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GENERAL INTRODUCTION, AIM AND OUTLINE OF THE THESIS

Based on:
How to reduce sudden cardiac death in patients with renal failure
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INTRODUCTION

The kidneys have several essential roles in the human body: they remove waste products, regulate volume status, maintain electrolyte balance and serve a crucial role in mineral homeostasis. Chronic kidney disease (CKD) causes a gradual decline in renal function ranging from only slight dysfunction (CKD Stage I) which can progress toward a state in which the kidneys are no longer able to remain homeostasis (CKD Stage V). In this state, also known as end stage renal disease (ESRD), either dialysis therapy or renal transplantation is necessary to prevent death. Currently, ~400,000 patients are receiving dialysis treatment in the United States (2,000 per 1,000,000 people in the population) and in the Netherlands there are currently ~6,500 patients on dialysis therapy (1,000 per 1,000,000).[1] These numbers are expected to increase exponentially in the future.

With an annual death rate of ~20%, the mortality of patients on dialysis treatment is extremely high.[1] The majority of deaths in patients with ESRD are caused by cardiovascular disease (~42%) and roughly 60% of these are defined as sudden cardiac death (SCD) (Figure 1).[1] Given this high event rate of SCD in dialysis patients it is of paramount importance to gain insights in this detrimental relationship between the kidneys and the heart, to identify those patients with a high risk of SCD and to explore preventive strategies in these patients. This is the aim of the current thesis.

MECHANISMS OF SCD IN CKD

The mechanisms underlying SCD in patients with CKD are complex and multiple factors have been associated with the increased risk of SCD in this population. The key factors will be discussed below and are summarized in table 1. The first part of the current thesis will further explore methods to detect patients at risk for the development of SCD.

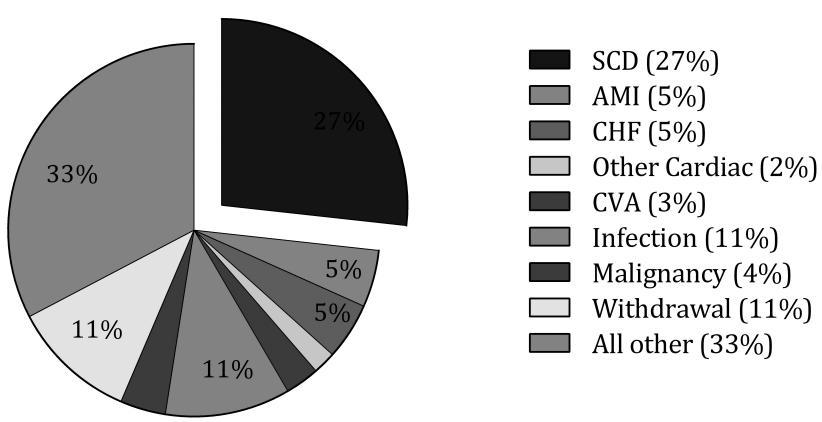

Figure 1: Causes of death in prevelant dialysis patients 2009-2011. Data from the 2013 USRDS Annual Data reports.

Table 1: Mechanisms associated with SCD in patients with CKD

Ischemic Heart Disease	• Highly prevalent and more severe in patients with CKD[2-5] • Most important predictor of SCD in patients with ESRD[6-7] • In patients with CAD severity of CKD is associated with the occurrence of SCD[7]
Left Ventricular Hypertrophy and Myocardial fibrosis	• Already present in the early stages of CKD and prevalence increases with severity of CKD[8] • Results in phenomena predisposing to cardiac arrhythmias (i.e. decreased myocardial capillary density, diastolic and systolic dysfunction.)[9] • Development and especially worsening of LVH is associated with increased risk for SCD[12-13]
Vascular calcification	• Intima calcification leads to luminal narrowing resulting in ischemia • Media calcification leads to a reduced vascular compliance resulting in vascular stiffening[14] • Disorders of the mineral-bone-axis play an important role in vascular calcification in CKD (this thesis)
Sympathetic overactivation	• Important mechanism for cardiovascular complications[15] • In dialysis patients norepinephrine predicts survival and cardiovascular events[15] • Damaged kidneys themselves trigger sympathetic over activation[16]
Dialysis treatment	• Timely relation between occurrence of SCD and dialysis treatment[17] • Fluid and electrolyte shifts might play an important role[17]
Other risk factors	• Including: age, diabetes mellitus, malnutrition, inflammation, electrolyte abnormalities and the use of vascular access catheters

SCD: Sudden Cardiac Death; CKD: Chronic Kidney Disease; ESRD: End Stage Renal Disease; LVH: Left Ventricular Hypertrophy.

Ischemic heart disease

Coronary artery disease (CAD) is common among patients with CKD and more severe in this group compared to patients without renal dysfunction.[2] In dialysis patients, the incidence of CAD is believed to be ~30-40% and since patients are often asymptomatic, this incidence might be even higher.[3-5] Like in the general population, in dialysis patients the presence of CAD is an important risk factor in the development of SCD.[6] Moreover, among patients with CAD, every 10 ml/min/1.73m^2 decrease in estimated glomerular filtration rate (eGFR) is associated with an 11% increase in the risk of SCD.[7] Furthermore, in patients with significant CAD, those on dialysis therapy have a 6-fold higher risk of SCD compared to those with a GFR>60ml/min/1.73m^2.[7] **Chapter III** and **Chapter IV** of this thesis focus on biomarkers associated with CAD in clinically stable dialysis patients, whereas **Chapter V** describes the value of a plain abdominal X-ray in predicting the presence of CAD in asymptomatic dialysis patients.

Left ventricular hypertrophy

Left ventricular hypertrophy (LVH) already starts to develop in the early stages of CKD and its prevalence increases to ~75% in patients with ESRD.[8] Causes for the development of LVH in patients with CKD can be roughly divided in (1) preload-related factors such

as hypervolemia and anaemia, (2) afterload-related factors such as systemic arterial resistance, elevated blood pressure and large-vessel compliance and (3) factors related to mineral homeostasis, oxidative stress and micro inflammation.[9] FGF-23, a phosphate-regulating hormone pivotal in mineral homeostasis, has recently emerged as an important factor associated with LVH, and mortality in patients with CKD.[10, 11] More information on this subject is found in **Chapter IV** of this thesis. The development of LVH is a strong predictor for mortality and especially SCD.[12, 13] **Chapter III** of this thesis explores the value of cardiac specific troponins for the detection of LVH in dialysis patients.

Vascular calcification

Vascular calcification in the general population generally occurs in the intima of the vessel wall. This is a consequence of inflammation and ossification of atherosclerotic plaques and leads to luminal narrowing of the vessel. In patients with CKD, however, media calcification develops which leads to stiffening of the vessel and thereby a reduced vascular compliance. In these patients, vascular stiffness has been linked to both cardiovascular mortality and SCD.[14] Disorders of the mineral-bone-axis and especially Klotho, a protein linked to aging, have been suggested as important causes of vascular calcification in patients with kidney dysfunction. **Chapter IV** of this thesis further elaborates on this subject**.**

Sympathetic overactivity

Increased sympathetic activity is recognized as an important mechanism of cardiovascular complications. In dialysis patients it has been demonstrated that plasma norepinephrine, a marker of sympathetic activity, is an independent predictor of survival and cardiovascular events.[15] Sustained overactivation of the sympathetic nervous system is highly prevalent among patients with CKD and this condition develops early in the course of CKD. The damaged kidneys themselves may be the trigger for this overactivity, since the augmented sympathetic drive declines after bilateral nephrectomy.[16]

Haemodialysis treatment

On top of the factors mentioned above, the haemodialysis (HD) procedure itself is an important risk factor for the occurrence of SCD in patients with ESRD. The incidence of SCD is related to the timing of HD treatment, with a significantly higher incidence of SCD in the first twelve hours from the start of HD an in the 48-72 hours after start of HD (Figure 2).[17] The rapid fluid and electrolyte shifts that occur during dialysis treatment as well as the volume overload between dialysis procedures might explain this association.[17] To further explore the pro-arrhythmogenic role of the dialysis procedure, the association between atrial arrhythmias and the dialysis treatment were explored in **Chapter II** of this thesis.

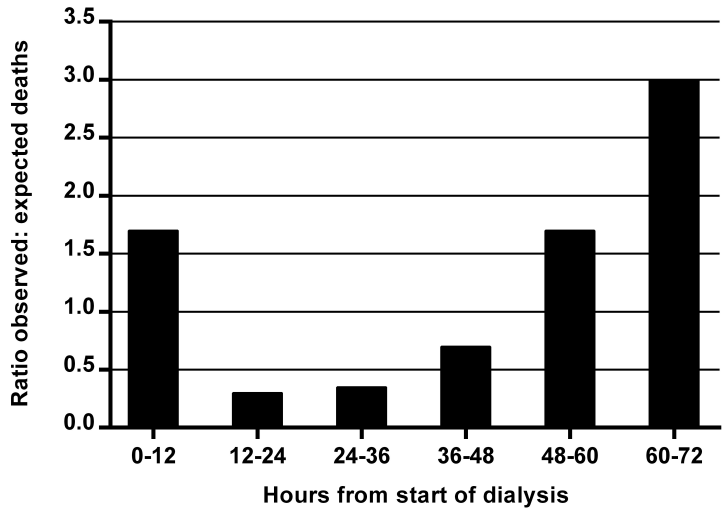

Figure 2: Incidence of SCD in relation to the dialysis therapy. Ratio of observed versus expected death, assuming that the occurrence of death would be evenly distributed over time, in relation to the start of the dialysis therapy. Reproduced from Bleyer et al with permission of Nature Publishing Group.

PREVENTION STRATEGIES

Various treatment strategies have been investigated with regard to the prevention of SCD in patients with CKD. The majority of treatment options interact with one of the risk factors mentioned previously. In the following section the most important treatment strategies will be discussed (table 2 & table 3). Moreover, the second part of this thesis will focus on a particular treatment strategy in preventing SCD, the implantable cardioverter defibrillator (ICD).

Medical therapy

β-blockers interfere with the deleterious actions of the sympathetic nervous system and are an effective and widely used therapy for the prevention of SCD in the general population. Unfortunately, data on the beneficial effects of β-blockers in patients with CKD are limited. A reduction in acute myocardial infarction or SCD rates has been described in a single post-hoc analysis of patients with CKD stages I-IV.[18] Furthermore, a survival benefit of the β-blocker carvedilol has been shown in a single small randomized trial performed in dialysis patients.[19]

Statins have beneficial effects on cardiovascular endpoints in various patient groups. The SHARP trial recently concluded that treatment of patients with CKD stages I-V with simvastatine+ezetimibe significantly reduces major events related to coronary atherosclerosis.[20] Furthermore, a recent meta-analysis demonstrated a significant reduction of major cardiovascular events in patients with all stages of CKD using

Table 2: Strategies to reduce SCD in CKD patients stages I-IV.

β-blocker	• Demonstrated to have a reduction in acute myocardial infarction and/or SCD rates in a single trial[18]
Statins	• Associated with improved cardiovascular outcomes among all stages of CKD in several studies[20, 21]
ACEi/ARB	• Beneficial effects on cardiovascular and renal endpoints[24-25]
Revascularization	• Prophylactic revascularization is not beneficial on top of optimal medical therapy in stable CAD[27]
ICD Implantation	• Current guidelines do not advice against prophylactic ICD implantation in CKD patients who meet the current criteria. Prospective data however is scarce[34] • ICD implantation in CKD patients meeting the current guidelines is beneficial compared to no ICD[37, 38] • Among ICD recipients, CKD patients have a significantly worse prognosis despite the presence of an ICD[35, 36]

SCD: Sudden Cardiac Death; CKD: Chronic Kidney Disease; ACEi: Angiotensin Converting Enzyme inhibitor; ARB: Angiotensin type II Receptor Blockers; CAD: Coronary Artery Disease; ICD: Implantable Cardioverter Defibrillator; AF: Atrial Fibrillation

statins.[21] On the other hand, two recent randomized trials failed to show significant beneficial effects of statins on cardiovascular outcomes in dialysis patients.[22, 23] Furthermore, none of these studies specifically described SCD as an endpoint.

In various populations angiotensin converting enzyme inhibitors (ACEi) and angiotensin type II receptor blockers (ARB) have been associated with beneficial effects regarding cardiovascular and renal endpoints. The data in CKD patients, however, is ambiguous. The RENAAL trial showed that losartan significantly reduced the incidence of death in patients with type 2 diabetes and nefropathy (as part of a composite endpoint), while candesartan significantly reduced the incidence of cardiovascular events in dialysis patients.[24, 25] A prospective study investigating fosinopril in CKD, on the other hand, failed to show a beneficial effect on cardiovascular events.[26]

Revascularization

Even though CAD is strongly associated with SCD, the current literature does not show a benefit of revascularization over optimal medical therapy in the reduction of mortality in patients with stable CAD.[27] Thus, prophylactic revascularization in patients with CKD stages I-V is controversial. Most trials however, excluded dialysis patients and results in this population might be different. Indeed, several studies demonstrated that revascularization in dialysis patients with stable CAD improved prognosis.[28, 29] *Herzog et al*, on the other hand, showed that all-cause mortality and arrhythmic mortality in optimally revascularized dialysis patients was comparable to that of dialysis patients without revascularization.[30] These results suggest that despite optimal treatment of CAD, a substantial risk of SCD remains in these patients.

Table 3: Strategies to reduce SCD in dialysis patients.

β-blocker	• One single prospective trial demonstrated a beneficial effect in a subset of dialysis patients [19]
Statins	• 2 recent large trials failed to demonstrate a benefit for statins in dialysis patients[22, 23] • Large meta-analysis showed beneficial effect on mortality along the whole spectrum of CKD stages[21]
ACEi/ARB	• Conflicting results regarding benefit [24-26]
Changing dialysis modality	• No results regarding cardiovascular mortality[32, 33] • Increasing dialysis frequency beneficial for LVH[32, 33]
Revascularization	• In dialysis patients with documented CAD revascularization improves outcome[28, 29] • No difference in all-cause mortality or SCD between optimally revascularized dialysis patients and the general dialysis population[30]
ICD Implantation	• For both primary and secondary prevention indications, conflicting results on survival improvement have been reported in retrospective cohorts [38-41, 44] • Dialysis treatment strongly predicts time to appropriate shock [42, 43] • Prophylactic ICD implantation in dialysis patients who do not meet ICD implantation criteria is currently being investigated in the ICD-2 trial[45]

SCD: Sudden Cardiac Death; CKD: Chronic Kidney Disease; ACEi: Angiotensin Converting Enzyme inhibitor; ARB: Angiotensin type II Receptor Blockers; LVH: Left ventricular Hypertrophy; CAD: Coronary Artery Disease; ICD: Implantable Cardioverter Defibrillator; AF: Atrial Fibrillation

Changing dialysis modality

Given the suggested relationship between SCD and the dialysis procedure, numerous modifications of the dialysis procedure itself have been investigated to prevent SCD, such as altering the dialysis frequency, dose and hemofiltration.[31-33] Increasing the frequency of (nocturnal) haemodialysis has shown promising results with regard to left ventricular mass and survival.[32, 33] However, no beneficial effects regarding SCD rate have been reported thus far.

Prophylactic ICD implantation in CKD patients (Stage I-IV)

ICD therapy is effective in the prevention of SCD in a wide range of patients.[34] However, mostly due to a lack of prospective data, the current literature regarding the benefit of ICDs in CKD patients, remains inconclusive . Numerous retrospective studies in patients who received an ICD according to current guidelines, have tried to shed a light on this subject, with conflicting results. Among ICD recipients, a step-wise association has been found between CKD stage and mortality, despite the presence of an ICD.[35, 36] On the other hand, a recent meta-analysis demonstrated that patients with CKD stages I-IV and who received an ICD (for primary or secondary prevention) had a significantly better survival than those without an ICD.[37] Furthermore, a retrospective analysis of the MADIT-II trial showed a beneficial effect of an ICD in patients with mild to moderate renal dysfunction.[38] This study also demonstrated however, that

the presence of co-morbidity (age>70years, atrial fibrillation, NYHA class >II, QRS duration of >120ms) significantly reduced this benefit. Thus, among patients with CKD eligible for an ICD for primary or secondary prevention according to current guidelines, an ICD might carry a survival benefit compared to CKD patients who do not receive an ICD. The mortality risk among ICD recipients with CKD, however, remains very high compared to those with better renal function, despite the presence of an ICD. With the current lack of prospective data, the question remains whether ICD's are (cost) effective in CKD patients and if so, in whom.

Prophylactic ICD implantation in dialysis patients

While scarce data exists on the benefit of ICD therapy in CKD stages I-IV, even less prospective data is available in dialysis patients. Several retrospective studies failed to show a benefit of the ICD in patients with ESRD.[38-40] A recent meta-analysis, however, demonstrated that dialysis patients with an ICD (for primary or secondary purposes) had a significantly better survival than a control group of dialysis patients without an ICD.[41] Furthermore, a decreased renal function is an independent predictor of appropriate ICD therapies, and dialysis therapy strongly predicts time to appropriate shock.[42, 43] Moreover, a retrospective analysis of dialysis patients surviving an out of hospital cardiac arrest, documented a substantial survival benefit for those who received an ICD.[44] Nonetheless, these retrospective studies are subject to several limitations and more prospective data is needed to assess the (cost) effectiveness of an ICD in dialysis patients.

The currently ongoing ICD2 trial will attempt to answer some of these questions. This ongoing trial evaluates the potential benefit of prophylactic ICD implantation in dialysis patients without a current indication for ICD therapy.[45] Two hundred dialysis patients are randomized for an ICD or no ICD. All participants are between 55 and 80 years old, are treated with dialysis, and have a left ventricular ejection fraction ≥35%. An extensive pre-randomization screening protocol is being conducted in all participants in order to establish potential predictors for SCD and/or appropriate ICD therapies. The data gathered during the screening phase of this trial forms the foundation of the current thesis.

Safety of ICD treatment in patients with renal failure

ICD implantation in patients with renal failure is not without complications. For instance, it has been established that CKD is associated with an increased risk of cardiac device infections and hematoma compared to the general population.[35, 46, 47] Cardiac device infections are a potentially life-threatening complication necessitating device extraction in nearly all cases. Another important complication in patients with ESRD is stenosis of the vessel related to the ICD-lead. In the general population, central venous obstruction has little consequence; however, since central venous access is necessary in patients with ESRD to perform dialysis, it could have major implications in this population.[48] **Chapter VI** of this thesis further explores the association between CKD and ICD-related

complications. Finally, **Chapter VII** describes the effectiveness and safety of a left ventricular lead placed on the epicardium. Since this lead is not located transvenously, both the risk of lead infections and venous obstruction might be reduced.

CONCLUSIONS AND AIM OF THIS THESIS

Sudden cardiac death (SCD) is the leading cause of death in patients with renal failure. Since the interaction between heart and kidney is a dynamic one, many factors have been associated with this increased risk of SCD. Accordingly, a wide range of therapeutic options have been investigated in CKD, mostly with disappointing results. The ongoing ICD-2 trial investigates the benefit of a prophylactic ICD for the prevention of SCD in dialysis patients and is the cornerstone of the current thesis. The extensive pre-randomization screening protocol of the ICD-2 trial provided unique data to investigate predictors of cardiovascular disease and to gain insights in the detrimental relationship between heart and kidneys in this population. The aim of this thesis was to identify dialysis patients at risk for SCD and to assess the potential values of ICD therapy in this fragile population.

Part 1: Detecting dialysis patients at risk for CVD

The first chapter of this thesis starts with a study on the dialysis procedure as a risk factor for the development of atrial fibrillation **(Chapter II).** Subsequently, several biomarkers (including sKlotho, FGF-23, PTH, vitamin D and cardiac-specific troponin-I and troponin-T) are investigated to evaluate their value in identifying cardiovascular disease in dialysis patients **(Chapter III and IV).** The last chapter in this part of the thesis explores the value of a plain x-ray for the identification of dialysis patients with significant CAD **(Chapter V)**.

Part 2: Complications related to ICD therapy

The second part of this thesis will focus on complications associated with ICD therapy. **Chapter VI** describes ICD-related complications in relation to renal function in a large cohort of device recipients. Lastly, **Chapter VII** describes performance, durability and safety of the epicardial lead, a lead that might have several advantages in overcoming ICD-related complications.

REFERENCE LIST

1 U.S. Renal data system, usrds 2013 annual data report: Atlas of chronic kidney disease and end-stage renal disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda,2013.

2 Russo D, Palmiero G, De Blasio AP, Balletta MM, Andreucci VE. Coronary artery calcification in patients with crf not undergoing dialysis. *American Journal of Kidney Diseases*. 2004;**44**:1024-1030

3 Charytan D, Kuntz RE, Mauri L, DeFilippi C. Distribution of coronary artery disease and relation to mortality in asymptomatic hemodialysis patients. *American Journal of Kidney Diseases*. 2007;**49**:409-416

4 Ohtake T, Kobayashi S, Moriya H, Negishi K, Okamoto K, Maesato K, et al. High prevalence of occult coronary artery stenosis in patients with chronic kidney disease at the initiation of renal replacement therapy: An angiographic examination. *Journal of the American Society of Nephrology*. 2005;**16**:1141-1148

5 Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *American Journal of Kidney Diseases*. 1998;**32**:S112-119

6 Cheung AK, Sarnak MJ, Yan G, Berkoben M, Heyka R, Kaufman A, et al. Cardiac diseases in maintenance hemodialysis patients: Results of the hemo study. *Kidney International*. 2004;**65**:2380-2389

7 Pun PH, Smarz TR, Honeycutt EF, Shaw LK, Al-Khatib SM, Middleton JP. Chronic kidney disease is associated with increased risk of sudden cardiac death among patients with coronary artery disease. *Kidney International*. 2009;**76**:652-658

8 Paoletti E, Bellino D, Cassottana P, Rolla D, Cannella G. Left ventricular hypertrophy in nondiabetic predialysis ckd. *American Journal of Kidney Diseases*. 2005;**46**:320-327

9 Glassock RJ, Pecoits-Filho R, Barberato SH. Left ventricular mass in chronic kidney disease and esrd. *Clinical Journal of the American Society of Nephrology*. 2009;**4** Suppl 1:S79-91

10 Gutierrez OM, Mannstadt M, Isakova T, Rauh-Hain JA, Tamez H, Shah A, et al. Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. *The New England Journal of Medicine*. 2008;**359**:584-592

11 Gutierrez OM, Januzzi JL, Isakova T, Laliberte K, Smith K, Collerone G, et al. Fibroblast growth factor 23 and left ventricular hypertrophy in chronic kidney disease. *Circulation*. 2009;**119**:2545-2552

12 Paoletti E, Specchia C, Di Maio G, Bellino D, Damasio B, Cassottana P, et al. The worsening of left ventricular hypertrophy is the strongest predictor of sudden cardiac death in haemodialysis patients: A 10 year survey. *Nephrology, Dialysis, Transplantation*. 2004;**19**:1829-1834

13 Zoccali C, Benedetto FA, Mallamaci F, Tripepi G, Giacone G, Stancanelli B, et al. Left ventricular mass monitoring in the follow-up of dialysis patients: Prognostic value of left ventricular hypertrophy progression. *Kidney International*. 2004;**65**:1492-1498

14 Blacher J, Safar ME, Guerin AP, Pannier B, Marchais SJ, London GM. Aortic pulse wave velocity index and mortality in end-stage renal disease. *Kidney International*. 2003;**63**:1852-1860

15 Zoccali C, Mallamaci F, Parlongo S, Cutrupi S, Benedetto FA, Tripepi G, et al. Plasma norepinephrine predicts survival and incident cardiovascular events in patients with end-stage renal disease. *Circulation*. 2002;**105**:1354-1359

16 Converse RL, Jr., Jacobsen TN, Toto RD, Jost CM, Cosentino F, Fouad-Tarazi F, et al. Sympathetic overactivity in patients with chronic renal failure. *The New England Journal of Medicine*. 1992;**327**:1912-1918

17 Bleyer AJ, Hartman J, Brannon PC, Reeves-Daniel A, Satko SG, Russell G. Characteristics of sudden death in hemodialysis patients. *Kidney International*. 2006;**69**:2268-2273

18 Chonchol M, Benderly M, Goldbourt U. Beta-blockers for coronary heart disease in chronic kidney disease. *Nephrology, Dialysis, Transplantation*. 2008;**23**:2274-2279

19 Cice G, Ferrara L, D'Andrea A, D'Isa S, Di Benedetto A, Cittadini A, et al. Carvedilol increases two-year survival in dialysis patients with dilated cardiomyopathy: A prospective, placebo-controlled trial.

Journal of the American College of Cardiology. 2003;**41**:1438-1444

20 Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, et al. The effects of lowering ldl cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (study of heart and renal protection): A randomised placebo-controlled trial. *Lancet*. 2011;**377**:2181-2192

21 Hou W, Lu J, Perkovic V, Yang L, Zhao N, Jardine MJ, et al. Effect of statin therapy on cardiovascular and renal outcomes in patients with chronic kidney disease: A systematic review and meta-analysis. *European Heart Journal*. 2013;**34**:1807-1817

22 Wanner C, Krane V, Marz W, Olschewski M, Mann JF, Ruf G, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *The New England Journal of Medicine*. 2005; **353**:238–248

23 Fellstrom BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *The New England Journal of Medicine*. 2009; **360**:1395–1407

24 Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *The New England Journal of Medicine*. 2001;**345**:861-869

25 Takahashi A, Takase H, Toriyama T, Sugiura T, Kurita Y, Ueda R, et al. Candesartan, an angiotensin ii type-1 receptor blocker, reduces cardiovascular events in patients on chronic haemodialysis--a randomized study. *Nephrology, Dialysis, Transplantation*. 2006;**21**:2507-2512

26 Zannad F, Kessler M, Lehert P, Grunfeld JP, Thuilliez C, Leizorovicz A, et al. Prevention of cardiovascular events in end-stage renal disease: Results of a randomized trial of fosinopril and implications for future studies. *Kidney International*. 2006;**70**:1318-1324

27 Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, et al. ESC guidelines on the management of stable coronary artery disease: The task force on the management of stable coronary artery disease of the european society of cardiology. *European Heart Journal*. 2013;**34**:2949-3003

28 Hemmelgarn BR, Southern D, Culleton BF, Mitchell LB, Knudtson ML, Ghali WA. Survival after coronary revascularization among patients with kidney disease. *Circulation*. 2004;**110**:1890-1895

29 Kumar N, Baker CS, Chan K, Duncan N, Malik I, Frankel A, et al. Cardiac survival after pre-emptive coronary angiography in transplant patients and those awaiting transplantation. *Clinical Journal of the American Society of Nephrology*. 2011;**6**:1912-1919

30 Herzog CA, Strief JW, Collins AJ, Gilbertson DT. Cause-specific mortality of dialysis patients after coronary revascularization: Why don't dialysis patients have better survival after coronary intervention? *Nephrology, Dialysis, Transplantation*. 2008;**23**:2629-2633

31 Cheung AK, Levin NW, Greene T, Agodoa L, Bailey J, Beck G, et al. Effects of high-flux hemodialysis on clinical outcomes: Results of the hemo study. *Journal of the American Society of Nephrology*. 2003;**14**:3251-3263

32 Culleton BF, Walsh M, Klarenbach SW, Mortis G, Scott-Douglas N, Quinn RR, et al. Effect of frequent nocturnal hemodialysis vs conventional hemodialysis on left ventricular mass and quality of life: A randomized controlled trial. *JAMA*. 2007;**298**:1291-1299

33 Group FHNT, Chertow GM, Levin NW, Beck GJ, Depner TA, Eggers PW, et al. In-center hemodialysis six times per week versus three times per week. *The New England Journal of Medicine*. 2010;**363**:2287-2300

34 Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA, 3rd, Freedman RA, Gettes LS, et al. American College of Cardiology/American Heart Association Task Force on Practice G, American Association for Thoracic S, Society of Thoracic S. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities. *Journal of the American College of Cardiology*. 2008;**51**:e1-62

35 Hess PL, Hellkamp AS, Peterson ED, Sanders GD, Al-Khalidi HR, Curtis LH, et al. Survival after primary prevention implantable cardioverter-defibrillator placement among patients with chronic kidney disease. *Circulation. Arrhythmia and Electrophysiology*. 2014;**7**:793-799

36 Sakhuja R, Keebler M, Lai TS, McLaughlin Gavin C, Thakur R, Bhatt DL. Meta-analysis of mortality in dialysis patients with an implantable cardioverter defibrillator. *The American Journal of Cardiology*. 2009;**103**:735-741

37 Makki N, Swaminathan PD, Hanmer J, Olshansky B. Do implantable cardioverter defibrillators improve survival in patients with chronic kidney disease at high risk of sudden cardiac death? A meta-analysis of observational studies. *Europace*. 2014;**16**:55-62

38 Goldenberg I, Vyas AK, Hall WJ, Moss AJ, Wang H, He H, et al. Risk stratification for primary implantation of a cardioverter-defibrillator in patients with ischemic left ventricular dysfunction. *Journal of the American College of Cardiology*. 2008;**51**:288-296

39 Borleffs CJ, van Welsenes GH, van Bommel RJ, van der Velde ET, Bax JJ, van Erven L, et al. Mortality risk score in primary prevention implantable cardioverter defibrillator recipients with non-ischaemic or ischaemic heart disease. *European Heart Journal*. 2010;**31**:712-718

40 Hager CS, Jain S, Blackwell J, Culp B, Song J, Chiles CD. Effect of renal function on survival after implantable cardioverter defibrillator placement. *The American Journal of Cardiology*. 2010;**106**:1297-1300

41 Chen TH, Wo HT, Chang PC, Wang CC, Wen MS, Chou CC. A meta-analysis of mortality in end-stage renal disease patients receiving implantable cardioverter defibrillators (icds). *PloS One*. 2014;**9**:e99418

42 Hreybe H, Ezzeddine R, Bedi M, Barrington W, Bazaz R, Ganz LI, et al. Renal insufficiency predicts the time to first appropriate defibrillator shock. *American Heart Journal*. 2006;**151**:852-856

43 Robin J, Weinberg K, Tiongson J, Carnethon M, Reddy M, Ciaccio C, et al. Renal dialysis as a risk factor for appropriate therapies and mortality in implantable cardioverter-defibrillator recipients. *Heart Rhythm*. 2006;**3**:1196-1201

44 Herzog CA, Li S, Weinhandl ED, Strief JW, Collins AJ, Gilbertson DT. Survival of dialysis patients after cardiac arrest and the impact of implantable cardioverter defibrillators. *Kidney International*. 2005;**68**:818-825

45 de Bie MK, Lekkerkerker JC, van Dam B, Gaasbeek A, van Buren M, Putter H, et al. Prevention of sudden cardiac death: Rationale and design of the implantable cardioverter defibrillators in dialysis patients (icd2) trial--a prospective pilot study. *Current Medical Research and Opinion*. 2008;**24**:2151-2157

46 Tompkins C, McLean R, Cheng A, Brinker JA, Marine JE, Nazarian S, et al. End-stage renal disease predicts complications in pacemaker and icd implants. *Journal of Cardiovascular Electrophysiology*. 2011;**22**:1099-1104

47 Lekkerkerker JC, van Nieuwkoop C, Trines SA, van der Bom JG, Bernards A, van de Velde ET, et al. Risk factors and time delay associated with cardiac device infections: Leiden device registry. *Heart*. 2009;**95**:715-720

48 Dasgupta A, Montalvo J, Medendorp S, Lloyd-Jones DM, Ghossein C, Goldberger J, et al. Increased complication rates of cardiac rhythm management devices in esrd patients. *American Journal of Kidney Diseases*. 2007;**49**:656-663