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Effect of Angiotensin-Converting Enzyme Inhibitors and/or Angiotensin Receptor Blockers on the Prevention of Death in Patients with Type 2 Diabetes and Undetermined Nephropathy : Five-Year Survival Data

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Abstract

Background: Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin Receptor Blockers (ARBs) are popular first-line agents for delaying the onset of diabetic nephropathy and diabetic kidney disease in diabetic patients without nephropathy and for reducing all causes of mortality in diabetic patients with nephropathy. However, long-term data showing a reduction in mortality from all causes or renal failure in type 2 diabetes patients with undetermined nephropathy taking ACEIs/ARBs are not available.

Objective: To compare renal and other causes of death between those treated and not treated with ACEIs/ARBs in type 2 diabetes patients who are non-nephropathic, nephropathic and have an undetermined nephropathy status.

Methods: Type 2 diabetes patients (n = 7,946) who registered with the Thailand Diabetes Registry Project (TDRP) in 2003 were followed-up prospectively for 5 years until January 25, 2008. Baseline demographic data and diabetic nephropathy status were recorded when the patient registered in the TDRP. Living statuses were retrieved from the database of each study site and causes of death were retrieved from the death certificates from the Bureau of Registration Administration of Thailand.

Results: There were 716 type 2 diabetic patients that died within 5 years of registration in the TPDR from all causes of death. Of these cases, 66 died from renal causes. The mortality incidence from renal causes in undetermined nephropathy patients who were treated and not treated with ACEIs/ARBs was 1.25 and 1.30 per 1000 person-years, respectively. After controlling for the propensity score, the competing risk analysis showed that treatment with ACEIs/ARBs was not significantly associated with prevention of death from renal or other causes in type 2 diabetes patients with an undetermined nephropathy status (HR = 0.83, 95% CI: 0.33-2.09, p-value = 0.688 for renal causes; HR = 1.26, 95% CI: 0.97-1.63, p-value = 0.085 for other causes). Treatment with ACEIs/ARBs was significantly associated with the prevention of renal and other causes of death in type 2 diabetes patients with nephropathy (HR = 0.49, 95% CI: 0.25-0.95, p-value = 0.034 for renal causes; HR = 0.73, 95% CI: 0.56-0.95, p-value = 0.019 for other causes).

Conclusions: Treatment with ACEIs or ARBs is not necessary for everyone, especially in type 2 diabetes patients with an undetermined nephropathy status. Healthcare services teams should screen for microalbuminuria before the treatment of all newly diagnosed type 2 diabetes patients with ACEIs or ARBs.

Introduction

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are popular first-line agents for delaying the onset of diabetic nephropathy and diabetic kidney disease because they are effective in reducing microalbuminuria [1-4]. The American Diabetes Association (ADA) recommends that for the treatment of non-pregnant patients with microalbuminuria, either ACEIs or ARBs should be prescribed [5]. A previous study has suggested that all middle-aged patients who meet the older diagnostic criteria for diabetes (glucose level ≥ 7.8 mmol/L) should receive ACEIs because it is a more cost-effective strategy in the diabetes population to give all middle-aged patients ACEIs than to screen for microalbuminuria [6]. A meta-analysis showed that ACEI treatment reduced all causes of mortality more than treatment with placebo and slowed progression from micro to macroalbuminuria [7,8]. However, long-term data showing a reduction in mortality from renal failure or all other causes in type 2 diabetes patients with an undetermined nephropathy status taking ACEIs/ARBs are not available. To fill this important gap in the current knowledge, we performed a retrospective

cohort study comparing the five-year mortality incidence to evaluate the effect of treatment with ACEIs/ARBs within the groups of different nephropathy statuses on the prevention of death in type 2 diabetes patients registered by Thailand Diabetes Registry Project (TDRP).

Methods

Study design and study population

For this retrospective cohort study, we included type 2 diabetes

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patients in the Thailand Diabetes Registry Project who were eighteen years or older and had no history of renal replacement or dialysis. This multi-center, hospital-based project was carried out from eleven tertiary care centers in university and regional hospitals across Thailand with one private hospital participating in the project.

Our study was conducted only in the ten tertiary care centers in the university and regional hospitals and included 7,946 type 2 diabetes patients who were classified by their nephropathy status. The patients were followed from their registration date until January 25, 2008, and the study endpoint was five-year mortality. The subjects were separated into three groups, non-nephropathic, nephropathic and undetermined nephropathy status, as shown in Figure 1. The study was approved by the ethical committees at each of the hospitals.

Data measurements

The baseline characteristics measured at registration were demographic data, clinical status of diabetes, diabetic complications and specific medication. These variables were retrieved from the Diabetes Registry Project's database for 2003.

The demographic data and clinical status of the diabetes patients were determined by interviewing and examining the patients. The measurement of diabetic complications was based on clinical diagnoses documented in medical records [9]. Microalbuminuria status was defined by a urine albumin to creatinine ratio above or equal to 3.5 mg/mmol or dipstick with proteinuria or creatinine levels greater than or equal to 152.52 μmol/L [10]. Patients with nephropathy were defined by the presence of at least two out of the three criteria for positive microalbuminuria. Patients without nephropathy were defined by the presence of at least two out of the three criteria for negative microalbuminuria. The subjects who did not have completed laboratory measurements were defined as the undetermined nephropathy group. The laboratory measurements were performed at each site [11].

Treatment with ACEIs or ARBs and other specific treatments were reviewed from the medical records by nurses and verified by clinicians. Specific treatment was classified into 3 groups. First, the antihyperglycemic drug group was defined by the use of sulfonylurea, glinide, metformin, thiazolidinedione and/or alpha-glucosidase inhibitors. Second, the antihypertensive drug group was defined by the use of beta-blockers, alpha-blockers, calcium channel blockers and/or diuretics. Third, the antidyslipidemia drug group was defined by the use of statins and/or fibrates.

Outcome measures were the vital status and the cause of death. The vital status was determined from each hospital's database. For the vital status of patients who lost to follow up was determined from the Bureau of Registration Administration of Thailand's database. The cause of death was determined by examining the death certificate from the Bureau of Registration Administration of Thailand. For each patient, the study had two possible outcomes: a renal cause of death or another cause of death. The other causes of death were cerebrovascular disease, cardiovascular disease, infection, diabetes, cancer and/or suicide.

Statistical analysis

Descriptive statistics such as the frequency, percentage, mean and standard deviation were used to describe the study subjects. The log-rank test was used to compare the differences in cumulative survival for the various treatment groups. Logistic regression was used to calculate the propensity score, which evaluates confounding by indication. The propensity score was calculated by the age, sex, duration of diabetes,

systolic blood pressure, diastolic blood pressure, HbA1C level, total cholesterol level, triglyceride level, high density lipoprotein level, low density lipoprotein level, blood creatinine level, history of ischemic heart disease, smoking, alcohol consumption and the use of insulin or antihyperglycemic, antihypertensive or antidyslipidemic drugs. We utilized the propensity score in the model to adjust for differences between the treatment groups. A Cox proportional hazards model was used to assess the impact of treatment with ACEIs/ARBs on patient mortality from all causes of death after adjusting for the propensity score.

A competing risk model was used to assess the impact of treatment with ACEIs/ARBs on patient mortality from renal failure and other causes of death. The reported probability values were two-sided. All statistical analyses were performed with STATA software version 11.0.

Results

Characteristics at registration

The baseline characteristics of 7,946 type 2 diabetes patients at registration, classified by nephropathy history and ACEI/ARBs used, are shown in Table 1. The percentages of non-nephropathic, nephropathic and undetermined nephropathy status subjects were 23.2%, 33.1% and 43.7%, respectively. The diabetes patients without nephropathy who were treated with ACEIs/ARBs had been diagnosed with diabetes for longer, a higher body mass index, a higher blood pressure and a more frequent history of hypertension than patients not prescribed ACEI/ARBs. For diabetes patients with nephropathy, those treated with ACEI/ARBs had lower creatinine levels than the patients not prescribed ACEI/ARBs. In diabetes patients with undetermined nephropathy, those treated with ACEIs/ARBs had similar characteristics to the diabetes patients without nephropathy. We then calculated the propensity score to determine confounding by indication. The propensity scores in subjects treated with ACEIs/ARBs for all nephropathy status groups were higher than for those patients who were not prescribed ACEIs/ARBs.

Survival time before death

Within 5 years, 716 patients died from various causes. In non-nephropathic, nephropathic and undetermined nephropathy status patients treated with ACEI/ARBs, there were 35 deaths from 5181.1

Figure 1: Patient exclusion criteria and classification.
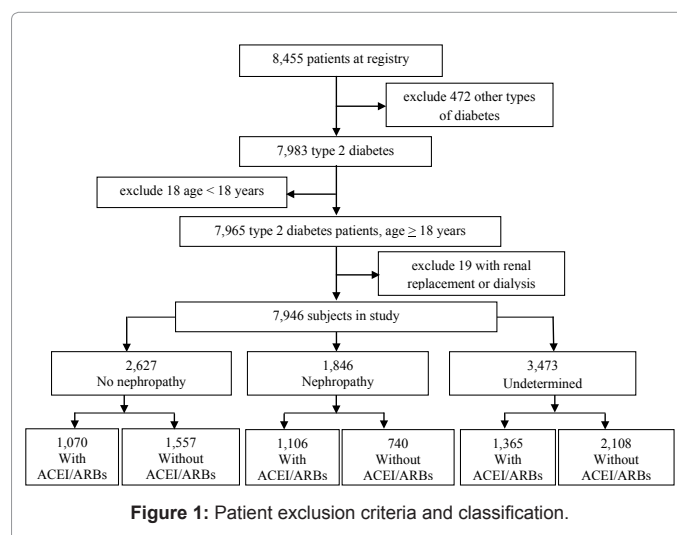
person-years of total follow-up, 152 deaths from 5062.4 person-years of total follow-up and 140 deaths from 6388.2 person-years of total follow-up, respectively. For subjects not treated with ACEIs/ARBs, in the non-nephropathic, nephropathic and undetermined nephropathy status patients there were 73 deaths from 7,536.9 person-years of total follow-up, 141 deaths from 3,226.7 person-years of total follow-up and 175 deaths from 100001.7 person-years of total follow-up, respectively. There were 66 patients who died from causes of renal failure and 650 who died of other causes. The incidence mortality from renal causes and other causes, grouped according to nephropathy history and ACEIs/ARBs treatment status, are displayed in Table 2.

When the cumulative hazards function for death from renal failure was compared between those treated with or without ACEIs/ARBs in non-nephropathic, nephropathic and undetermined nephropathy status subjects, there were statistically significant differences between the groups only in nephropathic subjects ($p = 0.034$). In regards to the cumulative hazards function for death from other causes between those treated with or without ACEIs/ARBs in non-nephropathic, nephropathic and undetermined nephropathy status subjects, there were statistically significant differences between the groups in the nephropathic group ($p = 0.019$) and the not nephropathic group ($p = 0.018$). However, in undetermined nephropathy subjects, there was no statistically significant difference between those treated with or without ACEIs/ARBs ($p = 0.085$) as displayed in Figure 2.

Role of ACEIs/ARBs in death from all causes

In the univariate Cox model, treatment with ACEIs/ARBs was associated with all causes of death in the non-nephropathic, nephropathic and the undetermined nephropathy status groups with the respective crude hazard ratios 0.70 (95% CI 0.47-1.04; $p = 0.081$), 0.68 (95% CI 0.55-0.87; $p = 0.001$) and 1.25 (95% CI 1.01-1.56; $p =$

Baseline characteristics	No Nephropathy		Nephropathy		Undetermined	
	ACEIs/ARBs (n=1,070)	No ACEIs/ARBs (n=1,557)	ACEIs/ARBs (n=1,106)	No ACEIs/ARBs (n=740)	ACEIs/ARBs (n=1,365)	No ACEIs/ARBs (n=2,108)
Male	380 (35.5)	464 (29.8)	460 (41.6)	244 (33.0)	398 (29.2)	601 (28.5)
Age, (year)	61.8±10.2	59.2±11.5	62.4±10.6	62.1±12.0	62.4±10.4	59.6±11.8
Duration of DM, (year)	10.1±7.2	9.1±7.4	12.1±8.1	11.9±8.3	10.7±7.2	9.1±7.1
Onset of DM, (year)	51.7±10.9	50.1±11.1	50.3±11.3	50.2±12.1	51.6±10.5	50.4±11.3
Body mass index, (kg/m²)	26.0±3.9	25.2±4.1	26.0±4.4	25.8±4.7	26.1±4.5	25.4±4.3
Systolic blood pressure, (mmHg)	145.1±21.3	137.0±19.9	150.3±24.7	147.1±24.8	146.9±21.6	138.1±19.9
Diastolic blood pressure, (mmHg)	79.0±11.2	77.0±10.7	79.4±12.6	77.4±11.6	80.6±10.8	79.0±10.3
HbA1C, (%)	7.9±1.7	7.9±1.7	8.5±2.1	8.4±2.0	8.2±1.8	8.2±1.9
Cholesterol, (mmol/L)	4.9±0.9	5.0±1.0	5.1±1.2	5.3±1.4	5.2±1.1	5.2±1.1
Triglyceride, (mmol/L)	1.6±0.9	1.5±0.9	1.9±1.6	2.0±1.6	1.8±1.0	1.8±1.3
High density lipoprotein, (mmol/L)	1.4±0.4	1.3±0.4	1.3±0.4	1.3±0.3	1.4±0.4	1.3±0.4
Low density lipoprotein, (mmol/L)	2.8±0.8	2.9±0.8	3.0±1.0	3.0±1.1	3.1±0.9	3.0±0.9
Creatinine, (µmol/L)	89.5±44.7	86.9±100.5	121.2±68.2	152.8±121.9	103.1±44.8	96.4±41.0
Ischemic heart disease	88 (8.3)	89 (5.7)	119 (10.8)	80 (10.9)	147 (10.9)	148 (7.1)
History of dyslipidemia	874 (81.7)	1,130 (72.6)	876 (79.2)	563 (76.1)	1,023 (74.9)	1,386 (65.8)
History of hypertension	991 (92.6)	609 (39.1)	984 (89.0)	530 (71.6)	1,275 (93.4)	939 (44.5)
Smoking	200 (18.7)	276 (17.7)	303 (27.4)	165 (22.3)	234 (17.1)	376 (17.8)
Alcohol drinking	195 (18.2)	245 (15.7)	260 (23.5)	143 (19.3)	242 (17.7)	412 (19.5)
Use of insulin	221 (20.7)	300 (19.3)	393 (35.5)	310 (41.9)	325 (23.8)	461 (21.9)
Use of antihyperglycemic drugs	999 (93.4)	1,246 (91.4)	941 (85.1)	522 (70.5)	1,246 (91.3)	1,891 (89.7)
Use of antihypertensive drugs	573 (53.6)	484 (31.1)	656 (59.3)	478 (64.6)	818 (59.9)	794 (37.7)
Use of antidyslipidemic drugs	712 (66.5)	895 (57.5)	708 (64.0)	442 (59.7)	746 (54.7)	917 (43.5)
Propensity score	0.50±0.12	0.42±0.12	0.51±0.14	0.48±0.14	0.47±0.13	0.40±0.13

Numbers are n (%) or mean ± standard deviation (SD)

Table 1: Baseline characteristics of patients prescribed (n=3,541) or not prescribed (n=4,405) ACEIs/ARBs, classified by nephropathy status at registration.

Outcome parameters	No Nephropathy		Nephropathy		Undetermined	
	ACEIs/ARBs (n=1,070)	No ACEIs/ARBs (n=1,557)	ACEIs/ARBs (n=1,106)	No ACEIs/ARBs (n=740)	ACEIs/ARBs (n=1,365)	No ACEIs/ARBs (n=2,108)
Total follow-up time (year)	5181.1	7536.9	5062.4	3226.7	6388.2	10001.7
Mean follow-up time (year)	4.84±0.73	4.84±0.72	4.58±1.12	4.36±1.36	4.68±0.99	4.74±0.89
Death from renal causes						
Number (n=66)	3	1	18	23	8	13
Incidence (per 1,000 person-years)	0.58	0.13	3.56	7.13	1.25	1.30
Death from other causes						
Number (n=650)	32	72	134	118	132	162
Incidence (per 1,000 person-years)	6.18	9.55	26.47	36.57	20.66	16.20
Death from all causes						
Number (n=716)	35	73	152	141	140	175
Incidence (per 1,000 person-years)	6.76	9.69	30.03	43.70	21.92	17.50

Table 2: Follow-up time and survival time in patients prescribed (n=3,541) and not prescribed (n=4,405) ACEIs/ARBs, classified by nephropathy status at registration.
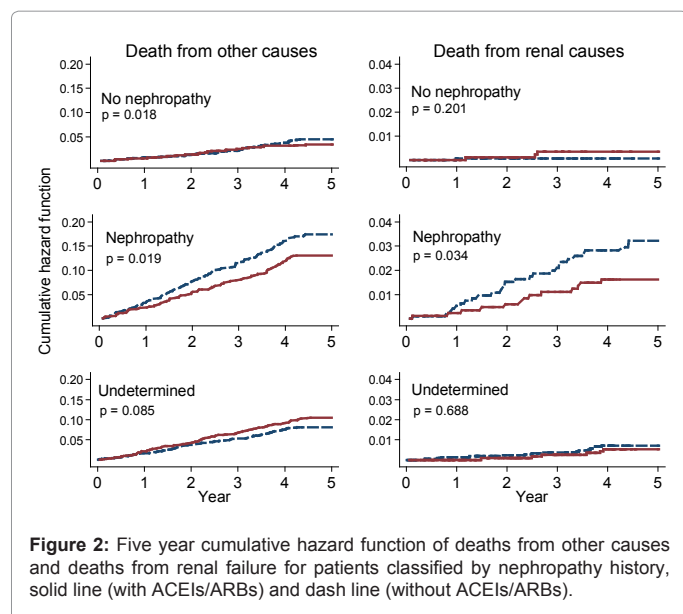
Figure 2: Five year cumulative hazard function of deaths from other causes and deaths from renal failure for patients classified by nephropathy history, solid line (with ACEIs/ARBs) and dash line (without ACEIs/ARBs).

0.048). Hazard ratios for death after adjusting for the propensity score in non-nephropathic, nephropathic and undetermined nephropathy status groups were 0.65 (95% CI 0.42-1.00; $p = 0.049$), 0.69 (95% CI 0.54-0.88; $p = 0.003$) and 1.22 (95% CI 0.95-1.56; $p = 0.122$), as shown in Table 3.

Role of treatment with ACEIs/ARBs in deaths from renal failure

In the competing risk model, we examined the relationship between treatment with ACEIs/ARBs and death from renal failure in the non-nephropathic, nephropathic and undetermined nephropathy status groups as displayed in Table 3. Crude hazard ratios were 4.38 (95% CI 0.46-42.07; $p = 0.201$), 0.50 (95% CI 0.27-0.3 $p = 0.027$) and 0.97 (95% CI 0.40-2.23; $p = 0.938$) for the non-nephropathic, nephropathic, and undetermined nephropathy status groups, respectively. After controlling for the propensity score, treatment with ACEIs/ARBs was associated with prevented deaths from renal failure in the group of patients with nephropathy (HR = 0.49, 95% CI: 0.25-0.95, $p = 0.034$). The adjusted hazard ratio for death from renal failure in the undetermined nephropathy patients was 0.83 (95% CI: 0.33-2.09, p-value = 0.688). The adjusted hazard ratio for death from renal failure in the non nephropathic group could not be calculated due to too small a number of events.

Role of treatment with ACEIs/ARBs in deaths from non-renal causes

The crude hazard ratio result showed that deaths from other causes were significantly different between those treated with or without ACEI/ARBs in all nephropathy status groups (P < 0.05). After controlling for the propensity scores in the competing risk model, the occurrence of other causes of death was significantly altered by treatment with ACEIs/ARBs in non nephropathic and nephropathic patient groups with the respective hazard ratios of 0.65 (95% CI 0.42-0.99; $p = 0.049$) and 0.69 (95% CI 0.54-0.88; $p = 0.003$). Treatment with ACEIs/ARBs was not associated with the prevention of other causes of death in the undetermined nephropathy status group and had a hazard ratio of 1.22 (95% CI 0.95-1.56; $p = 0.122$).

Discussion

This study was a retrospective cohort study. A major issue with this study design is that observational studies are more exposed and prone to biases, especially intention to treat bias, which can partly be addressed through rigorous study design or statistical analysis. Propensity score techniques are the most frequently used method of addressing this problem. The propensity score is the probability that an individual would receive a certain treatment based on his/her treatment characteristics [12,13]. The study used propensity scores to achieve a balance among confounders between the treatment groups in the model.

After controlling for the propensity scores in the competing risk model and Cox model to evaluate the effect of treatment with ACEIs/ARBs on the prevention of renal causes, other causes and all causes of death, treatment with ACEIs/ARBs was associated with the prevention of death from renal causes, other causes and all causes at a level that was significantly different from those not treated with ACEIs/ARBs in diabetes patients with nephropathy. This finding confirms the meta-analysis study that found that treatment with ACEIs/ARBs can reduce renal-cause, other-cause and all-cause mortality in diabetes patients with nephropathy [14,15]. Initial studies by Lewis have demonstrated that a slowing of the nephropathy progression rate was reflected in a significant increase in the time until the serum creatinine concentration doubles, which approximates a halving of the glomerular filtration rate [16]; ARBs were effective in reducing the doubling time of creatinine in type 2 diabetics [17]. Treatment with ARBs reduced the pressure against the filter by dilating the blood vessels that take blood away from the filter in the kidney. Usually, diabetes nephropathy patients should be treated with ACEIs/ARBs. However, in our study, approximately 40% of nephropathy patients did not receive ACEIs/ARBs. There was a systematic review study which reported specific adverse events of ACEIs/ARBs treatment, including coughing, headaches, dizziness, fatigue, upper respiratory infection, nausea, viral infection, ankle edema, back pain, palpitations, myalgia, diarrhea, malaise, and hypotension [18]. Potentially, a large portion of patients in this study were not prescribed ACEIs/ARBs because their doctors forgot to prescribe them or they were known to have a predisposition to the side effects mentioned above.

In type 2 diabetes patients without nephropathy, treatment with ACEIs/ARBs was associated with the prevention of death from other causes and renal causes of death at a level that was significantly different from those not treated with ACEIs/ARBs. This finding fulfills the knowledge gap and shows that the treatment with ACEIs/ARB is beneficial for the prevention of death in diabetes patients without nephropathy. Eurich's study found that the use of ACEIs was associated with a significant reduction in all-cause and cardiovascular-related mortality in a broad spectrum of patients with type 2 diabetes and no cardiovascular disease [19]. Because ACEIs/ARBs work by interfering with the formation of a hormone that can narrow blood vessels and increase blood pressure, they are prescribed to reduce blood pressure and ease the workload on the heart. A previous study suggested that ACE inhibitors may provide special advantages in addition to blood pressure control and may be superior to alternative antihypertensive agents [20].

Our study finds that treatment with ACEIs/ARBs could not prevent mortality from renal causes, other causes and all causes of death in type 2 diabetes patients with an undetermined nephropathy status. There was a trend that patients who received ACEIs/ARBs had more deaths from other causes than patients who did not receive treatment with

	No Nephropathy		Nephropathy		Undetermined	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Death from renal causes						
Crude	4.38 (0.46-42.07)	0.201	0.50 (0.27-0.93)	0.027	0.97 (0.40-2.33)	0.938
Adjusted for PS [a]	NC [b]	-	0.49 (0.25-0.95)	0.034	0.83 (0.33-2.09)	0.688
Death from other causes						
Crude	0.65 (0.43-0.98)	0.041	0.73 (0.57-0.93)	0.011	1.27 (1.01-1.60)	0.039
Adjusted for PS [a]	0.58 (0.37-0.91)	0.018	0.73 (0.56-0.95)	0.019	1.26 (0.97-1.63)	0.085
Death from all causes						
Crude	0.70 (0.47-1.04)	0.081	0.68 (0.55-0.87)	0.001	1.25 (1.01-1.56)	0.048
Adjusted for PS [a]	0.65 (0.42-0.99)	0.049	0.69 (0.54-0.88)	0.003	1.22 (0.95-1.56)	0.122

[a]PS: Propensity Score (age, sex, duration of diabetes, systolic blood pressure, diastolic blood pressure, HbA1C, total cholesterol, triglyceride, high density lipoprotein, low density lipoprotein, creatinine, history of ischemic heart disease, smoking, alcohol drinking, use of insulin, antihyperglycemic drugs, antihypertensive drug and antidyslipidemic drugs)
[b]NC: Non-calculable due to small number of events

Table 3: Hazard ratio (HR) and 95% confidence interval (CI) for death from renal causes, other causes and all causes in patients prescribed with ACEIs/ARBs, classified by nephropathy status at registration.

ACEIs/ARBs (HR = 1.26; 95% CI; 0.97-1.63, p = 0.085). We explored baseline characteristics between the groups separated by nephropathy status (Table 1). The data showed that subjects with an undetermined nephropathy status had a higher diastolic blood pressure level, Hba1c and history of ischemic heart disease than subjects with and without nephropathy. These factors are diabetes control quality indicators. We recommend that the next study explore causes of death related to diabetes control in undetermined nephropathy status patients.

Of the studied subjects in the tertiary hospitals, 43.7% of type 2 diabetes patients were not screened for microalbuminuria because the screening tools in Thailand are expensive and the method of urine collection is not convenient for patients willing to complete the test necessarily for 3 times. We have estimated from this information that type 2 diabetes patients in a general hospital may not have a determined nephropathy status in more than 80% of cases. In the future, if there were a simple screening test that was highly predictive and practical to use to detect microalbuminuria, type 2 diabetes patients would obtain more suitable treatment and care.

There are several limitations to this study. First, the World Health Organization (WHO) standard decision rule, in which specific ICD-10 codes for the cause of death were identified, should be applied. Our study utilized causes of death from the death certificates from the Bureau of Registration Administration of Thailand. The cause of death in the document can be completed by a health care team or a doctor. However, the outcome event of this study is similar to the outcome event of the project predicting death and causes of death in Thai diabetic patients [21]. The cause of death of diabetic patients in that study was defined by a panel of two independent physicians after reviewing the medical records, and causes of death were categorized according to the International Classification of Disease, Tenth Revision (ICD-10). Cardiovascular disease is the most common cause of death (29.0%), followed by infection (21.9%), cancer (19.5%) and chronic kidney disease (8.6%). For our study, cardiovascular disease was the most common cause of death (26.7%), followed by infection (23.5%), cancer (16.2%) and renal failure (9.3%).

Second, the laboratory and clinical factors in this study were based on a single baseline measurement at the time of registration without repeated measures during the five years of follow-up. Last, this study did not collect the dosage of administered ACEIs/ARBs. The next study should consider changes in treatment and other variables. However, the strength of this study is in its prospective nature and its large number of type 2 diabetes patients who can represent diabetic patients in a hospital. Moreover, other developing countries have similar diabetes characteristics as Thailand, so the study may be representative of other developing countries.

In conclusion, diabetic nephropathy patients who received ACEIs/ARBs had lower mortality than subjects who did not receive the drugs. The effect on mortality of treatment with ACEIs/ARBs was not statistically significant in subjects who were not diagnosed with diabetic nephropathy. A screening test for diabetic nephropathy should be performed to determine the administration of ACEIs and ARBs.

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