# 8

# SUMMARY AND GENERAL DISCUSSION

In this thesis, which focuses on outcomes in patients with CKD stage 4 and 5, our aim was twofold. First, we aimed to provide insight in health related quality of life (further referred to as quality of life) as an outcome in pre-dialysis patients by investigating appropriate ways to measure this construct and by investigating factors affecting quality of life. Second, we aimed to increase the understanding of the different associations between several cardiovascular risk factors and traditional outcomes in pre-dialysis and dialysis patients. In this chapter we present a summary of our main findings, discuss strengths and limitations of our research and consider its implications. We also provide recommendations for future research and end the chapter with our main conclusions.

## Summary of main findings

In **chapter 2** we investigated the impact of the number and severity of symptoms on quality of life in 1079 elderly pre-dialysis patients. We assessed this by investigating both the effect of symptoms and their importance relative to kidney function, and other clinical variables on quality of life. We found that both an increase in number of symptoms and in symptom severity were associated with a decrease in quality of life. In addition, baseline symptoms were related to quality of life after six months of follow-up. The impact of symptoms on quality of life was substantial, explaining 21 and 22% of the variance in quality of life, especially compared to eGFR which did not impact any of the components of quality of life.

Subsequently, we studied the validity of the SF-12 and EQ-5D questionnaire in pre-dialysis patients in **chapter 3**. The PREPARE-2 population was used to investigate whether these two questionnaires could substitute the SF-36 as quality of life measurement tool whenever this questionnaire is impractical to use, for example in larger questionnaires when the SF-36 is too time consuming. We found a better agreement between the SF-12 and the SF-36 as compared with the agreement between the EQ-5D and the SF-36, both for measurements at a single point in time and for changes over time. This was most pronounced in direct comparisons with the SF-36, while in external validations, relating the different questionnaires to external constructs, the EQ-5D largely corresponded with the physical component summary of the SF-36. Overall, the SF-12 had good agreement with the SF-36 and, although losing some information, can be used as a substitute for the SF-36 when a shorter questionnaire is needed.

In **chapter 4** we focus on traditional outcomes. First, we assessed the association between dyslipidemia and start of dialysis, kidney transplantation or death among the 502 pre-dialysis patients in PREPARE-2. During the study 376 (75%) patients started dialysis or had a kidney transplantation, and 47 (9%) patients died. Dyslipidemia was defined based on the levels of total cholesterol, LDL cholesterol, HDL cholesterol, HDL/LDL ratio, and triglycerides. We used continuous values of these lipid levels and determined thresholds, creating categories, to investigate the association with start of dialysis, kidney transplantation or death. Our results indicate there is no association between dyslipidemia and these traditional outcomes.

In **chapter 5** our focus was on the cardiovascular risk factor hypertension and the traditional outcomes start of dialysis, kidney transplantation, death and kidney function decline. More specifically, we compared dual with no or single renin–angiotensin system (RAS) blockade regarding kidney function decline, and risk of renal replacement therapy or death among incident pre-dialysis patients. RAS inhibitors, such as angiotensin converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB), both lower systolic and diastolic blood pressure, and have extensively been proven to be renoprotective agents.[1-6] Since ACEi or ARBs alone do not block the entire RAS and work via different pathways, it has been hypothesized that dual RAS blockade can improve renoprotective and anti-hypertensive effects.[7, 8] However, so far only negative effects of dual RAS blockade use have been found.[1-6] In the PREPARE-2 population we found a 20-25% lower risk of renal replacement therapy or death in patients treated with dual RAS blockade or single ACEi-users compared to non-RAS blockade-users. Dual RAS blockade medication use did not accelerate kidney function decline compared to patients with single or no RAS blockade. This lack of an increased risk of renal replacement therapy or mortality in dual RAS inhibition users suggests that there might be room for dual RAS inhibition when treating severe hypertension or proteinuria in pre-dialysis patients.

In **chapter 6 and 7** our focus was on vitamin K antagonists in both pre-dialysis and dialysis patients. This drug is used to decrease the risk for cardiovascular events in patients with increased clotting of the blood. However, vitamin K antagonists could cause damage to the kidneys by vascular calcifications due to the inhibition of matrix Gla protein or by glomerular haemorrhage which could lead to tubular obstruction.[9-14] In **chapter 6** we investigated the association between vitamin K antagonist use and the traditional outcomes rate of kidney function decline and time until start of dialysis in incident pre-dialysis patients. In the cohort of 984 pre-dialysis patients from PREPARE-1 and 2, we found no difference in annual kidney function decline between vitamin K antagonist users and non-users. Furthermore, vitamin K antagonist use as compared with non-use was not associated with an increased risk of start of dialysis within two years of follow-up.

In **chapter 7** we shifted focus to dialysis patients. It is plausible that pre-existing platelet dysfunction, routine heparin use during hemodialysis treatment and a suboptimal dose of vitamin K antagonists leads to increased risks of bleeding complications in dialysis patients.[15, 16] Because of the higher bleeding risk in dialysis patients compared to the general population, it could be that vitamin K antagonists are only beneficial in dialysis patients with higher stroke risks (estimated by $CHA_2DS_2$-VASc scores). Therefore, we investigated the association between vitamin K antagonist use and mortality for different $CHA_2DS_2$-VASc scores in a cohort of end-stage renal disease patients receiving dialysis treatment. We found that vitamin K antagonist use compared to no vitamin K antagonist use was associated with an increased all-cause mortality risk in dialysis patients. Furthermore, we showed that the mortality risk increased with increasing $CHA_2DS_2$-VASc scores. In addition, it was shown that within patients with a low $CHA_2DS_2$-VASc score (equal to or less than one),

vitamin K antagonist use was associated with an increased mortality risk as compared with no vitamin K antagonist use, while vitamin K antagonist use within patients with a higher $CHA_2DS_2$-VASc score (two or more) was not associated with an increased mortality risk.

## The bigger picture

### Quality of life

There is a substantial body of literature studying low quality of life as a risk factor in patients with CKD. These studies show that a low quality of life is associated with important outcomes such as impaired renal function, risk of end stage renal disease, and mortality in both pre-dialysis and dialysis patients.[17-21] As an outcome, however, quality of life has been largely neglected in renal literature.[22, 23] The main reason offered for this is the claim that quality of life is too subjective as a clinically relevant outcome. However, patients stress the need for more research into quality of life, since this reflects their health status and the impact their disease has on their daily life, which is much more relevant than traditional, more objective outcomes from their point of view.[22, 24] In this thesis we found that symptoms are a risk factor for quality of life, and impact quality of life much more than clinical factors such as eGFR, albumin, proteinuria, demographics or comorbidities. Earlier cross-sectional research did show similar associations between symptoms and quality of life. The comparison with clinical variables, however, has not been made before.[21, 25, 26]

A possible mechanism explaining the contrasting effects of symptoms versus clinical variables on quality of life can be found in the common-sense model of self-regulation of health and illness by Leventhal, Nerenz and Steele.[27] In this model patients develop their own cognitive and emotional perceptions of a health threat to make sense of this threat. These perceptions determine how a patient copes with their disease, which will determine outcomes, including quality of life. The development of the perceptions is determined by multiple factors, such as the cause, the timeline, and the consequences of the illness, the symptoms that are associated with the illness, and the influence of the patient's behaviour and treatment on the control of the illness.[27, 28] In this model, symptoms have a prominent role in determining the outcome quality of life. Clinical variables however, are not of any significance in this model. This is further confirmed by the later developed model of Wilson ***et al.*** where clinical variables only affect quality of life through intermediate variables, such as symptom status and functional status.[29] Both reflect and support the results we found in **chapter 2**.

To enhance the possibilities to investigate the outcome quality of life in patients with CKD, we validated the SF-12 and EuroQol in a pre-dialysis population. The SF-12 has already been validated in dialysis patients, and the EuroQol has been validated in patients with a kidney transplant. With the results from **chapter 3** we widen the range of possibili-

ties to measure quality of life on a large scale in patients with different stages of CKD. This step enables quality of life to gain more attention and thereby fulfil patient research aims.

*Cardiovascular risk factors and traditional outcomes*

Classic modifiable cardiovascular risk factors such as hypertension and diabetes are important drivers for the development of CKD. The association between high cholesterol LDL levels and kidney function decline is less clear. Lifestyle factors, such as smoking of cigarettes and adiposity, may increase the risk of hypertension and diabetes. All previous mentioned risk factors can have an unfavourable effect on kidney function owing to increased inflammation, oxidative stress, endothelial dysfunction, and disturbed coagulation, which may contribute to glomerular and interstitial fibrosis.

Our rationale to explore the effect of cardiovascular risk factors and pharmacotherapy in pre-dialysis patients, is the fact that pre-dialysis patients are a special group of patients, who might respond differently to cardiovascular risk factors and medication as compared with patients in the earlier CKD stages, due to different pathophysiological mechanisms. Pre-dialysis patients on specialized nephrological care are often under-represented or excluded from clinical trials. The PREPARE study allowed us to evaluate real world effectiveness of cardiovascular risk factors and medication in pre-dialysis patients. Given the results of the performed studies, the effects of the investigated cardiovascular risk factors seems to be comparable to the effects in patients in earlier CKD stages, especially the effects of dyslipidemia and dual RAS blockade.

In **chapter 4** we did not find an association between dyslipidemia and start of RRT or death. Other studies, performed in patients with a less impaired renal function showed the same lack of an association between lipoprotein levels and risk of ESRD.[30, 31] This is in concordance with a recent guideline, stating that CKD patients ≥50y should be treated with a statin, independent of lipid or triglyceride levels, without aiming at a target level.[32, 33]

In **chapter 5** the focus was on hypertension by investigating the use of ACE inhibitors and/ or ARBs and their association with the start of RRT or death and renal function decline. We found that incident pre-dialysis patients had a 20-25% lower risk of RRT when treated with dual RAS blockade or single ACEi-users compared to non-RAS blockade-users. Renal function decline in dual RAS blockade users did not accelerate as compared with single or no RAS blockade users. Similar results have been found in other studies in patients with a less impaired renal function, where dual RAS blockade was as effective as single RAS blockade.[34, 35] This implies there might be room for dual RAS blockade when treating severe hypertension or proteinuria in pre-dialysis patients.

Finally, we found no association between vitamin K antagonists and start of RRT or rate of renal function decline in vitamin K antagonist users as compared with non-users (**chapter 6**). Other benefits and risks of vitamin K antagonist use in pre-dialysis patients are not known, since trials exclude these patients because of a high bleeding risk. Guidelines mention this knowledge gap concerning risks and benefits of anticoagulation with vitamin K antagonists for stroke prevention.[36]

The overlap in results between the outcomes RRT and renal function decline is not surprising (**chapter 5 and 6**), since a major part of the decision to start RRT is based on renal function. However, it could be that RAS blockade use and vitamin K antagonist use were associated with RRT initiation through other pathways than renal function decline. For example, initiation of vitamin K antagonist use could be involved in the development of fluid overload, leading up to the decision to start RRT.

In **chapter 7** risk of mortality was the main outcome and compared for vitamin K antagonist users and non-users in incident dialysis patients. There was no protective effect on mortality of vitamin K antagonists in this population. Most of the previous studies that investigated the effect of vitamin K antagonists in dialysis patients with atrial fibrillation did not show a beneficial effect of vitamin K antagonists on survival.[37-39] In addition, we found an increased mortality risk for vitamin K antagonist use in dialysis patients with a low $CHA_2DS_2$-VASc score, which to our knowledge has not been investigated before.

Although all chapters in this thesis provide additional evidence for guidelines in pre-dialysis and dialysis patients, **chapter 5, 6, and 7** add information that is either missing in current guidelines, or provide conflicting evidence. This can either be a welcome addition, like the results in **chapter 7**, or a challenge to decide how much impact one additional observational study (**chapter 5**) has on current beliefs and guidelines.

## Study strengths and limitations

In this section the strengths and limitations of our studies in the EQUAL study, PREPARE-I study, PREPARE-II study, and NECOSAD study are discussed.

### Strengths

**Chapter 2** was performed with data from the EQUAL study. The EQUAL study is a prospective cohort study performed in elderly patients with CKD progressing towards ESRD. Main strength of this study is the large size of the study population, especially for pre-dialysis 1486 patients is a large cohort. Additional strengths are the longitudinal character of the study, the inclusion of incident pre-dialysis patients (who for the first time passed a pre-specified eGFR level), and the collection of detailed information on quite a wide range of subjects. Finally, the generalizability of the study due to the low number of exclusion criteria and the participation of multiple European countries is an important strength.

The PREPARE-II population was used in **chapter 3, 4 and 5**. The entire PREPARE study, combining PREPARE-I and PREPARE-II, was used for **chapter 6**. The PREPARE study is a multicenter follow-up study in 1049 patients, starting specialized pre-dialysis care in the Netherlands. The PREPARE study consists of a retrospective (PREPARE-I) and a prospective part (PREPARE-II). Main strength of this study is the well-defined cohort of incident pre-dialysis patients who received standardized treatments and check-ups by nephrologists. A wide range of incident pre-dialysis patients was included, making the results generalizable

to the clinical practice of pre-dialysis care. An extra strength of PREPARE-I is that the retrospective character made it possible to include all consecutive patients resulting in a high generalizability. An extra strength of the PREPARE-II study is its prospective longitudinal design, resulting in specific, complete information and the opportunity to track kidney function over time. Finally, the measurements of both the SF-36 and the EuroQol (over time) in PREPARE-II make it possible to validate the SF-12 and the EuroQol questionnaire in pre-dialysis patients, which we did in **chapter 3**.

Data from the NECOSAD study were used in **chapter 7**. NECOSAD is a prospective Dutch multicenter study, which included over 2000 incident dialysis patients. After inclusion, patients were followed up to ten years during which clinical variables were collected every six months, and events of death and censoring due to other reasons were recorded. The general strength of this study was the large and well-defined Dutch cohort of incident dialysis patients with available data on an extensive range of patient characteristics, laboratory measurements, quality of life, and death. An extra strength is the fact that follow-up of events of death, transplants and modality changes are continued to this day via linkage to the Dutch national renal registry, resulting in an extremely complete registration of outcomes.

## Limitations

### *Study design limitations*

All studies used in this thesis are observational follow-up studies. Inherent to this study design are several methodological limitations.

The first important limitation in observational aetiological studies is (residual) confounding. In every study there are factors that influence the outcome in addition to the investigated exposure. When these factors also affect the exposure - a so-called common cause - they are called confounders. As confounders are unequally divided over the compared patient groups they will disturb the relation between the exposure and the outcome. In well- performed randomized controlled trials patients by design are randomly divided into different groups with concealed allocation, which is expected to result in a balanced division of confounders. In the observational studies used in this thesis we try to solve confounding after performing the study by adjusting the models for all measured confounders and stratifying results. However, this is no guarantee that all confounding is solved. It is impossible to measure every confounder, simply because there are too many, they are subjective and thereby hard to measure, or they are unknown, leaving the possibility of residual confounding in any observational study. This is especially a concern when intended effects are studied, since unintended effects are less influenced by unmeasured confounding, such as expectations from the treating nephrologist. However, with adjusting for confounding and the use of sensitivity analyses it is often possible to show the limited effect residual confounding could have on the conclusions in the performed observational

research. Therefore, when performed correctly, observational research is often a good alternative for a randomized controlled trial. Especially since randomized controlled trials are often not feasible, due to ethical problems, sample size problems, a lack of randomization possibilities, or other practical problems.

A second limitation is the occurrence of missing data, a problem in all study designs. There are three types of missing data; data missing completely at random (MCAR), data missing at random (MAR), and data missing not at random (MNAR). There are several ways to deal with missing data MCAR and MAR.[40] The best way to handle these and the method used in this thesis is by using multiple imputation. This way, the risk of bias is minimized.[41, 42] There are some sophisticated methods to deal with MNAR. However, in this thesis we did not use these methods.

A final limitation is the selection of patients for all three studies. Although the aim was to include consecutive patients in outpatient clinics and consecutive incident dialysis patients in the dialysis centers, treating nephrologists could always decide not to include a patient, for example due to the severity of a patients illness. In addition, patients were asked for a written informed consent before inclusion and could refuse to participate. Sicker patients might find study participation too much of a burden, which might lead to a higher refusal rate as compared with the refusal rate in healthier patients. Both issues might have affected the generalizability of the cohorts, since included patients might be healthier than the average population of pre-dialysis patients and dialysis patients.

***Medication study limitations***

In **chapter 5, 6, and 7** of this thesis the investigated exposure is medication use. This type of study is associated with some extra limitations.

The main limitation in these studies is the possibility of confounding by indication. The indication for prescribing dual RAS blockade as well as vitamin K antagonists is based on the presence of certain risk factors, as well as the (immeasurable) experience and gut feeling of the treating nephrologist.[43-45] All these factors are associated with the probability of receiving dual RAS blockade or vitamin K antagonists and with the risk of kidney function decline. Therefore, patients receiving dual RAS blockade have a higher probability of developing ESRD, not because of the dual RAS blockade, but because of their increased intrinsic risk.[35] For example, patients with a worse kidney function would receive vitamin K antagonists less often leading to a possible underestimation of negative effects of vitamin K antagonists. However, confounding by indication is less of a problem when the outcome is an unintended effect, since the immeasurable factors that influence the nephrologists decisions do not apply to unintended effects. Since RAS inhibition is mainly prescribed for blood pressure control and vitamin K antagonists for thrombosis prevention, the effect on kidney function and start of RRT are for the largest part unintended effects. In combination with the correction for multiple confounders, this reduced the possible confounding by indication. In **chapter 7** preventing premature death is an indirect goal of prescribing

vitamin K antagonists, the main aim remains thrombosis prevention, making death at least a partial unintended effect.[46]

Another limitation is the inclusion of patients who were prevalent users or non-users of RAS-blockade medication in **chapter 5** and vitamin K antagonists in **chapter 6 and 7**. We had no information about the duration of medication use in these patients. However, in **chapter 5** 29 (24%) of the non-users started an ACEi or ARB during follow-up, which may have resulted in underestimation of the beneficial effect of ACEi-use or ARB-use. The inclusion of prevalent vitamin K antagonist users in **chapter 6** could have led to an underestimation of the negative effects on kidney function and start of dialysis in vitamin K antagonist users. In **chapter 7** this could have led to an underestimation of the mortality risks associated with vitamin K antagonist use. However, since there is no positive effect of the vitamin K antagonist use, and even a negative effect in patients with low $CHA_2DS_2$-VASc scores this could only result in larger negative effects.

A third limitation is the possible lack of therapy adherence. It is known that adherence to pharmacotherapy is rarely 100%.[47] A lack of therapy adherence in a study could lead to an underestimation of effects. However, it does represent clinical practice resulting in a realistic estimation of the effects in clinical practice. This means an RCT could result in an overestimation of effects when adherence is monitored closely.

Finally, we had no information about the indication of vitamin K antagonist use in our patients in **chapter 6 and 7**. Therefore, it could be that vitamin K antagonists were used for other indications than atrial fibrillation in dialysis patients with a low risk score ($CHA_2DS_2$-VASc) for thrombotic events. However, based on the high risk of atrial fibrillation in dialysis patients, it is likely that an important proportion of the patients had atrial fibrillation and that the impact on the found results is minimal.[48]

## Implications and recommendations

In this thesis we showed the importance of symptoms and relative unimportance of clinical variables in determining quality of life. Both the prevalence and severity of symptoms emphasize the need for attention on symptoms during outpatient clinic visits. The effect of symptoms on a clinically relevant outcome measure which in turn affects other important outcomes, indicates that symptoms should have a more prominent role in clinical decision making and guidelines in CKD should emphasize this.

After the validation of the SF-12 and the EuroQol, we would recommend to use the SF-12 as a shorter substitute for the SF-36, since this questionnaire has a better agreement with the SF-36 as compared with the EuroQol. Since both are now validated, use of the SF-12 and the EuroQol to measure quality of life in pre-dialysis patients could now be justified, however, additional validations in different countries would enhance this first evidence. In clinical practice the use of these shorter questionnaires is useful when large amounts of patients are asked to fill in multiple questionnaires. To measure quality of life and re-

lated topics more in depth, such as its relation with coping, illness perceptions, or coping mechanisms, a larger questionnaire such as the SF-36, is more appropriate.

For future research on quality of life in patients with CKD, we would recommend to broaden research on factors influencing quality of life. This could be achieved by intensifying research on symptoms, for example by studying the impact of individual symptoms or clusters of symptoms on QoL or testing whether interventions on symptoms improve QoL. A second method to achieve this is by investigating other aspects of the common-sense model by Leventhal, Nerenz and Steele, for example illness perceptions.[27]

In this thesis we also investigated several cardiovascular risk factors and their association with the traditional outcomes renal function decline, start of RRT and mortality. Finding no clear association between dyslipidemia and start of dialysis, RRT or death, we suggest focusing on the direct effects and mechanisms of lipid lowering drugs in pre-dialysis patients instead of the absolute lipid and triglyceride levels. The lack of a negative association between dual RAS blockade and start of RRT and renal function decline suggests that there might be room for dual RAS blockade when treating severe hypertension or proteinuria in CKD 4-5 patients with single RAS blockade.

The results in our studies on vitamin K antagonist use emphasize the need for randomized controlled trials comparing vitamin K antagonists with placebo or direct oral anticoagulants. This would provide better insight into the adverse effects of vitamin K antagonists and more personalized prescription of anticoagulant drugs in pre-dialysis and dialysis patients.

## Conclusion

In elderly pre-dialysis patients symptoms have a substantial impact on quality of life. The effect of symptoms on a clinically relevant outcome measure indicates that these symptoms, which in turn affect other important outcomes, should have a more prominent role in clinical decision making, and guidelines in CKD should emphasize this. An appropriate way to measure the construct quality of life in pre-dialysis patients with a short questionnaire is by using the SF-12. In the future additional validation of this questionnaire in different countries could strengthen this evidence.

No association between dyslipidemia and start of dialysis, RRT or death in pre-dialysis patients was found. In pre-dialysis patients, both dual RAS blockade as well as single ACEi-use were associated with a lower risk of RRT or death, as compared with no RAS blockade. Kidney function decline in the single or dual RAS inhibition groups was not accelerated as compared with non-RAS inhibition drug users. This implies there there might be room for dual RAS blockade when treating severe hypertension or proteinuria in CKD 4-5 patients with single RAS blockade. There is no association between vitamin K antagonist use and rate of renal function decline or time until start of dialysis in the pre-dialysis population, which provides support to continue the use of vitamin K antagonists in this population.

Vitamin K antagonist use compared to no vitamin K antagonist use is associated with an increased all-cause mortality risk in dialysis patients, which increases with increasing CHA2DS2-VASc scores. Within patients with a CHA2DS2-VASc score of equal to or less than one, vitamin K antagonist use is associated with an increased mortality risk as compared with no vitamin K antagonist use. This implies the need to evaluate the indication for vitamin K antagonist use when starting dialysis.

In short, in pre-dialysis patients quality of life is an important outcome measure which can be measured with the SF-12 in addition to the SF-36, and which is affected by the symptom burden of a patient. Cardiovascular risk factors remain important treatment targets in pre-dialysis and dialysis patients, and often have similar effects on traditional outcomes compared to their effects in earlier CKD stages.

## References


1. Perkovic V, Ninomiya T, Arima H*, et al.* Chronic kidney disease, cardiovascular events, and the effects of perindopril- based blood pressure lowering: data from the PROGRESS study. *J Am Soc Nephrol* 2007; 18: 2766-2772
2. Mann JF, Schmieder RE, McQueen M*, et al.* Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. *Lancet* 2008; 372: 547-553
3. Ruggenenti P, Perna A, Gherardi G*, et al.* Renoprotective properties of ACE-inhibition iin non-diabetic nephropathies with non-nephrotic proteinuria. *Lancet* 1999; 354: 359-364
4. Berl T, Hunsicker LG, Lewis JB*, et al.* Cardiovascular outcomes in the Irbesartan Diabetic Nephropathy Trial of patients with type 2 diabetes and overt nephropathy. *Ann Intern Med* 2003; 138: 542-549
5. Yusuf S, Teo KK, Pogue J*, et al.* Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008; 358: 1547-1559
6. Brenner BM, Cooper ME, de Zeeuw D*, et al.* Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001; 345: 861-869
7. Teo K, Yusuf S, Sleight P*, et al.* Rationale, design, and baseline characteristics of 2 large, simple, randomized trials evaluating telmisartan, ramipril, and their combination in high-risk patients: the Ongoing Telmisartan Alone and in Combination with Ramipril GlobalEndpoint Trial/Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (ONTARGET/TRANSCEND) trials. *Am Heart J* 2004; 148: 52-61
8. van den Meiracker AH, Man in 't Veld AJ, Admiraal PJ*, et al.* Partial escape of angiotensin converting enzyme (ACE) inhibition during prolonged ACE inhibitor treatment: does it exist and does it affect the antihypertensive response? *J Hypertens* 1992; 10: 803-812
9. Brodsky SV, Satoskar A, Chen J*, et al.* Acute kidney injury during warfarin therapy associated with obstructive tubular red blood cell casts: a report of 9 cases. *Am J Kidney Dis* 2009; 54: 1121-1126
10. Brodsky SV, Nadasdy T, Rovin BH*, et al.* Warfarin-related nephropathy occurs in patients with and without chronic kidney disease and is associated with an increased mortality rate. *Kidney Int* 2011; 80: 181-189
11. Holbrook AM, Pereira JA, Labiris R*, et al.* Systematic overview of warfarin and its drug and food interactions. *Arch Intern Med* 2005; 165: 1095-1106
12. Wheeler DS, Giugliano RP, Rangaswami J. Anticoagulation-related nephropathy. *J Thromb Haemost* 2016; 14: 461-467
13. Chatrou ML, Winckers K, Hackeng TM, Reutelingsperger CP, Schurgers LJ. Vascular calcification: the price to pay for anticoagulation therapy with vitamin K-antagonists. *Blood Rev* 2012; 26: 155-166
14. Schurgers LJ, Joosen IA, Laufer EM*, et al.* Vitamin K-antagonists accelerate atherosclerotic calcification and induce a vulnerable plaque phenotype. *PLoS One* 2012; 7: e43229
15. Rabelink TJ, Zwaginga JJ, Koomans HA, Sixma JJ. Thrombosis and hemostasis in renal disease. *Kidney Int* 1994; 46: 287-296

16. Pokorney SD, Simon DN, Thomas L*, et al.* Patients' time in therapeutic range on warfarin among US patients with atrial fibrillation: Results from ORBIT-AF registry. *Am Heart J* 2015; 170: 141-148, 148 e141
17. Knight EL, Ofsthun N, Teng M, Lazarus JM, Curhan GC. The association between mental health, physical function, and hemodialysis mortality. *Kidney Int* 2003; 63: 1843-1851
18. Lowrie EG, Curtin RB, LePain N, Schatell D. Medical utcomes study short form-36: a consistent and powerful predictor of morbidity and mortality in dialysis patients. *Am J Kidney Dis* 2003; 41: 1286-1292
19. Thong MS, Kaptein AA, Benyamini Y*, et al.* Association between a self-rated health question and mortality in young and old dialysis patients: a cohort study. *Am J Kidney Dis* 2008; 52: 111-117
20. Tsai YC, Hung CC, Hwang SJ*, et al.* Quality of life predicts risks of end-stage renal disease and mortality in patients with chronic kidney disease. *Nephrol Dial Transplant* 2010; 25: 1621-1626
21. de Goeij MC, Ocak G, Rotmans JI, Eijgenraam JW, Dekker FW, Halbesma N. Course of symptoms and health-related quality of life during specialized pre-dialysis care. *PLoS One* 2014; 9: e93069
22. Chong K, Unruh M. Why does quality of life remain an under- investigated issue in chronic kidney disease and why is it rarely set as an outcome measure in trials in this population? *Nephrol Dial Transplant* 2017; 32: ii47-ii52
23. Finkelstein FO, Wuerth D, Finkelstein SH. Health related quality of life and the CKD patient: challenges for the nephrology community. *Kidney Int* 2009; 76: 946-952
24. Tong A, Sainsbury P, Carter SM*, et al.* Patients' priorities for health research: focus group study of patients with chronic kidney disease. *Nephrol Dial Transplant* 2008; 23: 3206-3214
25. Abdel-Kader K, Unruh ML, Weisbord SD. Symptom burden, depression, and quality of life in chronic and end-stage kidney disease. *Clin J Am Soc Nephrol* 2009; 4: 1057-1064
26. Yong DS, Kwok AO, Wong DM, Suen MH, Chen WT, Tse DM. Symptom burden and quality of life in end-stage renal disease: a study of 179 patients on dialysis and palliative care. *Palliat Med* 2009; 23: 111-119
27. Leventhal H, Nerenz, D.R., Steele, D.J. Illness representations and coping with health threats. *A handbook of psychology and health. Social psychological aspects of health*. Erlbaum: Hillsdale, NJ; 1984, 219-252.
28. Jansen DL, Heijmans MJ, Rijken M*, et al.* Illness perceptions and treatment perceptions of patients with chronic kidney disease: different phases, different perceptions? *Br J Health Psychol* 2013; 18: 244-262
29. Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. *JAMA* 1995; 273: 59-65
30. Rahman M, Xie D, Feldman HI*, et al.* Association between chronic kidney disease progression and cardiovascular disease: results from the CRIC Study. *Am J Nephrol* 2014; 40: 399-407
31. Rahman M, Yang W, Akkina S*, et al.* Relation of serum lipids and lipoproteins with progression of CKD: The CRIC study. *Clin J Am Soc Nephrol* 2014; 9: 1190-1198
32. Stone NJ, Robinson JG, Lichtenstein AH*, et al.* 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American Col-

lege of Cardiology/American Heart Association Task Force on Practice Guidelines. ***Circulation*** 2014; 129: S1-45

33. Kidney Disease: Improving Global Outcomes (KDIGO) Lipid Work Group. KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease. ***Kidney International, Supplement*** 2013; 3: 259-305
34. Fernandez Juarez G, Luno J, Barrio V***, et al.*** Effect of dual blockade of the renin-angiotensin system on the progression of type 2 diabetic nephropathy: a randomized trial. ***Am J Kidney Dis*** 2013; 61: 211-218
35. Imai E, Chan JC, Ito S***, et al.*** Effects of olmesartan on renal and cardiovascular outcomes in type 2 diabetes with overt nephropathy: a multicentre, randomised, placebo-controlled study. ***Diabetologia*** 2011; 54: 2978-2986
36. Herzog CA, Asinger RW, Berger AK***, et al.*** Cardiovascular disease in chronic kidney disease. A clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). ***Kidney Int*** 2011; 80: 572-586
37. Zimmerman D, Sood MM, Rigatto C, Holden RM, Hiremath S, Clase CM. Systematic review and meta-analysis of incidence, prevalence and outcomes of atrial fibrillation in patients on dialysis. ***Nephrol Dial Transplant*** 2012; 27: 3816-3822
38. Winkelmayer WC, Liu J, Setoguchi S, Choudhry NK. Effectiveness and safety of warfarin initiation in older hemodialysis patients with incident atrial fibrillation. ***Clin J Am Soc Nephrol*** 2011; 6: 2662-2668
39. Wizemann V, Tong L, Satayathum S***, et al.*** Atrial fibrillation in hemodialysis patients: clinical features and associations with anticoagulant therapy. ***Kidney Int*** 2010; 77: 1098-1106
40. Donders AR, van der Heijden GJ, Stijnen T, Moons KG. Review: a gentle introduction to imputation of missing values. ***J Clin Epidemiol*** 2006; 59: 1087-1091
41. Lee KJ, Simpson JA. Introduction to multiple imputation for dealing with missing data. ***Respirology*** 2014; 19: 162-167
42. de Goeij MC, van Diepen M, Jager KJ, Tripepi G, Zoccali C, Dekker FW. Multiple imputation: dealing with missing data. ***Nephrol Dial Transplant*** 2013; 28: 2415-2420
43. Hillege HL, Fidler V, Diercks GF***, et al.*** Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. ***Circulation*** 2002; 106: 1777-1782
44. Williams JD, Coles GA. Proteinuria--a direct cause of renal morbidity? ***Kidney Int*** 1994; 45: 443-450
45. Psaty BM, Koepsell TD, Lin D***, et al.*** Assessment and control for confounding by indication in observational studies. ***J Am Geriatr Soc*** 1999; 47: 749-754
46. Vandenbroucke JP. Why do the results of randomised and observational studies differ? ***BMJ*** 2011; 343: d7020
47. Sontakke S, Budania R, Bajait C, Jaiswal K, Pimpalkhute S. Evaluation of adherence to therapy in patients of chronic kidney disease. ***Indian J Pharmacol*** 2015; 47: 668-671
48. Shah M, Avgil Tsadok M, Jackevicius CA***, et al.*** Warfarin use and the risk for stroke and bleeding in patients with atrial fibrillation undergoing dialysis. ***Circulation*** 2014; 129: 1196-203