International Urology and Nephrology (2019) 51:1219–1227
https://doi.org/10.1007/s11255-019-02157-7

NEPHROLOGY - ORIGINAL PAPER

Incidence and risk of major adverse cardiovascular events in middle-aged patients with chronic kidney disease: a population-based cohort study

Shiauyee Chen[1,2] · Wen-yen Hsu[1] · Yen-Nung Lin[1,3] · Chien-Yung Wang[1] · Chien-Hua Wu[4] · Kwang-Hwa Chang[1,3]

Received: 17 January 2019 / Accepted: 16 April 2019 / Published online: 24 April 2019

Abstract

Purpose For early prevention, information regarding the incidence of major adverse cardiovascular events (MACEs) in middle-aged patients with chronic kidney disease (CKD) may be more beneficial than that regarding MACE prevalence. But, literature comparing the incidence and risk of MACEs in middle-aged patients with CKD with the controls using a population-based cohort study is scant. Our aim was to estimate the incidence and risk of MACEs, such as congestive heart failure (CHF) and ischemic heart disease (IHD), in middle-aged patients with advanced (stages 3–5) CKD.

Methods From the National Health Insurance Research Database, 261 patients aged 35–65 years who had received advanced CKD diagnoses in 2000 and 1305 age-, sex-, and comorbidity-matched controls were recruited. Patients with CHF alone (MACE 1), IHD alone (MACE 2), or CHF and IHD (MACE 3) diagnoses between January 1, 2001, and December 31, 2008, were identified in the CKD and control groups.

Results Patients (mean age ± standard deviation, 50.0 ± 8.3 years; female, 56%) exhibited a higher incidence of MACE 1, MACE 2, and MACE 3 (11.9 vs. 1.4/1000, 30.7 vs. 13.4/1000, and 13.4 vs. 1.7/1000 person-years, respectively, all $p < 0.001$) and were at a higher risk of experiencing MACEs than the controls (adjusted hazard ratios: MACE 1, MACE 2, and MACE 3: 8.57, 2.26, and 3.80, respectively, all $p < 0.001$).

Conclusions CKD is an independent risk factor for CHF and IHD among patients aged 35–65 years. Early intervention for preventing CHF and IHD in middle-aged patients with CKD is crucial.

Keywords Chronic kidney disease · Congestive heart failure · Ischemic heart disease · Incidence

Introduction

Chronic kidney disease (CKD) is common worldwide, with a prevalence of 10–20% [1]. Patients with CKD often exhibit multimorbidity, and CKD has a high mortality rate [2]. CKD occurred before the age of 65 years in 39% of patients who died of it [3]. Furthermore, major adverse cardiovascular events (MACEs), such as congestive heart failure (CHF) and ischemic heart disease (IHD), which are the leading causes of mortality in the general population [4], are prevalent in patients with CKD [5]. Patients with stage 3–5 (advanced) CKD exhibited a higher probability of experiencing MACEs than those with stage 1–2 CKD [5, 6]. Additionally, the MACE-related mortality is > 20-fold higher in patients on dialysis aged < 65 years than in the general population of the same age [7]. Being an outcome evaluation [8], MACEs often include CHF, IHD, fatal arrhythmia, and death [9]. Of them, both CHF and IHD are two established cardiovascular diseases [10] which have long-term clinical course and are preventable [11]. They share similar pathophysiologic mechanisms and have close interaction [12]. Therefore, preventing CHF and IHD in middle-aged patients with advanced CKD is crucial for reducing MACE-related mortality [13].

✉ Kwang-Hwa Chang
chang2773@gmail.com

1 Department of Physical Medicine and Rehabilitation, Wan Fang Hospital, Taipei Medical University, 111, Section 3, Hsing-Long Rd., Taipei 116, Taiwan

2 School of Respiratory Therapy, College of Medicine, Taipei Medical University, Taipei, Taiwan

3 Graduate Institute of Injury Prevention and Control, College of Public Health, Taipei Medical University, Taipei, Taiwan

4 Department of Applied Mathematics, Chung-Yuan Christian University, Chungli, Taoyuan, Taiwan

Although most studies have estimated the prevalence of MACEs in patients with CKD to assess its burden on these [14, 15], for early prevention, information regarding the incidence and risk of MACEs in middle-aged patients with CKD may be more beneficial than that regarding MACE prevalence. However, a long-term follow-up study is necessary to estimate the incidence of a medical condition [16]. In addition, when studies are conducted over many years, the reliability of the follow-up data often causes concern.

Under the Taiwanese law, *National Health Insurance (NHI) Act*, the NHI program has been implemented in Taiwan since 1995. The program is a mandatory comprehensive medical care program, which covers 99% of the population of Taiwan. The program's healthcare providers and the insured are regulated by the National Health Insurance Administration, Ministry of Health and Welfare. The diagnosis of a major illness is often made based on the medical associations' guideline. For example, the Taiwan society of cardiology has regularly released guidelines for the diagnosis of hypertension [17] and CHF [18]. All health record data of more than 22 million participants, including longitudinal medical claims, such as diagnoses and medical services, for each enrollee in Taiwan, were compiled to construct the NHI Research Database (NHIRD). The data of the NHIRD are continuously collected by the National Health Insurance Administration and are managed and periodically released by the government. Since medical claims are submitted for payment under the NHI program and are regularly audited by the program's authority, the accuracy of data from the NHIRD is acceptable. Cheng et al. demonstrated that the NHIRD can offer a valid source of health information related to cardiovascular diseases [19]. Using data from the NHIRD, more than 2700 peer-reviewed articles have been published since 2001 [20]. Since the NHIRD offers comprehensive longitudinal medical information regarding Taiwan's population [21], it was used to conduct a population-based cohort study for measuring the incidence and risk of MACEs in patients with CKD. However, information regarding the severity of medical conditions is limited in the NHIRD. Patients to whom a disability identification document has been issued are exempted from copayment and can be identified in the NHIRD. Patients with long-term functional impairment after an illness can apply for disability evaluation and verification in the Eligibility Determination System of Disability in Taiwan [22]. Patients with renal function impairment with a creatinine clearance rate of < 60 mL/min (stages 3–5) after medical treatment for at least 3 months are issued an official identification document for urinary disability. Thus, patients with advanced (stage 3–5) CKD can be identified in the NHIRD.

To our knowledge, literature comparing the incidence and risk of MACEs in middle-aged patients with CKD with those in age-, sex-, and comorbidity-matched controls using a population-based cohort study is scant. This comparison may be crucial for establishing a suitable MACE prevention policy for middle-aged patients with CKD. In this study, we used data from the NHIRD to estimate the incidence and risk of CHF and IHD in middle-aged patients with advanced CKD.

Methods

For this prospective population-based cohort study, NHIRD data between January 1, 2000, and December 31, 2008, were analyzed. The NHIRD contains data of 1 million patients randomly selected in 2000. The research process included two phases (Fig. 1). Phase I identified the study sample from January 1, 2000 to December 31, 2000 in the database. This phase focused on achieving balance in the covariates between the CKD and control patients. Those patients who had had a prior history of CHF and IHD were also excluded during the baseline period. Phase II identified the secondary conditions among the participants from January 1, 2001 to December 31, 2008. The study analyzed those MACE-related factors and estimated their contribution to the risk of developing CHF and IHD during the follow-up period.

Phase I

We identified patients who had received CKD diagnoses in 2000 using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 582–586. The patients aged 35–65 years with disability identification documents were included in the study. The ages of the patients were calculated according to the dates of their first medical claims in the database. In total, 296,885 patients aged 35–65 years, including 290 CKD patients and 296,595 non-CKD patients were identified between January 1, 2000 and December 31, 2000 in the database.

In addition to CKD, the other most common disability-related health conditions, based on the Taiwan Data Bank of Persons with Disabilities [23], include schizophrenia (ICD-9-CM code 295), intellectual disabilities (317–319), autism (299.0), intractable epilepsy (345), hearing impairment (389), retinal disorder (362), glaucoma (365), cataract (366), visual impairment (369), optic neuropathy (377), cleft palate and cleft lip (749), organic sleep apnea (780.5 and 327.2), cardiac dysrhythmias (426–427), congenital heart disease (745–746), cerebral vascular accident (431–438), cerebral palsy (343), poliomyelitis (045 and 138), scar conditions and fibrosis of skin (709.2), and burn injury (941–949). Those health conditions may be also at risk of MACE. Patients with these conditions, alone or in combination with CKD, were hence identified between January 1, 2000, and December 31, 2000 and excluded from the study.

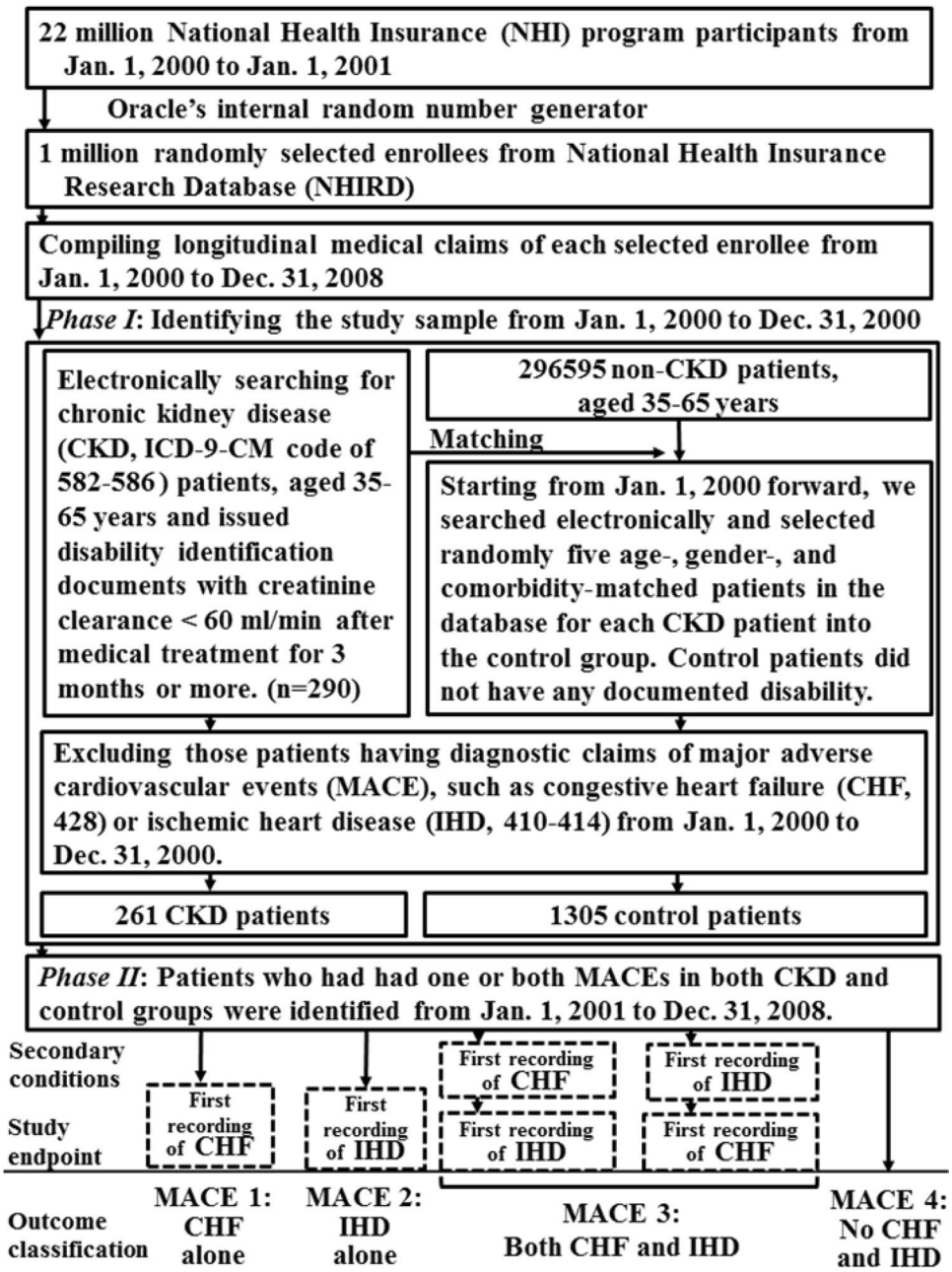

Fig. 1 Flowchart and outcome classifications of the study. Phase I: recruitment of patients with chronic kidney disease (CKD) and the controls in 2000. Phase II: identification of patients experiencing congestive heart failure (CHF) and ischemic heart disease (IHD) during the follow-up period (2001–2008)

For each patient with CKD, 5 age-, sex-, and comorbidity-matched patients were recruited as controls. Each control patient was no more than 1 year older or younger than the matched patient with CKD. MACEs and CKD often coexist and have similar risk factors such as hypertension (ICD-9-CM codes 401–405), diabetes mellitus (250), and hyperlipidemia (272.0–272.4) [24]. Therefore, comorbidity matching was based on these illnesses. The controls did not have any documented disabilities. Due to dealing with a small number of covariates [25] and a more than 1:1 matching ratio [26], the study searched electronically and selected randomly the age-, sex-, hypertension-, diabetes-, and hyperlipidemia-matched controls from the 296,595 non-CKD patients, rather than using a propensity-score technique. The study monitored the outcome variables of CHF (ICD-9-CM code 428) and IHD (ICD-9-CM codes 410–414) for 1 year before enrolling our participants. The patients with diagnostic claims for CHF and IHD in the records of ambulatory or inpatient care before January 1, 2001 were considered to have a prior history of these illnesses and were excluded from this study.

To improve the identification accuracy of an illness, patients were only included if they had received one corresponding diagnosis during inpatient care, at least three

corresponding diagnoses during ambulatory visits with at least one of which being the primary diagnosis, or both. The identification criteria may be rigorous. For the identification of CKD and the matching comorbidities, patients were included if they met these criteria between January 1, 2000, and December 31, 2000. For CHF and IHD, patients were included if they had met the aforementioned criteria between January 1, 2001, and December 31, 2008.

Phase II

Figure 1 presents the flowchart and outcome classifications of the study. Patients with diagnostic claims for CHF alone, IHD alone, or both in the CKD and control groups during the follow-up period were identified. Thus, this study identified four mutually exclusive outcome classifications, namely CHF alone (MACE 1), IHD alone (MACE 2), both CHF and IHD (MACE 3), and neither CHF nor IHD (MACE 4). The study counted only the first MACEs. For patients with CHF alone or IHD alone, the end date of the study coincided with the date of the first record of CHF or IHD in the database (Fig. 1). Among patients experiencing both CHF and IHD, the CHF records of some patients were dated before their IHD records, while the CHF records of the other patients were dated after their IHD records. The end date coincided with the first record date of the condition that was identified later. For patients without CHF or IHD during the study period, in both groups, the end date of the study was December 31, 2008. Considering that a MACE may also be associated with other medical conditions, we calculated the frequencies of comorbidities in the CKD and control groups during the follow-up period. The comorbidities with significantly higher frequencies in the patients with MACEs than in those without MACEs, and those with significantly higher frequencies in the CKD group than in the control group between January 1, 2001, and December 31, 2008 were considered MACE-related factors. The study was approved by the Joint Institutional Review Boards of Taipei Medical University.

Statistical analysis

The differences in the clinical characteristics and incidence of each MACE outcome classification between the CKD and control groups were compared using the Pearson Chi squared test or Poisson regression test. Since the results were not normally distributed (Kolmogorov–Smirnov test, $p < 0.05$), patients' ages at the beginning and at the endpoint of the study were analyzed using the Mann–Whitney U test. Cox proportional hazards regression analyses with a forward stepwise method were used to assess the risk factors for each MACE outcome. Variables entered into the analyses included CKD, sex, age, and MACE-related factors. In addition to hypertension, diabetes mellitus, and hyperlipidemia, the MACE-related factors included cardiac dysrhythmias, chronic bronchitis, and cataract. Patients with those MACE-related factors were included if they had met the aforementioned identification criteria between January 1, 2001, and December 31, 2008. Those variables found to be significantly associated in the univariate analyses were entered into the multivariate analyses. Before performing the multivariate analyses, independent variables were checked for multicollinearity using phi coefficient (φ) or univariate logistic model. The interactions of any two significant variables were also entered for analyses in different regression models. The study used -2 log likelihood value for assessing the goodness-of-fit of each model. Kaplan–Meier curves were used to estimate the cumulative MACE-free probability of the CKD and control groups during the study. These two curves for each MACE outcome classification were compared using the log-rank test. The data were analyzed using the SAS software (version 9.1, SAS Institute Inc, Cary, NC, USA). The differences between the two groups were considered significant if the corresponding p values were < 0.05. After applying the Bonferroni correction, the variables entered into Cox proportional hazards models were considered significant if the corresponding p values were < 0.005.

Results

In this study, 261 patients (mean age ± standard deviation, 50.0 ± 8.3 years; female, 56%) who had received CKD diagnoses between January 1, 2000, and December 31, 2000, as well as 1305 control patients were identified from the NHIRD. The distributions of age and sex, and the frequencies of the matching comorbidities were similar between the CKD and control groups (Table 1). In the CKD group, 22, 53, and 25 patients (incidence: 11.9/1000, 30.7/1000, and 13.4/1000 person-years, respectively) exhibited MACE 1, MACE 2, and MACE 3, respectively, during the 8-year study period (Table 2). The incidence of MACEs (1–3) was significantly higher in all patients with CKD group than in the control group. In the CKD and control groups, the incidence of MACEs 1–3 did not differ significantly between sexes. In the CKD group, the occurrence of MACE-related factors in patients with and without MACEs was similar (Table 3). Patients with CKD exhibited a lower cumulative MACE-free (1–3) probability than the controls (Fig. 2).

Using the phi coefficient, diabetes mellitus was correlated to hypertension ($\varphi = 0.18$, $p < 0.001$), hyperlipidemia ($\varphi = 0.05$, $p = 0.04$), and cataract ($\varphi = 0.10$, $p < 0.001$); sex was correlated to hyperlipidemia ($\varphi = -0.13$, $p < 0.001$), diabetes mellitus ($\varphi = 0.08$, $p = 0.002$), and cardiac dysrhythmias ($\varphi = 0.05$, $p = 0.04$); and cataract was correlated

Table 1 Clinical characteristics of patients with CKD and controls

Group	Patients with CKD			Controls		
	Female ($n=148$)	Male ($n=113$)	Total ($n=261$)	Female ($n=740$)	Male ($n=565$)	Total ($n=1305$)
Age, year	50.4 ± 8.3	49.5 ± 8.2	50.0 ± 8.3	50.4 ± 8.3	49.5 ± 8.2	50.0 ± 8.2
Study duration, years/person	7.2 ± 1.6	7.1 ± 1.8	7.1 ± 1.7	7.6 ± 1.2	7.5 ± 1.2	7.6 ± 1.2
Diabetes mellitus	18 (12.2%)	20 (17.7%)	38 (14.6%)	90 (12.2%)	100 (17.7%)	190 (14.6%)
Hypertension	51 (34.5%)	40 (35.4%)	91 (34.9%)	255 (34.5%)	200 (35.4%)	455 (34.9%)
Hyperlipidemia	15 (10.1%)	4 (3.5%)	19 (7.3%)	75 (10.1%)	20 (3.5%)	95 (7.3%)

Data of categorical variables are expressed as numbers and percentages, and those of age and study duration as mean ± standard deviations

CKD chronic kidney disease

Table 2 Incidence (per 1000 person-years) of MACEs in the patients with CKD and controls

MACE outcome classification	Patients with CKD			Controls			Incidence rate ratio
	N (%)	Incidence	Age[a], year	*N* (%)	Incidence	Age, year	
MACE 1[b]							
Female	15 (10.1%)	14.3‡	57.6 ± 7.7	8 (1.1%)	1.4	62.5 ± 5.6	10.2
Male	7 (6.2%)	8.7†	49.5 ± 8.5	6 (1.1%)	1.4	61.7 ± 7.1	6.2
Total	22 (8.4%)	11.9‡	55.0 ± 8.7	14 (1.1%)	1.4	62.1 ± 6	8.5
MACE 2							
Female	27 (18.2%)	27.4‡	53.7 ± 8.9	66 (8.9%)	12.3	57.1 ± 8.7	2.2
Male	26 (23.0%)	34.9‡	54.9 ± 7.4	59 (10.4%)	14.8	57.9 ± 8.2	2.4
Total	53 (20.3%)	30.7‡	54.3 ± 8.2*	125 (9.6%)	13.4	57.5 ± 8.4	2.3
MACE 3							
Female	15 (10.1%)	14.1‡	54.9 ± 9.9	11 (1.5%)	2.0	58.2 ± 7.3	7.1
Male	10 (8.9%)	12.5‡	59.6 ± 7.2	6 (1.1%)	1.4	57.7 ± 7.2	8.9
Total	25 (9.6%)	13.4‡	56.8 ± 9.1	17 (1.3%)	1.7	58.1 ± 7.0	7.9

MACE major adverse cardiovascular event, *CKD* chronic kidney disease

* $p<0.05$, † $p<0.005$, ‡ $p<0.001$ (Poisson regression test, compared with the control group)

[a]Mean ± standard deviation of age at the first record of the MACE outcome classification

[b]MACE 1, congestive heart failure only; MACE 2, ischemic heart disease only; and MACE 3, congestive heart failure and ischemic heart disease during the study period

Table 3 Comparisons of comorbidities between patients with and without MACEs in the CKD and control groups

Variable, units	CKD group			Control group			Intergroup comparison[b]
MACE	Yes ($n=100$)	No ($n=161$)	Intragroup comparison[a]	Yes ($n=156$)	No ($n=1149$)	Intragroup comparison[a]	
Diabetes mellitus	21 (21)	22 (13.7)	0.12	48 (30.8)	166 (14.5)	< 0.0001	–
Hypertension	36 (36)	41 (25.5)	0.07	71 (45.5)	307 (26.7)	< 0.0001	–
Hyperlipidemia	11 (11)	18 (11.2)	0.96	30 (19.2)	149 (13)	0.03	–
Cardiac dysrhythmias	4 (4)	10 (6.2)	0.44	10 (6.4)	16 (1.4)	0.0004	0.0001
Chronic bronchitis	11 (11)	14 (8.7)	0.54	15 (9.6)	38 (3.3)	0.0002	0.02
Cataract	20 (20)	9 (5.6)	0.0003	5 (3.2)	12 (1)	0.04	< 0.0001

Values are represented as number (%)

MACE major adverse cardiovascular event, *CKD* chronic kidney disease

[a]Comparisons between patients with and without MACEs in each group (Pearson's Chi squared test or Fisher's exact test)

[b]Comparisons between the CKD and control groups (McNemar test)

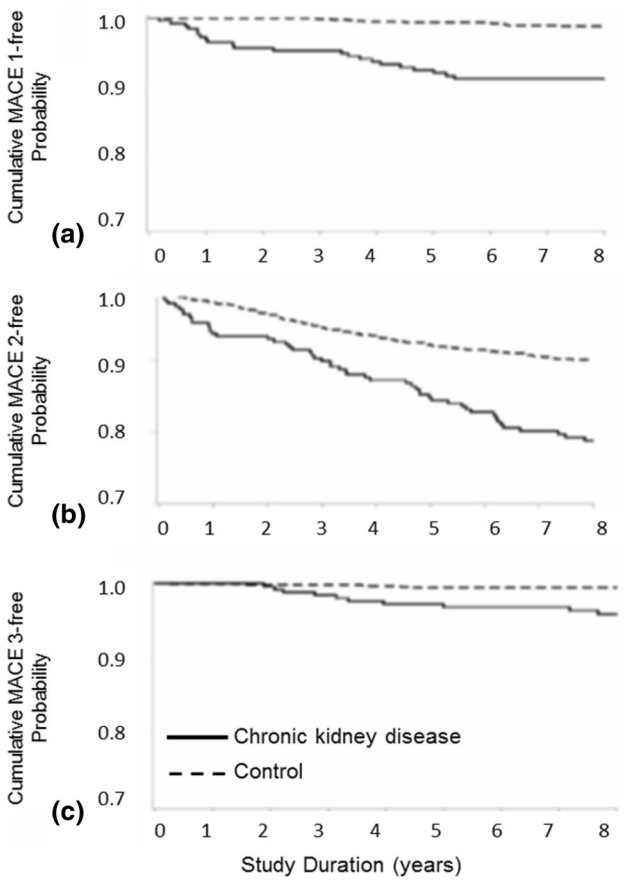

Fig. 2 Kaplan–Meier plots for cumulative major adverse cardiovascular event (MACE)-free probability with age for **a** congestive heart failure alone (MACE 1), **b** ischemic heart disease alone (MACE 2), and **c** congestive heart failure and ischemic heart disease (MACE 3) among patients with chronic kidney disease (CKD, solid line, $n=261$) and controls (dashed line, $n=1305$). **a** The estimated cumulative MACE 1-free probability (±standard error) of patients with CKD at the end of the study (0.914 ± 0.017) was significantly lower than that of the controls (0.989 ± 0.003) (log-rank test, $p<0.001$). **b** The estimated cumulative MACE 2-free probability of patients with CKD at the end of the study (0.788 ± 0.026) was significantly lower than that of the controls (0.901 ± 0.008) ($p<0.001$). **c** The estimated cumulative MACE 3-free probability of patients with CKD at the end of the study (0.900 ± 0.019) was significantly lower than that of the controls (0.987 ± 0.003) ($p<0.001$)

to hypertension ($\varphi=0.06$, $p=0.02$) and chronic bronchitis ($\varphi=0.16$, $p<0.001$). Using univariate logistic model, age was correlated to diabetes mellitus (odds ratio (OR) = 1.05, $p<0.001$), hypertension (OR = 1.03, $p<0.001$), hyperlipidemia (OR = 1.04, $p=0.004$), sex (OR = 0.99, $p=0.03$), cataract (OR = 1.22, $p=0.002$), and chronic bronchitis (OR = 1.15, $p=0.001$). Table 4 presents the univariate and multivariate analyses of the potential risk factors for MACEs 1–3. After adjustment for the significant variables identified in the univariate analyses, CKD, age, and coexisting hypertension were significant risk factors for IHD (MACEs 2 and 3); CKD and coexisting diabetes mellitus were significant factors for MACE 1; and CKD and coexisting hyperlipidemia were significant factors for MACE 2. The risk of MACEs during the 8-year study was higher in patients with CKD than for controls, thus yielding adjusted hazard ratios (95% confidence interval) of 8.57 (4.38–16.77), 2.26 (1.64–3.11), and 3.80 (2.96–4.89) for MACE 1, MACE 2, and MACE 3, respectively (all $p<0.001$).

Discussion

In this study, the incidence and additional risk of MACEs in patients with advanced CKD was estimated. Compared with the age-, sex-, and comorbidity-matched controls, middle-aged patients with CKD stage 3–5 exhibited a higher incidence of MACEs 1–3 (Table 2), an adjusted hazard ratio (of MACEs 1–3) of > 2 (Table 4), and a lower estimated cumulative MACE-free (1–3) probability throughout the study period (Fig. 2).

MACEs and their risk factors such as hypertension, diabetes mellitus, and hyperlipidemia are prevalent in patients with CKD [2]. The interactions among MACEs, CKD, and the concordant comorbidities are complex; hence, the contribution of CKD itself to the risk of MACEs remains unclear. To minimize the possible effects confounding factors between CKD and age, CKD and sex, and CKD and concordant comorbidities on the risk of MACEs, age as well as the distribution of sex, hypertension, diabetes mellitus, and hyperlipidemia were equalized between patients with CKD and their matched controls. Similarly, to account for the effect of sex on MACEs [11], the incidence of MACEs in female and male patients was separately analyzed. In the CKD group, the frequencies of MACE-related factors in patients with and without MACE were similar (Table 3). Considering all these variables, this study demonstrated that middle-aged patients with advanced CKD were at a higher risk of experiencing MACEs than the controls.

Focusing on early prevention of MACEs among middle-aged patients with CKD, the study estimated the incidence and risk of CHF and IHD which represents two established cardiovascular diseases [10] and are preventable [11]. Among adults with a mean age of 74.4 years, Americans with CKD stage 3–4 have a CHF incidence of 23/1000 person-years and an IHD incidence of 12/1000 person-years [27]. Compared with those findings, our participants experienced a similar CHF (MACEs 1 and 3, Table 2) incidence and a higher IHD (MACEs 2 and 3) incidence partly because our participants included CKD stage 5 and belonged to different races. In a cohort study on patients with CKD, Rahman et al. found that CHF can worsen patients' kidney function and cause progression to end-stage renal disease [28]. Our study revealed that middle-aged patients with

Table 4 Cox proportional hazards regression analyses of potential risk factors for MACEs in patients aged 35–65 years ($n=1566$)

Dependent variables	Univariate analyses		Multivariate analyses[a]		Goodness-of-fit statistics[b]
Independent variables, unit	Hazard ratio (95% confidence intervals)	*p* value	Adjusted hazard ratio (95% confidence intervals)	*p* value	
MACE 1[c]					475.0
CKD group, yes[d]	8.28 (4.24–16.19)	< 0.001	8.57 (4.38–16.77)	< 0.001	
Age, year	1.01 (1.01–1.1)	0.01	–	–	
Diabetes mellitus, yes	3.79 (1.94–7.40)	< 0.001	4.03 (2.06–7.88)	< 0.001	
Hypertension, yes	2.05 (1.01–3.95)	0.03	–	–	
Sex, male	0.74 (0.38–1.47)	0.40	–	–	
Cardiac dysrhythmias, yes	0	1.00	–	–	
Chronic bronchitis, yes	2.91 (0.40–21.24)	0.30	–	–	
Hyperlipidemia, yes	1.12 (0.34–3.66)	0.85	–	–	
Cataract, yes	17.79 (5.45–58.06)	< 0.001	–	–	
MACE 2					2515.1
CKD group, yes[d]	2.26 (1.64–3.12)	< 0.001	2.26 (1.64–3.11)	< 0.001	
Age, year	1.04 (1.02–1.06)	< 0.001	1.07 (1.04–1.10)	< 0.001	
Diabetes mellitus, yes	1.68 (1.18–2.40)	0.004	–	–	
Hypertension, yes	1.90 (1.42–2.55)	< 0.001	30.92 (4.33–221.01)	< 0.001	
Hyperlipidemia, yes	1.72 (1.10–2.71)	0.02	3.03 (1.70–5.38)	< 0.001	
Sex, male	1.22 (0.91–1.63)	0.19	–	–	
Cardiac dysrhythmias, yes	2.10 (0.52–8.47)	0.30	–	–	
Chronic bronchitis, yes	1.16 (0.29–4.68)	0.83	–	–	
Cataract, yes	1.90 (0.47–7.64)	0.37	–	–	
Age × hypertension			0.95 (0.91–0.99)	0.006	
Hyperlipidemia × hypertension			0.29 (0.11–0.77)	0.013	
MACE 3					3556.4
CKD group, yes[d]	3.77 (2.93–4.85)	< 0.0001	3.80 (2.96–4.89)	< 0.001	
Age, year	1.04 (1.03–1.06)	< 0.001	1.06 (1.03–1.08)	< 0.001	
Diabetes mellitus, yes	2.06 (1.55–2.73)	< 0.0001	–	–	
Hypertension, yes	1.96 (1.54–2.51)	< 0.0001	10.87 (2.19–54.00)	0.003	
Sex, male	1.07 (0.83–1.37)	0.60	–	–	
Cataract, yes	7.41 (3.66–14.99)	< 0.001	–	–	
Cardiac dysrhythmias, yes	1.43 (0.36–5.74)	0.61	–	–	
Chronic bronchitis, yes	1.20 (0.39–3.76)	0.75	–	–	
Hyperlipidemia, yes	1.45 (0.97–2.17)	0.07	–	–	
Age × hypertension			0.97 (0.94–1.00)	0.03	

MACE major adverse cardiovascular event, *CKD* chronic kidney disease

[a]After applying the Bonferroni correction, those variables found to be significantly associated in the univariate analyses ($p<0.005$) were entered into the multivariate analyses with a forward stepwise method. Only significant variables were shown in the multivariate models

[b]The study used −2 log likelihood value for goodness-of-fit statistics

[c]MACE 1, congestive heart failure alone; MACE 2, ischemic heart disease alone; and MACE 3, congestive heart failure and ischemic heart disease during the study period

[d]CKD group, patients with stages 3–5 chronic kidney disease; control group, age-, sex-, and comorbidity-matched patients without any documented disability (comorbidities: hypertension, diabetes mellitus, and hyperlipidemia)

CKD had a sevenfold higher CHF risk than the controls (Table 4). Thus, a vicious cycle of CKD and CHF develops. Djousse et al. demonstrated that healthy lifestyle habits, such as the performance of regular exercise, maintenance of an ideal body weight, abstinence from smoking, and moderate consumption of alcohol, as well as healthy dietary habits such as the sufficient intake of fruits, vegetables, and cereals, are associated with a lower CHF risk among healthy men [29]. The promotion of healthy lifestyle and dietary habits is necessary for patients with CKD to break the vicious cycle

and prevent a secondary condition of CHF. Bae et al. found that patients with advance CKD often experience non-ST elevation myocardial infarction [30]. In addition to changes in healthy lifestyle and dietary habits and managements of body weight and risk factors [31], the IHD prevention program for advance CKD patients should achieve a balance between myocardial oxygen supply and demand. Thus, middle-aged patients with CKD undoubtedly require integrated care provided by multidisciplinary teams of physicians, physiotherapists, dietitians, and nurses. For the early detection and prevention of left ventricular systolic dysfunction, a precursor of CHF, assessments using an electrocardiogram and echocardiogram may be required, particularly for asymptomatic patients with CKD who are at a risk of CHF [32, 33]. Drug therapy involving statins, low-dose aspirin, and antihypertensives can also reduce the risk of CHF and IHD [34]. However, patients with CKD should be cautious of using aspirin because they are also at risk of peptic ulcer disease [35]. Further work to measure the incidence and risk of other MACEs, such as cardiac dysrhythmias may be needed.

The study had several strengths, such as its population-based 8-year cohort design; the use of age-, sex-, and comorbidity-matched patients and controls to clarify the contribution of CKD to MACEs; the use of a reliable database that is audited and regulated by a national authority; and its focus on middle-aged patients for whom early prevention of secondary conditions is possible.

Limitations

The study had three major limitations. First, information regarding patients' clinical manifestations, blood pressure, severity of renal impairment, body weight, lifestyle status, smoking, drinking, and dietary habits could not be obtained from the secondary data analysis of NHIRD. But, the clinical practice guidelines to help physicians diagnose hypertension and CHF are regularly announced by the Taiwan society of cardiology [17, 18]. Those health record data are also regularly audited and regulated by the NHI program's authority [19]. And, the study used rigorous criteria to identify an illness, including hypertension and CHF. Taking all these factors into consideration, the identification accuracy of hypertension and CHF may be acceptable in the study. Contrariwise, because of the rigorous criteria, patients with newly developed CHF or IHD may not have been identified if the third record of the corresponding diagnoses during their ambulatory visits occurred after December 31, 2008. Second, because information about traveling history and mortality was lacking in the database, the study may exhibit a loss-to-follow-up bias if patients traveled abroad or died during the follow-up period. Thus, the incidence of MACEs could have been underestimated in the study. And third, the multivariate models did not have a good fit. Further work to analyze other clinical and sociodemographic information, such as body weight, lifestyle status, smoking, and dietary habits is needed.

Conclusions

The study offers crucial information regarding the incidence and added risks of MACEs in middle-aged patients with advanced CKD. CKD is an independent risk factor for MACEs. Early intervention is crucial for preventing secondary MACEs in patients with CKD. Studies on additional resource utilization by patients with CKD and the mortality rates of these patients who have experienced MACEs are recommended.

Acknowledgements This study is based in part on data from the National Health Insurance Research Database provided by the Bureau of National Health Insurance, Department of Health and managed by the National Health Research Institutes. The interpretation and conclusions contained herein do not represent those of the Bureau of National Health Insurance, Department of Health, or National Health Research Institutes. This manuscript was edited by Wallace Academic Editing.

Funding This study was supported by the Social and Family Affairs Administration, Ministry of Health and Welfare (Grant No. 104037), Taipei, and Wan Fang Hospital, Taipei Medical University (Grant No. 106TMU-WFH-02), Taipei, Taiwan. The funding sources had no role in the study design, collection, analysis or interpretation of the data, writing the manuscript, or the decision to submit the paper for publication.

Compliance with ethical standards

Conflict of interest The authors report no conflicts of interest.

References

1. Hill NR, Fatoba ST, Oke JL et al (2016) Global prevalence of chronic kidney disease—a systematic review and meta-analysis. PLoS ONE 11:e0158765
2. Tonelli M, Wiebe N, Guthire B et al (2015) Comorbidity as a driver of adverse outcomes in people with chronic kidney disease. Kidndy Int 88:859–866
3. Wen CP, Cheng TY, Tsai MK et al (2008) All-cause mortality attributable to chronic kidney disease: a prospective cohort study based on 462293 adults in Taiwan. Lancet 371:2173–2182
4. Mozaffarian D, Benjamin EJ, Go AS et al (2015) Heart disease and stroke statistics–2015 update: a report from the American Heart Association. Circulation 131:e29–e322
5. de Lusignan S, Chan T, Stevens P et al (2005) Identifying patients with chronic kidney disease from general practice computer records. Fam Pract 22:234–241
6. Limori S, Noda Y, Okado T et al (2013) Baseline characteristics and prevalence of cardiovascular disease in newly visiting or referred chronic kidney diseases patients to nephrology centers in Japan: a prospective cohort study. BMC Nephrol 14:152–163

7. Sarnak MJ, Levey AS, Schoolwerth AC et al (2003) Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Circulation 108:2154–2169
8. Kip KE, Hollabaugh K, Marroquin OC et al (2008) The problem with composite end points in cardiovascular studies: the story of major adverse cardiac events and percutaneous coronary intervention. J Am Coll Cardiol 51:701–707
9. Lin YS, Liu PH, Wu LS et al (2014) Major adverse cardiovascular events in adult congenital heart disease: a population-based follow-up study from Taiwan. BMC Cardiovasc Disord 14:38
10. Covic A, Gusbeth-Tatomir P, Goldsmith DJ (2006) The epidemics of cardiovascular disease in elderly patients with chronic kidney disease–two facets of the same problem. Int Urol Nephrol 38:371–379
11. McSweeney JC, Rosenfeld AG, Abel WM et al (2016) Preventing and experiencing ischemic heart disease as a woman: state of the science: a scientific statement from the American Heart Association. Circulation 133:1302–1331
12. Remme WJ (2000) Overview of the relationship between ischemia and congestive heart failure. Clin Clin Cardiol 23:IV4–IV8
13. Keith DS, Nichols GA, Gullion CM et al (2004) Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. Arch Intern Med 164:659–663
14. Levin A (2003) Clinical epidemiology of cardiovascular disease in chronic kidney disease prior to dialysis. Semin Dialysis 16:101–105
15. Foley RN, Parfrey PS, Sarnak MJ (1998) Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis 32:S112–S119
16. Brinks R, Landwehr S (2015) A new relation between prevalence and incidence of a chronic disease. Math Med Biol 32:425–435
17. Chiang CE, Wang TD, Lin TH et al (2017) The 2017 focused update of the guidelines of the Taiwan Society of Cardiology (TSOC) and the Taiwan Hypertension Society (THS) for the management of hypertension. Acta Cardiol Sin 33:213–225
18. Wang CC, Chen JH, Yu WC et al (2012) 2012 guidelines of the Taiwan Society of Cardiology (TSOC) for the diagnosis and treatment of heart failure. Acta Cardiol Sin 28:161–195
19. Cheng CL, Lee CH, Chen PS et al (2014) Validation of acute myocardial infarction cases in the national health insurance research database in Taiwan. J Epidemiol 24:500–507
20. Lin LY, Warren-Gash C, Smeeth L et al (2018) Data resource profile: the National Health Insurance Research Database (NHIRD). Epidemiol Health 40:e2018062
21. Wu CH, Liou TH, Hsiao PL et al (2011) Contribution of ischemic stroke to hip fracture risk and the influence of gender difference. Arch Phys Med Rehabil 92:1987–1991
22. Chiu WT, Yen CF, Teng SW et al (2013) Implementing disability evaluation and welfare services based on the framework of the international classification of functioning, disability and health; experiences in Taiwan. BMC Health Serv Res 13:416–424
23. Chang KH, Liao HF, Yen CF et al (2015) Association between muscle power impairment and WHODAS 2.0 in older adults with physical disability in Taiwan. Disabil Rehabil 37:712–720
24. Wilson PW, D'Agostino RB, Levy D et al (1998) Prediction of coronary heart disease using risk factor categories. Circulation 97:1837–1847
25. D'Agostino RB Jr (2007) Propensity scores in cardiovascular research. Circulation 115:2340–2343
26. Deb S, Austin PC, Tu JV et al (2016) A review of propensity-score methods and their use in cardiovascular research. Can J Cardiol 32:259–265
27. Chang TI, Tabada GH, Yang J et al (2016) Visit-to-visit variability of blood pressure and death, end-stage renal disease, and cardiovascular events in patients with chronic kidney disease. J Hypertens 34:244–252
28. Rahman M, Xie D, Feldman HI et al (2014) Association between chronic kidney disease progression and cardiovascular disease: results from the CRIC study. Am J Nephrol 40:399–407
29. Djousse L, Driver JA, Gaziano JM (2009) Relation between modifiable lifestyle factors and lifetime risk of heart failure. J Am Med Assoc 302:394–400
30. Bae EH, Lim SY, Cho KH et al (2012) GFR and cardiovascular outcomes after acute myocardial infarction: results from the Korea Acute Myocardial Infarction Registry. Am J Kidney Dis 59:795–802
31. Kohli P (2015) Primary and secondary prevention of ischemic heart disease in women. Curr Atheroscler Rep 17:38
32. Gencer B, Butler J, Bauer DC et al (2014) Association of electrocardiogram abnormalities and incident heart failure events. Am Heart J 167:869–875.e3
33. Atherton JJ (2010) Screening for left ventricular systolic dysfunction: is imaging a solution? JACC-Cardiovasc Imaging 3:421–428
34. Karmali KN, Lloyd-Jones DM, Berendsen MA et al (2016) Drugs for primary prevention of atherosclerotic cardiovascular disease: an overview of systematic reviews. JAMA Cardiol 1:341–349
35. Liang CC, Muo CH, Wang IK et al (2014) Peptic ulcer disease risk in chronic kidney disease: ten-year incidence, ulcer location, and ulcerogenic effect of medications. PLoS ONE 9:e87952