EPIDEMIOLOGICAL STUDY OF CHRONIC KIDNEY DISEASE

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EPIDEMIOLOGICAL STUDY OF CHRONIC KIDNEY DISEASE

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ABSTRACT

Background: Chronic kidney disease (CKD) is globally one of the leading causes of disease burden. Risk of death from cardiovascular disease was twice as high in CKD as non-CKD patients. Thus, knowing its risk and prognostic factors should help to identify patients at risk, and establish effective strategies for prevention of CKD occurrence. Therefore, CKD progression can be properly managed. A series of three studies were conducted to address these issues.

Objectives: 1) To compare efficacy of renin angiotensin system (RAS) blockers with other active drugs or placebo with respect to end-stage renal disease (ESRD), doubling of serum creatinine, macro-albuminuria, micro-albuminuria, and promotion of albuminuria regression in type 2 diabetic subjects. 2) To determine the median time of changing glomerular filtration rate (GFR) categories and probability of kidney failure (KF)/death separately in diabetic and non-diabetic subjects. 3) To assess the role of small solute clearance index (rKt/V, tKt/V, and tCrcl) on death in continuous ambulatory peritoneal dialysis (CAPD) patients.

Methods: For the first objective, a systematic review and network meta-analysis of randomized controlled trials was performed to evaluate the reno-protective effects of RAS blockers. Randomized controlled trials were identified from Medline and Embase up to April 2011. Data were independently extracted by two reviewers. A random effect model was applied to pool treatment effects. For the second objective, a population-based retrospective cohort of CKD progression was conducted using community-health screening, hospitals, and death registry data in Ubon Ratchathani province from 1997-2011. A competing risk model was applied to estimate the probability of KF and median time for CKD progression. For the last objective, a retrospective cohort study of patients receiving CAPD was conducted during 2008 and 2011. A receiver operating characteristic curve was applied to calibrate the cutoffs of rKt/V, tKt/V, and tCrcl. Kaplan-Meier and time-varying covariate cox-regression were applied to estimate overall death and prognosis.

Results: For efficacy of RAS blockers, a network meta-analysis detected significant treatment effects across all outcomes, i.e., 62% significantly lower risk of ESRD (pooled risk ratio (RR)=0.38, 95% CI: 0.31, 0.47); 77% significantly lower risk of serum creatinine doubling (pooled RR=0.23, 95% CI: 0.09, 0.57); 39% significantly lower risk of macro-albuminuria (pooled RR=0.61, 95% CI: 0.47, 0.77); 39% significantly lower risk of micro-albuminuria (pooled RR=0.61, 95% CI: 0.45, 0.83) when compared to other anti-hypertensive drugs; and 16% more likely to promote regression of albuminuria when compared to dihydropyridine calcium channel blockers (d-CCB). For CKD progression, diabetic subjects progressed more rapidly through GFR categories with the median times for CKD progression from GFR categories G1 to G2, G2 to G3a, G3a to G3b, G3b to G4, and G4 to G5 of 4.4, 6.1, 4.9, 6.3, and 9.0 years, respectively. Non-diabetic subjects had the corresponding median time of 9.4, 14.0, 11.0, 13.8, and >14.3 years. Diabetic subjects were 49% (case-specific hazard ratio (HR)=1.49, 95% CI: 1.37, 1.42) more likely to develop KF than non-diabetic subjects. For CAPD, the rKt/V and tKt/V cutoffs were 0.25 and 1.75, respectively. The risks of death for those above these cutoffs were 57% (HR=0.43, 95% CI: 0.31, 0.60), and 29% (HR=0.71, 95% CI: 0.52, 0.98) lower for rKt/V and tKt/V, respectively.

Conclusion: We have demonstrated the specific reno-protective effects of RAS blockers in real clinical outcomes, i.e., ESRD & doubling of serum creatinine in type 2 diabetic subjects compared with other anti-hypertensive drugs and placebo using a network meta-analysis. CKD progression from less advanced GFR categories to KF was twice as rapid in diabetic as non-diabetic subjects. We have calibrated the cutoffs of rKt/V and tKt/V which could be used to predict prognosis in CAPD patients.

KEY WORDS: RENO-PROTECIVE EFFECT, RAS BLOCKADE, CKD PROGRESSION, CAPD

121 pages

การศึกษาเชิงระบาดวิทยาของโรคไตเรื้อรัง

EPIDEMIOLOGICAL STUDY OF CHRONIC KIDNEY DISEASE

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บทคัดย่อ

ความเป็นมาและความสำคัญของปัญหา: โรคไตเรื้อรังเป็นสาเหตุการเจ็บป่วยที่สำคัญทั่วโลก ผู้ป่วยโรคไตเรื้อรังเสียชีวิตจากโรคหลอดเลือดหัวใจมากกว่าผู้ที่ไม่มีโรคไตเรื้อรัง 2 เท่า การทราบปัจจัยเสี่ยงหรือปัจจัยพยากรณ์ของโรคไตเรื้อรังจะทำให้เราสามารถวางมาตรการในการป้องกันและชะลอการดำเนินโรคไตเรื้อรังได้ ดุษฎีนิพนธ์นี้ประกอบไปด้วย 3 การศึกษา

วัตถุประสงค์: 1) เพื่อศึกษาประสิทธิภาพของยากลุ่ม RAS blockers เปรียบเทียบกับยาลดความดันโลหิตอื่น ๆ หรือยาหลอกในการลดไตวาย, serum creatinine doubling, macro-albuminuria, micro-albuminuria, และ albuminuria regression ในผู้ป่วยเบาหวานชนิดที่ 2 2) เพื่อศึกษาค่ามัธยฐานของเวลาที่ใช้ในการเปลี่ยนระยะของโรคไตเรื้อรัง และความน่าจะเป็นของการเกิดไตวาย /ตาย ในผู้ป่วยที่เป็นและไม่เป็นเบาหวาน 3) เพื่อศึกษาบทบาทของ tKt/V, tKt/V, และ tCrcl ต่อการตายในผู้ป่วยที่ล้างไตทางช่องท้อง

วิธีดำเนินการวิจัย: สำหรับวัตถุประสงค์ข้อ 1 ทำการศึกษาแบบ การทบทวนวรรณกรรมอย่างเป็นระบบและวิเคราะห์อภิมานแบบเครือข่าย เพื่อ ประเมินผลป้องกันไตของยากลุ่ม RAS blockers โดยสืบค้นข้อมูลจากฐานข้อมูล Medline และ Embase จนถึง พ.ศ. 2554 ผู้วิจัย 2 คน คัดเลือกและสกัดข้อมูลอย่างอิสระต่อกัน ใช้ random effect model ในการรวมผลของ RAS blockers สำหรับวัตถุประสงค์ข้อ 2 การศึกษาแบบโคฮอรทย้อนหลัง ในผู้ป่วยโรคไตเรื้อรังในจังหวัดอุบลราชธานี ตั้งแต่ 2548 ถึง 2554 ใช้ competing risk model ในการคำนวณความน่าจะเป็นของการเกิดไตวายและค่ามัธยฐานของเวลาที่ใช้ในการเปลี่ยนระยะของโรคไตเรื้อรัง สำหรับวัตถุประสงค์ข้อ 3 การศึกษาแบบโคฮอรทย้อนหลัง ในผู้ป่วยที่ล้างไตทางช่องท้องระหว่าง พ.ศ. 2551 ถึง 2554 ใช้ ROC curve เพื่อหาจุดตัดขอ rKt/V, tKt/V, และ tCrcl ใช้ Kaplan Meier และ Cox regression เพื่อหาอัตราการตายทั้งหมด และความเสี่ยงของการตาย

ผลการวิจัย: สำหรับการประเมินผลของ RAS blockers การวิเคราะห์อภิมานแบบเครือข่ายในผู้ป่วยเบาหวานชนิดที่ 2 พบว่า RAS blockers ลดการเกิดไตวาย 62% (pooled RR=0.38, 95% CI: 0.31, 0.47), ลดการเพิ่มของครีเอตินีนเป็น 2 เท่า 77% (pooled RR=0.23, 95% CI: 0.09, 0.57), ลดการเกิด macro-albuminuria 39% (pooled RR=0.61, 95% CI: 0.47, 0.77), ลดการเกิด micro-albuminuria 39% (pooled RR=0.61, 95% CI: 0.45, 0.83), เมื่อเปรียบกับยาความดันอื่น ๆ และเพิ่ม albuminuria regression 16% เมื่อเปรียบเทียบกับยาลดความดันกลุ่มต้านแคลเซี่ยมชนิดไดไฮโดรไพริดีน สำหรับการพยากรณ์โรคไตเรื้อรัง ผู้ป่วยเบาหวานมีค่ามัธยฐานเวลาที่ใช้ในการเปลี่ยนระยะจาก G1-G2, G2-G3a, G3a-G3b, G3b-G4, G4-G5 เป็น 4.4, 6.1, 4.9, 6.3, และ 9 ปี ผู้ป่วยอื่นมีค่ามัธยฐานเวลาเป็น 9.4, 14.0, 11.0, 13.8, และ >14.3 ปี ตามลำดับ ผู้ป่วยเบาหวานมีความเสี่ยงในการเกิดไตวายเพิ่มขึ้น 49% ($_{cs}$HR=1.49, 95% CI: 1.37, 1.42) เมื่อเปรียบเทียบกับผู้ป่วยอื่น ๆ 3) จุดตัดของ rKt/V และ tKt/V คือ 0.25 และ 1.75 ตามลำดับ ค่าที่สูงกว่าจุดตัดดังกล่าวมีความเสี่ยงต่อการตายเพิ่มขึ้น 57% และ 29% ตามลำดับ

สรุปผลการวิจัย: การทบทวนวรรณกรรมอย่างเป็นระบบและวิเคราะห์อภิมานแบบเครือข่ายแสดงให้เห็นผลการป้องกันไตเสื่อมจากกลุ่มยา RAS blockers สามารถลดการเกิด ไตวาย และการเพิ่มขึ้นของครีเอตินีนเป็น 2 เท่าในผู้ป่วยเบาหวานชนิดที่ 2 เมื่อเปรียบเทียบกับยาลดความดันชนิดอื่น ๆ หรือยาหลอก ผู้ป่วยเบาหวานมีการดำเนินโรคที่เร็วและเกิดไตวายสูงกว่าผู้ป่วยกลุ่มอื่น ๆ ถึง 2 เท่า ค่า rKt/V, และ tKt/V สามารถใช้ทำนายการตายของผู้ป่วยล้างไตทางช่องท้องได้

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eGFR	Estimated GFR
EC	Ethical committee
ESRD	End-stage renal disease
Hb	Hemoglobin
HbA_{1c}	Hemoglobin A1c
HR	Hazard ratio
HT	Hypertension
ICD	International classification of disease
IDMS	Isotope-dilution mass spectrometry
KDIGO	Kidney disease: Improving global outcomes
KDOQI	Kidney Disease Outcome Quality Initiative
KF	Kidney failure
K-M	Kaplan-Meier
LR+	Likelihood ratio positive
LR-	Likelihood ration negative
NCD	Non-communicable disease
nd-CCB	Non-dihydropyridine calcium channel blocker
NHSO	National Health Security Office
PCR	Protein-to-creatinine ratio
RAS	Renin-angiotensin system
RBC	Red blood cell
RCT	Randomized controlled trial
rKt/V	Renal Kt/V
ROC	Receiver operatiing characteristic
RR	Relative risk
SBP	Systolic blood pressure

LIST OF ABBREVIATIONS(cont.)

Scr	Serum creatinine
SD	Standard deviation
sdHF	Subdistribution hazards function
tKt/V	Total Kt/V
SEEK	Study for the Evaluation of Early Kidney disease
UA	Urine analysis
UF	Ultrafiltration
UKPDS	United kingdom prospective diabetes study
UBPHO	Ubon Ratchathani Public Health Office
WBC	White blood cell

CHAPTER I
INTRODUCTION

1.1 Background and Rationale

Chronic kidney disease (CKD) is now recognized as one of the leading causes of disease burden globally. The prevalence of CKD with glomerular filtration rate (GFR) categories 1 (G1) to 4 (G4) were 13.1% to 17.5% in the adult US and Thai populations, respectively (1, 2). Although a small numbers of CKD subjects from G1 to G4 (approximately 1.1% to 19.9%) progress to G5 (kidney failure, KF) requiring dialysis or kidney transplantation, a large numbers of CKD subjects die from any cause before reaching dialysis state (i.e., 19.5% to 45.7%) (3-6).

Comparing to those without CKD, subjects with CKD were approximately 2 times more likely to die from any cause or from cardiovascular disease (CVD) (3, 7). Thus, knowing the risk factors of CKD or prognostic factors of CKD progression to KF/death should lead to identify subjects who are at risk. Effective strategies for prevention of CKD occurrence and its progression could therefore be properly implemented.

Many studies had reported risk factors of CKD/KF and diabetes was one among those important risks (8, 9), i.e., diabetic subjects were approximately 2.6 times higher risk of CKD than non-diabetic subjects. Effective treatments for prevention of KF and CVD events in general population have been demonstrated by recent meta-analyses (10-12). These treatments included renin-angiotensin system (RAS) blockers, beta-blockers, and statins for either primarily treating CKD or treating associated co-morbidities (e.g., diabetes, hypertension, or dyslipidemia). However, the reno-protective effects of RAS blockers in type 2 diabetes, have been controversial.

Several previous community-based studies (3, 5-7, 13-16) have assessed the course of CKD progression in general populations, although, none has yet estimated the time for changing kidney function and the probability of KF or death according to each GFR category, particularly for early stages of G1 and G2. Although

some studies had large overall sample sizes (3, 14), most of them had relatively low numbers of subjects for each GFR category, lacked information on progression through GFR categories (3, 5-7, 13, 14, 16), had short follow-up times (5, 6, 14, 15), and were thus unable to assess the probability of KF or death. In addition, a high proportion of CKD subjects died before reaching KF, therefore estimating the rate of KF occurrence without taking into account death as a competing risk would yield biased results (17).

As CKD advances, the kidney progressively loses its excretory and homeostasis functions and eventually becomes KF. Renal replacement therapy (i.e., renal transplantation or dialysis) is usually required for KF subjects. Two dialysis modalities, i.e., hemo-dialysis and continuous ambulatory peritoneal dialysis (CAPD), have been widely used. The numbers of patients on CAPD has been growing rapidly in Asian countries, representing about 71% of dialysis patients in Hong Kong, and 21% in Thailand in 2011 (18). The usage of four 2-L daily exchanges with double-bag disconnected systems has been a standard CAPD regime which has been covered by a benefit package of the universal coverage scheme in Thailand since 2008. Adequacy targets for CAPD are primarily based on the weekly clearances of urea (Kt/V) or creatinine (Crcl) which are expressed as renal Kt/V (rKt/V), peritoneal Kt/V (pKt/V), total Kt/V (tKt/V); or renal Crcl (rCrcl), peritoneal Crcl (pCrcl), and total Crcl (tCrcl), respectively. The effect of rKt/V on survival in CAPD patients has been well-documented (19-27), but the roles of pKt/V, tKt/V and tCrcl are controversial. Some studies (22, 28) found that higher pKt/V and/or tKt/V were associated with longer survival times, whereas some observational studies (19-21, 23-25) and randomized controlled trials (26, 27) did not find such associations.

This thesis was therefore conducted, which consisted of a series of three studies as follows: first, a systematic review and meta-analysis of RAS blockade (Chapter II); second, epidemiological study of chronic kidney disease progression among a large-scale population-based cohort (Chapter III); and third, prognostic factors of all-cause mortalities in patients receiving continuous ambulatory peritoneal dialysis (Chapter IV).

1.2 Research questions

For systematic review:

1.2.1 Did RAS blockers have specific reno-protective effects beyond blood pressure lowering effects when compared to other anti-hypertensive drugs in type 2 diabetic subjects?

For CKD progression:

1.2.2 What were the median times of changing from lower GFR categories to higher GFR categories in diabetes and non-diabetes?

1.2.3 What were the probabilities of death according to each GFR/albuminuria category in diabetes and non-diabetes?

1.2.4 What were prognostic factors of CKD progression to KF, death before and after KF?

For CAPD:

1.2.5 Were tKt/V, rKt/V, and tCrcl associated with death in KF subjects treated with CAPD? If yes, what were their cutoff thresholds that could be used to discriminate dead and alive subjects?

1.2.6 What were prognostic factors of death in patients receiving CAPD treatments?

1.3 Research objectives

For systematic review:

To compare the reno-protective effects of RAS blockers with other antihypertensive drugs including beta-blockers, calcium channel blockers, and diuretics and placebo in type 2 diabetic subjects with following specific objectives

1.3.1 To estimate direct and indirect effect of angiotensin converting

enzyme inhibitor (ACEI) / angiotensin receptor blocker (ARB) on end-stage renal disease (ESRD)

1.3.2 To estimate direct and indirect effect of ACEI/ARB on doubling creatinine

1.3.3 To estimate direct and indirect effect of ACEI/ARB on micro-vascular complications

1.3.4 To estimate direct and indirect effect of ACEI/ARB on micro-/macro-albuminuria

1.3.5 To estimate direct and indirect effect of ACEI/ARB on micro-/macro-albuminuria

1.3.6 To estimate direct and indirect effect of ACEI/ARB on albuminuria regression

For CKD progression:

1.3.7 To estimate probability of CKD progression changing forward from G1 to G2, G2 to G3a, G3a to G3b, G3b to G4, and G4 to G5 separately by diabetes and non-diabetes

1.3.8 To estimate cause specific hazard ratio of diabetes on kidney failure and death using a competing risk model with adjusting for baseline characteristics and co-morbidities

1.3.9 To identify the other prognostic factors of CKD progression to KF/death

For CAPD:

1.3.10 To assess the optimum cutoffs of tKt/V, rKt/V, and tCrcl on death in subjects receiving CAPD treatments

1.3.11 To identify the prognostic factors of death in subjects receiving CAPD treatments

1.4 Conceptual framework

The conceptual framework has been shown in Figure 1.1

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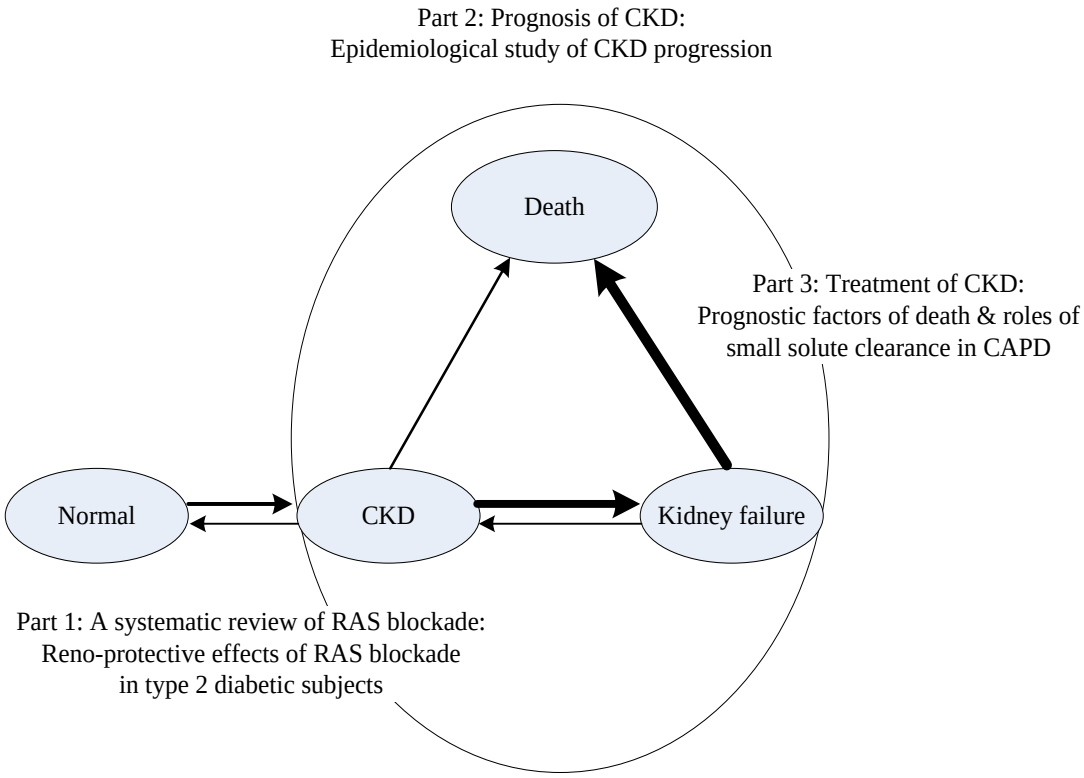

CKD, chronic kidney disease; CAPD, continuous ambulatory peritoneal dialysis; DM, diabetes mellitus; HT, hypertension; CVD, cardiovascular disease; BMI, body mass index; RAS, renin-angiotensin system

Figure 1.1 Conceptual framework

CHAPTER II
RENO-PROTECTIVE EFFECTS OF RENIN–ANGIOTENSIN SYSTEM BLOCKADE IN TYPE 2 DIABETIC PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

2.1 Introduction

Diabetic nephropathy is a significant health and economic burden across the world. The prevalence of micro- and macroalbuminuria in type 2 diabetes is as high as 37 – 40% in western countries and 57.4 – 59.8% in Asian countries (1-3). Microalbuminuria is a well-established risk factor for cardiovascular disease and is also associated with ESRD (4-7). Preventive treatments have been prescribed for type 2 diabetes with or without hypertension with the aim of lowering BP, and delaying or even preventing the progression of diabetic nephropathy. The reno-protective effects of RAS blockers in type 2 diabetes have been controversial (8). A few systematic reviews have been conducted (9-11), but these reviews pooled studies with mixed populations of participants with type 1 and type 2 diabetes, with and without diabetic nephropathy, and the focus was mainly on surrogate rather than clinical outcomes. We therefore conducted a systematic review and meta-analysis comparing the effects of ACEI/ARB with other antihypertensive drugs and placebo on ESRD, doubling of serum creatinine, microvascular complications, micro- and macro-albuminuria and regression of albuminuria.

2.2 Methods

2.2.1 Study selection

English-language publications were identified from Medline (1949 – July 2011) and Embase (1974 – April 2011) using PubMed and Ovid search engines.

Search terms and strategies for Medline were as follows: (type 2 diabetes or type 2 diabetes mellitus or type 2 DM or non-insulin dependent diabetes) and (ACEI or angiotensin-converting enzyme inhibitors or ACE inhibitors or ARB or angiotensin receptor blockers*) and (nephropathy or overt nephropathy or micro-albuminuria or macro-albuminuria or micro-vascular complications or doubling serum creatinine or ESRD or end-stage renal disease or urinary albumin excretion). We also searched for any additional studies in the reference lists of identified publications. Data from the most recent or the most complete report by the same authors were used. We restricted our searches to clinical trials.

Studies with the following criteria were included:

- Type 2 diabetic adult individuals
- Randomized controlled trial (RCT) comparing any single ACEI/ARB with other single agents (i.e., beta-blocker (BB), calcium channel blocker (CCB), diuretics) or placebo
- Had at least one of the following outcomes (i.e., microalbuminuria, macroalbuminuria, albuminuria regression, micro-vascular complications, serum creatinine doubling and/or ESRD),
- Reported number of patients and events in each treatment arm

Studies with the following criteria were excluded:

- Crossover trials,
- Used dual therapies
- Compared different dosages of ACEI/ARB

2.2.2 Outcome measures

The outcomes of interest were ESRD, doubling of serum creatinine, micro-vascular complications, macro-albuminuria, micro-albuminuria and regression of albuminuria. ESRD was defined as a requirement for renal replacement therapy or dialysis. Doubling of serum creatinine was defined as an increase in serum creatinine level of at least two times compared with baseline level. Micro-vascular complications were defined as a composite of having nephropathy and/or retinopathy. Micro-albuminuria was defined as urine albumin excretion rate of 30 – 300 mg/24 h for 24-hour urine collection, 3.5 – 35 mg/mmol for urinary albumin/creatinine ratio from a

spot urine collection, or 20 – 199 μg/min for timed urine collection. Macro-albuminuria was defined as urine albumin excretion rate ≥ 300 mg/24 h, ≥ 25 mg/mmol creatinine or ≥ 200 μg/min for the same specimens, respectively. Regression of albuminuria was defined as a change from a higher to a lower stage of albuminuria.

2.2.3 Data extraction

Two investigators (P. Vejakama and D. Lertrattananon) independently extracted data, including study and participant characteristics (e.g. age, blood pressure, albuminuria stage, serum glucose, and HbA1c) and numbers of events across intervention groups. Discrepancies were discussed with a third party (A. Thakkinstian) and resolved by consensus.

2.2.4 Risk of bias assessment

Risk of bias was assessed using the Cochrane Collaboration's tool addressing six domains: sequence generation, allocation concealment, blinding of participants and outcome assessors, incomplete outcome, selective outcome reporting and other source of bias. Risk of bias was considered low if plausible bias was unlikely to seriously alter the results (low risk for all key domains within study and most information at low risk across studies), unclear if it raises some doubt about the results (unclear risk for one or more key domains within study & most information at low or unclear risk across studies), and high if it seriously weakens the confidence of the results (high risk for one or more key domains within study & proportion of information at high risk across studies is sufficient to affect the interpretation of the results). Two investigators (P. Vejakama and D. Lertrattananon) independently completed the assessments and discrepancies were discussed with a third party (A. Thakkinstian) and resolved by consensus.

2.2.5 Statistical analysis

For direct meta-analysis, the intervention of interest was ACEI/ARB mono-therapy, while the comparator group was any antihypertensive drug or placebo. Pooled RRs were used to compare treatment effects using a fixed or random-effect model where appropriate as in the following equations:

Fixed effect model (Inverse-variance method)

$$ln\,OR_{IV} = \frac{\sum_j^K w_j\, ln\, OR_j}{\sum_j^k w_i}$$

$$Var\, ln(OR_j) = \frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}$$

$$w_j = \frac{i}{Var_j}$$

95% Confidence interval (CI) = $OR_{IV} \pm 1.96\sqrt{Var(lnOR_{IV})}$

Random effect model

$$ln\, OR_{dl} = \frac{\sum_{j=1}^k W_j^* \times ln\, OR_j}{\sum_{j=1}^k W_j^*}$$

$$W_J^* = \frac{1}{V_j + \tau^2}$$

$$\tau^2 = \frac{Q-(k-1)}{\sum_{j=1}^k W_j - \frac{\sum_{j=1}^k W_j^2}{\sum_{j=1}^k W_j}}$$

$$V_j = Var(ln\, OR_j)$$

Q test and I^2 statistic were used to assess the presence and degree of heterogeneity as equations below:

$$Q = \sum_{i=1}^k W_i(\theta_i - \theta_p)^2$$

$\theta_i = \ln(effect\ size)$ *e.g.*, $\ln OR_i$, $\ln RR_i$, $\ln HR_i$

$\theta_p = \ln(pool\ effect\ size)$

$$W_i = \frac{1}{varln(\theta_i)}$$

Q ~Chi-square with k-1 degree of freedom

If heterogeneity was present or I^2 > 25%, the random-effects model was applied, otherwise the fixed-effects model was used. Sources of heterogeneity including clinical and methodological variation were explored using meta-regression. The Harbord test and a funnel plot were applied to assess publication bias (12). If

either suggested asymmetry of the funnel, contour-enhanced funnel plots were used to distinguish the cause of asymmetry (i.e. heterogeneity and reporting bias) (13, 14).

A network meta-analysis (15-17) was performed to compare indirectly all treatment effects. Summary data for treatments and outcomes were expanded to the individual patient level. A Poisson regression analysis was applied by fitting treatment variable on dichotomous outcome as in the following equation:

$$y_{ij} = \beta_0 + \beta_j Treatment_j + \zeta_j + \varepsilon_{ij},$$

Where y_{ij} binary distribution, which linked with independent variables using a family of *log-link function* ζ_i is random effect with normal distribution as $\zeta_i \sim N(0, \psi)$. The error term ϵ_{ij} is normal distribution with mean 0 and variance of θ, $\epsilon_{ij} \sim N(0, \theta)$.

The pooled RRs and 95% CIs were then estimated by exponential coefficients estimated from the Poisson regression. The point estimate (incidence rate ratio) along with 95% CI for each treatment comparison was computed by linear combinations of estimators. All analyses were performed using STATA version 11 (Stata Corp., College Station, TX, USA). P values less than 0.05 were considered statistically significant, except for the test of heterogeneity where $p < 0.10$ was used. For more details in statistical analysis commands, see Appendix I.

2.3 Results

Of the 673 articles located, full papers of 153 plus four additional studies from reference lists were reviewed, leading to data pooling for 28 studies (see Figure 2.1). The characteristics of these studies have been described in Table 2.1. The major ACEI/ARBs used were enalapril 32%), followed by lisinopril (10.7%) and ramipril (10.7%). The majority of comparators were dihydropyridine CCBs (d-CCBs; 43%), placebo (39%), or BB/diuretic/non-dihydropyridine CCBs (nd-CCBs; 18%). The assessments of risk of bias have been described in Table 2.2. Numbers of individuals are summarized according to the treatments and outcomes of interest (Tables 2.3 -

2.9). Problems with incomplete outcome reports were least frequent in 2/28 (7.1%) studies (18, 19), followed by other sources of bias in 5/28 (17.9%) (18, 20-23) and selective reporting of outcomes in 5/28 studies (17.9%) (18, 21, 22, 24, 25). Although all studies were RCTs, only 14 (50.0%) studies clearly described randomization (21, 25-37) and allocation concealment (21, 22, 26-29, 31, 33-39).

2.3.1 Direct meta-analysis

ESRD

Nine studies (20, 21, 24, 26, 29, 30, 33, 34, 40) reported the effect of ACEI/ARB on ESRD (n = 13,295). Of these, five studies (20, 21, 26, 30, 40) compared ACEI with other anti-hypertensive drugs (three BB, two d-CCB), three (24, 29, 34) compared ACEI with placebo, and one (33) compared ARB with d-CCB and placebo (Table 2.3).

Six studies (20, 21, 26, 30, 33, 40) directly compared ACEI/ARB with other active drugs (n = 1,090 vs 1,055); four were trials that studied patients with macro-albuminuria whereas the other two studied mixed patients with micro- and macro-albuminuria.

The treatment effects were homogeneous (χ^2 = 1.54, df = 5, p = 0.908, I^2 = 0.0%), suggesting that ACEI/ARB reduced the risk of ESRD by 18% (pooled RR = 0.82, 95% CI: 0.64, 1.05, see Figure 2.2A). However, this result was not statistically significant (Table 2.3). Neither the Harbord test nor a funnel plot (Figure 2.4A.i) suggested publication bias (coefficient = −0.001, SE = 0.436, p = 0.998).

For placebo controls, pooled estimates based on four studies (24, 29, 33, 34) (n = 5,581 vs 5,569) demonstrated homogeneous treatment effects (χ^2 = 1.11, df = 3, p = 0.774, I^2 = 0.0%; Figure 2.2A) despite a mix of patients with normo-, micro- and macro-albuminuria. ACEI/ARB significantly decreased the risk of ESRD by 20% (pooled RR = 0.80, 95% CI: 0.69, 0.93, Table 2.6). Although the Harbord test was not significant (coefficient = 1.220, SE = 0.311, p = 0.059), the contour-enhanced funnel plot showed asymmetry (Figure 2.4A.ii). One high-precision study fell in the significant area (grey shading) whereas the other three (one high and two low precision) were in the non-significant area. Applying ‘trim and fill’ suggested two

low-precision studies (square symbols) were missing and adding these studies yielded a pooled RR of 0.78 (95% CI: 0.68, 0.91) with I^2 = 0%.

Doubling of serum creatinine

Six studies (20, 24, 29, 33, 34, 39) reported the effect of ACEI/ARB vs other anti-hypertensive drugs on doubling of serum creatinine (n = 16,216), and five studies (24, 29, 33, 34, 39) reported ACEI/ARB vs placebo (Table 2.4).

The treatment effects of ACEI/ARB vs antihypertensive drugs (n = 597 vs 601) were homogeneous (χ^2 = 0.76, df = 1, p = 0.382, I^2 = 0.0%) with a pooled RR of 0.66 (95% CI: 0.53, 0.83; Figure 2.2B), suggesting a significant reduction in risk of 34%.

The ACEI/ARB effects were also present when compared with placebo (n = 7,831 vs 7,784). The pooled RR was 0.76 (95% CI: 0.69, 0.84), indicating a 24% lower risk of serum creatinine doubling. The pooled effect was homogeneous (χ^2 = 1.67, df = 4, p = 0.796, I^2 = 0.0%) without publication bias (Harbord test coefficient = 0.629, SE = 0.908, p = 0.538; Figure 2.4B).

Micro-vascular complications

Of five studies (24, 26, 31, 32, 37) (n = 6,489), only one (26) compared ACEI/ARB with active drug; the other four (24, 31, 32, 37) compared ACEI/ARB with placebo (Table 2.5). Compared with placebo controls (n = 2,847 vs 2,884), ACEI/ARB significantly reduced the risk of micro-vascular complications by 15% (pooled RR = 0.85, 95% CI: 0.76, 0.97), with low heterogeneity (χ^2 = 3.34, df = 3, p = 0.342, I^2 = 10.3%; Figure 2.2C) and without publication bias (Harbord test coefficient = −1.51, SE = 0.53, p = 0.105; Figure 3.4C). In addition, the ACEI/ARB group (n = 2,884) had a significantly lower risk of retinopathy (13% lower, pooled RR = 0.87, 95% CI: 0.76, 0.99) with low heterogeneity (χ^2 = 3.51, df = 3, p = 0.319, I^2 = 14.6%).

Macro-albuminuria

Twelve studies (19, 21-26, 32, 36, 38, 41, 42) reported ACEI/ARB effects on macro-albuminuria (n = 5,151) with ACEI/ARB vs other therapies (five with

d-CCB, one with diuretic, one with BB and one with BB/diuretic) in eight studies (19, 21-23, 25, 26, 36, 38) and placebo in five studies (24, 32, 36, 41, 42) (Table 2.6). Eight trials (19, 22, 25, 26, 32, 36, 38, 41) (n = 1,401) studied patients with micro-albuminuria, and four (21, 23, 24, 42) (n = 3,761) studied mixed patients with normo- and micro-albuminuria.

Direct pooled estimates of treatment effects between ACEI/ARB and other anti-hypertensive drugs (n = 641 vs 653) of eight trials (19, 21-23, 25, 26, 36, 38) were homogeneous (χ^2 = 5.24, df = 7, p = 0.631, I^2 = 0.0%; Figure 2.2D) with borderline significant risk reduction of 29% (pooled RR = 0.71, 95% CI: 0.50, 1.00). Neither the Harbord test nor the funnel plot suggested publication bias (coefficient = −0.733, SE = 0.828, p = 0.410; Figure 2.4D.i).

Among five placebo-controlled trials (24, 32, 36, 41, 42) (n = 1,950 vs 1,918), the pooled RR was 0.45 (95% CI: 0.26, 0.79) with moderate heterogeneity (χ^2 = 8.64, df = 4, p = 0.071, I^2 = 53.7%; Figure 2.2D). This suggested that ACEI/ARB significantly reduced risk of macroalbuminuria by 55%. The Harbord test suggested asymmetry of the funnel plot (coefficient = −2.043, SE = 0.547, p = 0.033). The contour enhanced funnel plot showed that one-half of the studies included were in the high- and non-significance areas (Figure 2.4D.ii), suggesting treatment-effect heterogeneity. Meta-regression analysis fitting type of patient (micro-albuminuria and mixed patients) reduced the degree of heterogeneity (I^2) from 53.7% to 0%. Subgroup analysis performed in patients with micro-albuminuria and mixed micro- and macro-albuminuria yielded pooled RRs of 0.31 (95% CI: 0.18, 0.57) and 0.45 (95% CI: 0.26, 0.79), respectively.

Micro-albuminuria

Nine studies (19, 21, 22, 25, 26, 31, 35, 39, 43) had micro-albuminuria outcomes (n = 7,891): six (19, 21, 22, 25, 26, 43) looking at ACEI vs other anti-hypertensive drugs, two looking at ACEI vs placebo (31, 43) and two looking at ARB vs placebo (35, 39) (Table 2.7).

The pooled treatment effects between ACEI/ARB and other anti-hypertensive drugs were somewhat heterogeneous (χ^2 = 7.70, df = 5, p = 0.174, I^2 = 35.1%) with a pooled RR of 0.84 (95% CI: 0.61, 1.15), see Table 2.7 and Figure

2.2E. The Harbord test suggested no asymmetry of the funnel plot (coefficient = −0.281, SE = 1.367, p = 0.847; Figure 2.4E.i).

Compared with placebo in four studies (31, 35, 39, 43) (n = 3,290 vs 3,472), the pooled effect of ACEI/ARBs (24, 28, 32, 37) was 0.82 (95% CI: 0.64, 1.05; Figure 2.2E) with moderate heterogeneity (χ^2 = 5.93, df = 3, p = 0.115, I^2 = 49.4%). Meta-regression could not identify the source of the heterogeneity. The Harbord test suggested asymmetry of the funnel (coefficient = −2.626, SE = 0.360, p = 0.018), and the contour-enhanced funnel plot suggested that this heterogeneity might be the cause of the asymmetry (Figure 2.4E.ii).

Albuminuria regression

Ten studies (18, 21, 25, 27-29, 36, 38, 44, 45) reported regression of albuminuria (n = 3,710; Table 2.8). The treatment effect between ACEI/ARB and other anti-hypertensive drugs, which was based on nine studies (18, 21, 25, 27, 28, 36, 38, 44, 45) (n = 646 vs 640), was homogeneous (χ^2 = 8.74, df = 8, p = 0.365, I^2 = 8.4%) with a borderline non-significant effect of 16% (pooled RR = 1.16, 95% CI: 0.99, 1.39, see Table 2.8 and Figure 2.2F). Neither the Harbord test nor a funnel plot suggested publication bias (coefficient = −0.086, SE = 0.718, p = 0.907; Figure 2.4F).

For the placebo-controlled trials (n = 947 vs 948), the likelihood of albuminuria regression was 17% higher with ACEI/ARB, which was on the borderline of non-significance (RR = 1.17, 95% CI: 1.00, 1.37; Table 2.8).

2.3.2 Network meta-analysis

ESRD

A network meta-analysis was applied to assess all treatment comparisons, (Figure 2.3A and Table 2.9). Arrows and tails refer to interventions and comparators, bold and dashed lines refer to direct and indirect comparisons, respectively. Numbers under the line refer to the number of studies for the direct comparator data, whereas numbers above the line indicate pooled RRs. The analysis suggested that the ACEI/ARB (n = 6,092) significantly decreased the risk of ESRD when compared with d-CCB (n = 644) and placebo (n = 5,569) with pooled RRs of 0.25 (95% CI: 0.07, 0.96) and 0.77 (95% CI: 0.64, 0.92), respectively. However, the risk of ESRD was

2.00 (95% CI: 0.35, 11.55) times higher, but not significantly so, compared with the BB group (n = 411). Comparing ACEI/ARB with all antihypertensive drugs (d-CCB + BB) resulted in 62% significantly lower risk of ESRD (pooled RR = 0.38, 95% CI: 0.31, 0.47).

Pooling mean BPs from four studies (21, 26, 30, 40) showed non-significant differences between groups, with mean differences of 1.27 (95% CI: −1.42, 3.95) for systolic BP (SBP) and −0.71 (95% CI: −3.88, 2.46) for diastolic BP (DBP).

Doubling of serum creatinine

Figure 2.3B and Table 2.9 show that ACEI/ARBs (n = 7,831) significantly reduced the risk of serum creatinine doubling by 77% (pooled RR = 0.23, 95% CI: 0.09, 0.57), 72% (pooled RR = 0.28, 95% CI: 0.11, 0.71), and 21% (pooled RR = 0.79, 95% CI: 0.75, 0.84) compared with d-CCB (n = 567), nd-CCB/BB (n = 34), and placebo (n = 7,784), respectively. Combining all anti-hypertensive drugs (n = 601) and comparing with ACEI/ARB resulted in 77% significantly lower risk (pooled RR = 0.23, 95% CI: 0.09, 0.58).

Micro-vascular complications

The number of participants in each treatment arm has been described in Table 2.5, with total number of patients in ACEI/ARB and placebo of 3,284 vs 2,847, respectively. ACEI/ARBs significantly reduced the risk of micro-vascular complications by 19% (pooled RR = 0.81, 95% CI: 0.71, 0.92) when compared with placebo, but increased the risk almost twofold when compared with BB (Figure 2.3C and Table 2.9).

Macro-albuminuria

Network meta-analysis was performed based on 12 studies (19, 21-26, 32, 36, 38, 41, 42) (n = 5,151; Table 2.9). ACEI/ARBs (n = 2,580) significantly reduced macro-albuminuria by 29% (pooled RR = 0.71, 95% CI: 0.62, 0.83) compared with BB/diuretic (n = 441), 55% (pooled RR = 0.45, 95% CI: 0.29, 0.70) vs d-CCB (n = 212), and 33% (pooled RR = 0.67, 95% CI: 0.49, 0.92) vs placebo (n = 1,918; Figure 2.3D and Table 2.9). The ACEI/ARBs significantly reduced macro-albuminuria

by 40% (pooled RR = 0.60, 95% CI: 0.47, 0.77) compared with all anti-hypertensive drugs (n = 653).

Pooling SBP and DBP in three studies (21, 38, 41), the mean SBP and DBP differences were 2.82 (95% CI: 0.32, 5.31) and 0.33 (95% CI: −0.93, 1.60) mmHg, respectively.

Micro-albuminuria

Based on pooling of results from nine studies (19, 21, 22, 25, 26, 31, 35, 39, 43) (n = 7,891), ACEI/ARB (n = 3,704) had significantly better benefit than d-CCB (n = 238) with a pooled RR of 0.50 (95% CI: 0.38, 0.65), but significantly worse outcomes than BB (i.e. favoring BB) with the pooled RR of 0.48 (95% CI: 0.35, 0.66; Figure 2.3E and Table 2.9). When compared with nd-CCB (n = 303) and placebo (n = 3,472), ACEI/ARBs did not reduce micro-albuminuria with pooled RRs of 0.93 (95% CI: 0.71, 1.22) and 1.01 (95% CI: 0.82, 1.25), respectively. Compared with all anti-hypertensive drugs, the ACEI/ARB significantly reduced the risk by 39% (pooled RR = 0.61, 95% CI: 0.45, 0.83).

Regression of albuminuria

Using data from ten studies (18, 21, 25, 27-29, 36, 38, 44, 45) (n = 3,710), ACEI/ARB (n = 1,582) significantly promoted regression of albuminuria compared with placebo (n = 948), but not with diuretic (n = 283) and RRs were 1.35 (95% CI: 1.07, 1.70) in favor of ACEI/ARB and 1.28 (95% CI 1.02, 1.60) in favor of diuretic, respectively (Figure 2.3F and Table 2.9). The pooled RR was1.16 (95% CI: 0.83, 1.63) for ACEI/ARB vs d-CCB (n = 357).

In six of ten studies where data were available (21, 27-29, 44, 45), the mean SBP was significantly higher for ACEI/ARB (mean difference = 2.35, 95% CI: 1.07, 3.64) than placebo, but not so for DBP (mean difference = 0.54 mmHg, 95% CI: −0.40, 1.48 mmHg).

2.4 Discussion

The direct and indirect comparisons in our study confirm the clear benefit of ACEI/ARB over placebo for all outcomes (ESRD, serum creatinine doubling, micro-vascular complications, macro-albuminuria and regression of albuminuria) except micro-albuminuria. The lack of a statistically significant treatment effect for micro-albuminuria outcome is likely to result partly from the heterogeneity of treatment effects across the studies. Our study extends the results of Strippoli et al. (11), who showed borderline significant benefit for ACEI/ARB vs placebo for doubling of serum creatinine (RR = 0.79, 95% CI: 0.75, 0.84 vs 0.60, 95% CI: 0.34, 1.05) and ESRD (RR = 0.77, 95% CI: 0.64, 0.92 vs 0.64, 95% CI: 0.4, 1.03). The addition of new data and the use of network meta-analysis methods increase the power and allow us to demonstrate the reno-protective effects of RAS blockade more confidently. The major contribution of our study is in teasing out the potential reno-protective effect of ACEI/ARBs over other anti-hypertensive drugs. Overall, the direct meta-analysis suggests a potential benefit of ACEI/ARB in reducing macro-albuminuria and doubling of serum creatinine, and in promoting regression of albuminuria. The results of network meta-analysis suggest additional benefits of the ACEI/ARB in reducing the risk of ESRD. These benefits contradict the previous meta-analysis (9), which found reno-protective effects of ACEI/ARB in patients without diabetes but not in patients who had already developed diabetic nephropathy. This discrepancy with previous work may be due partly to the addition of new data, thereby improving power, or may be driven partly by the fact that the major active comparators were CCBs. In some comparisons, BBs and diuretics are significantly better than ACEI/ARBs, though the numbers in these comparisons are small and driven largely by the UK Prospective Diabetes Study. In the studies that reported BP change, there was no significant difference in BP decrease between ACEI/ARB and other anti-hypertensive drugs, suggesting that there is a specific reno-protective effect of ACEI/ARBs beyond their anti-hypertensive effect. This runs contrary to the conclusion of Casas et al., (9) who found the effect of RAS blockade to depend on its BP-lowering effect. In their study, Casas et al. showed that the benefit of RAS blockers compared with active controls was associated with the extra degree of BP decrease. These results are hard to reconcile with summary level data. It is of course

possible for both conclusions to be true, i.e. the effect of RAS blockers is linked to the level of BP control but that for two agents that bring about the same drop in BP, RAS blockers would have an additional benefit. This possibility would be better teased out with a meta-analysis of individual patient data or a direct test of this hypothesis in a large-scale RCT.

Our study has some strengths. We have applied a network meta-analysis to increase the power of the tests and reduce type I errors (15-17). We applied a mixed model, which is thought to be the most appropriate method for this kind of pooling. The network method 'borrows' treatment information from other studies and increases the total sample size. As a result, treatment effects that could not be detected or treatment effects of borderline significance in direct meta-analysis could be identified. In addition, all possible treatment comparisons have been mapped and displayed. The weakness of our study is that despite the large overall numbers, some comparator groups still have small numbers, leading to poor precision of estimates. The lack of BP data for some studies also limits our ability to judge the specific reno-protective effects.

In conclusion, there appears to be a consistent benefit of ACEI/ARB on all outcomes in type 2 diabetes, including the 'hard clinical endpoints' of ESRD and doubling of serum creatinine, when compared with other antihypertensive drugs (mainly CCBs) and placebo, both in direct and indirect meta-analyses. This is seen in the context of no difference in BP decrease, suggesting a specific reno-protective effect. Other antihypertensives, particularly BBs and diuretics, may have even greater reno-protective effects, but this needs to be investigated in further studies or individual patient meta-analysis.

2.5 Acknowledgement

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Table 2.1. Characteristics of studies in meta-analysis

Author[reference]	Type of Participants at Baseline					Intervention (mg/day)	Comparators (mg/day)	Outcomes	Follow up (y)
	Age (y)	HbA_{1c}[a]	Renal Function	Albuminuria	HT				
UKPDS(26), 1998	56	7.0/53		Normoalb[b] Microalb[c] Macroalb[d]	Yes	Captopril 25-50	Atenolol 50-100	Microalb Macroalb ESRD	8.4
HOPE (24), 2000	65	-	93.9[e]	Normoalb Microalb	Mix	Ramipril 10	Placebo	Macroalb ESRD	4.5
Ahmad J(41), 1997	50	8.1/65	124[f]	Microalb	No	Enalapril 10	Placebo	Macroalb	5
Baba S(25), 2001	60	-	-	Normoalb Microalb	Yes	Enalapril 5-50	Nifedipine R 20-60	Microalb Macroalb, Albuminuria regression	2
Bakris GL(20), 1996	63	10.7/93	63.6[g]	Macroalb	Yes	Lisinopril	Verapamil / Diltiazem Atenolol	ESRD	6

Table 2.1. Continued

Author[reference]	Type of Participants at Baseline					Intervention (mg/day)	Comparators (mg/day)	Outcomes	Follow up (y)
	Age (y)	HbA_{1c}[a]	Renal Function	Albuminuria	HT				
Chan JC(21), 2000	58	-	-	Normoalb Microalb Macroalb	Yes	Enalapril 10-40	Nifedipine SR 40-80	Microalb Macroalb Albuminuria regression ESRD	5
Fogari R(27), 2005	60	6.9/52	-	Microalb	Yes	Lisinopril 10	Manidipine 10	Albuminuria regression	2
Fogari R(28), 2002	63	7.1/54	88.4[e]	Microalb	Yes	Fosinopril 10-30	Amlodipine 5-15	Albuminuria regression	4
Fogari R(40), 1999	56	7.2/55	43.8[g]	Macroalb	Yes	Ramipril 5	Nitrendipine 20	ESRD	2
Lacourciere Y(22), 1993	57	9.3/78	77.8[e]	Macroalb[d]	Yes	Captopril 50-100	Metoprolol50-100 HCTZ 25-50	Microalb Macroalb	3

Table 2.1. Continued

Author[reference]	Type of Participants at Baseline					Intervention (mg/day)	Comparators (mg/day)	Outcomes	Follow up (y)
	Age (y)	HbA_{1c}[a]	Renal Function	Albuminuria	HT				
Lebovitz HE(42), 1994				Normoalb[f] Microalb	Yes	Enalapril 5-40	Placebo	Macroalb	3
Marre M(29), 2004	60	7.8/62	92.5[g]	Microalb Macroalb	Mixed	Ramipril 1.25	Placebo	Albuminuria regression ESRD	4
Marre M(38), 2004	65	7.6/60	89.2[e]	Microalb	Yes	Enalapril 10	Indapamide 1.5	Macroalb, Albuminuria regression	1
Mosconi L(44), 1996	-	-	64.6[f]	Microalb	Yes	Enalapril 5-20	Nitrendipine 10-40	Albuminuria regression	2
Nielson FS(30), 1997	61	8.6/71	74.5[f]	Macroalb	Yes	Lisinopril 10-20	Atenolol 50-100	ESRD	3.5
Ogawa S(45), 2007	61	6.8/51	65.8[d]	Microalb	Yes	Temocapril 4	Nifedipine CR 40	Albuminuria regression	2

Table 2.1. Continued

Author[(reference)]	Type of Participants at Baseline					Intervention (mg/day)	Comparators (mg/day)	Outcomes	Follow up (y)
	Age (y)	HbA_{1c}[a]	Renal Function	Albuminuria	HT				
Ravid M(31), 1998	55	9.3/78	107.7 [g]	Normoalb	No	Enalapril 10	Placebo	Microalb	6
Ravid M(32), 1993	44	10.4/90	104.6[e]	Microalb[e]	No	Enalapril 10	Placebo	Macroalb	5
Ruggenenti P(43), 2004	62	5.8/40	79.6[e]	Normoalb	Yes	Tranadolapril 2	Verapamil SR 240 Placebo	Microalb	3.6
Shiba T(23), 2000	61	8.1/65	-	Normoalb Microalb	Yes	Delapril 60	Manidipine 10	Macroalb	2
Brenner B(34)	60	8.4/68	168[e]	Macroalb		Losartan 50 - 100	Placebo	ESRD Doubling Scr	3.4
Jerums G(36)	53	8.1/65	92	Microalb	No	Perindopril	Nifedipine	Macroalb Albuminuria regression	6

Table 2.1. Continued

Author[reference]	Type of Participants at Baseline					Intervention (mg/day)	Comparators (mg/day)	Outcomes	Follow up (y)
	Age (y)	HbA_{1c}[a]	Renal Function	Albuminuria	HT				
Haller H(39)	57.7	7.7/61	84.9	Normoalb	Mixed	Olmesartan 40	Placebo	Microalb Doubling Scr	3.2
Lewis E(33)	59	8.2/66	147.6[e]	Proteinuria	Yes	Irbesartan	Amlodipine Plaebo	Doubling Scr ESRD	2.6
Uzu T(18)	62	-	-	Microalb	Yes	Valsartan	Amlodipine	Albuminuria regression	0.5
Bilous R(35)	56.9	-	90	Normoalb	Mixed	Candesartan	Placebo	Microalb	4.7
Sjolie AK(37)	57	8.2/66	-	Normoalb	Mixed	Candesartan	Placebo	Microvascular complication	4.7
Estacio RO(19), 2000	58	11.6/103	-	Normoalb Microalb Macroalb	Yes	Enalapril 5-40	Nisoldipine 10-60	Microalb Macroalb	5.3

[a] Normo-albuminuria, [b] Micro-albuminuria, [c] Macro-albuminuria , [d] Serum creatinine (mmol/l), [e] estimated GFR (ml/min/1.73 m^2), [f] Creatinine clearance (ml/min)

Table 2.2. Risk of bias assessment

Study	Sequence generation	Allocation concealment	Blinding	Incomplete outcome	Selective outcome report	Free of other bias	Description of other bias
UKPDS(26)	Y	Y	Y	Y	Y	Y	
HOPE Study(24)	U	U	Y	Y	N	Y	
Ahmad J(41)	U	U	Y	Y	Y	Y	
Baba S(25)	Y	U	N	Y	N	Y	
Bakris GL(20)	U	U	Y	Y	Y	N	Imbalanced baseline BP
Chan JC(21)	Y	Y	Y	Y	N	N	Imbalanced baseline SBP
Brenner B(34)	Y	Y	Y	Y	Y	Y	
Fogari R(27)	Y	Y	Y	Y	Y	Y	
Fogari R(28)	Y	Y	Y	Y	Y	Y	
Fogari R(40)	U	U	U	Y	Y	Y	
Lacouciere Y(22)	U	Y	Y	Y	N	N	Imbalanced baseline BP
Lebovitz HE(42)	U	U	Y	Y	Y	Y	
Marre M(29)	Y	Y	Y	Y	Y	Y	
Marre M(38)	U	Y	Y	Y	Y	Y	
Mosconi L(44)	U	U	Y	Y	Y	Y	

Table 2.2. Continued

Study	Sequence generation	Allocation concealment	Blinding	Incomplete outcome	Selective outcome report	Free of other bias	Description of other bias
Nielsen FS(30)	Y	U	Y	Y	Y	Y	
Ogawa S(45)	U	U	Y	Y	Y	Y	
Ravid M(31)	Y	Y	Y	Y	Y	Y	
Ravid M(32)	Y	N	Y	Y	Y	Y	
Ruggenenti P(43)	U	U	Y	Y	Y	Y	
Shiba T(23)	U	U	U	Y	Y	N	Imbalanced baseline BP, HbA1c
Jerums G(36)	Y	Y	Y	Y	Y	Y	
Haller H(39)	U	Y	Y	Y	Y	Y	
Lewis E(33)	Y	Y	Y	Y	Y	Y	
Uzu T(18)	U	U	U	N	N	N	
Bilous R(35)	Y	Y	Y	Y	Y	Y	
Sjolie AK(37)	Y	Y	Y	Y	Y	Y	
Estacio RO(19)	U	U	N	N	Y	Y	

Y=low risk, N=high risk, U=unclear

Table 2.3. ESRD between ACEI/ARB and active drugs or placebo

Study[(Reference)]	Mean Age	Mean Crcl[a]	Albuminuria	Treatments	SBP (sd)	DBP (sd)	No. of Events	N	RR (95%CI)
ACEI/ARB vs Active drugs									
UKPDS(26)	56	-	Mixed	Captopril	144 (14)	83 (8)	4	400	0.90 (0.23, 3.55)
				Atenolol	143 (14)	81 (7)	4	358	
Bakris GL(20)	62	62.9	Macroalb[b]	Lisinopril	-	-	0	18	0. 21 (0.01, 3.60)
				Atenolol	-	-	4	16	
				nd-CCB	-	-	0	18	
Chan JC(21)	58	75.3	Mixed	Enalapril	137 (11.8)	72.1 (14.6)	6	50	1. 25 (0.41, 3.83)
				Nifedipine SR	132.2 (9.4)	72.6 (7.8)	5	52	
Fogari R(40)	56	43.8	Macroalb	Ramipril	147.8 (10)	89.9 (6)	1	26	0.96 (0.06, 14.55)
				Nitrendipine	149.4 (12)	91 (7)	1	25	
Nielsen FS(30)	61	74.5[c]	Macroalb	Lisinopril	145 (16.5)	76 (8.3)	1	17	1. 12 (0.08, 16.52)
				Atenolol	148 (8.7)	82 (8.7)	1	19	
Lewis E(33)	59	-	Proteinuria	Irbesartan	140(-)	77(-)	87	579	0.80 (0.62, 1.04)
				Amlodipine	141(-)	77(-)	105	569	
Pooled RR									0.82 (0.64, 1.05)

Table 2.3. Continued

Study(Reference)	Mean Age	Mean Crcl[a]	Albuminuria	Treatments	SBP (sd)	DBP (sd)	No. of Events	N	RR (95%CI)
ACEI/ARB vs Placebo									
HOPE Study(24)	65	-	Norrrmoalb[d] & Microalb[e]	Ramipril	-	-	10	1,808	1.22 (0.48, 3.09)
				Placebo	-	-	8	1,769	
Marre M(29)	65	-	Microalb & Macroalb	Ramipril	-	-	11	2,443	0.93 (0.41, 2.10)
				Placebo	-	-	12	2,469	
Brenner B(34)	60	-	Macroalb	Losartan	140(-)	74(-)	147	751	0.77 (0.64, 0.93)
				Placebo	142(-)	74(-)	194	762	
Lewis E(33)	59	-	Proteinuria	Irbesartan	140(-)	77(-)	87	579	0.81 (0.63, 1.06)
				Placebo	144(-)	80(-)	106	567	
Pooled RR									0.80 (0.69, 0.93)

[a] Creatinine clearance (ml/min), [b] Macro-albuminuria,[c]Glomerular filtration rate (ml/min/1.73 m^2), [d] Normo-albuminuria,

[e] Micro-albuminuria

Table 2.4. Doubling of serum creatinine between ACEI/ARB and active drugs or placebo

	Mean Age	Mean Crcl[a]	Albuminuria	Treatments	SBP (sd)	DBP (sd)	No. of Events	N	RR (95%CI)
RASB vs Active drugs									
Bakris GL(20)	62	62.9	Macroalb[b]	Lisinopril	-	-	1	18	0.27 (0.34, 2.03)
				Atenolol/nd-CCB	-	-	7	34	
Lewis E(33)	59	-	Proteinuria	Irbesartan	140(-)	77(-)	98	579	0.67 (0.53, 0.84)
				Amlodipine	141(-)	77(-)	144	567	
Pooled RR									0.66 (0.53, 0.83)
RASB vs Placebo									
HOPE Study(24)	65	-	Norrrmoalb[c] & Microalb[d]	Ramipril	-	-	118	1,808	0.78 (0.61, 0.98)
				Placebo	-	-	149	1,769	
Marre M(29)			Micro& macroalb	Ramipril	-	-	48	2,443	0.81 (0.56, 1.18)
				Placebo	-	-	60	2,469	

Table 2.4. Continued

	Mean Age	Mean Crcl[a]	Albuminuria	Treatments	SBP (sd)	DBP (sd)	No. of Events	N	RR (95%CI)
Brenner B(34)	60	-	Macroalb	Losartan	140(-)	74(-)	162	751	0.83 (0.69, 0.10)
				Placebo	142(-)	74(-)	198	762	
Haller H(39)	57.7	84.9	Normoalb	Olmesartan	125.7(-)	74.3(-)	23	2,232	0.99 (0.56, 1.76)
				Placebo	128.7(-)	76.2(-)	23	2,215	
Lewis E(33)	59	-	Proteinuria	Irbesartan	140(-)	77(-)	98	579	0.71 (0.57, 0.90)
				Placebo	144(-)	80(-)	135	478	
Pooled RR									0.79 (0.71, 0.89)

[a] Creatinine clearance (ml/min), [b] Macro-albuminuria, [c] Normo-albuminuria, [d] Micro-albuminuria

Table 2.5. Major micro-vascular complications between ACEI/ARB and active drugs or placebo

Study	Mean Age	Mean Crcl[a]	Albuminuria	Treatments	SBP (SD)	DBP (SD)	No. of Events	N	RR (95%CI)
ACEI/ARB vs Active drugs									
UKPDS(26)	56	-	Microalb[b]	Captopril	144 (14)	83 (8)	40	400	1.28 (0.81, 2.03)
				Atenolol	143 (14)	81 (7)	28	358	
ACEI/ARB vs Placebo									
HOPE Study(24)	65	-	Norrmoalb & Microalb	Ramipril	-	-	273	1,808	0.86 (0.74, 0.99)
				Placebo			312	1,769	
Ravid M(32)	44	-	Normoalb	Enalapril			9	49	0.64 (0.30, 1.34)
				Placebo			13	45	
Ravid M(31)	55	108	Microalb	Enalapril	-	-	6	77	0.41 (0.17, 1.00)
				Placebo	-	-	15	79	
Sjolie AK(37)	57	-	Normoalb	Candesartan			161	950	0.89 (0.73, 1.08)
				Placebo			182	954	
Pooled RR									0.85 (0.74, 0.97)

Table 2.6. Macro-albuminuria between ACEI/ARB and active drugs or placebo

Study	Mean Age	Mean Crcl[a]	Albuminuria	Treatments	SBP (SD)	DBP (SD)	No. of Events	N	RR (95%CI)
ACEI/ARB vs Active drugs									
UKPDS(26)	-	-	Microalb[b]	Captopril	-	-	7	153	0.48 (0.20, 1.15)
				Atenolol	-	-	14	146	
Baba S(25)	60	110.4	Microalb	Enalapril	-	-	3	53	0.91 (0.21, 3.87)
				Nifedipine SR	-	-	4	64	
Chan JC(21)	-	-	Normoalb[c] & Microalb	Enalapril	137 (11.8)	72.1(14.6)	4	39	0.65 (0.20, 2.12)
				Nifedipine SR	132.2 (9.4)	72.6 (7.8)	6	38	
Lacourciere Y(22)	-	-	Microalb	Captopril	-	-	0	9	0.26 (0.01, 4.83)
				Metoprolol/ HCTZ	-	-	2	12	
Marre M(38)	60	92.5	Microalb	Enalapril	139.3(14.3)	81.4 (7.9)	18	286	0.69 (0.38, 1.22)
				Indapamide	137.3 (12)	81.0 (8.1)	26	283	
Shiba T(23)	61	-	Normoalb & Microalb	Delapril	-	-	0	23	0.08 (0.01, 1.37)
				Manidipine	-	-	4	16	
Jerums G(36)	53		Microalb	Perindopril	-	-	2	11	2.00 (0.21, 18.98
				Nifedipine	-	-	1	11	

Table 2.6. Continued

Study	Mean Age	Mean Crcl[a]	Albuminuria	Treatments	SBP (SD)	DBP (SD)	No. of Events	N	RR (95%CI)
Estacio RO(19)	58	-	Microalb	Enalapril	-	-	13	67	0.95 (0.50, 1.81)
				Nisoldipine	-	-	17	83	
Pooled RR									0.71 (0.50, 1.00)
ACEI/ARB vs Placebo									
HOPE Study(24)	65	-	Norrmoalb & Microalb	Ramipril	-	-	117	1,808	0.77 (0.61, 0.97)
				Placebo	-	-	149	1,769	
Ahmad J(41)	50	124[e]	Microalb	Enalapril	134 (5.7)	80 (4.6)	4	52	0.33 (0.11, 0.95)
				Placebo	134 (5.7)	83 (5.1)	12	51	
Lebovitz HE(42)	-	-	Norrmoalb & Microalb	Enalapril	-	-	2	30	0.32 (0.07, 1.38)
				Placebo	-	-	8	38	
Ravid M(32)	44	-	Microalb	Enalapril	-	-	6	49	0.29 (0.13, 0.66)
				Placebo	-	-	19	45	
Jerums G(36)	53		Microalb	Perindopril	-	-	2	11	0.39 (0.10, 1.53)
				Placebo	-	-	7	15	
Pooled RR									0.67 (0.54, 0.83)

[a] Creatinine clearance (ml/min), [b] Micro-albuminuria, [c] Normo-albuminuria, [d] not include in the direct meta-analysis,

[e] Glomerular filtration rate (ml/min/1.73 m^2)

Table 2.7. Micro-albuminuria between ACEI/ARB and active drugs or placebo

Study[Reference]	Mean Age	Mean Crcl[a]	Albuminuria	Treatments	SBP (SD)	DBP (SD)	No. of Events	N	RR (95%CI)
RASB vs Active drugs									
UKPDS(26)	56	-	Norrmoalb[b]	Captopril	-	-	48	153	1.21 (0.84, 1.73)
				Atenolol	-	-	38	146	
Baba S(25)	60	110.4	Norrmoalb	Enalapril	-	-	15	95	0.73 (0.40, 1.31)
				NifedipineSR	-	-	23	106	
Chan JC(21)	58	75.3	Norrmoalb	Enalapril	-	-	4	18	1.11 (0.35, 3.57)
				NifedipineSR	-	-	5	25	
Lacourciere Y(22)	57	-	Norrmoalb	Captopril	-	-	1	25	0.56 (0.05, 5.81)
				Metoprolol / HCTZ	-	-	2	28	
Ruggenenti P(43)	62	-	Norrmoalb	Trandolapril	139 (12)	81 (6)	18	301	0.50 (0.29, (0.87)
				Verapamil	142 (12)	83 (6)	36	303	
Estacio RO(19)	58	85	Norrmoalb	Enalapril	-	-	25	123	0.87 (0.53, 1.42)
				Nisoldipine	-	-	25	107	
Pooled RR									0.84 (0.61, 1.15)

Table 2.7. Continued

Study(Reference)	Mean Age	Mean Crcl[a]	Albuminuria	Treatments	SBP (SD)	DBP (SD)	No. of Events	N	RR (95%CI)
RASB vs Placebo									
Ravid M(31)	55	107.7	Norrmoalb	Enalapril	-	-	5	7,785	0.34 (0.13, 0.90)
				Placebo	-	-	15	79	
Ruggenenti P(43)	62	-	Norrmoalb	Trandolapril	139 (12)	81 (6)	18	301	0.60 (0.34, 1.05)
				Placebo	141 (10)	82 (6)	30	300	
Haller H(39)	57.7	84.9	Normoalb	Olmesartan	125.7 (-)	74.3 (-)	178	1,961	0.93 (0.77, 1.12)
				Placebo	128.7 (-)	76.2 (-)	210	2,139	
Bilous R(35)	56.9	-	Normoalb	Candesartan	-	-	114	951	0.92 (0.73, 1.17)
				Placebo	-	-	124	954	
Pooled RR									0.82 (0.64, 1.05)

[a] Creatinine clearance (ml/min), [b] Normo-albuminuria

Table 2.8. Albuminuria Regression between ACEI/ARB and active drugs or placebo

Study [Reference]	Mean Age	Mean Crcl[a]	Albuminuria	Treatments	SBP (SD)	DBP (SD)	No. of Events	N	RR (95%CI)
RASB vs Active drugs									
Baba S(25)	60	110.4	Microalb	Enalapril	-	-	11	53	0.70 (0.37, 1.34)
				Nifedipine SR	-	-	19	64	
Chan JC(21)	-	-	Microalb & Macroalb[d]	Enalapril	137 (11.8)	72.1 (14.6)	6	32	1.01 (0.35, 2.95)
				Nifedipine SR	132.2 (9.4)	72.6 (7.8)	5	27	
Fogari R(27)	60	93.4	Microalb	Lisinopril	126.8 (9.9)	74.4(4.1)	27	49	1.45 (0.94, 2.24)
				Manidipine	125.3 (9.3)	73.8(3.9)	19	50	
Fogari R (28)	63	-	Microalb	Fosinopril	142.3 (10.4)	87.3 (5.6)	47	102	1.40 (0.99,1.97)
				Amlodipine	140.4 (10.1)	86.5 (5.4)	34	103	
				Fosinopril + Amlodipine[c]	132.4 (9.9)	82.3 (5.1)	70	104	
Marre M(38)	60	92.5	Microalb	Enalapril	139.3 (14.3)	81.4 (7.9)	120	286	1.06 (0.87, 1.29)
				Indapamide	137.3 (12)	81 (8.1)	112	283	
Mosconi (44)	-	64.6[e]	Microalb	Enalapril	146.6 (12.4)	93.7 (7.8)	4	6	1.17 (0.50, 2.74)
				Nitrendipine	150.3 (11.7)	84.9 (3.6)	4	7	

Table 2.8. Continued

Study [Reference]	Mean Age	Mean Crcl[a]	Albuminuria	Treatments	SBP (SD)	DBP (SD)	No. of Events	N	RR (95%CI)
Ogawa S(45)	62	-	UACR 100 - 300 mg/g Cr	Temocapril	130 (4.5)	78.5(3.3)	5	34	1.32 (2.9, 6.16)
				Nifedipine			2	18	
Jerums G(36)	53	90	Microalb	Perindopril	-	-	1	11	0.33 (0.04, 2.73)
				Nifedipine	-	-	3	11	
Uzu T(18)	62		Microalb	Valsartan	-	-	17	73	1.99 (0.95, 4.18)
				Amlodipine	-	-	9	77	
Pooled RR									1.16 (1.00, 1.34)
RASB vs Placebo									
Marre M(29)	65	-	Microalb & Macroalb	Ramipril	-	-	253	936	1.17 (1.00, 1.37)
				Placebo	-	-	215	933	
Jerums G(36)	53	90	Microalb	Perindopril	-	-	1	11	0.46 (0.05, 3.81)
				Nifedipine	-	-	3	15	
Pooled RR									1.17 (1.00, 1.37)

[a] Creatinine clearance (ml/min), [b] Micro-albuminuria, [c] not include in the direct meta-analysis, [c] Macro-albuminuria,

[e] Glomerular filtration rate (ml/min/1.73 m^2)

Table 2.9. Estimate effects of ACEI/ARB on renal and micro-vascular outcomes: A network meta-analysis

A) ESRD		
Treatments	RR	95% CI
ACEI/ARB vs d-CCB	0.25	0.07, 0.96
ACEI/ARB vs Placebo	0.77	0.64, 0.92
BB vs ACEI/ARB	0.50	0.09, 2.88
BB vs d-CCB	0.13	0.04, 0.41
BB vs Placebo	0.38	0.06, 2.57
Placebo vs d-CCB	0.33	0.08, 1.43
B) Doubling serum creatinine		
Treatments	RR	95% CI
ACEI/ARB vs d-CCB	0.23	0.09, 0.57
ACEI/ARB vs nd-CCB/BB	0.28	0.11, 0.71
ACEI/ARB vs Placebo	0.79	0.75, 0.84
nd-CCB vs d-CCB	0.81	0.81, 0.81
Placebo vs d-CCB	0.29	0.11, 0.74
Placebo vs nd-CCB/BB	0.35	0.14, 0.91

Table 2.9. Continued

C) major micro-vascular complications		
Treatments	RR	95% CI
ACEI/ARB vs Placebo	0.81	0.71, 0.92
BB vs ACEI/ARB	0.53	0.46, 0.60
BB vs Placebo	0.43	0.40, 0.45
D) macro-albuminuria		
Treatments	RR	95% CI
ACEI/ARB vs BB/Diuretic	0.72	0.62, 0.83
ACEI/ARB vs d-CCB	0.45	0.29, 0.70
ACEI/ARB vs Placebo	0.67	0.49, 0.92
BB/Diuretic vs d-CCB	0.63	0.39, 1.02
BB/Diuretic vs Placebo	0.94	0.64, 1.37
Placebo vs d-CCB	0.67	0.37, 1.24

Table 2.9. Continued

E) Micro-albuminuria		
Treatments	RR	95% CI
ACEI/ARB vs BB/Diuretic	0.48	0.35, 0.66
ACEI/ARB vs d-CCB	0.50	0.38, 0.65
ACEI/ARB vs nd-CCB	0.93	0.71, 1.22
ACEI/ARB vs Placebo	1.00	0.82, 1.25
d-CCB vs BB/Diuretic	0.97	0.70, 1.35
nd-CCB vs BB/Diuretic	0.52	0.37, 0.72
nd-CCB vs d-CCB	0.53	0.50, 0.56
Placebo vs BB/Diuretic	0.48	0.33, 0.69
Placebo vs d-CCB	0.49	0.41, 0.59
Placebo vs nd-CCB	0.92	0.77, 1.09

Table 2.9. Continued

F) Albuminuria regression Treatments	RR	95% CI
ACEI/ARB vs d-CCB	1.17	0.83, 1.63
ACEI/ARB vs Placebo	1.35	1.07, 1.70
d-CCB vs Placebo	1.16	0.83, 1.61
Diuretic vs ACEI/ARB	1.28	1.02, 1.60
Diuretic vs d-CCB	1.49	1.07, 2.07
Diuretic vs Placebo	1.72	1.71, 1.73

Figure 2.1. Flow of study selection

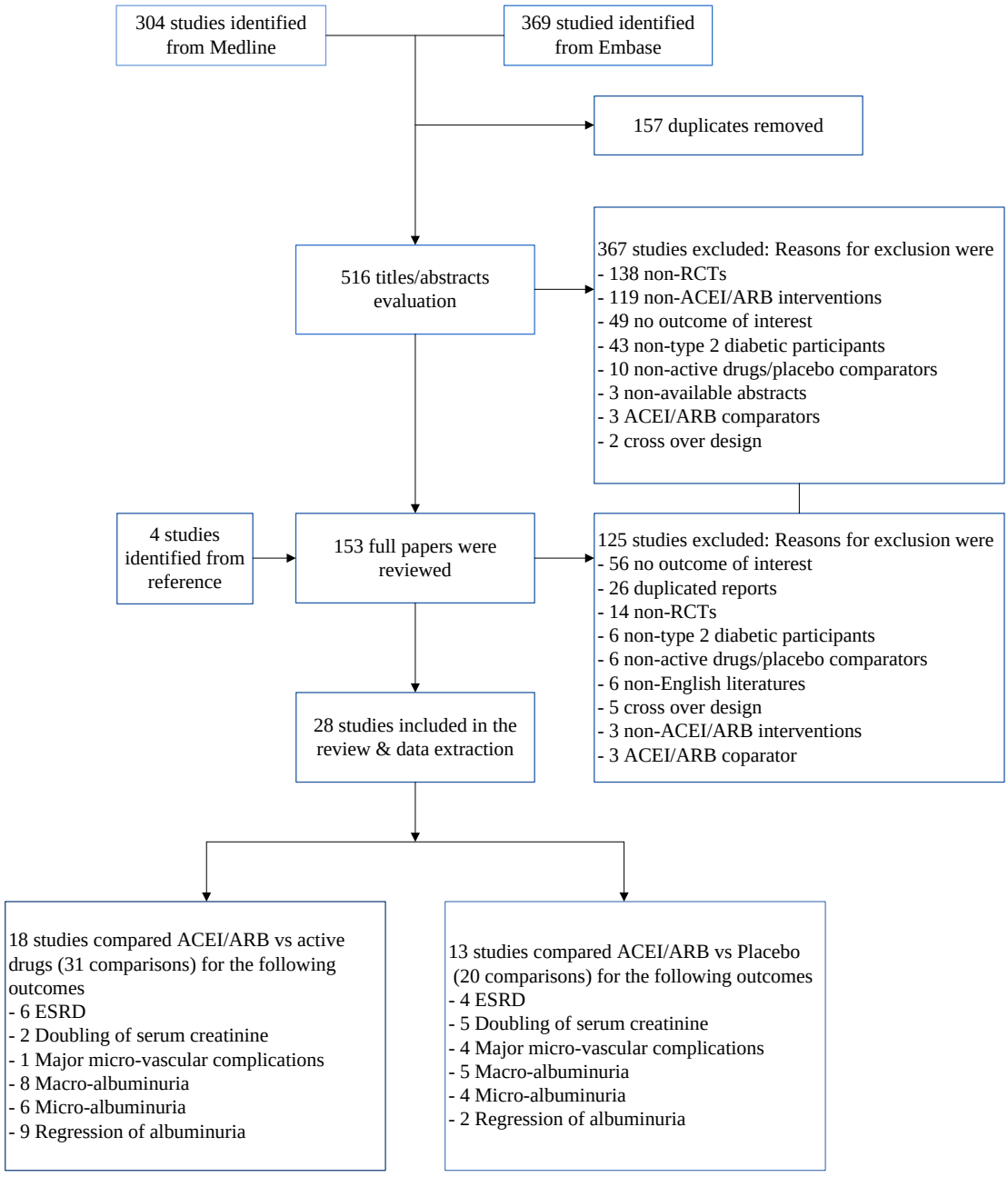


Figure 2.2. Forest plots

A) ESRD

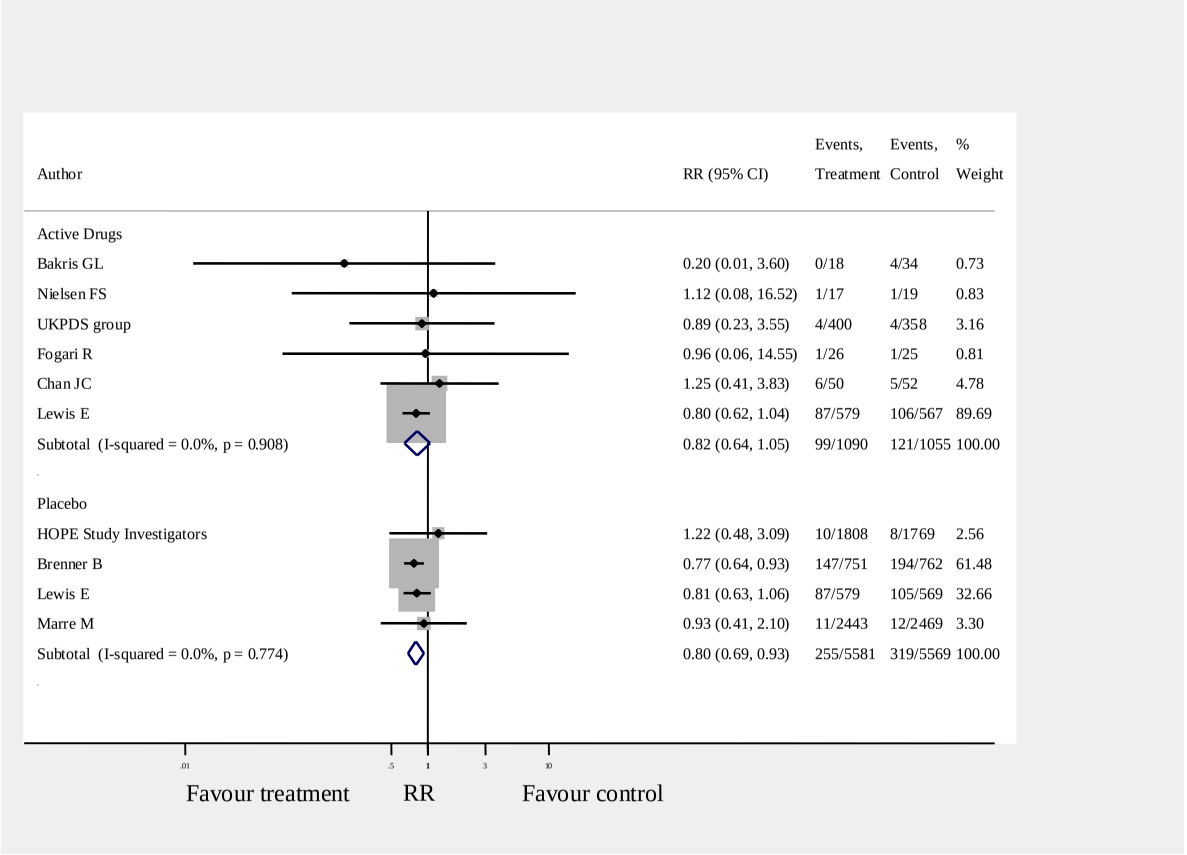


Figure 2.2. Continued

B) Doubling of serum creatinine

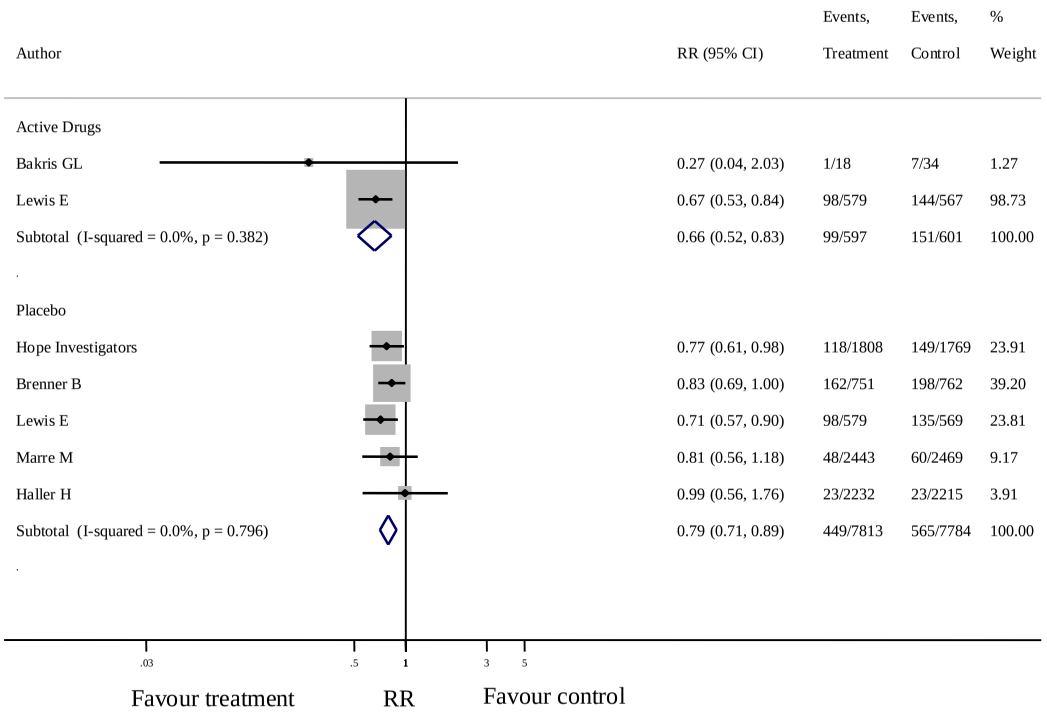


Figure 2.2. Continued

C) Major micro-vascular complications: ACEI/ARB vs placebo

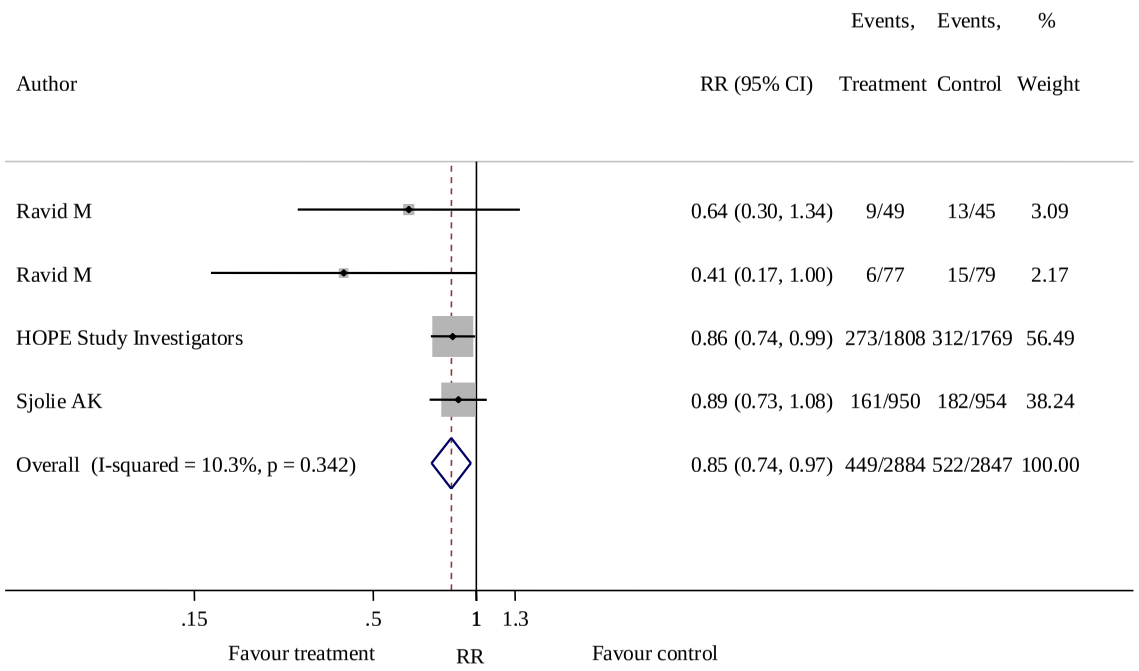


Figure 2.2. Continued

D) Macro-albuminuria

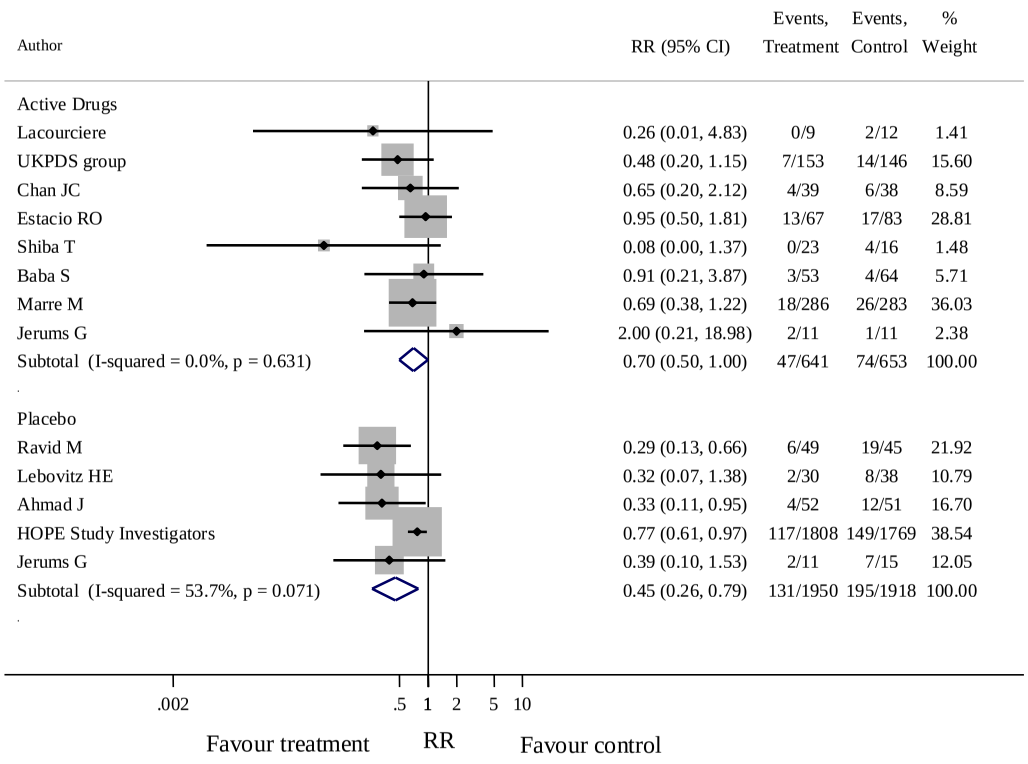


Figure 2.2. Continued

E) Micro-albuminuria

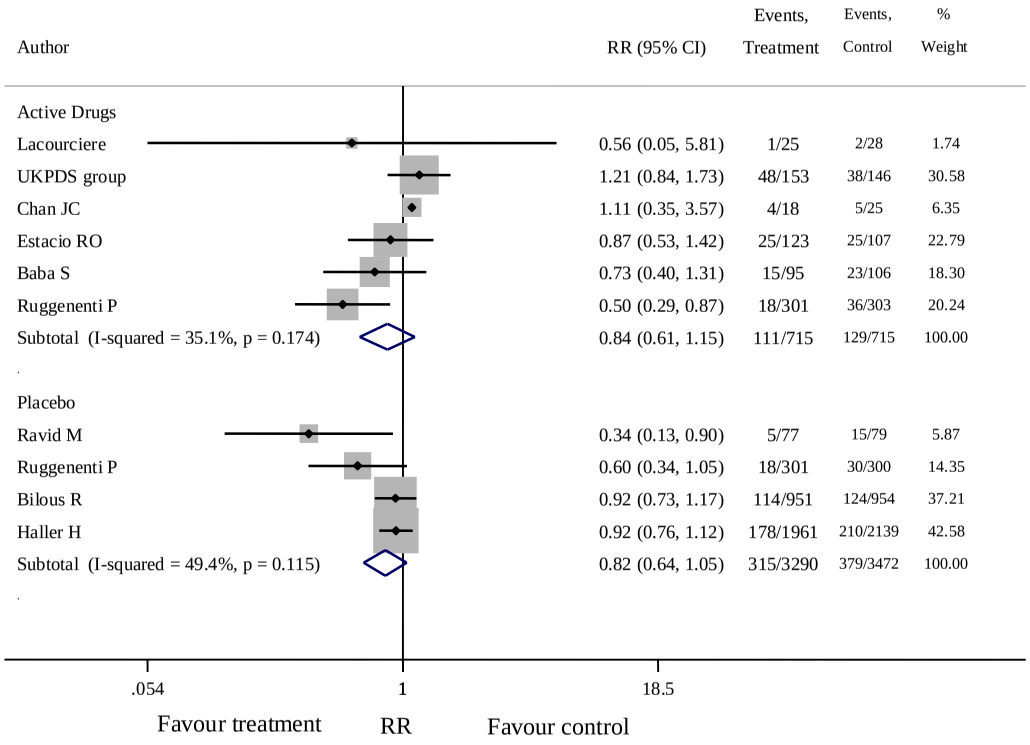


Figure 2.2. Continued

F) Albuminuria regression

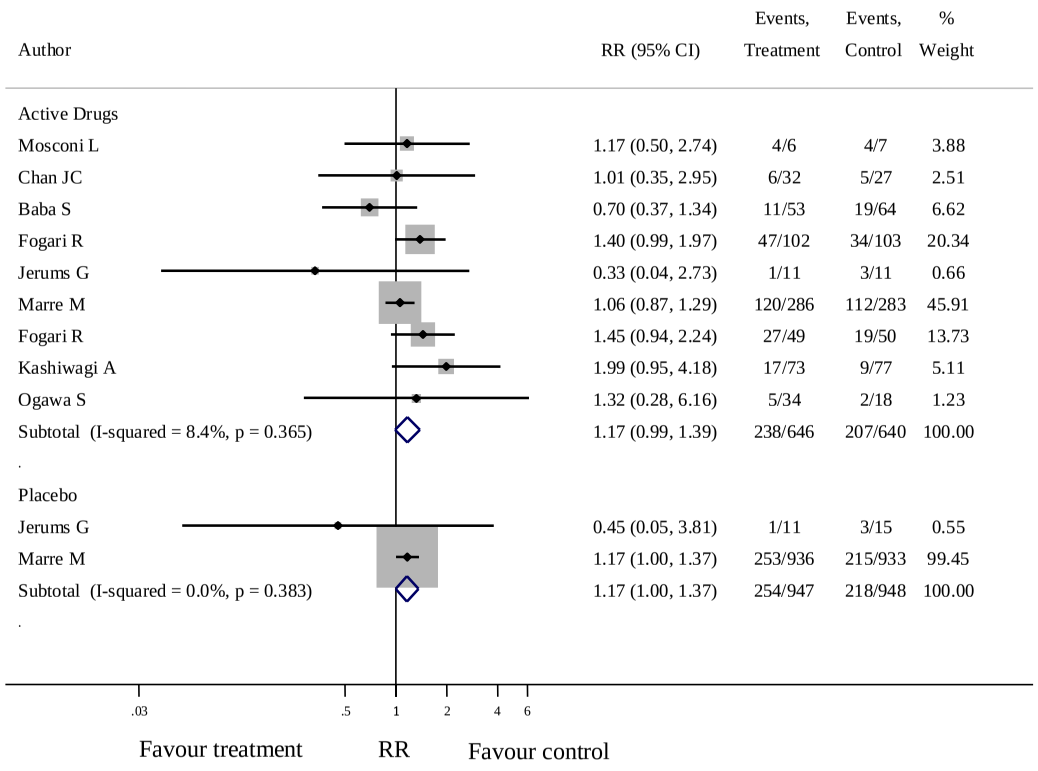
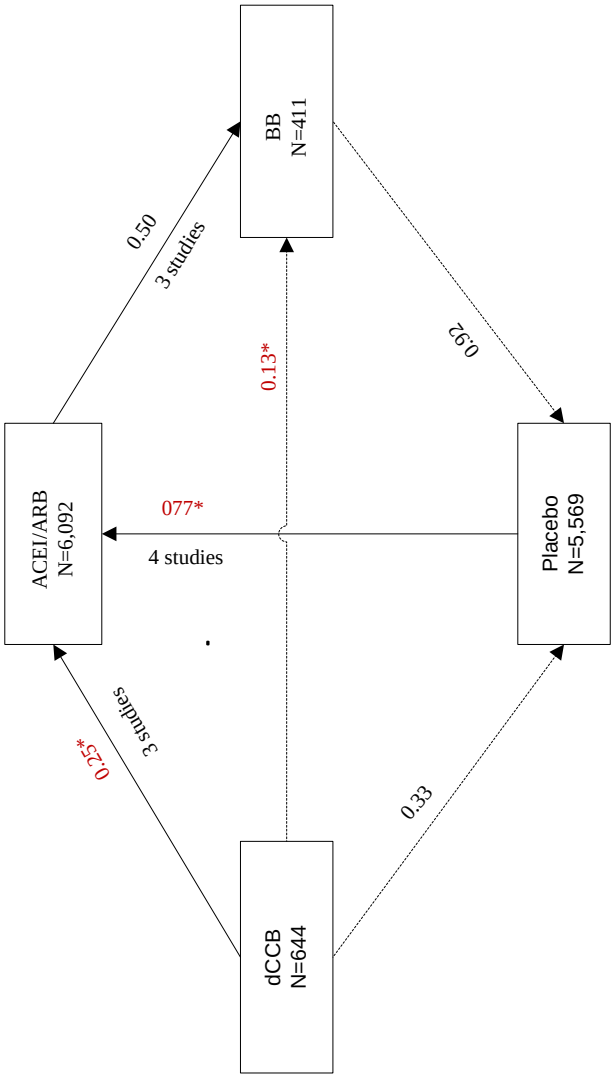


Figure 2.3. Network meta-analysis of treatment effects between ACIE/ARB, other active drugs, and placebo

A) ESRD



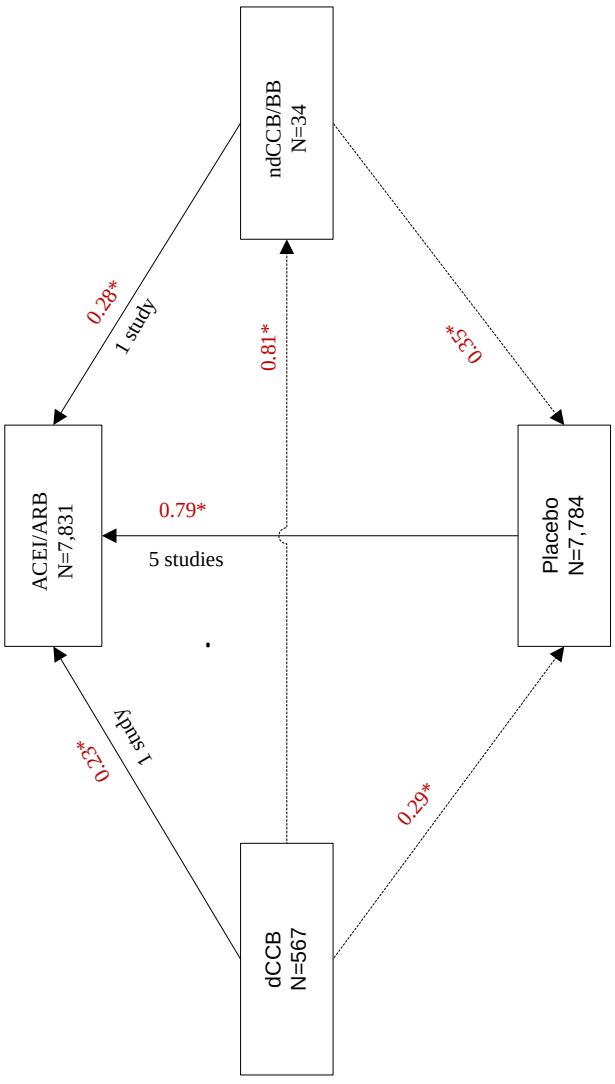
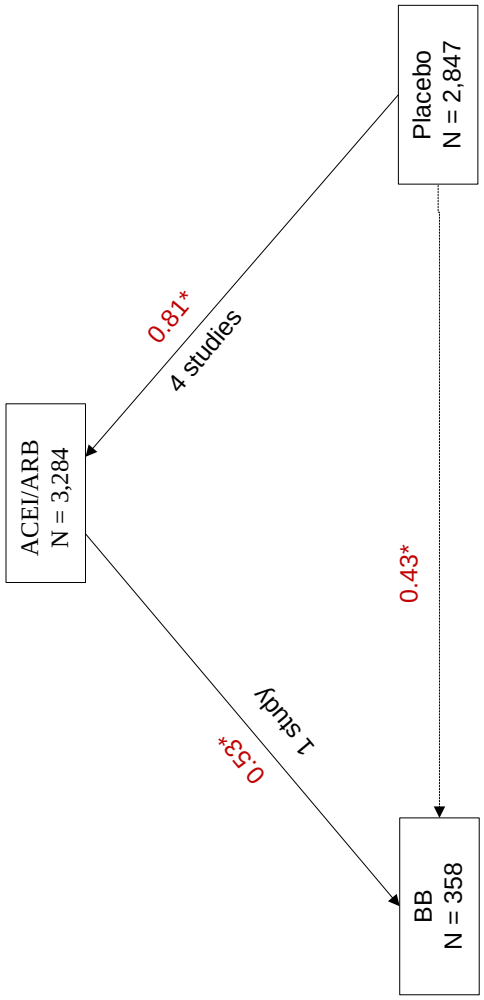


Figure 2.3. Continued

B) Doubling of serum creatinine

Figure 2.3. Continued

C) Major micro-vascular complications



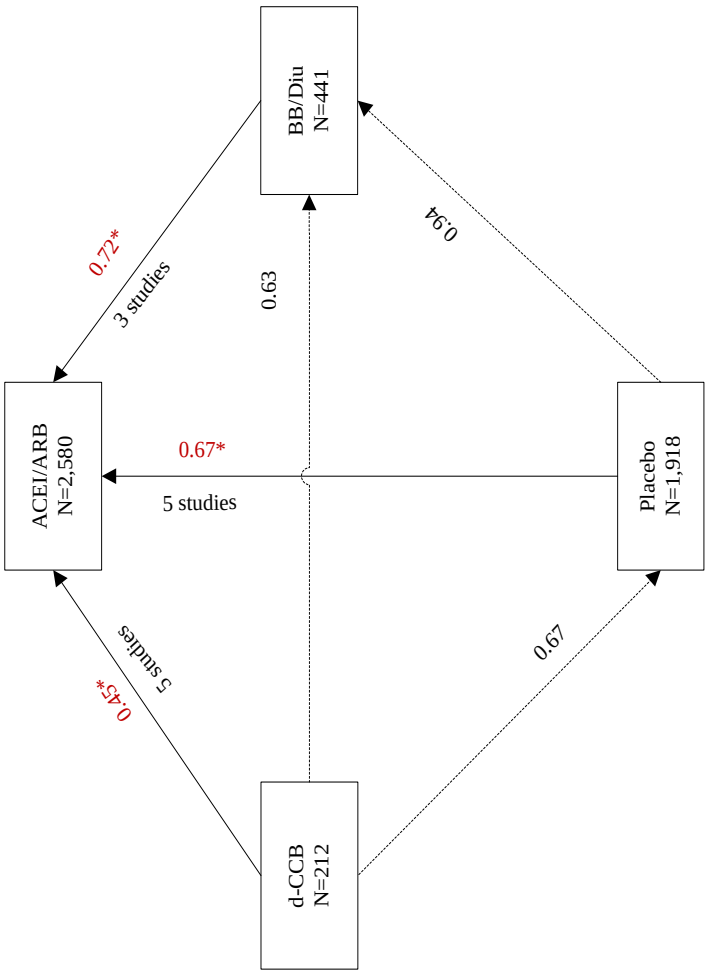


Figure 2.3. Continued

D) Macro-albuminuria

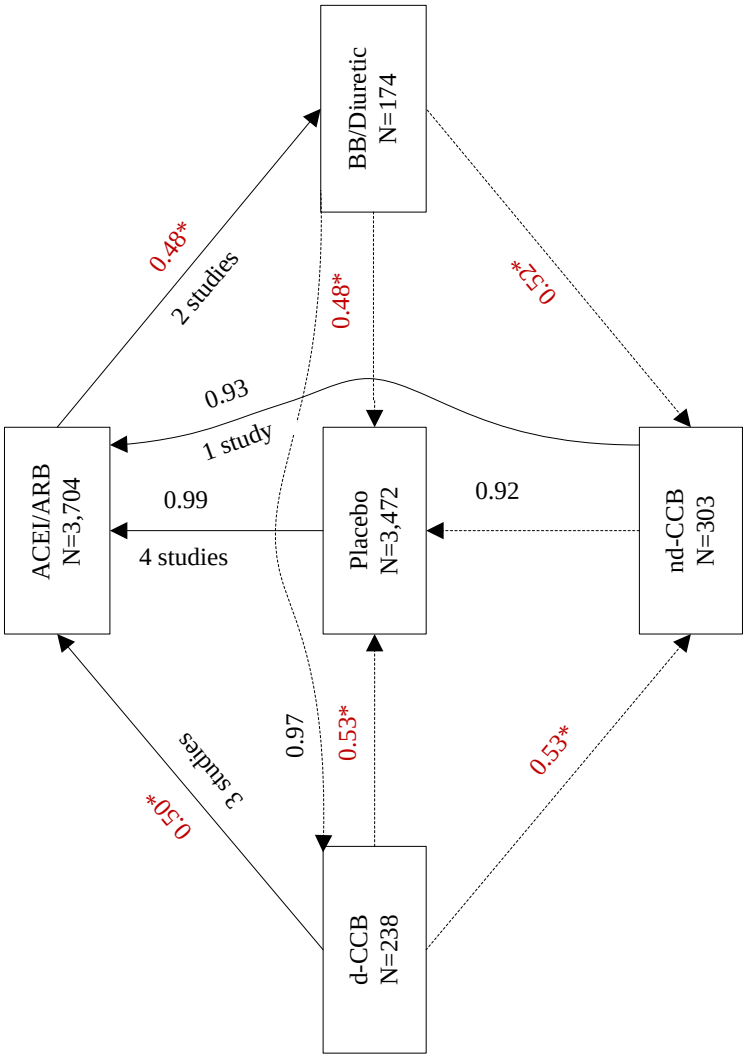


Figure 2.3. Continued

E) Micro-albuminuria

Figure 2.3. Continued

F) Regression of albuminuria

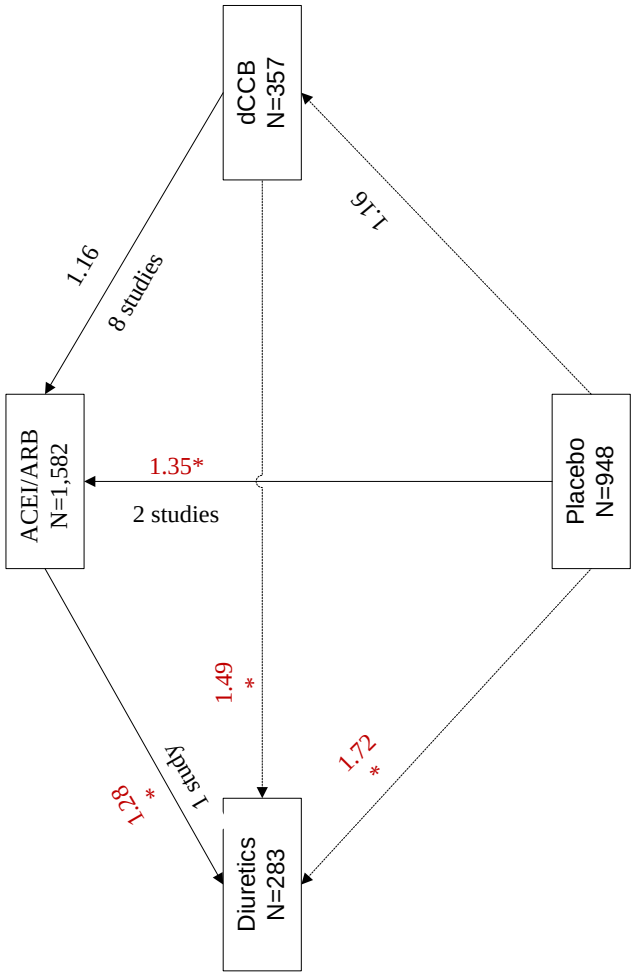


Figure 2.4. Funnel plots

A) ESRD

i. ACEI/ARB vs active drugs

ii. ACEI/ARB vs placebo

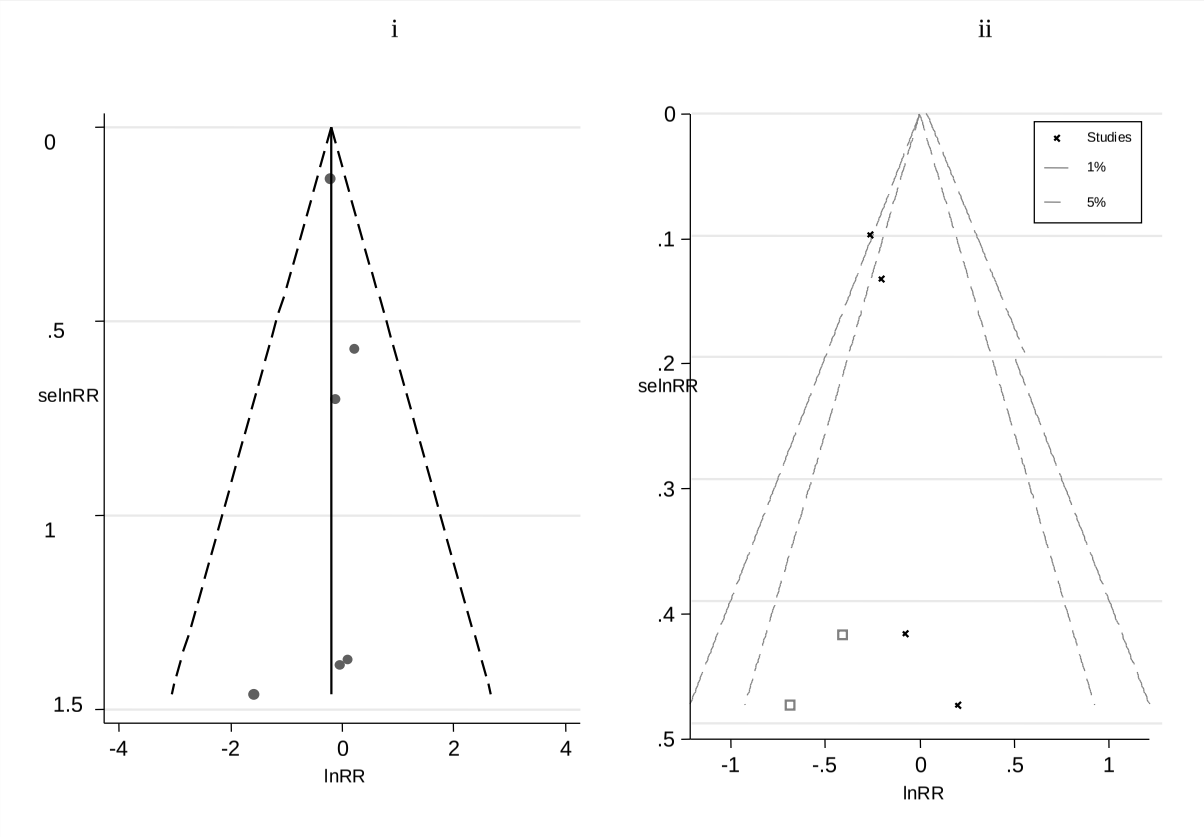


Figure 2.4. Continued

B) Doubling of serum creatinine: ACEI/ARB vs placebo

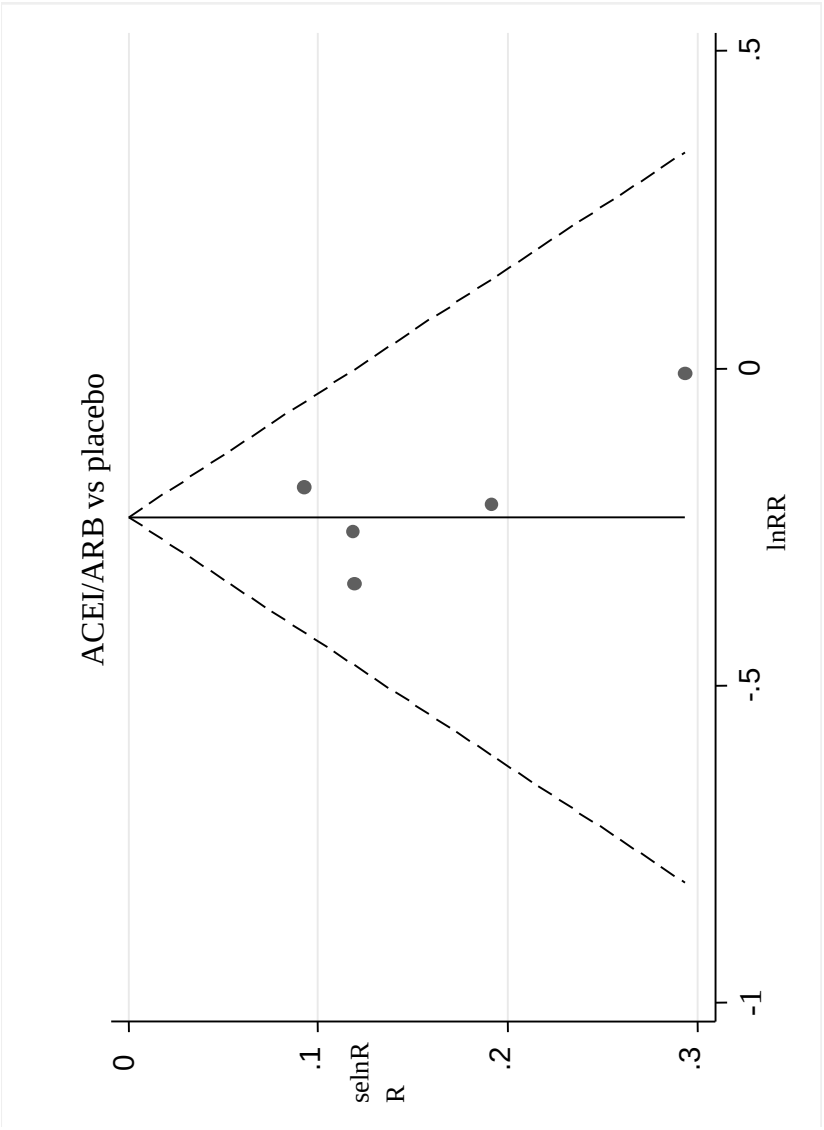


Figure 2.4. Continued

C) Micro-vascular outcome: ACEI/ARB vs placebo

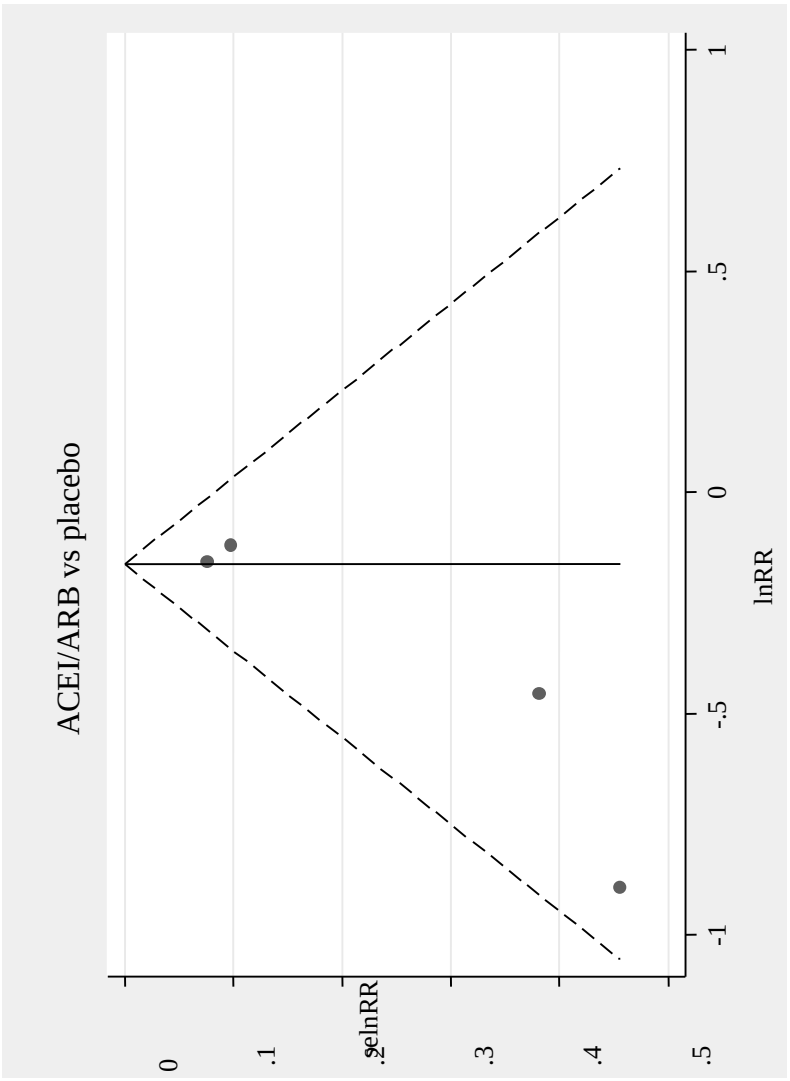


Figure 2.4. Continued

D) Macro-albuminuria

i. ACEI/ARB vs active drugs

ii. ACEI/ARB vs placebo

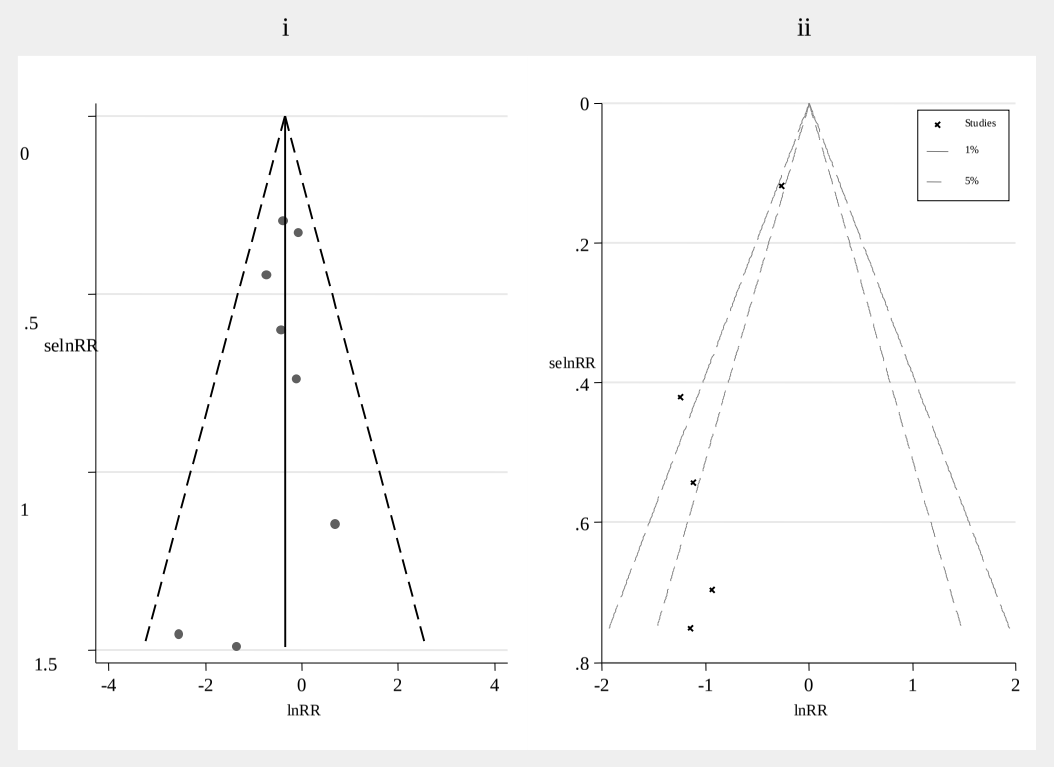


Figure 2.4. Continued

E) Micro-albuminuria

i. ACEI/ARB vs active drugs

ii. ACEI/ARB vs placebo

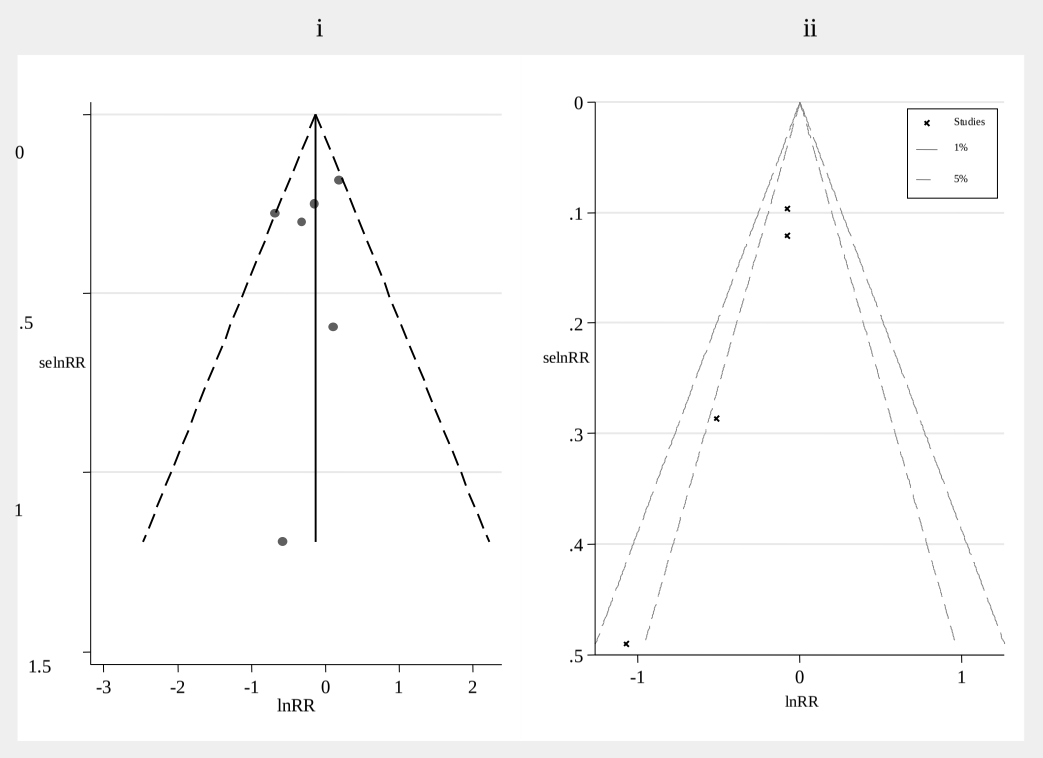
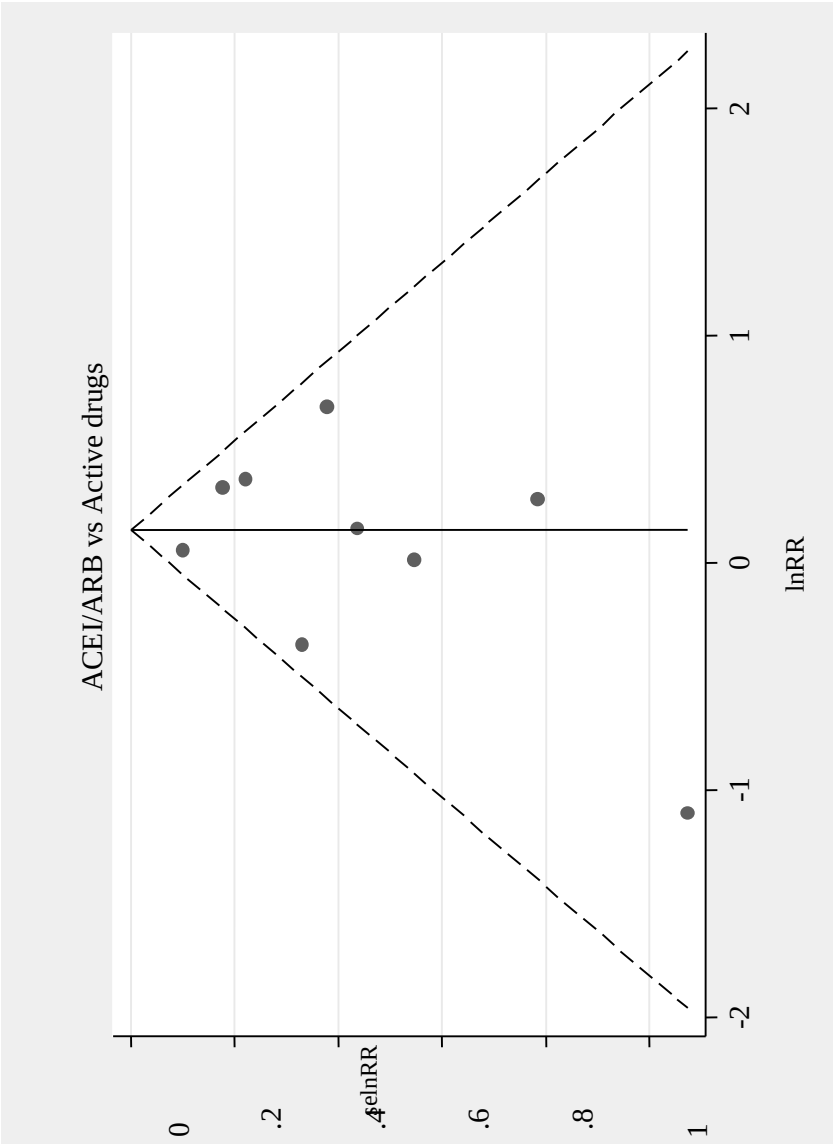


Figure 2.4. Continued

F) Albumin regression: ACEI/ARB vs active drugs



CHAPTER III
EPIDEMIOLOGICAL STUDY OF CHRONIC KIDNEY DISEASE PROGRESSION: A LARGE-SCALE POPULATION-BASED COHORT STUDY

3.1 Introduction

CKD is now recognized as one of the leading causes of disease burden globally. The prevalence of CKD with GFR categories 1 (G1) to 4 (G4) were 13.1% to 17.5% in the adult US and Thai population, respectively (1, 2). Although several previous community-based studies (3-10) have assessed the prognosis of CKD in general populations, none has yet estimated the time for changing kidney function and the probability of kidney failure or death according to each GFR category, particularly for early stages of G1 and G2. Although some studies had large overall sample sizes (4, 7), most of them had relatively low numbers of subjects for each GFR category, lacked information on progression through GFR categories (3, 4, 6-10), had short follow-up times (4-6, 8), and were thus unable to assess the probability of kidney failure or death. In addition, a high proportion of CKD subjects died before reaching kidney failure, therefore estimating the rate of kidney failure occurrence without taking into account death as a competing risk would yield biased results (11). We therefore conducted a large retrospective cohort study considering death as a competing risk, which aimed to quantify CKD progression starting forward from G1 to kidney failure, separately in diabetic and non-diabetic patients.

3.2 Literature review

A systematic review was performed by identifying studies assessing the natural histories and/or prognostic factors of CKD progression. Studies were identified from the Medline database (up to July 22, 2012) using the PubMed search engine. The

search strategies were *(“Chronic kidney disease” OR “CKD” OR “eGFR” OR “GFR” OR “glomerular filtration rate” OR “kidney function” OR “renal function”) AND (“mortality” OR “end stage renal disease” OR ESRD OR “progressive chronic kidney disease” OR “natural history” OR “progression”) AND (“population base” OR “community base”) AND (“cohort” OR "follow up").* Studies were reviewed if they were community-based or population-based cohorts and evaluated the natural history of CKD, with or without prognostic factors of CKD progression. Studies which enrolled too specific groups of participants, i.e., CVD, HIV-positive, age-specific (children and elderly) and sex-specific were excluded.

Of 514 articles located, full papers of 21 articles plus 13 additional studies from reference lists met the criteria for review. Seven studies (5-9, 12, 13) which evaluated the kidney failure and/or death were located. These studies enrolled 13,117 to 2,583,911 participants and had the median follow up time of 2 to 7.5 years. Among these studies, 4 (6-8, 12) provided information on CKD progression, and 3 (5, 9, 13) were risk studies of CKD and thus were excluded, see Figure 3.1.

Among 4 studies which provided information on CKD progression, 1 (7) reported the probability of kidney failure/death at 5 years, 2 (6, 8) reported the kidney failure/death rate stratified by levels of proteinuria, and 1 (12) did not take into account proteinuria. Only 1 study (12) reported the prognostic factors and their prognostic effects on CKD progression to kidney failure.

3.2.1 Kidney failure outcome

Probability of kidney failure

The probability of kidney failure at 5 years was 1.1%, 1.3%, and 19.9% for CKD stages 2, 3, and 4 respectively.

Rate of kidney failure

The rate of kidney failure ranged from 0.005 to 0.13/100 patient-years for CKD stages 1 and 2 with mild proteinuria, and 0.1 to 0.48/100 patient-years for CKD stages 1 and 2 with heavy proteinuria, 0.02 to 0.08/100 patient-years for CKD stage 3a with normal proteinuria, 0.07 to 0.22/100 patient-years for CKD stage 3a with mild proteinuria, 0.43 to 0.80/100 patient-years for CKD stage 3a with heavy proteinuria, 0.13 to 0.16/100 patient-years for CKD stage 3b with normal proteinuria, 0.42 to

0.44/100 patient-years for CKD stage 3b with mild proteinuria, 1.59 to 1.61/100 patient-years for CKD stage 3b with heavy proteinuria, 0.57 to 1.27/100 patient-years for CKD stages 4 and 5 with normal proteinuria, 1.6 to 2.52/100 patient-years for CKD stages 4 and 5 with mild proteinuria, and 5.79 to 6.59/100 patient-years for CKD stages 4 and 5 with heavy proteinuria. When proteinuria was not considered, the rate of kidney failure was 0.77, 3.53, and 24.74/100 patient-years for CKD stages 3a, 3b and 4 and 5 respectively.

Prognostic factors for kidney failure

Diabetes vs. non-diabetes (HR = 6.10, 95% CI: 4.57, 8.13), age (≥ 55 vs < 55 years, HR = 1.60, 95% CI: 1.21, 2.10), sex (male vs. female, HR = 1.49, 95% CI: 1.10, 2.01), SBP (/1 unit increased, HR = 1.44, 95% CI: 1.31, 1.59), race (African American vs white, HR = 2.47, 95% CI: 1.17, 5.21), coronary heart disease (CHD) vs non-CHD, HR = 1.60, 1.05, 2.43), BMI (/1 kg/m^2 increase, HR = 1.13, 95% CI: 1.00, 1.29), smoking status (current vs never, HR = 1.93, 95% CI: 1.38, 2.70, former vs never, HR = 1.64, 95% CI: 1.18, 2.27), and triglyceride (ln[triglyceride], HR = 1.68, 95% CI: 1.23, 2.32), were significantly associated with kidney failure incidence.

3.2.2 Death outcome

Probability of death

The 5-year probabilities of death were 19.5% (95% CI: 17.6, 21.4), 24.3% (95% CI: 23.5, 25.1), and 45.7% (95% CI: 42.2, 49.5) for CKD stages 2, 3, and 4 respectively.

Rate of Death

The death rate ranged from 0.58 to 0.84/100 patient-years for CKD stages 1 and 2 with mild proteinuria, 0.72 to 1.10/100 patient-years for CKD stages 1 and 2 with heavy proteinuria, 0.29 to 0.44/100 patient-years for CKD stage 3a with normal proteinuria, 0.52 to 0.75/100 patient-years for CKD stage 3a with mild proteinuria, 0.72 to 0.97/100 patient-years for CKD stage 3a with heavy proteinuria, 0.40 to 0.59/100 patient-years for CKD stage 3b with normal proteinuria, 0.58 to 0.89/100 patient-years for CKD stage 3b with mild proteinuria, 0.75 to 0.98/100 patient-years for CKD stage 3b with heavy proteinuria, 0.67 to 0.93/100 patient-years for CKD stages 4 and 5 with normal proteinuria, 0.91 to 1.28/100 patient-years for CKD stages

4 and 5 with mild proteinuria, and 1.04 to 1.80/100 patient-years for CKD stage 4 and 5 with heavy proteinuria.

3.2.3 Conclusion from the literature review

Although several previous community-based studies (3-10) assessed the prognosis of CKD in general population, none has yet estimated the time for changing kidney function and the probability of kidney failure or death according to each GFR category, particularly for early GFR categories of G1 and G2. Although some studies had large overall sample sizes (4, 7), most of them had relatively low numbers of subjects for each GFR category, lacked information on progression through GFR categories (3, 4, 6-10), had short follow-up times (4-6, 8), and were thus unable to assess the probability of kidney failure or death. In addition, a high proportion of CKD subjects died before reaching kidney failure, therefore estimating the rate of kidney failure occurrence without taking into account death as a competing risk would yield the biased results (11).

3.3 Methods

3.3.1 Setting & participants

The design of this study was a retrospective cohort of CKD subjects living in Ubon Ratchathani province, Thailand. Subjects were enrolled to our cohort since they were first diagnosed as CKD. The province consists of 20 districts with a population of 1.8 million. The Ubon Ratchathani Public Health Office (UBPHO) has provided medical services under a universal coverage scheme launched by the Thai government since 2002. This scheme provides a health promotion service called a "core package", which includes annual screening for hypertension, diabetes, dyslipidemia, cardiovascular diseases (CVDs), and includes core laboratory tests (i.e., complete blood count (CBC), fasting plasma glucose (FPG), lipid profile, blood urea nitrogen (BUN), serum creatinine, and urine analysis (UA)). The UBPHO computerized databases were retrieved between 2002 and 2011 and then were merged with the hospital databases from 20 district hospitals (covering ~ 98% of records for

both out- and in-patients) from 1997 to 2011. The 2 databases were then linked to the Thailand death registry using individuals' unique personal identification numbers, see Figure 3.2.

Subjects were eligible if they had the following criteria:

- Aged 18 years or older,
- Had been diagnosed as having CKD at the time of screening or later at follow up of diseases/conditions identified at screening,
- Had at least 3 months of follow-up.

Subjects were excluded if they had the following criteria:

- Had received maintenance dialysis and/or transplantation

3.3.2 Studied variables and measurements

CKD & CKD Progression

We used the current CKD nomenclature recommended by the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 guideline to classify CKD and its progression (14). CKD, persistent abnormalities of kidney structure or function for longer than 3 months, were classified based on cause, GFR, and albuminuria category (CGA) as follows: cause included diabetes and non-diabetes, GFR category consisted of normal or high (≥ 90 ml/min/1.73 m^2, G1), mildly decreased (60 - 89 ml/min/1.73 m^2, G2), mildly to moderately decreased (45 - 59 ml/min/1.73 m^2, G3a), moderately to severely decreased (30 - 44 ml/min/1.73 m^2, G3b), severely decreased (15 - 29 ml/min/1.73 m^2, G4), and kidney failure (< 15 ml/min/1.73 m^2, G5). Albuminuria category was classified as normal to mild (albumin-to-creatinine ration (ACR) < 30 mg/g, or protein reagent strip negative to trace, A1), moderate (ACR 30 - 300 mg/g, or protein reagent strip +, A2), and severe (ACR > 300 mg/g, or protein reagent strip ≥ ++, A3). GFR and albuminuria were repeatedly assessed every 3 - 6 months depending on patients' conditions. CKD progression was defined as a change of GFR category with 25% or greater drop in e-GFR from baseline.

The serum creatinine was measured using the Modified Jaffe method at each hospital's laboratory unit. The automated clinical analyzers used in district hospitals were ABX Pentra 400®, Cobas®, and Erba Mannheim®. The laboratory tests of these hospitals were standardized and calibrated every 3 months by the Department

of Medical Science, Ministry of Public Health of Thailand. The modified Jaffe method was then converted to the Isotope Dilution Mass Spectrometry (IDMS) equivalent using the calibration equation from the Thai SEEK study (2). The e-GFR was then calculated using the CKD-EPI equation (15). To avoid acute changes in creatinine due to intercurrent illness, only out-patient determinations of serum creatinine and urine analysis were used. The urine analysis was done using a urine dipstick for testing urine protein (CYBOW^{TM}, Gyung-Num, Republic of Korea) and microscopic examinations. The result was reported as negative, trace, or ≥ 1+.

Diabetes mellitus

Diabetes was identified from the databases according to the ICD10 code which codes E10-E14. Diagnosis of diabetes was made by physicians based on elevated fasting plasma glucose (≥ 126 mg% on 2 consecutive occasions) along with clinical presentations of diabetes. In addition, this diagnosis was verified by the evidence of repeated determinations of fasting plasma glucose or prescriptions of anti-diabetic medications.

All-cause mortality

All-cause mortality was retrieved from the Bureau of Strategy and Statistics, Ministry of Public Health database from January 01, 1997 to December 31st, 2011. The data were validated by verifying with death certificate information from the Ministry of the Interior. It is mandatory that all deaths are registered in Thailand, so death registries were considered complete and no loss to follow up was assumed.

3.3.3 Statistical analysis

Imputation

Among 32,106 eligible subjects, the data for body weight, height, albuminuria at baseline were missing in 0.5%, 12.4% and 25% of subjects, respectively. The missing data were thus imputed using multivariate chain equation assuming that the data were missing at random (16, 17), as in the following equations:

$$X_1^{(t+1)} \sim g_1(X_1 | X_2^t, \ldots, X_p^{(t)}, Z, \emptyset_1)$$

$$X_2^{(t+1)} \sim g_2(X_2 | X_1^{(t+1)}, X_3^t, \ldots, X_p^t, Z, \emptyset_2$$

...

$$X_p^{(t+1)} \sim g_p(X_p | X_1^{(t+1)}, X_2^{(t+1)}, \ldots, X_{p-1}^{(t+1)}, Z, \emptyset_p$$

Where X_i *are imputation variables i for iteration at t = 0, 1, …, T until convergence at t = T,*

$\emptyset_J$ *are corresponding model parameters with a uniform prior,*

$g_j(\cdot)$ *are multivariate imputation models with logit link function for dichotomous variable, identical link for continuous variable, and multi-logit link for categorical variable.*

Twenty imputations were constructed using linear regression to obtain the summarized estimates for further analysis (18). More details of imputation using STATA commands have been described in Appendix II.

Competing risk model

Time from diagnosis of CKD to CKD progression or death, whichever occurred first, was calculated for each subject. Subjects were censored if they were free from interested events and competing risk event at the end of the study period, i.e., December 31st, 2011. Our outcomes of interest were CKD progressions, which were changes forward from G1 to G2, G2 to G3a, G3a to G3b, G3b to G4, and G4 to G5, whereas higher GFR category for each change and death were considered as competing risk events. For instance, G3a, G3b, G4, G5, and death were considered as competing-risk events for a change from G1 to G2. The subdistribution hazard function ($_{sd}$HF) (19-21) was used to estimate the cumulative incidence function (CIF) and the median times of CKD progression for each change separately by diabetic and non-diabetic subjects. GFR category was treated as time varying covariates.

The cause specific hazard function ($_{cs}$HF) (19-21) was used to estimate the cause specific hazard ratio ($_{cs}$HR) of diabetes on kidney failure (i.e., interested event) and death (i.e., competing risk event) adjusting for baseline characteristics and co-morbidities, i.e., sex, body mass index (BMI), hypertension, CVDs and albuminuria category. Age was not included in the multivariate cause specific hazard model because it had already been taken into account in the GFR estimation. In addition, the naïve Kaplan-Meier (KM) method was also applied to estimate the probability of interested events without accounting for competing risk of death. All analyses were

performed using STATA version 13.0, and P-value less than 0.05 was taken as the threshold for statistical significance (for more details of statistical analysis, see Appendix III).

3.4 Ethical considerations

The study protocol was reviewed and approved by the Ramathibodi Hospital Ethical Committee and the Ethical Committee of Ubon Ratchathani Public Health Office. Permissions for obtaining and describing data were approved. The patient records/information was anonymized and de-identified prior to analysis.

3.5 Results

A flow chart of data retrieval for our cohort has been demonstrated in Figure 3.2. Among approximately 1.3 million adult population, 646,618; 434,493 and 216,151 were in age groups of 18 - 39, 40 - 59, and 60 years or older, respectively. Of these, 51,384 (7.9%), 87,662 (20.2%), and 80,319 (37.2%) in the corresponding age groups were screened for CKD between 1997 and 2011, respectively. A total of 32,106 subjects were classified as CKD according to the criteria of GFR and albuminuria. Among them, 17,074 (53.2%) and 15,032 (46.8%) subjects were respectively non-diabetes and type 2 diabetes, respectively.

Their baseline characteristics have been described in Table 3.1. Among diabetic subjects, the mean age was 60.6 years, 27% were males, and the median follow-up time was 4.7 years (range: 0.3, 14.2) with 70,414 person-years of observation. The median duration of diabetes was 2.0 years (range: 0, 11.8 years), and most subjects (70.5 %) received oral hypoglycaemic drugs, followed by insulin (14.6 %), both oral hypoglycaemic drugs and insulin (8.0 %), and diet control only (6.9%).

Among non-diabetic subjects, the mean age was 65.3 years, 45% were males, and the median follow-up time was 4.2 years (range: 0.3, 14.3) with 72,879 person-years of observation. All covariate distributions were statistically different between diabetic and non-diabetic groups, except the mean systolic blood pressure and diastolic blood pressure, respectively. Notably, the proportion of subjects on renin-

angiotensin system blockade agents was significantly higher in the diabetic than non-diabetic groups (26.8% vs 13.3%, $p < 0.001$), see Table 3.1.

3.5.1 CKD progression

The numbers of GFR categories G1, G2, G3a, G3b, G4, and G5 at baseline enrollment have been described in Table 2.1. Additional baseline characteristics of subjects by GFR category have also been described in Table 3.3. The median times for CKD progression were estimated separately by diabetic and non-diabetic group, see Figure 3.3. This suggested that diabetic subjects progressed more rapidly through GFR categories with the median times for CKD progression from GFR category G1 to G2, G2 to G3a, G3a to G3b, G3b to G4, and G4 to G5 of 4.4, 6.1, 4.9, 6.3, and 9.0 years, respectively. Non diabetic subjects took longer to progress with the corresponding median times of 9.4, 14.0, 11.0, 13.8, and > 14.3 years, respectively.

3.5.2 Kidney failure

The overall kidney failure rates were 2.8% (95% CI: 2.7, 2.9) and 1.8% (95% CI: 1.7, 1.9) in diabetic and non-diabetic subjects, respectively. The CIF curves of kidney failure were plotted against the KM-methods, see Figure 3.4. This suggested that the probabilities of kidney failure by CIFs at 2, 5, and 10 years from index date were respectively 3.7%, 11.0%, and 25.3% for diabetic subjects; and 3.1%, 7.5%, and 13.8% for non-diabetic subjects. The naïve KM method tended to overestimate the probabilities of kidney failure when compared to the CIFs, i.e., the probabilities at 2, 5, and 10 years were 3.8%, 11.8%, and 30.8% for diabetic subjects and 3.2% , 8.2%, and 17.3% for non-diabetic subjects, respectively.

After adjusting for sex, body mass index (BMI), hypertension, CVDs, and albuminuria at baseline, the $_{cs}$HR of diabetes was 1.49 (95% CI: 1.37, 1.62), indicating diabetic subjects were 49% significantly higher risk to develop kidney failure than non-diabetic subjects, see Table 3.2. Albuminuria at baseline was strongly associated with kidney failure with the $_{cs}$HRs of 1.71 (95% CI: 1.53, 1.92) and 3.40 (95% CI: 3.07, 3.76) for albuminuria category A2 and A3 compared to A1, respectively. In addition, having hypertension and CVDs at baseline were also at higher risk to develop kidney failure with the $_{cs}$HRs of 1.47 (95% CI: 1.35, 1.60) and 1.49 (95% CI:

1.37, 1.63), respectively. Conversely, higher BMIs were approximately 28% (95% CI: 21%, 34%) and 55% (52%, 59%) lower risk of kidney failure for the BMIs of 22 - 24.9 and $\geq$ 25 relative to BMI < 22 kg/m^2, respectively.

3.5.3 Death rate

The overall death rates were 5.3% (95% CI: 5.1%, 5.5%) and 5.9% (95% CI: 5.8%, 6.1%) in diabetic and non-diabetic subjects, respectively. The overall probabilities of death at 2, 5, and 10 years from index date were respectively 6.0%, 21.1%, and 48.9% for diabetic subjects and 8.3%, 24.2% and 48.1% for non-diabetic subjects. The death rates of these two groups were stratified by GFR and albuminuria category, see Figure 3.3. This suggested that, for each albuminuria category, the death rates gradually increased from G1 to G4 and sharply increased from G4 to G5 in both non-diabetic and diabetic subjects. For each GFR category, the death rate increased as albuminuria increased particularly in diabetic subjects, which was approximately two times higher in A3 compared to A1. The death rates were slightly different from G1 to G4 in both groups, but were substantially higher in diabetic than non-diabetic groups in G5.

After adjusting for age, sex, BMI, hypertension, CVDs, and albuminuria at baseline, the risks of death was 6% ($_{cs}$HR = 1.06: 95% CI: 1.01, 1.12) significantly higher for diabetic subjects when compared to non-diabetic subjects, see Table 3.2. CVDs had the strongest effect on death with the $_{cs}$HR of 3.11 (95% CI: 2.84, 3.41). Albuminuria categories A2 and A3 were 1.28 (95% CI: 1.18, 1.39) and 2.01 (95% CI: 1.87, 2.17) times more likely to die relative to albumin category A1. Older age was higher risk of death with the $_{cs}$HRs of 1.38 (95% CI: 1.11, 1.72) and 2.41 (95% CI: 1.93, 2.00) for age groups 40 - 59 and $\geq$ 60 compared to age group < 39 years, respectively. Hypertension was approximately 17% (95% CI: 5%, 30%) higher risk of death than non-hypertension. Female and higher BMI were preventive factors of death, i.e., females were 22% (95% CI: 16%, 28%) lower risk than males, whereas BMIs of 22 - 24.9 and $\geq$ 25 kg/m^2 were 35% (95% CI: 28%, 42%) and 55% (95% CI: 52%, 59%) respectively lower risk of death than BMI of < 22 kg/m^2.

3.6 Discussion

We conducted a large cohort study of CKD patients with a median follow-up time of 4.5 years in the context of normal primary care. This allowed us to clearly quantify the progression of CKD in both general and diabetic populations. CKD progressed more rapidly through kidney failure in diabetic subjects, and on average, the rate of progression was about double, while the median times for progression were respectively about 5 to more than 8 years shorter for changing GFR category in diabetic subjects compared to non-diabetic subjects. Albuminuria, CVD, and hypertension were associated with kidney failure progression, but conversely BMI was found to reduce such risk.

Huge numbers of studies have assessed the risk of CKD occurrence in general and high risk populations. Contrastingly, not many studies have determined the progression of disease after CKD occurrence, and our systematic search in Medline database (up to July 22, 2012) could only identify six studies of CKD progression (6-8, 12, 13, 22). None of them provided times for changing GFR and albuminuria categories, so our study should be able to fill in this remaining gap of knowledge. Like other previous prognostic studies (6-9, 13, 22), our study also showed consistent association between increased GFR and albuminuria categories and rate of death. In addition to these studies, the prognosis of death among diabetic subjects were slightly higher than non-diabetic subjects, but paradoxically the overall rate of dying at each GFR category were higher in non-diabetic subjects, except for GFR category G4 and G5 (data not shown). This may be because diabetic subjects progressed through the GFR category more rapidly which resulted in opportunities for other unobserved competing events (i.e., death in our case) to play more roles in non-diabetic than diabetic subjects. However, such competing event effects were blunted by the presence of severely increased albuminuria.

The association between BMI and CKD among general population has been clear. However, association between BMI and kidney failure progression among established CKDs has been controversial. This paradoxical inverse association was consistent to findings obtained from previous studies (23-27), which probably reflected better nutritional status among subjects with higher BMI and this may contribute to the delayed kidney failure progression.

The impacts of CKD on clinical outcomes have received less concern given that globally more people are living with CKD than at any previous time (28). The cost of renal replacement therapy in Thailand has risen steadily, i.e., 53, 467, 900, 1066 and 1300 million US$ in 2008, 2009, 2010, 2011, and 2012 respectively (29). Unfortunately, policy makers and communities have paid insufficient attention to CKD, i.e., limited resources have been allocated to CKD and to risk factors such as diabetes. To decrease disease and economic burden of the country, the governments, policy makers, and health care providers should implement effective treatment managements, not only aiming at delaying CKD progression, but also implement effective health promotion programs aiming at prevention of diabetes. In addition, intensive treatments and health promotion programs should be urgently launched and these should be included in the Universal Health Coverage program in Thailand.

Our study has some strengths. This is a large cohort of CKD subjects recruited from real life practice that should be able to reflect the CKD progression of Asian population. The sources of the studied populations were from both general and high-risk populations, thus making the comparison of CKD prognosis in general and high-risk CKD populations feasible. The follow up time was as long as 14 years with a median of 4.5 years, which allowed us to estimate the median time of disease progression from lower to higher GFR categories. The CKD misclassification was less likely because the diagnosis of CKD required evidence of persistent abnormal urine findings or decreased e-GFR on several occasions at least 3 months apart. Our study investigated the outcomes of routine clinical practice currently provided for people with CKD in real-world conditions.

Finally, we properly applied the subdistribution hazard model to predict the disease prognosis (i.e., CIF of CKD progression) and the cause-specific hazard model to evaluate the prognostic effects (i.e., $_{cs}$HRs) on kidney failure/death separately by non-diabetic and diabetic subjects (21, 30). The probability of CKD progression was estimated in the presence of competing risks (i.e., higher GFR category and death), which yielded more accurate estimates than the naïve KM method (19-21). The KM method treats death as censoring, given the basic assumption of constant hazard that censored subjects are independent and thus are good representatives for those subjects who are still observed. In other words, the censored event should not alter or

preclude (as in our case) kidney failure occurrence. In a real situation of chronic illness such as CKD, subjects may die from other causes before reaching kidney failure leaving only surviving subjects in the cohort. As such, the remaining subjects are prone to survival bias, and thus they are not good representatives for the whole cohort (11). Performing a proportional hazard assumption test for our data found highly significant violation of this assumption ($p < 0.001$, data have not been shown). If such assumption is not met, applying the naïve KM method would lead to overestimation of kidney failure rate. This is like what we observed in our data, the KM method tended to yield higher probability of kidney failure than the CIF method because it treated dead subjects as if they were still at risk of having kidney failure (31). In this case, the KM method overestimated the cumulative probabilities of kidney failure as a result of high rate of competing risk (32, 33). Although the competing risk models have been applied and acknowledged more in cardiovascular and oncology research, their methodological issues have only recently been discussed in Nephrology (11, 30, 32, 33).

Our study also had some limitations. This study was a retrospective cohort in which the data were retrieved from databases of routine practice. Data quality controls, standardised laboratory tests, and completeness of data were not as good as a prospective cohort with research purpose. Information on treatments of co-morbidity (i.e., DM, HT, CVD, dyslipidemia) such as types of drug, drug dosage, drug compliance, achievement of treatment targets or treatments of CKD itself were lacking. This may result in biased prognostic effects of the studied co-variables. This cohort was conducted using data from only one province located in North Eastern Thailand, where the CKD prevalence was highest compared to other regions, except Bangkok (2). The healthcare resources, in terms of density of nephrologists, clinicians, nurses, and other health professionals were low compared to other regions of the country. Consequently, the pattern of CKD progression obtained under these conditions may not be similar to other developed countries, but may be generalisable to developing countries with similar structures.

In conclusion, our study has described CKD progression in a Thai population with current clinical practice. The CKD progressed more rapidly and was more likely to reach to kidney failure in diabetic than non-diabetic subjects. These

subjects may need more aggressive assessments and treatments in order to delay their disease progression and increase survival.

3.7 Acknowledgement

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Table 3.1. Baseline characteristics of subjects by non-diabetic and diabetic groups

Characteristics	Non-diabetic N=17,074	Diabetic N=15,032	P-value
Follow-up time, years, median (range)	4.2 (0.3, 14.3)	4.7 (0.3, 14.2)	<0.001
Age, year, mean (SD)	65.3 (13.9)	60.6 (11.0)	<0.001
Male, no (%)	7659 (44.4)	4048 (26.9)	<0.001
BMI[a], mean (SD)	22.0 (4.4)	23.8 (4.1)	<0.001
e-GFR[b], ml/1.73 m^2, mean (SD)	45.8 (22.5)	47.8 (18.9)	<0.001
SBP[c], mmHg, mean (SD)	127.6 23.1)	127.6 (19.6)	0.898
DBP[d], mmHg, mean (SD)	77.1 (13.2)	77.0 (11.2)	0.337
Co-morbidity, no (%)			
HT[e]	6190 (36.3)	6455 (42.9)	<0.001
CVD[f]	2472 (14.5)	1569 (10.4)	<0.001
Dyslipidemia	3657(26.7)	5416 (39.1)	<0.001
RAS[g] blockade use, no (%)	2276 (13.3)	4023 (26.8)	<0.001
GFR category, no (%)			
G1	902 (5.3)	601 (4.0)	<0.001
G2	1439 (8.4)	1069 (7.1)	<0.001
G3a	6347 (37.2)	7001 (46.6)	<0.001
G3b	4475 (26.2)	4152 (27.6)	0.005
G4	2759 (16.1)	1825 (12.1)	<0.001
G5	1152 (6.8)	384 (2.6)	<0.001
Albuminuria category, no (%)			
A1	6867 (53.4)	5170 (44.8)	<0.001
A2	3485 (27.1)	3367 (29.2)	<0.001
A3	2510 (19.5)	3008 (26.1)	<0.001

[a] body mass index, [b] estimated glomerular filtration rate, [c] systolic blood pressure, [d] diastolic blood pressure, [e] hypertension, [f] cardiovascular disease, g[ρ] renin-angiotensin system

Table 3.2. Risk effect of diabetes on kidney failure and death: A cause specific hazard competing risk model

Characteristics	Kidney failure		Death	
	$_{cs}$HR[a] (95% CI)	p-value	$_{cs}$HR (95% CI)	p-value
Diabetes				
No	1		1	
Yes	1.49 (1.37, 1.62)	<0.001	1.06 (1.01, 1.12)	0.027
Albuminuria at baseline				
A1	1		1	
A2	1.71 (1.53, 1.92)	<0.001	1.28 (1.18, 1.39)	<0.001
A3	3.40 (3.07, 3.76)	<0.001	2.01 (1.87, 2.17)	<0.001
HT[b]				
No	1		1	
Yes	1.47 (1.35, 1.60)	<0.001	1.17 (1.05, 1.30)	0.006
CVD[c]				
No	1		1	
Yes	1.49 (1.37, 1.63)	<0.001	3.11 (2.84, 3.41)	<0.001
Age				
18 - 39	NA[d]		1	
40 - 59	NA		1.38 (1.11, 1.72)	<0.001
≥60	NA		2.32 (1.93, 3.00)	<0.001
Sex				
Male	1		1	
Female	1.01 (0.93, 1.98)	0.802	0.78 (0.72, 0.84)	<0.001
BMI[e]				
< 22	1		1	
22 - 24.9	0.72 (0.66, 0.79)	<0.001	0.65 (0.58, 0.72)	<0.001
≥ 25	0.60 (0.54, 0.66)	<0.001	0.45 (0.41, 0.48)	<0.001

[a] cause specific hazard ratio, [b] hypertension, [c] cardiovascular disease, [d] not applicable, [e] body mass index

Table 3.3. Baseline characteristics of subjects by GFR category and diabetic groups

	GFR category					
Group	G1	G2	G3a	G3b	G4	G5
Non-diabetic	n=902	n=1,439	n=6,348	n=4,480	n=2,796	n=1,109
Age, year, mean (SD)	41.7 (12.3)	53.7 (14.8)	66.7 (11.5)	69.2 (11.3)	69.7 (12.0)	64.6 (13.1)
Male, no. (%)	474 (52.6)	783 (54.4)	2,843 (44.8)	2,032 (45.4)	1,143 (40.9)	384 (34.6)
Co-morbid, no. (%)						
HT	90 (10.0)	221 (15.4)	3,004 (47.3)	1,821 (40.7)	810 (29.0)	244 (22.0)
CVD	90 (10.0)	130 (9.0)	1,062 (16.7)	697 (15.6)	394 (14.1)	99 (8.9)
Dyslipidemia	171 (25.9)	268 (23.0)	1661 (30.3)	996 (27.0)	457 (22.0)	104 (16.2)
	G1	G2	G3a	G3b	G4	G5
Diabetic	n=601	n=1,069	n=7,002	n=4,152	n=1,845	n=363
Age, year, mean (SD)	47.1 (10.2)	52.5 (10.8)	60.8 (10.2)	62.9 (10.5)	63.4 (10.5)	63.3 (10.9)
Male, no. (%)	185 (30.8)	341 (31.9)	1,913 (27.3)	1,047 (25.2)	469 (25.4)	93 (25.6)
Co-morbid, no. (%)						
HT	128 (21.3)	343 (32.1)	3,167 (45.2)	1,868 (45.0)	766 (41.5)	183 (50.4)
CVD	56 (9.3)	97 (9.1)	700 (10.0)	463 (11.2)	205 (11.1)	48 (13.2)
Dyslipidemia	212 (37.1)	413 (40.5)	2,069 (39.1)	1,490 (39.3)	628 (40.5)	64 (28.1)

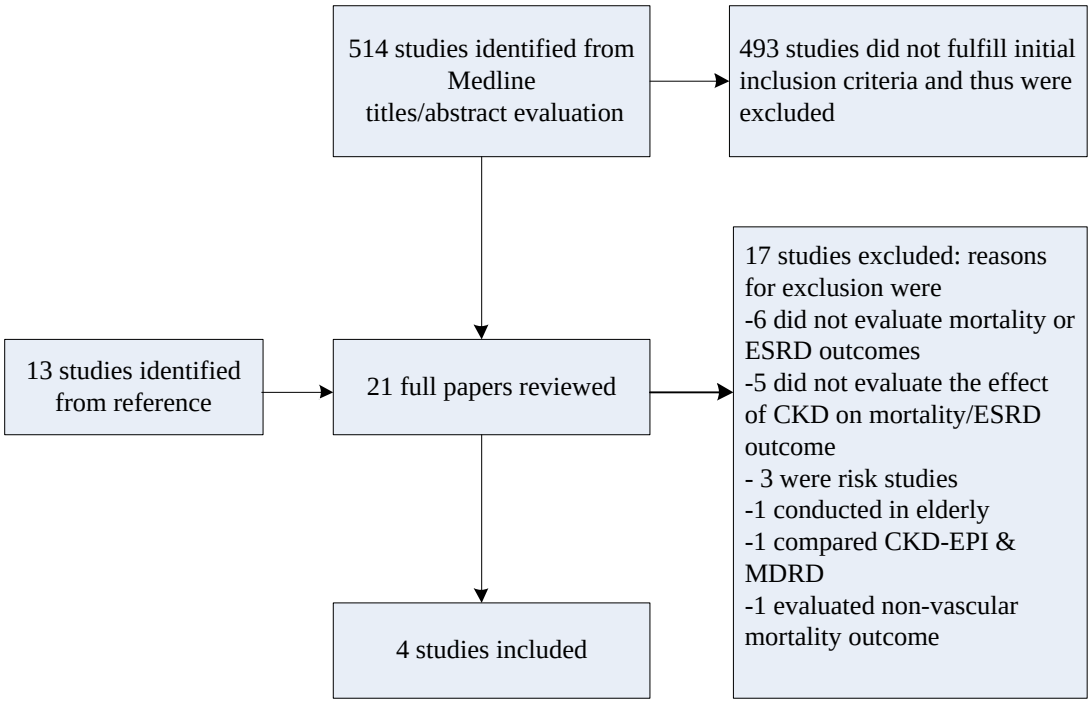

Figure 3.1. Flows of selected studies

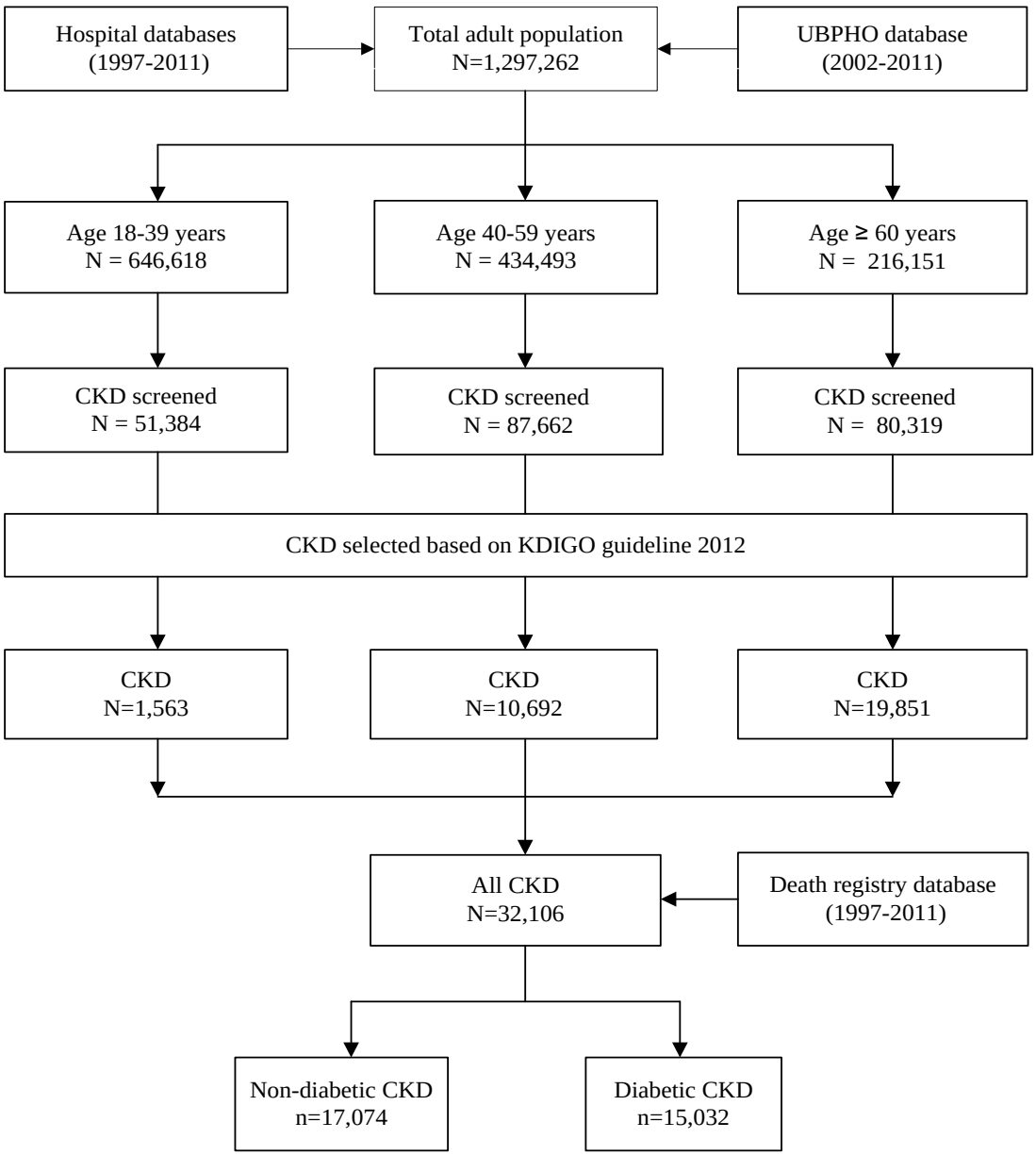

Figure 3.2. Flow of cohort study and data retrieval

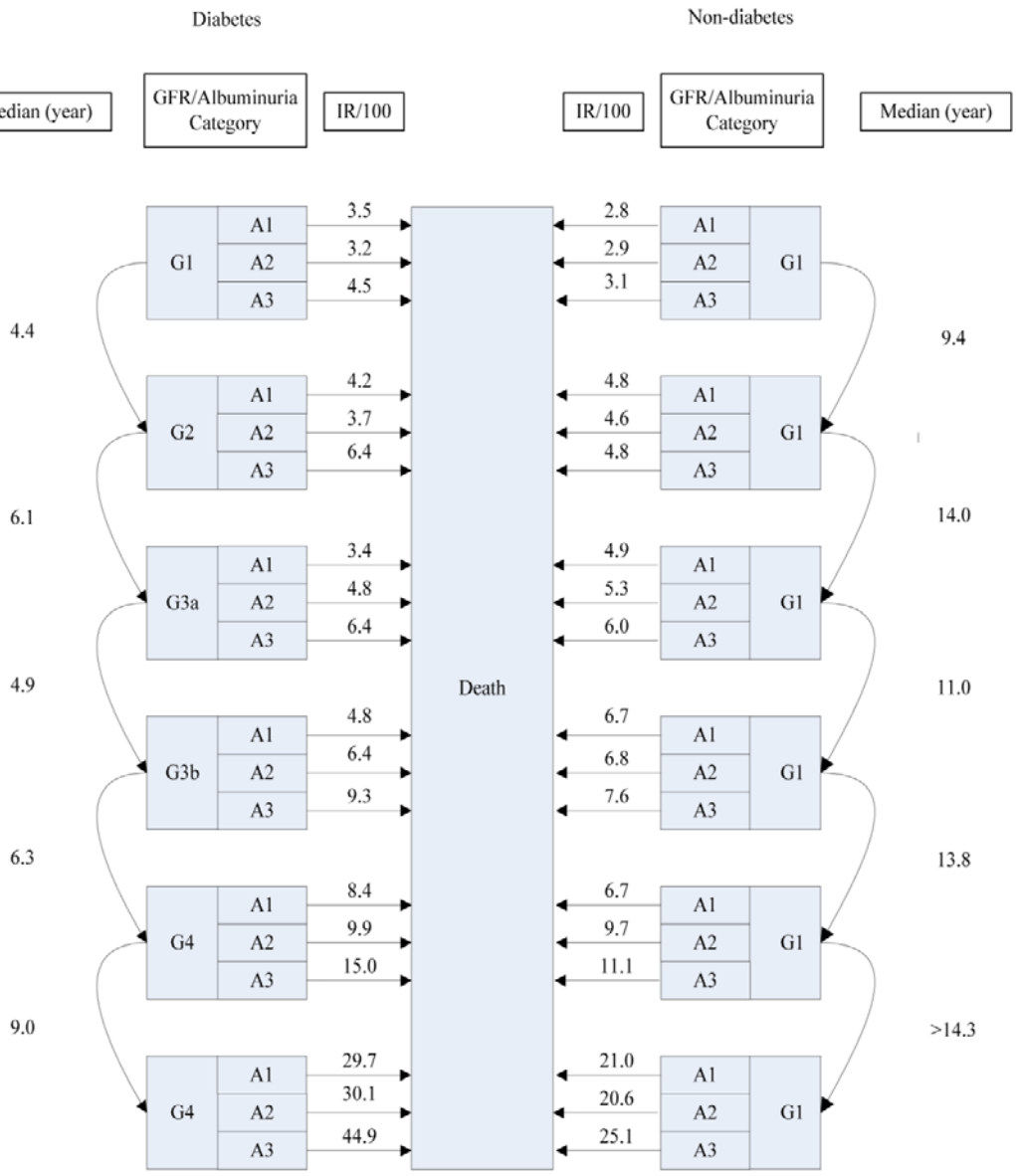

Figure 3.3. Estimation of median time of CKD progression from lower to higher GFR category and death rate by non-diabetic and diabetic subjects

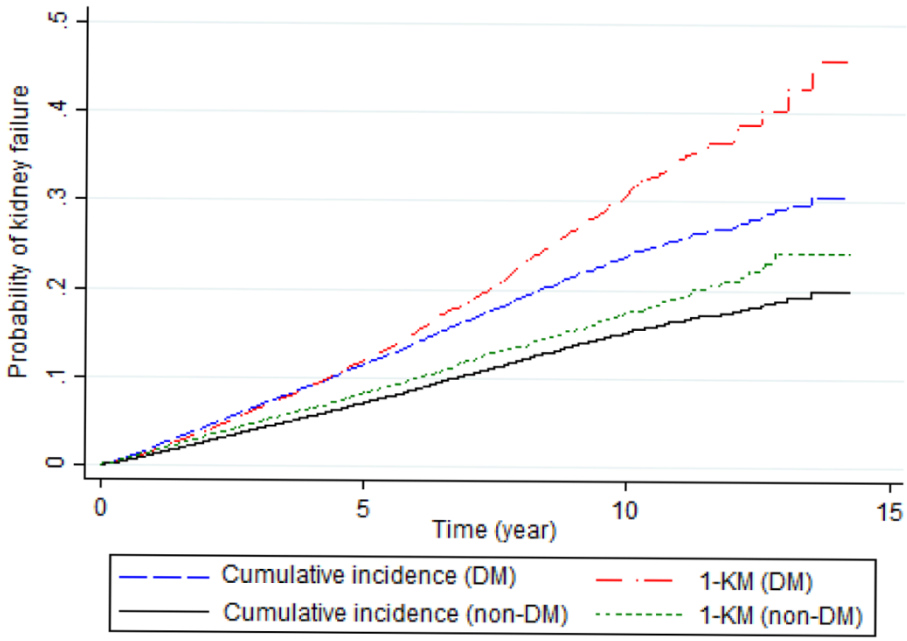

Figure 3.4. Estimation of probability of kidney failure by diabetic groups: Subdistribution hazard vs KM method

CHAPTER IV
PROGNOSTIC FACTORS OF ALL-CAUSE MORTALITIES IN CONTINUOUS AMBULATORY PERITONEAL DIALYSIS: A COHORT STUDY

4.1 Introduction

The global burden of ESRD is increasing rapidly (1-3) with a prevalence of 0.2% in the USA, and 0.3% in Thailand respectively (4, 5). Renal replacement therapy (i.e., renal transplantation or dialysis) is required for ESRD patients, and 2 dialysis modalities, hemo-dialysis and CAPD, have been widely used. The numbers of patients on CAPD has been growing rapidly in Asian countries, representing about 71% of dialysis patients in Hong Kong, and 21% in Thailand in 2011 (6). A health care reform scheme for all Thai citizens, called the "Universal Coverage" scheme (UC) was first initiated in 2002, and it has covered renal replacement therapy for CAPD-first treatment since 2008. The usage of four 2-L daily exchanges with double-bag disconnected systems has been a standard CAPD regime in Thailand.

Adequacy targets for CAPD are primarily based on the weekly clearances of urea (Kt/V) or creatinine (Crcl) which are expressed as renal Kt/V (rKt/V), peritoneal Kt/V (pKt/V), total Kt/V (tKt/V); or renal Crcl (rCrcl), peritoneal Crcl (pCrcl), and total Crcl (tCrcl) respectively. The effect of rKt/V on survival in CAPD patients has been well-documented (7-15), but the roles of pKt/V, tKt/V and tCrcl are controversial. Some studies(10, 16) found that higher pKt/V and/or tKt/V were associated with longer survival times, whereas some observational studies (7-9, 11-13) and randomized controlled trials (14, 15) did not find such associations. Many factors may affect these outcomes, such as dialysis dosage, residual renal function, power of test, cutoff threshold used, and follow-up period.

We therefore conducted a cohort study with 3 years' follow up to answer the following research questions: Can tKt/V, rKt/V, and tCrcl significantly predict

disease prognosis in CAPD patients? If so, what are the cutoffs that can be used to predict patient's outcomes?

4.2 Methods

4.2.1 Setting & Participants

This cohort study covered patients receiving four 2-L CAPD exchanges at 82 general hospitals, belonging to the Ministry of Public Health, Thailand. Data from the National Health Security Office (NHSO) were retrieved between January 2008 and April 2011. The study was approved by the Ramathibodi Hospital Ethical Committee.

Patients aged 15 years or older were eligible if they met the following criteria: Firstly initiated CAPD and participated in the CAPD first-policy from January 2008 to April 2011, survived more than 1 month after initiating CAPD, and had at least 1 tKt/V during the studied period.

Patients were ineligible if they had the following criteria: on CAPD due to acute renal failure, aged > 100 years, tKt/V < 0.5 or > 5, tCrcl < 10 or > 400 L/week/1.73 m^2, serum albumin level < 0.3 or > 6 g/dl, hemoglobin level < 3 or > 20 g/dl, urine volume < 0 or > 4,000 ml, ultra-filtration (UF) volume < -2,000 or > 4,000 ml, SBP < 40 or > 300 mmHg, or DBP < 10 or > 200 mmHg.

4.2.2 Clinical endpoint

The primary outcome of the study was time since first initiation of CAPD therapy to death. Patients were censored if they were lost to follow up, or survived at the end of the study (May 2011). Death referred to all-cause mortalities and the data were validated by cross-referencing with the death certificate database from the Ministry of the Interior.

4.2.3 Prognostic factors

The studied prognostic factors were renal (i.e., rKt/V and rCrcl) and peritoneal (i.e., pKt/V and pCrcl) small solute clearances. The former clearance was estimated using a ratio of concurrent urea/creatinine excretion in 24-hour urine

whereas the latter clearance was estimated using 24-hour dialysate effluent. The total small solute clearance (e.g., tKt/V or tCrcl) was the summation of renal and peritoneal small solute clearances. Urea distribution volume (V) was measured using Watson's formula (17).

These small solute clearances (i.e., rKt/V, tKt/V, tCrcl) and other variables were considered in the prognostic model, which included age, gender, body mass index (BMI), serum albumin, hemoglobin, UF volume, SBP, DBP, and co-morbidities (i.e., diabetes, hypertension and/or CVD). Among these variables, tKt/V, rKt/V, tCrcl, BMI, serum albumin, hemoglobin, UF volume, SBP, and DBP were considered in the analysis as time-varying covariates, whereas the rest were fixed variables.

4.2.4 Statistical analyses

Imputation

Among 1,177 eligible patients, the data for UF volume, hemoglobin, serum albumin, rKt/V, BMI, tCrcl, and co-morbidities were missing in 0.3%, 1.1%, 3.3%, 6.5%, 11.5%, 16.7%, and 36.3% of patients, respectively. For each patient, the last observed value was carried forward to replace missing data. Then, the rest of the missing data were imputed using multivariate chain equations. A simulation-based procedure (18, 19) with the assumption that data were missing at random was applied. Logistic and linear regressions were applied to predict missing data for dichotomous and continuous data, respectively. Twenty imputations were performed to allow for the uncertainty of imputed data and the summarized values were then used (20) (for more details of imputation using STATA commands, see Appendix II).

Calibration of the cutoff threshold

The receiver operating characteristic (ROC) curve was used to determine the cutoffs of tKt/V, rKt/V, and tCrcl which could discriminate death from living patients. Each variable was separately fitted in the ROC model as both continuous and categorized variables. For categorical variables, they were categorized according to tertile distributions. The likelihood ratio positive (LR+) and Youden’s index (i.e., highest sensitivity + specificity - 1) (21) were then used to select the cutoff threshold.

The performance of the cutoff thresholds suggested by the two methods were incorporated which led to the final cutoffs (for more details, see Appendix IV).

KM was applied to estimate the overall death rate and probability of death at 12 -, 24 -, and 36 - months after first-initiated CAPD. A patient was censored if s/he had one of the following events: loss to follow-up, withdrew from the CAPD program, or alive at the end of follow up period. Cox-regression models with time varying covariates were applied to assess prognostic effects by fitting equations which separately contained rKt/V and tKt/V. Prognostic scores were then calculated from the final Cox models. The ROC curve analysis was used to estimate the area under the ROC curves (AUC) between the two prognostic scores (22).

All analyses were done using STATA software version 12. The p-value of less than 0.05 was considered statistically significant.

4.3 Results

We identified 11,523 patients in the CAPD registry and follow-up databases from January 2008 to May 2011. Among them, 11,352 patients were aged 15 years or older, but only 1,188 (10.5%) patients had at least one tKt/V data. Eleven patients had a tKt/V out of the acceptable range (i.e., tKt/V < 0.5 or > 5) and thus they were excluded, leaving 1,177 patients with 23,144 observations for the primary analysis, see Figure 4.1. Baseline characteristics of eligible versus ineligible subjects were compared which found that eligible patients were younger (50 vs. 53, $p < 0.001$), had slightly higher proportions of anuria (5.4% vs. 2.9%, $p < 0.001$), serum albumin (3.3 vs. 3.2, $p < 0.001$), hemoglobin (9.0 vs. 8.8, $p < 0.001$), and urine output (704 vs. 645 ml, $p < 0.001$), than ineligible patients. However, both groups had similar proportions of males (50.1% vs. 48.4%, $p = 0.26$, diabetes (33.2% vs.30.5%, $p = 0.12$), hypertension (39 vs. 36 years, $p = 0.08$), cardiovascular disease (4.4 vs. 3.1 years, $p = 0.06$), mean SBP (141 vs. 141 mmHg, $p = 0.99$), and mean DBP (81 vs. 80 mmHg, $p = 0.29$), see Table 4.1.

4.3.1 Calibration of tKt/V, rKt/V and tCrcl cutoffs

Data for the tKt/V were categorized as < 1.75 (n = 384), 1.75 - 2.19 (n = 384), and > 2.19 (n = 409) using a tertile distribution. Fitting a continuous tKt/V in the ROC curve analysis yielded an optimum cutoff based on Youden's index of 1.65. Sensitivity, specificity, and LR^+ of this cutoff were 0.40, 0.74, and 1.50, respectively. Fitting a categorical tKt/V in the ROC analysis suggested that a cutoff of 1.75 yielded sensitivity, specificity, and LR^+ of 0.45, 0.65, and 1.31, respectively. The AUCs were similar for both variables, i.e., 0.556 (95% CI: 0.544, 0.568) vs. 0.551 (95% CI: 0.540, 0.562), respectively. The final cutoff of 1.75 was chosen because it provided higher sensitivity.

Fitting rKt/V as a continuous variable in the ROC analysis resulted in an AUC of 0.632 (95% CI: 0.620, 0.643). Applying Youden's index suggested the cutoff of 0.15 with sensitivity, specificity, and LR^+ of 0.45, 0.77, and 1.96, respectively. The rKt/V was categorized into 3 groups according to a tertile distribution, i.e., < 0.25, 0.25 - 0.49, and > 0.49, and fitting this categorical variable yielded the AUC of 0.612 (95% CI: 0.602, 0.623). Although this cutoff yielded slightly inferior performance (i.e., sensitivity, specificity, and LR^+ of 0.53, 0.66, and 1.57 respectively), this rKt/V cutoff of 0.25 was chosen for further analyses because it provided higher sensitivity.

Fitting the tCrcl variable did not discriminate well between dead and surviving patients with the AUCs of 0.519 (95% CI: 0.506, 0.533) and 0.513 (95% CI: 0.501, 0.525) for continuous and categorical variables, respectively.

4.3.2 Prognostic factors of death

Among 1,177 patients, the person-time at risk was 21,831 patient-months with a median follow-up of 22.9 months (range: 1.8, 43.5). One-hundred and eighty eight patients died which resulted in an overall death rate of 9.9 (95% CI: 8.6, 11.4) per 100 patient-years. The probabilities of death at 12 -, 24 - and 36 - months were 6.7% (95% CI: 5.3%, 8.4%), 19.4% (95% CI: 16.7%, 22.4%) and 29.2% (95% CI: 24.7%, 34.4%), respectively.

KM curves were plotted by tKt/V groups (see Figure 4.2A). This suggested that the failure curves of tKt/V of 1.75 - 2.19 and > 2.19 groups were similar, but they were lower when compared with tKt/V < 1.75. The overall death

rates were 1.03 (95% CI: 0.83, 1.29), 0.72 (95% CI: 0.56, 0.94), and 0.71 (95% CI: 0.54, 0.92) per 100 patient-months for tKt/V < 1.75, 1.75 - 2.19, and > 2.19 respectively, see Table 4.2. The unadjusted hazard ratios (HRs) were 0.70 (95% CI: 0.49, 0.98), and 0.70 (95% CI: 0.50, 0.99) for tKt/V 1.75 - 2.19, and > 2.19 when compared to tKt/V < 1.75, respectively. These two tKt/V groups were then combined because their HRs were similar.

The estimated probability of death was decreased as the rKt/V increased (see Figure 4.2B). The estimated death rates were 1.65 (95% CI: 1.35, 2.01), 1.06 (95% CI: 0.80, 1.40), and 0.59 (95% CI: 0.41, 0.85) per 100 patient-months for rKt/V of < 0.25, 0.25 - 0.49, and > 0.49, respectively. The unadjusted HRs were 0.64 (95% CI: 0.45, 0.91), and 0.36 (95% CI: 0.23, 0.54) for the groups with rKt/V of 0.25 - 0.49 and > 0.49 when compared with the reference group of < 0.25, respectively. Other covariables with p < 0.25 in the univariate analysis were age, BMI, serum albumin, hemoglobin, UF volume, SBP, and diabetes (see Table 4.2).

After adjusting for covariables, patients with tKt/V 1.75 or higher had 29% (HR = 0.71 (95% CI: 0.52, 0.98) significantly lower risk of death than patients with tKt/V < 1.75 (see Table 4.3). The effects of rKt/V on death were stronger than tKt/V, with HRs of 0.56 (95% CI: 0.38, 0.80) and 0.30 (95% CI: 0.19, 0.47) for rKt/V 0.25 - 0.49 and > 0.49, respectively. This suggested higher rKt/V gave lower risk of death, i.e., patients with rKt/V 0.25 - 0.49 and > 0.49 had approximately 44% and 70% lower risk of death when compared to patients with rKt/V lower than 0.25. We further created predictions scores from model 1 and model 2 (see Table 4.3). Fitting these scores in the ROC curve analysis yielded the AUCs of 0.753 (95% CI: 0.743, 0.763) and 0.726 (95% CI: 0.716, 0.736) for model 1 and model 2, respectively, which indicated rKt/V was a better prognostic factor of death than tKt/V.

Age, serum albumin, hemoglobin, UF volume, and SBP were also significant prognostic factors of death in both tKt/V and rKt/V models, but BMI and diabetes were significant only in the tKt/V model. Patients aged 45 - 54 and 55 years or older had respectively 1.89 (95% CI: 1.17, 3.04) and 2.70 (95% CI: 1.77, 4.13) times higher risk of death than patients aged younger than 45 years. High serum albumin resulted in better prognosis with 52% (HR = 0.48, 95% CI: 0.34, 0.70), and

75% (HR = 0.25, 95% CI: 0.16, 0.40) lower risk of death for serum albumin 3.0 - 3.4 g/dl and > 3.4 g/dl respectively, when compared to albumin below 3.0 g/dl.

Hemoglobin showed an inverse dose-response relationship with death, and those with hemoglobin levels of 9.0 - 10.9 and > 10.9 g/dl had 32% (HR = 0.68, 95% CI: 0.47, 0.97) and 56% (HR = 0.44, 95% CI: 0.28, 0.69) respectively significantly lower risk of death than those with a hemoglobin level below 9.0 g/dl. UF volume 1,000 ml per day or higher reduced the risk of death by 47% (HR = 0.53, 95% CI: 0.37, 0.76). Patients whose SBP were 140 mmHg or higher had 31% (HR = 0.69, 95% CI: 0.51, 0.94) significantly lower risk of death than those whose SBP were below 140 mmHg.

Higher BMI were associated with lower mortality with the adjusted HR of 0.73 (95% CI: 0.53, 1.04) for BMI 21 kg/m^2 or higher when compared with BMI less than 21 kg/m^2, but this was not statistically significant. The presence of diabetes increased the risk of death by 43% with the adjusted HR of 1.43 (95% CI: 0.98, 2.09), but this was also not statistically significant.

After adjusting for covariables, patients with tCrcl $\geq$ 50 $L/week/m^2$ had 20% (HR = 0.80, 95% CI: 0.56, 1.13) lower risk of death than patients with tCrcl < 50 $L/week/m^2$, although this was not statistically significant, and data have not been shown.

4.4 Discussion

We conducted a retrospective cohort study of first-initiated CAPD patients with a median follow-up time of 22.9 months. The 12 -, 24 - and 36 - months probabilities of death were 6.7% (95% CI: 5.3%, 8.4%), 19.4% (95% CI: 16.7%, 22.4%), and 29.2% (95% CI: 24.7%, 34.4%), respectively with the overall death rate of 9.9 (95% CI: 8.6, 11.4) per 100 patient-years. Prognostic factors of death were explored suggesting that rKt/V was the strongest predictor of death followed by tKt/V. The cutoff thresholds of these parameters that discriminated poor from good prognosis were $\geq$ 0.25 for rKt/V and $\geq$ 1.75 for tKt/V. Patients with the rKt/V and tKt/V higher than the cutoffs had respectively 65% and 29% lower risk of death than patients with lower levels than the cutoffs.

The mortality rate for our cohort was quite low (i.e., 6.7% and 19.4% for 1- and 2-year probabilities of death) when compared with the mortality rates in other Asian countries, e.g., Indian (20% and 40%) (23), and China (10% and 21%) (17). This might be explained by our study included patients who were firstly initiated CAPD while those studies included both prevalent and incident CAPD cases. In addition, we used four 2-L CAPD exchanges whereas those studied used three 2-L CAPD exchanges. Although our study had higher prevalence of diabetes compared with the Chinese study (17), our patients were younger (mean age 50 vs. 54 years) and about three times lower CVD (4.4% vs. 14.2%) than the Chinese study. We included only patients who had tKt/V data and survived at least 1 month after first-initiated CAPD. Among patients who participated in the CAPD program, approximately 18% and 26% required temporary hemodialysis in the first 1, and 3 months respectively of their critically ill period before switching to CAPD modes. Overall, 4.3% and 7.7% died during the first 1 and 3 months respectively. As such, our mortality rates were lower than previous studies.

Unlike rKt/V, the roles of tKt/V on mortality have not been consistently demonstrated by previous studies (7, 8, 14, 18, 21, 24). Although there was a trend in favor of higher tKt/V, those studies could not demonstrate statistical significance (7, 8, 14, 18, 21, 24), but our study had sufficient power to detect this association. However, the prognostic effect of tKt/V needs to be confirmed by further studies since its effect was borderline significant.

A target small solute clearance has long been a critical issue. Since increasing the peritoneal dialysis prescription may increase the patients' discomfort, decrease the quality of life, and harm by metabolic glucose load, the advantages from increased dialysis dose and potential harms should be well-balanced. Unfortunately, the optimum target clearance has not been well-formulated due to lack of previous evidence and our study should be able to fill information for this issue. Both continuous and categorical variables for small solute clearances were explored in the ROC curve analyses and suggested the optimum cutoffs for tKt/V and rKt/V. These cutoffs were similar to the current tKt/V target suggested by the Kidney Disease Outcome Quality Initiative (KDOQI) guideline (21). Two randomized controlled trials (14, 21) have assessed the effects of tKt/V targets advocated by the previous KDOQI

guideline. The ADEMEX study (14) compared the modified prescriptions to achieve a target tCrcl of > 60 L/week/1.73 m^2 with the four 2-L daily exchanges of standard PD solution. They found no significant differences in patient survival, technique survival, and quality of life between intervention and control groups. The Hong Kong study (21) which had randomized patients to 3 different tKt/V targets also showed negative results.

Some studies (8, 12, 24) considered two or more indices of small solute clearance simultaneously in the regression models. Since tKt/V was the sum of pKt/V plus rKt/V, the two variables were highly correlated with the estimated correlation coefficient of 0.388 ($p < 0.001$). Although including them simultaneously in the same model did not cause multicolinearity, adding tKt/V in the model which already contained rKt/V did not improve the explanation of mortality with the area under curves of 0.753 vs. 0.755 ($p = 0.82$).

Increased serum albumin, hemoglobin, UF volume, and SBP > 140 mmHg were also associated with a lower risk of mortality. Interestingly, we found an inverse relationship between high SBP and risk of death. This finding is consistent with recent findings in chronic kidney disease/dialysis patients which suggested that low blood pressure could be related to coexisting co-morbidities such as heart failure, autonomic neuropathy, decreased food intake, and worse nutritional status (20, 25-27). These explanations may partly be attributable to these paradoxical findings, but the mechanism underlying this reverse relationship has not been clearly understood.

Our study has some strengths. Our study is a large CAPD cohort with a median follow up time of nearly 2 years. We properly calibrated the rKt/V and tKt/V cutoffs using ROC curve analysis. We considered study factors (i.e., rKt/V, tKt/V, and tCrcl) and other observed prognostic factors as time-varying co-variables in the survival analyses, which should be better in explaining disease prognosis than using only single measurements. However, our study also has some limitations. First, the study was not a randomized controlled trial and thus selection and unobserved confounding biases could not be avoided. Second, patients were only eligible if they had data for tKt/V, which was about 10% of the entire cohort; so the representativeness of the whole CAPD patients was limited. Third, we might face with survival bias because of our inclusion criteria and differences of characteristics of

eligible versus ineligible patients. Our results may be generalizable to patients who firstly received CAPD with stable conditions, not patients with critical conditions. The specific etiologies of death including their prognostic factors were not evaluated due to lack of information. Among eligible patients, some variables were missing and thus multiple imputations using regression analysis were applied to predict missing values. Twenty imputations were applied taking into account the between-imputation variability.

In conclusion, the cutoffs of 0.25 and 1.75 for rKt/V and tKt/V might be used to prevent mortality in CAPD patients. A minimum tKt/V of 1.75 should be targeted; although increased dialysis dosage to achieve tKt/V > 2.19 adds no further benefit, and potentially increases harm. Serum albumin, hemoglobin, SBP, and UF volume are also associated with mortality. However, our study may face with selection and other unobserved confounders. Further randomized control trial is required to confirm these cutoffs.

4.5 Acknowledgement

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Table 4.1. Comparisons of baseline characteristics of eligible versus ineligible patients

Variables	Eligible group		Ineligible group		P-value
	n	No (%)[a]	n	No (%)[a]	
Age, year	1,177	50 (14)	10,346	53 (15)	<0.001
Male	1,177	590 (50.1)	10,346	5,008 (48.4)	0.260
BMI[b], kg/m^2	1,037	22.4 (4.0)	5,886	22.1 (4.0)	0.090
Serum creatinine, mg/dL	1,177	6.8 (1.1)	10,346	6.8 (1.1)	0.990
Co-morbidities					
DM[c]	749	249 (33.2)	6,806	2,076 (30.5)	0.120
HT[d]	749	294 (39.2)	6,806	2,447 (36.0)	0.080
CVD[e]	749	33 (4.4)	6,806	211 (3.1)	0.060
Anuria, N (%)	1,177	63 (5.4)	10,346	311 (2.9)	< 0.001
Serum albumin, g/dL	1,138	3.3 (0.7)	8,309	3.2 (0.7)	< 0.001
Hemoglobin, g/dL	1,164	9.0 (2.0)	8,572	8.8 (1.9)	< 0.001
Urine volume, ml	1,154	705 (529)	9,234	645 (475)	< 0.001
SBP[f], mmHg	1,177	141 (25)	10,346	141 (26)	0.990
DBP[g], mmHg	1,177	81 (14)	10,346	80 (15)	0.021

[a] mean (SD) for continuous data, [b] Body mass index, [c] Diabetes, [d] Hypertension, [e] Cardiovascular disease, [f] Systolic blood pressure, [g] Diastolic blood pressure

Conversion factors for units: serum creatinine in mg/dL to mol/L, ×88.4; serum albumin in g/dL to g/L, ×10; hemoglobin in mg/dL to g/L, ×10

Table 4.2. Described death rates and HR according to prognostic factors: A univariate analysis

Variables	Rate/100 patient-months (95% CI[a])	Unadjusted HR[b] (95% CI)	P-value
tKt/V			
< 1.75	1.03 (0.83, 1.29)	1	
1.75 - 2.19	0.72 (0.56, 0.94)	0.70 (0.49, 0.98)	0.040
> 2.19	0.71 (0.54, 0.92)	0.70 (0.50, 0.99)	0.040
rKt/V			
< 0.25	1.65 (1.35, 2.01)	1	
0.25 - 0.49	1.06 (0.80, 1.40)	0.64 (0.45, 0.91)	0.010
> 0.49	0.59 (0.41, 0.85)	0.36 (0.23, 0.54)	< 0.001
tCrcl, ml/week/1.73 m^2			
< 50	0.88 (0.66, 1.16)	1	
50 – 64	0.66 (0.50, 0.87)	0.74 (0.50, 1.10)	0.140
> 64	0.78 (0.59, 1.03)	0.93 (0.63, 1.39)	0.730
Age, years			
< 45	0.52 (0.39, 0.70)	1	
45 – 54	0.81 (0.61, 1.07)	1.64 (1.09, 2.47)	0.020
> 54	1.12 (0.92, 1.37)	2.41 (1.68, 3.44)	< 0.001
Gender			
Female	0.83 (0.68, 1.01)	1	
Male	0.81 (0.66, 0.99)	0.96 (0.72, 1.28)	0.800
BMI[c], kg/m^2			
< 21.0	0.91 (0.71, 1.16)	1	
21.0 – 23.9	0.77 (0.58, 1.01)	0.78 (0.54, 1.13)	0.190
> 23.9	0.77 (0.59, 1.01)	0.71 (0.54, 1.11)	0.160
Serum albumin, g/dL			
< 3.0	1.72 (1.41, 2.10)	1	
3.0 - 3.4	0.76 (0.57, 0.99)	0.41 (0.29, 0.57)	< 0.001
> 3.4	0.37 (0.27, 0.50)	0.20 (0.13, 0.29)	< 0.001

Table 4.2. Continued

Variables	Rate/100 patient-months (95% CI[a])	Unadjusted HR[b] (95% CI)	P-value
Hemoglobin, g/dL			
< 9.0	1.08 (0.86, 1.36)	1	
9.0 - 10.9	0.84 (0.68, 1.05)	0.67 (0.48, 0.92)	0.010
> 10.9	0.49 (0.35, 0.68)	0.38 (0.25, 0.57)	< 0.001
UF[d] volume, ml			
< 500	0.89 (0.66, 1.18)	1	
500 – 999	0.93 (0.75, 1.15)	0.93 (0.65, 1.33)	0.690
> 999	0.64 (0.50, 0.84)	0.59 (0.40, 0.87)	0.010
SBP[e], mmHg			
< 140	0.91 (0.75, 1.11)	1	
≥ 140	0.74 (0.60, 0.90)	0.83 (0.62, 1.10)	0.190
DBP[f], mmHg			
< 90	0.85 (0.71, 1.01)	1	
≥ 90	0.76 (0.59, 98)	0.92 (0.67, 1.24)	0.570
Diabetes			
Yes	1.19 (0.95, 1.49)	1.74 (1.27, 2.38)	0.001
No	0.67 (0.56, 0.81)	1	
Hypertension			
Yes	0.85 (0.69, 1.04)	1.06 (0.75, 1.49)	0.740
No	0.79 (0.65, 0.97)	1	
CVD[g]			
Yes	0.82 (0.49, 1.38)	0.92 (0.48, 1.78)	0.810
No	0.82 (0.71, 0.95)	1	

[a] Confidence Interval, [b] Hazards Ratio [c] Body mass index, [d] Ultra-filtration, [e] Systolic blood pressure, [f] Diastolic blood pressure, [g] Cardio-vascular disease

Conversion factors for units: serum albumin in g/dL to g/L, ×10; hemoglobin in mg/dL to g/L, ×10

Table 4.3. Cox proportional hazards model for all-cause mortalities using tKt/V and rKt/V as prognostic factors

	Model 1: tKt/V				Model 2: rKt/V			
Variables	Coefficient	SE[a]	HR[b] (95% CI[c])	P–value	Coefficient	SE	HR (95% CI)	P–value
tKt/V								
< 1.75			1					
≥ 1.75	-0.34	0.11	0.71 (0.52, 0.98)	0.040				
rKt/V								
< 0.25							1	
0.25 - 0.49					-0.59	0.11	0.56 (0.38, 0.80)	0.010
> 0.49					-1.22	0.07	0.30 (0.19, 0.47)	< 0.001
Age, year								
< 45			1				1	
45 – 54	0.59	0.44	1.81 (1.12, 2.92)	0.020	0.64	0.46	1.89 (1.17, 3.04)	0.010
> 54	0.89	0.51	2.44 (1.61, 3.69)	< 0.001	0.99	0.59	2.70 (1.77, 4.13)	< 0.001
BMI[d], kg/m^2								
< 21			1				1	
≥ 21	-0.37	0.12	0.69 (0.50, 0.96)	0.030	-0.30	0.13	0.73 (0.53, 1.04)	0.080
Serum albumin, g/dL								
< 3.0			1				1	
3.0 - 3.4	-0.74	0.09	0.48 (0.33, 0.68)	< 0.001	-0.73	0.09	0.48 (0.34, 0.70)	< 0.001
> 3.4	-1.42	0.05	0.24 (0.16, 0.37)	< 0.001	-1.39	0.06	0.25 (0.16, 0.40)	< 0.001

Table 4.3. Continued

Variables	Model 1: tKt/V				Model 2: rKt/V			
	Coefficient	SE[a]	HR[b] (95% CI[c])	P–value	Coefficient	SE	HR (95% CI)	P–value
Hemoglobin, g/dL								
< 9.0			1				1	
9.0 - 10.9	-0.36	0.12	0.70 (0.49, 0.98)	0.040	-0.39	0.12	0.68 (0.47, 0.97)	0.030
> 10.9	-0.89	0.09	0.41 (0.26, 0.65)	< 0.001	-0.83	0.10	0.44 (0.28, 0.69)	< 0.001
UF[e] volume, ml								
< 1,000			1				1	
≥ 1,000	-0.38	0.12	0.69 (0.49, 0.96)	0.030	-0.63	0.10	0.53 (0.37, 0.76)	0.010
SBP[f], mmHg								
< 140			1				1	
≥ 140	-0.36	0.11	0.70 (0.51, 0.95)	0.020	-0.37	0.11	0.69 (0.51, 0.94)	0.020
Diabetes								
Yes	0.36	0.26	1.43 (1.00, 2.03)	0.050	0.36	0.28	1.43 (0.98, 2.09)	0.060
No			1				1	

[a] Standard Error, [b] Hazards Ratio, [c] Confidence Interval, [d] Body mass index, [e] Ultra-filtration, [f] Systolic blood pressure

Conversion factors for units: serum albumin in g/dL to g/L, ×10; hemoglobin in mg/dL to g/L, ×10

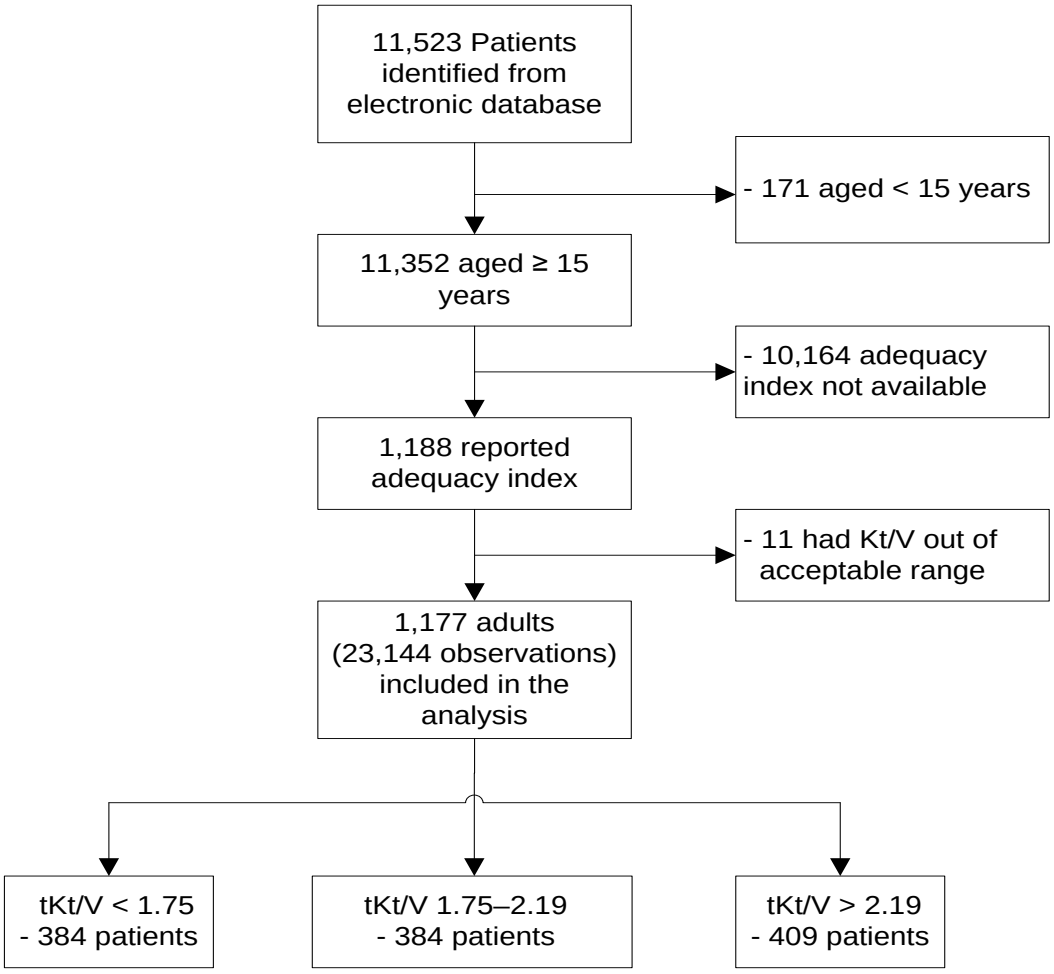

Figure 4.1. Flow of study design

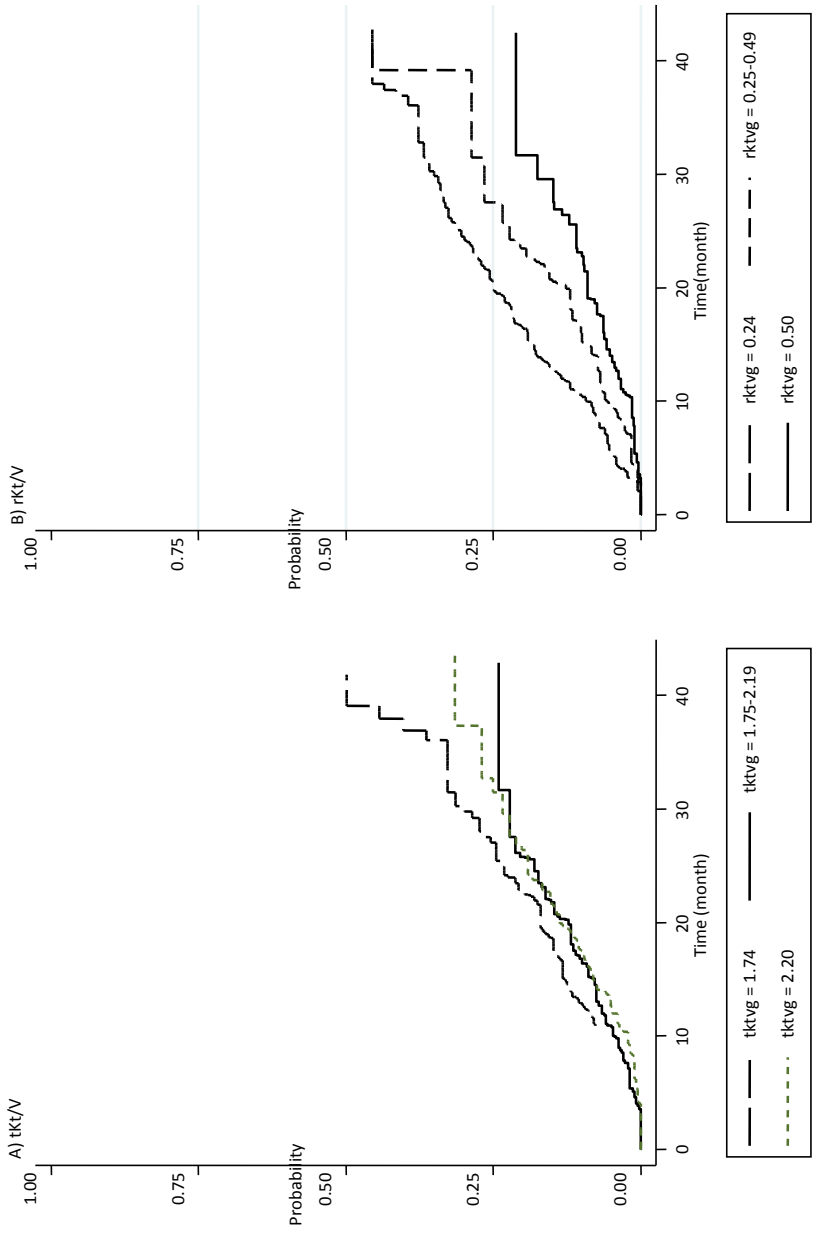

Figure 4.2. Kaplan-Meier curve of death by tKt/V and rKt/V

CHAPTER V
CONCLUSION

5.1 Summary

In this thesis, we have conducted series of studies which consisted of three parts as follows: first, a systematic review and meta-analysis of RAS blockade, second, epidemiological study of chronic kidney disease progression among large-scale population, and third, prognostic factors of all-cause mortalities in continuous ambulatory peritoneal dialysis.

For the systematic review, we have demonstrated a reno-protective effect, in all clinical hard outcomes including, i.e., ESRD and doubling of serum creatinine, of RAS blockers in type 2 diabetic subjects comparing with other anti-hypertensive drugs and placebo, from both direct and indirect comparison using conventional and network meta-analysis. The beneficial effects of RAS blockers were shown in the absence of blood pressure difference between the RAS blockade arm and other anti-hypertensive arm suggested their specific renal protection properties in type 2 diabetic subjects.

For the epidemiological study of CKD progression, we have demonstrated, separately in diabetic and non-diabetic subjects, the median times of changing GFR category, starting forward from lower to higher one along with death rate according to albuminuria category. In addition, we also assessed the prognostic factors of CKD progression. Diabetic subjects progressed through GFR categories and reached KF twice as rapidly as non-diabetic subjects. Hypertension, CVD, albuminuria, and lower BMI increased risk of KF. Diabetes, hypertension, CVD, albuminuria, older age, male gender, and lower BMI increased risks of death.

For CAPD study, we have demonstrated the effects of rKt/V and tKt/V but not tCrcl on survival. We have also applied the ROC curve to calibrate the cutoffs of rKt/V (0.25) and tKt/V (1.75) which could be used to predict prognosis in CAPD patients. Older age and diabetes increased risks of death, but higher BMI, serum

albumin level, hemoglobin concentration, ultrafiltration volume, and systolic blood pressure decreased such risks.

5.2 Suggestion for further studies

While working on these three series of studies, there are research questions that can be extended from these three studies which could not completely answer. Thus, a number of suggestions for further studies are as follows:

5.2.1 Determination of RAS blockade effectiveness in a routine clinical practice

The efficacy of RAS blockers in kidney protection has been well-demonstrated by our meta-analysis in the Chapter 2. However, evidence on its effectiveness in a real clinical practice has been scant. Since our previous epidemiological study of CKD progression was conducted within a routine practice in community-based setting, this should render further study an opportunity to determine the effectiveness of RAS blockade. A counterfactual framework approach will be used to assess treatment effectiveness (1, 2) in a routine clinical practice where treatment has not yet been randomly allocated. Probability of receiving treatment will be estimated using a logit model by regressing treatment variable (i.e., RAS vs non-RAS) on covariables including age, gender, BMI, diabetes, hypertension, CVD, and HLD. An augmented inverse-probability weighting will be then calculated and used to estimate potential outcome mean and average treatment effect from the outcome model, in which a Poisson regression will be used. Three outcomes will be considered and analysed separately, i.e., KF, death before and after KF.

5.2.2 Prognostic factors of CKD: An illness-death model

Better understanding of the prognostic factors of CKD will improve risk stratification and thus lead to better prevention/delay of progression to KF or death. Most studies of CKD progression applied standard survival analysis, treating death as a censoring event if KF was the outcome of interest, and censoring on KF if death was the outcome of interest. The standard survival analysis may lead to biased estimates if

the number of censored patients, which is a competing risk as such death, is high compared to the number of patients with the outcome of interest. The method also does not distinguish between probability of death between patients who do or do not reach KF. The competing risk model, either cause-specific or sub-distribution hazard model, handles this situation and yields less biased estimates than the standard Cox model (3-5). However, like our previous epidemiological study of CKD progression in Chapter 3, the competing risk model would only be able to estimate the probability of KF, and of death before KF, but not for of death after KF.

In order to estimate probability of being in each state as describe in Figure 5.1, an illness-death model will be applied (6). This method is an extension of a competing risk model, in which the probability of three transitions, i.e., transition 1: CKD G1-G4→death, transition 2: CKD G1-G4→KF, and transition 3: KF→death, will be further studied. In addition, prognostic factors of being in each state will also be estimated.

5.2.3 Effectiveness of CAPD versus hemodialysis

Studies comparing the outcomes of CAPD and hemodialysis have seemingly reported conflicting results. This might be due to limitations of most studies were observation studies, which were prone to bias, i.e., selection bias and confounding bias. A large scale randomized controlled trial is needed to avoid these biases. However, conducting this type of study is costly and time consuming, particularly for recruitment and follow up for the final outcome such as death. Data from a routine clinical practice should be made a benefit, in terms of assessing the effectiveness of CAPD and hemodialysis, using similar method as RAS blockade. A counterfactual framework approach should be applied for this purpose.

5.3 References

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APPENDICES

APPENDIX A
META-ANALYSIS

Direct meta-analysis (fixed and random effects)

: *metan varlist [if] [in] [weight] [, measure_and_model_options // options_for_continuous_data]*

(Where measure_and_model_options may be or rr rd fixed random fixedi peto cornfield chi2 breslow nointeger cc(#) wgt(weightvar) second(model or estimates and description) first(estimates and description))

(Where options_for_continuous_data may be cohen hedges glass nostandard fixed random)

Network meta-analysis

- Step 1: Expansion of summary data to individual patient data

  : Generate intervention & comparator groups

  : Reshape wide to long data format (2 steps, i.e., event and treatment groups)

- Step 2: Fitting treatment variable on dichotomous outcome using a Poisson regression method and obtain the pooled RRs and 95% CIs using exponential coefficients estimated from the Poisson regression

  : xi: xtpoisson event i.treatment, irr i(studyid)

- Step 3: Obtain the point estimate (incidence rate ratio) and 95% CIs for each treatment comparison using linear combinations of estimators

  : lincom _Itreatment_2-_Itreatment_1, irr

  : ……

  : lincom _Itreatment_7-_Itreatment_1, irr

APPENDIX B
IMPUTATION

- Step 1: Assess patterns of missing data (monotone or arbitrary) using "misstable pattern" command

  : *misstable patterns*
- Step 2: Set the data for use with mi

  : *mi set mlong*
- Step 3: Inform mi which variables contain missing values

  : *mi register imputed varlists*
- Step 4: Impute values using chained equations

  : *mi impute chained (uvmethod) ivars [=indepvars] [if] [weight] // [,impute_options options]*
- Step 5: Fit the model and combine the results (include variables with significant effects by univariate analysis)

  : *mi estimate [, options]: estimation_command*

APPENDIX C
CUMULATIVE INCIDENCE ESTIMATION

- Step 1: Set data for multiple-records-per-subject survival data
  : *stset timevar [if] [weight] , id(idvar) failure(failvar[==numlist]) // [multiple_options]*
- Step 2: Apply competing risk regression
  : *stcrreg [varlist] [if] [in], compete(crvar[==numlist]) [options]*
- Step 3: Obtain baseline hazards
  : *predict h0, basecshazard*
- Step 4: Obtain baseline cumulative incidence
  : *predict cif0, basecif*
- Step 5: Obtain 2-, 5-, or 10-year probability
  : *sort _t*
  : *sum cif0 if inrange(_t,1.99, 2.01)*
  : *sum cif0 if inrange(_t,4.99, 5.01)*
  : *sum cif0 if inrange(_t,9.99, 10.01)*

APPENDIX D
CALIBRATION OF THE CUTOFF THRESHOLD USING ROC CURVE

- Step1. Explore data

  : *roctab death rktv, detail*

  At this step we observed that *rktv* levels were inversely associated with likelihood ratio+ index, so we changed the *rktv* to inverse form and then execute the *roctab* again.

  : *gen rktv_inv=rktv*-1*

  : *roctab death rktv_inv, detail*

- Step2. Identification of Youden's index

  Visually, we could identify the rKt/V which gave maximum sensitivity & specificity (Youden's index) from the displayed table.

  The *roctab* also calculates the area under the ROC curves. The same steps were also applied for categorized values (according to their tertile distributions) and for tKt/V and tCrcl.

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