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Separate and Joint Effects of Diabetes Mellitus and Chronic Kidney Disease on the Risk of Acute Coronary Syndrome

A Population-Based Cohort Study

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Abstract: Patient with diabetes (DM) and chronic kidney disease (CKD) are at a higher risk of developing acute coronary syndrome (ACS). However, only a few studies have investigated the separate and joint effects of DM and CKD on the risk of ACS, especially population-based studies under age-, sex- and various cardiovascular risk factor-stratifications. By using a national diabetes cohort derived from the Taiwan National Health Insurance Research Database, we identified a total of 416,143 DM and 541,724 non-DM patients, including 51,208 DM/CKD and 8,894 non-DM/CKD patients, in 2000 who did not have a history of ACS (ICD-9: 410.X, 413.9, 411.1) before 2000. We then prospectively investigated the incidence of ACS by linking to inpatient claims data from 2000 to 2007. A Cox proportional hazard model was used to estimate the relative risk of ACS in individuals with DM and/or CKD under various stratifications.

Age- and sex-specific incidence rates were similar between the non-DM/CKD and DM/non-CKD groups, except for female patients under 45 years, in whom DM was associated with a higher risk of ACS than CKD (8.21 vs. 3.82 per 1000 person-years). In the group aged <45 years, the DM/non-CKD patients were associated with a higher relative hazard of ACS than those in the non-DM/CKD group when compared with the non-DM/non-CKD group (men: adjusted hazard ratios [AHR]:1.77; 95% confidence interval [CI]:1.61–1.93 vs. 1.42 [95% CI: 0.73–2.73]; women 1.97 [95% CI: 1.76–2.20] vs. 1.13 [95% CI: 0.36–3.52]). This discrepancy in AHR was reduced with increasing age. The co-existence of DM and CKD further enhanced the AHR in a multiplicative independent manner. A significant age-modification effect was noted in the DM individuals regardless of their CKD status, but not in the non-DM/CKD group. In stratification by various cardiovascular risk factors, diabetes had a higher risk of ACS than CKD in patients with ≤2 selected risk factors, with the exception of the hyperlipidemia and hypertension subgroup. When all three selected risk factors were included, CKD was associated with a higher risk of ACS than DM (AHR: 1.43 [1.27–1.60] vs. 1.25 [1.22–1.29]). In conclusion, DM and CKD were associated with different levels of risk for ACS according to age, sex and certain cardiovascular risk factors. Strategies aimed at preventing ACS should therefore be individualized according to the presence of DM, CKD and various cardiovascular risk factors.

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Abbreviations: ACS = acute coronary syndrome, AHR = adjusted hazard ratio, CHD = Coronary heart disease, CKD = chronic kidney disease, CV = cardiovascular, DM = diabetes mellitus, ESRD = end-stage renal disease, ICD-9 = International Statistical Classification of Diseases and Related Health Problems, 9th edition, ICD-9-CM = International Statistical Classification of Diseases and Related Health Problems, 9th edition, Clinical Modification, IR = incidence rate, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database.

INTRODUCTION

Diabetes mellitus (DM) and chronic kidney diseases (CKD) are a growing threat to public health.[1–6] The number of patients with CKD and DM had risen abruptly in the past few decades worldwide, and management for the related complications characteristic of both illnesses has been associated with a heavy medical financial burden in many countries.[5,7–9] Cardiovascular diseases, including acute coronary syndrome (ACS), are among the major causes of morbidity and mortality in patients with CKD and DM, and the risk for cardiovascular events has been reported to exit even in the early stages of both illnesses.[2,3,7,10] Therefore, patients with CKD or DM are considered to be at a very high risk of developing coronary heart disease (CHD), or even a CHD equivalent.[3,11–15]

Aging and male gender are two known detrimental risk factors for coronary events. DM and CKD have also been reported to increase the risk of developing coronary events; however, little is known about the age-specific coronary effects that occur in association with DM and/or CKD. In addition, only a very few studies have simultaneously investigated both the separate and the combined effects of DM and CKD on the risks of coronary events via head-to-head comparisons.[16–18] Moreover, DM and CKD usually co-exist with many common

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risk factors for coronary events, such as hyperlipidemia and hypertension. How the presence of DM and/or CKD per se, independently of these coronary disease risk factors, further increase the risk of coronary events is still unclear. This study aimed to investigate the risks for first ever cases of ACS onset in relation to DM and CKD both separately and jointly across different spectra, including age, sex, and selected cardiovascular risk factors (i.e., hypertension, hyperlipidemia, and previous CHD history) in a nationally representative diabetic cohort selected from the National Health Insurance Research Database (NHIRD).

METHODS

Data Source

The Taiwan National Health Insurance (NHI) program was initiated in March 1995.[19] Up to 99% of the 23 million residents of Taiwan currently receive medical care through the NHI program. In addition, over 96% of the hospitals (including over 100 regional and tertiary care hospitals) and clinics in Taiwan are contracted to provide health care services, which are reimbursed by the Bureau of NHI, and all data related to these services are collected and input into the NHIRD by the National Health Research Institutes (NHRI) to provide a comprehensive record of medical care.[19] The NHRI release these data for research purposes, and numerous high quality studies have been published based on data from the NHIRD.[20–24] The in-hospital health care database makes an epidemiological study of ACS in relation to DM and/or CKD possible, because nearly all patients with ACS are hospitalized to receive optimal medical care.

Identification of Diabetic, Non-diabetic, CKD and Dialysis Groups

In this study, we used an established diabetes cohort, which included 615,532 diabetic and 614,871 age- and sex-matched control subjects selected from the NHIRD from 1997 to 2000 after ethical approval by the NHRI. Details of this diabetes cohort have been described previously.[20] Briefly, a diabetes-related diagnosis was coded using the International Statistical Classification of Diseases and Related Health Problems, 9th edition (ICD-9) code 250 or A181. All patients who had an initial diabetes-related diagnosis in the year 2000 and another diagnosis within the same year were classified into the diabetes group, with the interval between these two visits of more than 30 days. Individuals who had been admitted to hospitals for any kind of malignancy (ICD-9: 140–208) from 1997 to 1999 were then excluded. The index date in this group was defined as the date of their first visit for diabetes care in 2000. In the non-diabetes group, any subject diagnosed as having diabetes or malignancy during 1997 to 1999 was excluded. Using a sex- and age-matched technique, a total of 614,871 non-diabetic individuals were chosen. The index date in the non-diabetes group was defined as the date when each subject enrolled in the NHI program. If the first date of enrolment was before January 1, 2000, the index date was set as January 1, 2000.

We defined the diagnosis of CKD as the following ICD-9-CM codes: 016.0, 095.4, 189.0, 189.9, 223.0, 236.91, 250.4, 271.4, 274.1, 283.11, 403.×1, 404.×2, 404.×3, 440.1, 442.1, 447.3, 572.4, 580–588, 591, 642.1, 646.2, 753.12–753.17, 753.19, 753.2, and 794.4, in accordance with the recommendations from the United States Renal Data System report.[25] Patients who had made at least two visits (with the interval between the two visits being more than 30 days) for CKD care in an outpatient clinic within 1 year or had been diagnosed with CKD from inpatient claims during 1997 to 1999 were defined as having CKD. Patients on dialysis were identified from outpatient or inpatient claims using ICD-9 code: 585.6 combined with copayment code "001", which indicated the presence of a catastrophic illness. In addition, patients with a diagnosis of ACS and those receiving dialysis during 1997 to 1999 were excluded.

The enrolled patients were further divided into the following groups: (1) non-DM/non-CKD group; (2) non-DM/CKD group; (3) DM/non-CKD group; and (4) DM/CKD group. The follow-up period, from January 1, 2000 to December 31, 2007, was used to establish the onset of ACS. The incidence of CKD during the follow-up period for the DM/non-CKD group was three to four times higher than that of the non-DM/non-CKD group, and this may have caused significant statistical bias in the analyses. Therefore, the patients in these two groups with new physician-diagnosed CKD during the follow-up period were excluded. Since the incidence of new-onset diabetes did not increase in the CKD patients,[26] they were not excluded (Figure 1).

Endpoint of the Study

The endpoint of this study was the initial onset of ACS during the 8-year follow-up period. Since nearly all patients with ACS are hospitalized for optimal medical care, only inpatients with a discharge diagnosis of ICD-9-CM codes 410.X (acute myocardial infarction), 413.9 (unstable angina), and 411.1 (intermediate syndrome) were defined as having reached the end point. The index date of the endpoint was defined as the first day of hospitalization. When patients died due to causes unrelated to ACS, or they required maintenance dialysis during the follow-up period, the date of mortality or receiving dialysis was defined as the date of censoring.

Identification of Clinical Risk Factors and Other Covariates

Certain clinical risk factors, including hypertension (ICD-9: 401–402, 405, A260), hyperlipidemia (ICD-9: 272.0–272.4, A182), and CHD (ICD-9: 414.8 and 414.9) were identified for analysis and risk factor-stratification. The patients who had been diagnosed as having these risk factors before reaching the endpoint or prior to censoring were considered to have these comorbidities. The age of each subject was calculated by the difference between the index date and the date of birth. Moreover, the geographic area of the patients was defined as the location of their NHI unit, which was likely the area of their residence or workplace.

Statistical Methods

The age- and sex-specific incidence rates (IRs) expressed as person-years were calculated using the Poisson assumption. Cox proportional hazard regression models were conducted to analyze the overall, sex- and age-specific effects of diabetes and CKD, both separately and jointly, on the risk of ACS. The Cox model was further used to assess the risk of ACS in the patients with diabetes or CKD and various cardiovascular risk factors. Aside from the common ACS risk factors, including age, sex, hypertension, hyperlipidemia, and previous CHD history,[15,27–30] we adjusted for insurance premium as a surrogate marker of socioeconomic status,[31] which was an independent risk factor for ACS, in the Cox model. Since an urban–rural difference has been reported to affect the accessibility and utilization of medical care in Taiwan,[32] geographic area was also adjusted for in the Cox model. The potential effect-modification by sex

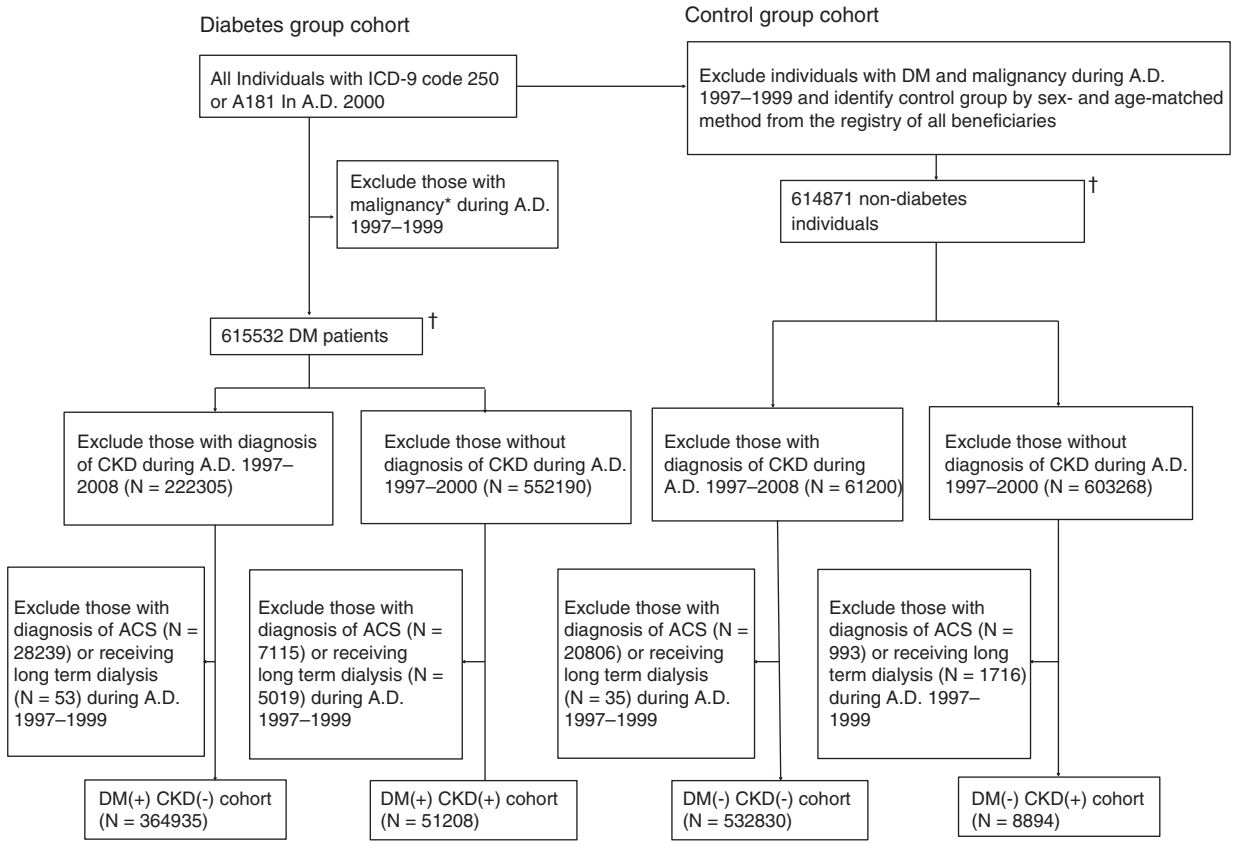

FIGURE 1. The flow diagram of individuals selection in our cohort study. ∗Malignancy: (ICD-9: 140–208). †The inconsistent number between diabetes and control cohort was due to the missing information in diabetes group (N = 661).

(or age) for the relationships between DM/CKD and ACS was assessed according to the statistical significance of the interaction term of DM/CKD and sex (or age). All statistical analyses were performed with SAS version 9.2 (SAS Institute, Cary, NC). A $P < 0.05$ was considered statistically significant.

RESULTS

The Baseline Characteristics of the Study Population

In total, 416,143 diabetic (51,208 with CKD) and 541,724 non-diabetic (8894 with CKD) patients were included in the study (Figure 1). The patients in the non-DM/CKD group were the oldest (66.5 ± 10.8 years), followed by those in the DM/CKD group (62.5 ± 12.4 years). The mean age of the patients in the non-DM/non-CKD and DM/non-CKD groups was similar (59.7 ± 13.0 and 59.5 ± 13.1 years, respectively). With the exception of the non-DM/CKD patients, the patients in the other three groups were mostly female. In addition, the distributions of insurance premium, geographic area, and urbanization were similar in the study groups. The patients in the DM/CKD group had the highest proportions of the selected comorbidities, while the lowest proportion was seen in the non-DM/non-CKD group (Table 1). The median follow-up period were 6.6, 7.7, 8.0, and 8.0 years in the DM/CKD, DM/non-CKD, non-DM/CKD, and non-DM/non-CKD groups, respectively.

Age- and Sex-Specific Incidence Rates and Adjusted Hazard Ratios of ACS in the Four Study Groups

Table 2 and Supplementary Table 1 (http://links.lww.com/MD/A97) show the overall, age- and sex-specific IRs, and adjusted hazard ratios (AHRs) of ACS. The IRs for ACS increased with increasing age in all study groups. The non-DM/non-CKD group had the lowest ACS event rates for men (12.82 per 1000 patient-years) and women (13.93 per 1000 patient-years) in the whole age-groups, whether the DM/CKD group had the highest overall ACS event rates of 30.97 and 31.84 per 1000 patient-years in men and women, respectively. In addition, the overall sex-specific IR was slightly higher in the non-DM/CKD group compared with the DM/non-CKD group (24.82 vs. 20.11 per 1000 patient-years in men; 23.80 vs. 21.53 per 1000 patient-years in women). Similar IRs were found in both the non-DM/CKD and the DM/non-CKD groups across all age stratifications, except in females aged <45 years, in which the DM/non-CKD group had a higher IR than the non-DM/CKD group (8.21 vs. 3.82 per 1000 person-years).

In male subjects, diabetes alone conferred a similar risks for ACS as CKD alone, with an AHR of 1.47 [95% CI: 1.37–1.59], when compared with the non-DM/non-CKD group (Table 2). The AHR increased to 1.99 [95% CI: 1.92–2.06] in male patients with DM/CKD. Similar magnitudes and patterns of AHRs were observed in the female subjects. Age-specific analysis showed that the increased risks of ACS in the non-DM/

TABLE 1. The Baseline Clinical Characteristics of the Study Subjects

	Non-DM				DM			
	Without-CKD‡		With CKD‡		Without-CKD‡		With CKD‡	
Variables*	n	%	n	%	n	%	n	%
Socio-demographic variables								
Age (years)								
<45	66,696	12.5	305	3.4	49,221	13.5	4519	8.8
45–64	265,475	49.8	3173	35.7	180,450	49.4	22,687	44.3
>64	200,659	37.7	5416	60.9	135,262	37.1	24,002	46.9
Mean (±SD)	59.7 ± 13.0		66.5 ± 10.8		59.5 ± 13.1		62.5 ± 12.4	
Sex								
Male	253,898	47.6	4688	52.7	172,892	47.5	25,277	49.4
Female	278,932	52.4	4206	47.3	191,466	52.5	25,904	50.6
Insurance premium (NTD)								
Dependent	132,936	25.0	2612	29.3	97,670	26.8	15,110	29.5.
<Median (19,200)	116,373	21.8	2167	24.4	79,291	21.7	12,120	23.7
≥Median	283,521	53.2	4115	46.3	187,974	51.5	23,978	46.8
Mean (±SD)†	20,534.5 ± 15,405.4		17498.7± 14299.2		20,023.8 ± 14,801.6		18,020.1 ± 13,796.7	
Geographic area								
Northern	236,525	44.9	4000	45.4	165,700	46.1	21,200	41.8
Central	129,724	24.6	2251	25.5	79,332	22.0	13,012	25.7
Southern	144,719	27.5	2348	26.7	103,769	28.8	15,065	29.7
Eastern	15,720	3.0	211	2.4	11,238	3.1	1402	2.8
Urbanization status								
Metropolis	212,652	40.3	3546	40.2	152,391	42.2	21,591	42.6
Satellite city/town	141,783	26.8	2356	26.7	95,388	26.4	12,807	25.2
Rural area	173,901	32.9	2924	33.1	113,087	31.3	16,339	32.2
Comorbidities§								
Hypertension								
No	248,255	46.6	1739	19.5	77,731	21.3	5909	11.5
Yes	284,575	53.4	7155	80.5	287,204	78.7	45,299	88.5
Hyperlipidemia								
No	364,265	68.4	4528	50.9	116,596	32.0	14,076	27.5
Yes	168,565	31.6	4366	49.1	248,339	68.0	37,132	72.5
Coronary heart diseases								
No	445,966	83.7	6301	70.8	274,002	75.1	34,381	67.1
Yes	86,864	16.3	2593	29.2	90,933	24.9	16,827	32.9
Total	532,830	100.0	8894	100.0	364,935	100.0	51,208	100.0

CKD = chronic kidney disease; DM = diabetes mellitus; NTD = New Taiwan dollars; SD = standard deviation.
* Inconsistency between the total population and the population summed for individual variable was due to missing information.
† Dependent insurers were not included.
‡ CKD ICD-9-CM codes: 016.0, 095.4, 189.0, 189.9, 223.0, 236.91, 250.4, 271.4, 274.1, 283.11, 403.×1, 404.×2, 404.×3, 440.1, 442.1, 447.3, 572.4, 580–588, 591, 642.1, 646.2, 753.12–753.17, 753.19, 753.2, and 794.4.
§ Hypertension (ICD-9: 401–402, 405, A260), Hyperlipidemia (ICD-9: 272.0–272.4, A182), Coronary heart diseases (ICD-9: 414.8 and 414.9).

CKD patients were similar across all age stratifications in both men and women, whereas age showed a significant modification effect on the risk of ACS in both DM/non-CKD and DM/CKD groups. The AHR associated with DM/non-CKD patients decreased gradually from 1.77, 1.52, to 1.39 for male subjects aged <45, 45 to 64, and >64 years, respectively ($P < 0.001$). The corresponding AHRs for male patients with DM/CKD also diminished from 2.34, 2.14 to 1.86 ($P < 0.001$). In contrast, the AHRs remained constant in the male subjects in the non-DM/CKD group aged <45 years, 45 to 64 years, and >64 years (1.42, 1.42 and 1.49, respectively; $P = 0.82$). Similar results were noted for the female subjects. Moreover, the magnitude of the increase in hazard ratios for ACS among the patients in the DM/CKD group was nearly equal to the direct multiplication product of the AHRs of DM and CKD, which indicated the multiplicatively independent effect of DM and CKD on the risk for ACS. For example, in the male subjects aged 45 to 64 years, the AHR of the DM/CKD group (2.14) was nearly the same as the direct product of AHRs of the non-DM/CKD and DM/non-CKD groups (2.16).

AHRs for ACS in Relation to Diabetes and CKD Alone With Other Selected Risk Factors

Table 3 shows the relative hazards of ACS in relation to diabetes and CKD according to the presence of various

TABLE 2. Overall and Age- and Sex-Specific Incidence Rates (IRs) and Relative Hazards of Acute Coronary Syndrome in Relation to Diabetes and CKD

		Overall and Age-Specific Incidence Rates (IRs) and Adjusted Hazard Ratios (HRs)* (95% Confidence Interval [CI])								#
		<45 years		45–64 years		>64 years		Total		
DM	CKD	IR† (per 1,000 Patient-Years)	Adjusted HR* (95% CI)	IR† (per 1000 Patient-Years)	Adjusted HR* (95% CI)	IR† (per 1,000 Patient-Years)	Adjusted HR* (95% CI)	IR† (per 1000 Patient-Years)	Adjusted HR* (95% CI)	*P*-value
Men										
No	No	3.72	1.00	11.11	1.00	20.34	1.00	12.82	1.00	
No	Yes	6.41	1.42 (0.73–2.73)	17.50	1.42¶ (1.22–1.64)	31.52	1.49¶ (1.36–1.63)	24.82	1.47¶ (1.37–1.59)†	0.82
Yes	No	8.74	1.77¶ (1.61–1.93)	18.92	1.52¶ (1.48–1.57)	29.15	1.39¶ (1.35–1.43)	20.11	1.47¶ (1.44–1.50)‡	<0.001
Yes	Yes	12.76	2.34¶ (1.99–2.74)	28.10	2.14¶ (2.02–2.25)	39.63	1.86¶ (1.77–1.95)	30.97	1.99¶ (1.92–2.06)§	<0.001
Women										
No	No	2.97	1.00	11.80	1.00	20.10	1.00	13.93	1.00	
No	Yes	3.82	1.13 (0.36–3.52)	18.76	1.47¶ (1.27–1.69)	28.76	1.39¶ (1.25–1.54)	23.80	1.42¶ (1.31–1.54)†	0.51
Yes	No	8.21	1.97¶ (1.76–2.20)	19.60	1.51¶ (1.47–1.56)	29.01	1.43¶ (1.39–1.46)	21.53	1.48¶ (1.45–1.51)‡	<0.001
Yes	Yes	13.16	2.80¶ (2.32–3.37)	29.10	2.16¶ (2.06–2.27)	39.13	1.91¶ (1.83–2.00)	31.84	2.04¶ (1.98–2.11)§	<0.001

CI = confidence interval; CKD = chronic kidney disease; DM = diabetes mellitus; HR = hazard ratio; IR = incidence rate.
* Based on Cox proportional hazard regression with adjustment for age, sex, insurance premium, geographic area, urbanization status, hypertension, hyperlipidemia, and coronary heart diseases.
† *P*-value for effect-modification by sex = 0.47.
‡ *P*-value for effect-modification by sex = 0.93.
§ *P*-value for effect-modification by sex = 0.65.
¶ $P < 0.05$.
# *P*-value for effect-modification by age.

cardiovascular (CV) risk profiles. After adjusting for baseline characteristics, the DM/CKD group still had the highest risk of ACS across various risk factors stratifications. In subjects without any selected risk factor, diabetes increased the risk of ACS by a magnitude of 146% (AHR: 2.46 [95% CI: 2.35–2.57]), while CKD only conferred an increased risk of 67% (AHR: 1.67 [95% CI: 1.34–2.08]). In contrast, in subjects with all three selected risk factors, CKD conferred a higher risk of ACS than diabetes (AHR: 1.43 [95% CI: 1.27–1.60] vs. 1.25 [95% CI: 1.22–1.29], respectively). The effect of diabetes on the risk of ACS was higher than CKD in the subjects with ≤2 selected CV risk factors, except in the hyperlipidemia + hypertension subgroup. Therefore, there was a tendency for the discrepancy in AHR between the DM/non-CKD and non-DM/CKD groups to be diminished as the number of risk factors increased. Furthermore, the multiplicative independent effect of diabetes and CKD on the risk for ACS was also observed in different risk factor-stratification subgroups.

DISCUSSION

In this population-based cohort study, diabetes and CKD were both found to be associated with a higher risk of ACS.

TABLE 3. Selected Clinical Risk Factor(s)-Specific Relative Hazards of Acute Coronary Syndrome in Relation to Diabetes (DM) and Chronic Kidney Disease (CKD)

	Acute coronary syndrome		
	No	Yes	AHR* (95% CI)
Non-DM/non-CKD subjects without clinical risk factors	182,838	9863	1.00 (reference)
DM/non-CKD subjects without clinical risk factors	25,363	2464	2.46† (2.35–2.57)
Non-DM/CKD subjects without clinical risk factors	948	81	1.67† (1.34–2.08)
DM/CKD subjects without clinical risk factors	1607	191	3.39† (2.94–3.92)
Non-DM/non-CKD subjects with hyperlipidemia only	38,030	2785	1.00 (reference)
DM/non-CKD subjects with hyperlipidemia only	37,825	3761	1.70† (1.61–1.78)
Non-DM/CKD subjects with hyperlipidemia only	443	42	1.30 (0.96–1.77)
DM/CKD subjects with hyperlipidemia only	2844	425	2.58† (2.33–2.86)
Non-DM/non-CKD subjects with hypertension only	113,137	13,704	1.00 (reference)
DM/non-CKD subjects with hypertension only	55,670	8571	1.53† (1.49–1.58)
Non-DM/CKD subjects with hypertension only	2102	287	1.44† (1.28–1.63)
DM/CKD subjects with hypertension only	7287	1082	2.01† (1.89–2.14)
Non-DM/non-CKD subjects with past-history of CHD only	7847	1500	1.00 (reference)
DM/non-CKD subjects with past-history of CHD only	2024	500	1.58† (1.43–1.75)
Non-DM/CKD subjects with past-history of CHD only	105	23	1.39 (0.91–2.12)
DM/CKD subjects with past-history of CHD only	201	42	1.61† (1.19–2.19)
Non-DM/non-CKD subjects with hyperlipidemia + hypertension	76,537	9072	1.00 (reference)
DM/non-CKD subjects with hyperlipidemia + hypertension	123,600	16,748	1.31† (1.28–1.35)
Non-DM/CKD subjects with hyperlipidemia + hypertension	2087	311	1.34† (1.20–1.51)
DM/CKD subjects with hyperlipidemia + hypertension	17,788	3157	1.99† (1.91–2.07)
Non-DM/non-CKD subjects with past-history CHD + hyperlipidemia	4547	845	1.00 (reference)
DM/non-CKD subjects with past-history CHD + hyperlipidemia	4716	1078	1.42† (1.30–1.56)
Non-DM/CKD subjects with past-history CHD + hyperlipidemia	79	18	1.22 (0.76–1.94)
DM/CKD subjects with past-history CHD + hyperlipidemia	484	115	1.53† (1.25–1.86)
Non-DM/non-CKD subjects with past-history CHD + hypertension	28,696	6680	1.00 (reference)
DM/non-CKD subjects with past-history CHD + hypertension	17,426	4578	1.32† (1.27–1.37)
Non-DM/CKD subjects with past-history CHD + hypertension	785	197	1.31† (1.14–1.51)
DM/CKD subjects with past-history CHD + hypertension	2889	777	1.76† (1.63–1.90)
Non-DM/non-CKD subjects with past-history of CHD, hyperlipidemia and hypertension	30,406	6343	1.00 (reference)
DM/non-CKD subjects with past-history of CHD, hyperlipidemia and hypertension	49,044	11,567	1.25† (1.22–1.29)
Non-DM/CKD subjects with past-history of CHD, hyperlipidemia and hypertension	1079	307	1.43† (1.27–1.60)
DM/CKD subjects with past-history of CHD, hyperlipidemia and hypertension	9553	2766	1.76† (1.69–1.85)

AHR = adjusted hazard ratio; CHD = coronary heart disease; CKD = chronic kidney disease; DM = diabetes mellitus.
* Based on Cox proportional hazard regression with adjustment for age, sex, insurance premium, geographic area, and urbanization status.
† $P < 0.05$.

However, the magnitude of association varied across different age-, sex- and risk factor-stratifications. In general, diabetes had a greater negative effects than CKD in the younger patients (<45 years) and in the patients without or with a small number of CV risk factors. On the other hand, CKD conferred a similar risk of ACS to that of diabetes in the older patients, especially in those aged >64 years of age, or with more selected CV risk factors. Moreover, we also noted that diabetes and CKD multiplicatively contributed to the risk of ACS regardless of age, gender, and cardiovascular risk factors, which is similar to findings reported in patients with diabetes and end-stage renal disease (ESRD).[28]

Our results revealed that age may modify the risk of ACS in diabetic patients regardless of CKD status, which is consistent with previous studies.[29,33] Younger diabetic patients have been reported found to be at a higher risk of CV diseases than older diabetic patients, mainly due to poor glycemic control, adverse health-related behaviors, and irregular assessment of diabetes-related complications in younger diabetic patients.[33] On the other hand, our study showed no significant modification effect by age for the relationship between CKD and ACS ($P = 0.820$ and 0.511, in men and women, respectively). Since we adjusted for several major traditional CV risk factors, a possible explanation is that non-traditional CV risk factors, such as mineral metabolism dysregulation and inflammation, can enhance vascular calcification and arterial stiffness, which therefore accelerates the process of vascular aging in patients with CKD.[34] Premature arterial aging can further contribute to the excess burden of ischemic heart disease in CKD patients, in concert with numerous other risk factors, including endothelial dysfunction, oxidative stress, accelerated thrombosis, and malnutrition.[34] In addition, even intensive modification of both traditional and non-traditional CV risk factors has been reported to be unable to reduce the incidence of ACS in CKD patients.[35] Thus, the presence of CKD may superpose a constant excess hazard with regard to the risk of ACS beyond an age effect, which might partly explain the mechanism related to the constant effect of CKD in the different age groups (Table 2). Evidence supporting the concept of acceleration of premature vascular aging in CKD patients was also revealed in the current study. The incidence rates of ACS in the CKD patients aged between 45 and 64 years were similar to those of the non-CKD patients older than 64 years in both the diabetes and the non-diabetes groups (Table 2), and this phenomenon was more prominent in the patients with diabetes. Large prospective clinical trials are needed to explore strategies to lower the risk of ACS in CKD patients.

Compared with the patients without DM and CKD, both diabetes and CKD were found to enhance the risk of ACS. However, different weights of the relative hazard of diabetes and CKD were found in various CV risk factor stratifications. Diabetes conferred a higher risk of ACS than CKD in the patients without any selected risk factors. As the number of risk factors increased, the effect of CKD approached that of diabetes and was even higher if all selected risk factors were present. The CKD patients were prone to have more selected risk factors if they were in the advanced stages of CKD, and it is biologically plausible that more non-traditional risk factors emerge as CKD stages progresses. This suggested an enhanced effect of non-traditional risk factors on the future risk of ACS in patients with advanced stage CKD. Previous studies have suggested that estimating the risk of future CV events using traditional CV risk factors only (via Framingham risk equation) is inadequate for patients with diabetes and CKD population.[36,37] Therefore, the different relative hazards related to diabetes and CKD in the various selected risk factor stratifications may highlight the distinct effect of non-traditional risk factors for ACS in these two populations. Preventing and controlling both traditional and non-traditional CV risk factors simultaneously may be essential to control the heavy burden of CV events burden in patients with diabetes and CKD populations.

Only a few studies revealed the effect of CKD on the risk of ACS in patients under the age of 45. The findings of this study suggest that younger (<45 years) female patients with CKD tended to have the lowest risk of ACS (AHR: 1.13 [95% CI: 0.36–3.52]). The biological mechanism may be a result of the fact that estrogen can ameliorate the negative impact induced by CKD. In one study comparing the effect of estrogen use and its relationship to renal function,[38] the use of estrogen was found to better preserve renal function than in those not receiving estrogen in cross-sectional analysis; however, these results were not found in prospective analysis. The interaction between estrogen and various CV risk factors in patients with CKD population still needs to be clarified in further studies.

In our previous study, diabetes and ESRD were demonstrated to contribute to the risk of acute myocardial infarction in a nearly multiplicative effect.[28] We speculated that different penetrations of disease-specific CV risk factors among diabetes and ESRD patients might explain this phenomenon. Similar findings related to the effect of diabetes and non-dialysis CKD on the risk of ACS in this study further extended our previous hypothesis to non-dialysis CKD patients. The magnitude of the increased risk for ACS in the patients with both diabetes and CKD also nearly reached the value of the direct multiplicative product of those with either diabetes or CKD alone. Because patients with ESRD were excluded before enrolment and the CKD patients were censored when they developed ESRD, the effect of CKD on ACS could not be explained by the presence of ESRD.

Several previous studies compared the effect of CKD and diabetes on the risk of CV events, and concluded that CKD conferred a similar CV risk as diabetes in different study populations.[14,15,17,18] However, our study results showed that this effect was not constant across various age-, sex- and risk factor-stratifications. Thus, it may not be appropriate to treat CKD in the same manner as diabetes in all patients. The graded differences in the risk of ACS in the DM and CKD patients with different ages and CV risk factors suggest that individualized management of ACS is warranted in different target populations to optimize the utilization of medical resources and avoid possible treatment-related side effects. For example, women with CKD who are >45 years old or CKD patients without any selected CV risk factors may not need as intensive management as diabetic patients. Different therapeutic goals, such as the control of hypertension or lipid profiles and the use of antiplatelet agents for primary prevention, should be considered according to the presence of diabetes, CKD, CV risk factors, and age. Intensive screening strategies and therapies may therefore be reserved for patients who value the potential benefits of the management to a greater extent than the potential harm, especially in CKD patients at a low risk of ACS because clinical evidence involving the effects of these treatments is still limited.[39,40]

This study has several strengths. First, the NHIRD covers most of the residents in Taiwan and contains data on most of the

medical services that beneficiaries receive. Such a sizable study population in a real-world setting can avoid most of the selection and recall bias or missing information related to medical conditions which can arise in referral subjects, volunteers, or clinical trial populations. Thus, the results of our study are probably more generalizable. Second, this large and diverse database provides sufficient power by which to investigate the effects of DM and CKD on the incidence of ACS, especially with regard to age, sex, and various CV risk factors. This allowed us to clarify the separate and joint effects of DM and CKD according to various clinical conditions.

There are several limitations to this study. First, the exclusive reliance on the claims data may have resulted in disease misclassification. However, we used at least two visits for diabetes or CKD-related diagnoses that were >30 days apart to reduce the likelihood of misclassification.[20,29] In our non-DM population, 1.64% of the patients were found to have CKD after excluding subjects with cancer and ACS before the start of follow-up. This is generally consistent with the proportion of patients having CKD (2.1%), including patients with cancer identified from a non-diabetic Medicare population using a method similar to that reported by Foley et al[41] Second, some individuals in the non-DM/CKD and non-DM/non-CKD groups may have developed diabetes during the follow-up period. However, the overall 5-year incidence of diabetes is 197.0 per 100,000 population in Taiwan.[42] The contribution of newly diagnosed diabetes to the non-DM/CKD group were therefore to be considered low. In addition, the misclassification in the non-DM/non-CKD (control) group is likely to be non-differential, which would tend to underestimate the true relative hazard. Third, due to limited information available from the claims data, not all traditional and non-traditional CV risk factors or confounders were adjusted for, such as smoking, body mass index, proteinuria amount, and the concurrent use of medications. Furthermore, a lack of the records for the estimated glomerular filtration rate made it impossible to provide detailed CKD stage information in our study population. Since the prevalence of hypertension is around 56.6% to 77.6% in CKD stage III–V patients in Taiwan,[1] which is consistent with the results found in our non-DM/CKD group, we speculate that most of our CKD patients were likely to have CKD stage III-V. Fourth, since dialysis per se has different impacts on ACS, we did not extend the follow-up period after the initiation of dialysis in our CKD patients. However, this is likely to have underestimated the risk of ACS in our non-dialysis-dependent CKD population because dialysis patients have a higher risk of ACS than non-dialysis-dependent CKD patients.

In summary, we found that diabetes conferred a higher risk of ACS than CKD in younger patients (<45 years) and in those with fewer CV risk factors, and that the difference in the risk was minimized in older patients (≥45 years) and in those with more CV risk factors. In addition, age was found to modify the risk of ACS in patients with diabetes, but not in those with CKD alone. Furthermore, the presence of both diabetes and CKD further enhance the risk of ACS in a multiplicatively independent effect. Management for the primary prevention of ACS in patients with diabetes/CKD should be individualized by taking into account age, sex, and CV risk factors.

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