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

A Population-Based Cohort Study

Yu-Tzu Chang, MSc, MD, Chih-Ching Liu, MSc, Liang-Miin Tsai, MD, Chung-Yi Li, PhD, and Junne-Ming Sung, MD

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.

(Author’s ORCID iDs: Yu-Tzu Chang, https://orcid.org/0000-0001-5978-4261; Chih-Ching Liu, https://orcid.org/0000-0001-5837-7709; Liang-Miin Tsai, https://orcid.org/0000-0001-8106-0159; Chung-Yi Li, https://orcid.org/0000-0001-5767-7436; Junne-Ming Sung, https://orcid.org/0000-0002-2434-7810)

INTRODUCTION

Diabetes mellitus (DM) and chronic kidney diseases (CKD) are a growing threat to public health. 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. 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. 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.

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 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. Moreover, DM and CKD usually co-exist with many common
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, 283.1, 403.1, 404.1–4, 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, 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
(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 \( \pm \) 10.8 years), followed by those in the DM/CKD group (62.5 \( \pm \) 12.4 years). The mean age of the patients in the non-DM/non-CKD and DM/non-CKD groups was similar (59.7 \( \pm \) 13.0 and 59.5 \( \pm \) 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 co-morbidities, 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/
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 risk factors.
| DM  | CKD  | <45 years | 45–64 years | >64 years | Total |
|-----|------|-----------|-------------|-----------|-------|
|     |      | IR (per 1,000 Patient-Years) | Adjusted HR* (95% CI) | IR (per 1,000 Patient-Years) | Adjusted HR* (95% CI) | IR (per 1,000 Patient-Years) | Adjusted HR* (95% CI) | IR (per 1,000 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 (1.22–1.64) | 24.82  | 1.47 (1.37–1.59) | <0.001 |
|     | 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-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\(^1\) (2.35–2.57) |
| Non-DM/CKD subjects without clinical risk factors | 948 | 81 | 1.67\(^1\) (1.34–2.08) |
| DM/CKD subjects without clinical risk factors | 1607 | 191 | 3.33\(^1\) (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\(^1\) (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\(^1\) (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\(^1\) (1.49–1.58) |
| Non-DM/CKD subjects with hypertension only | 2102 | 287 | 1.44\(^1\) (1.28–1.63) |
| DM/CKD subjects with hypertension only | 7287 | 1082 | 2.01\(^1\) (1.89–2.14) |
| **Non-DM/non-CKD subjects with past-history of CHD only** | 2087 | 311 | 1.34\(^1\) (1.20–1.51) |
| DM/non-CKD subjects with past-history of CHD only | 2024 | 500 | 1.58\(^1\) (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 | 2844 | 425 | 2.58\(^1\) (2.33–2.86) |
| **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\(^1\) (1.28–1.35) |
| Non-DM/CKD subjects with hyperlipidemia + hypertension | 2087 | 311 | 1.34\(^1\) (1.20–1.51) |
| DM/CKD subjects with hyperlipidemia + hypertension | 17,788 | 3157 | 1.99\(^1\) (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\(^1\) (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\(^1\) (1.25–1.86) |
| **Non-DM/non-CKD subjects with past-history CHD, hyperlipidemia and hypertension** | 28,696 | 6680 | 1.00 (reference) |
| DM/non-CKD subjects with past-history CHD, hyperlipidemia and hypertension | 17,426 | 4578 | 1.32\(^1\) (1.27–1.37) |
| Non-DM/CKD subjects with past-history CHD, hyperlipidemia and hypertension | 785 | 197 | 1.31\(^1\) (1.14–1.51) |
| DM/CKD subjects with past-history CHD, hyperlipidemia and hypertension | 2889 | 777 | 1.76\(^1\) (1.63–1.90) |
| **Non-DM/non-CKD subjects with past-history of CHD, hyperlipidemia and hypertension** | 9553 | 2766 | 1.76\(^1\) (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.

\(^1\) 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).38

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 the 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. Both 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 anti-platelet 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 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. 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 the 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. However, the overall 5-year incidence of diabetes is 197.0 per 100,000 population in Taiwan. 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, 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.

ACKNOWLEDGMENTS

The authors would like to extend grateful thanks to the National Health Research Institutes for kindly providing the data for analysis. The interpretation and conclusions in the current study do not represent those of the National Health Research Institutes.

REFERENCES

1. Wen CP, Cheng TY, Tsai MK, et al. All-cause mortality attributable to chronic kidney disease: a prospective cohort study based on 462 293 adults in Taiwan. Lancet. 2008;371:2173–2182.

2. Meguid El Nahas A, Bello AK. Chronic kidney disease: the global challenge. Lancet. 2005;365:331–340.

3. Levey AS, Coresh J, Balk E, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Ann Intern Med. 2003;139:137–147.

4. Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. Nature. 2001;414:782–787.

5. Danaei G, Finucane MM, Lu Y, et al. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. Lancet. 2011;378:31–40.

6. Herman WH, Zimmet P. Type 2 diabetes: an epidemic requiring global attention and urgent action. Diabetes care. 2012;35:943–944.

7. Couser WG, Remuzzi G, Mendis S, Tonelli M. The contribution of chronic kidney disease to the global burden of major noncommunica-

diseases. Kidney Int. 2011;80:1258–1270.

8. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. JAMA. 2007;298:2038–2047.

9. Chen L, Magliano DJ, Zimmet PZ. The worldwide epidemiology of type 2 diabetes mellitus – present and future perspectives. Nat Rev Endocrinol. 2012;8:228–236.

10. Chiu YL, Chen KL, Lin SL, et al. Outcomes of stage 3–5 chronic kidney disease before end-stage renal disease at a single center in Taiwan. Nephron Clin Pract. 2008;109:C109–118.

11. National Kidney F. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002;39(2 Suppl. 1):S1–S266.

12. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction – executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). Circulation. 2004;110:588–636.

13. Levey AS, Beto JA, Coronado BE, et al. Controlling the epidemic of cardiovascular disease in chronic renal disease: what do we know? What do we need to learn? Where do we go from here? National Kidney Foundation Task Force on Cardiovascular Disease. Am J Kidney Dis. 1998;32:853–906.

14. Raskin I, Sehgal AR, Rahman M, O’Connor AS. The case for chronic kidney disease, diabetes mellitus, and myocardial infarction being equivalent risk factors for cardiovascular mortality in patients older than 65 years. Am J Cardiol. 2008;102:1668–1673.

15. Reiner Z, Catapano AL, De Backer G, et al. ESC Committee for Practice Guidelines (CPG) 2004–2010 and 2010–2012 Committees. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J. 2011;32:1769–1818.

16. Weiner DE, Tighiouart H, Amin MG, et al. Chronic kidney disease as a risk factor for cardiovascular disease and all-cause mortality: a pooled analysis of community-based studies. J Am Soc Nephrol. 2004;15:1307–1315.
17. Debella YT, Gidumda HD, Light RP, Agarwal R. Chronic kidney disease as a coronary disease equivalent – a comparison with diabetes over a decade. *Clin J Am Soc Nephrol*. 2011;6:1385–1392.

18. Tonelli M, Munter P, Lloyd A, et al. Risk of coronary events in people with chronic kidney disease compared with those with diabetes: a population-level cohort study. *Lancet*. 2012;380:807–814.

19. Bureau of National Health Insurance. 2001 National Health Insurance Annual Statistical Report. Taipei, Taiwan; 2002.

20. Chen HF, Chen P, Li CY. Risk of malignant neoplasms of liver and biliary tract in diabetic patients with different age and sex stratifications. *Hepatology*. 2010;52:155–163.

21. Lai MN, Wang SM, Chen PC, et al. Population-based case-control study of Chinese herbal products containing aristolochic acid and urinary tract cancer risk. *J Natl Cancer Inst*. 2010;102:179–186.

22. Wu CY, Kuo KN, Wu MS, et al. Early Helicobacter pylori eradication decreases risk of gastric cancer in patients with peptic ulcer disease. *Gastroenterology*. 2009;137:1641–1648 e1641–1642.

23. Tsan YT, Lee CH, Wang JD, Chen PC. Statins and the risk of hepatocellular carcinoma in patients with hepatitis B virus infection. *J Clin Oncol*. 2012;30:623–630.

24. Lai MN, Lai JN, Chen PC, et al. Risks of kidney failure associated with consumption of herbal products containing Mu Tong or Fangchi: a population-based case-control study. *Am J Kidney Dis*. 2010;55:507–518.

25. US Renal Data System. Annual data report (2006) Appendix a. Bethesda, MD. Available from http://www.usrds.org/adr.htm, accessed 8 April 2014.

26. Pham H, Robinson-Cohen C, Biggs ML, et al. Chronic kidney disease, insulin resistance, and incident diabetes in older adults. *Clin J Am Soc Nephrol*. 2012;7:588–594.

27. Gao AS, Moraffarian D, Roger VL, et al. Heart disease and stroke statistics – 2014 update: a report from the American Heart Association. *Circulation*. 2014;129:e28–e292.

28. Chang YT, Wu JL, Hsu CC, et al. Diabetes and end-stage renal disease synergistically contributed to increased incidence of cardiovascular events: a nationwide follow-up study during 1998–2009. *Diabetes care*. 2014;37:277–285.

29. Chen HF, Li CY. Effect-modifications by age and sex on the risks of coronary artery disease and revascularization procedures in relation to diabetes. *Diabetes Res Clin Pract*. 2007;75:88–95.

30. Sarnak MJ, Levey AS. Cardiovascular disease and chronic renal disease: a new paradigm. *Am J Kidney Dis*. 2000;35(4 Suppl. 1):S117–131.

31. Kaplan GA, Keil JE. Socioeconomic factors and cardiovascular disease: a review of the literature. *Circulation*. 1993;88 (4 Pt. 1):1973–1998.

32. Tan HF, Tseng HF, Chang CK, et al. Accessibility assessment of the Health Care Improvement Program in rural Taiwan. *J Rural Health*. 2005;21:372–377.

33. O’Connor PJ, Desai JR, Solberg LI, et al. Variation in diabetes care by age: opportunities for customization of care. *BMC Fam Pract*. 2003;4:16.

34. London G, Covic A, Goldsmith D, et al. Arterial aging and arterial disease: interplay between central hemodynamics, cardiac work, and organ flow – implications for CKD and cardiovascular disease. *Kidney Int Suppl*. 2011;1:10–12.

35. Rakhi DJ, Marwick TH, Armstrong KA, et al. Effect of aggressive risk factor modification on cardiac events and myocardial ischaemia in patients with chronic kidney disease. *Heart*. 2006;92:1402–1408.

36. Coleman RL, Stevens RJ, Retnakaran R, Holman RR. Framingham, SCORE, and DECODE risk equations do not provide reliable cardiovascular risk estimates in type 2 diabetes. *Diabetes care*. 2007;30:1292–1293.

37. Weiner DE, Tighiouart H, Elsayed EF, et al. The Framingham predictive instrument in chronic kidney disease. *J Am Coll Cardiol*. 2007;50:217–224.

38. Fung MM, Poddar S, Bettencourt R, et al. A cross-sectional and 10-year prospective study of postmenopausal estrogen therapy and blood pressure, renal function, and albuminuria: the Rancho Bernardo Study. *Menopause*. 2011;18:629–637.

39. Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet*. 2011;377:2181–2192.

40. Palmer SC, Di Micco L, Razavian M, et al. Effects of antiplatelet therapy on mortality and cardiovascular and bleeding outcomes in persons with chronic kidney disease: a systematic review and meta-analysis. *Ann Intern Med*. 2012;156:445–459.

41. Foley RN, Murray AM, Li S, et al. Chronic kidney disease and the risk for cardiovascular disease, renal replacement, and death in the United States Medicare population, 1998 to 1999. *J Am Soc Nephrol*. 2005;16:489–495.

42. Tseng CH, Tseng CP, Chong CK, et al. Increasing incidence of diagnosed type 2 diabetes in Taiwan: analysis of data from a national cohort. *Diabetologia*. 2006;49:1755–1760.