CHAPTER II

The Current Status of Interventions Aiming at Reducing Sudden Cardiac Death in Dialysis Patients.

Mihály K. de Bie, Bastiaan van Dam, André Gaasbeek, Marjolijn van Buren, Lieselot van Erven, Jeroen J. Bax, Martin J. Schalij, Ton J. Rabelink, J. Wouter Jukema

Eur Heart J. 2009 Jul;30(13):1559-64

ABSTRACT

Mortality in dialysis patients is extremely high, with an annual death rate of ~23%. Sudden cardiac death (SCD) is the single largest cause of death in dialysis patients accounting for ~60% of all cardiac deaths and 25% of all-cause mortality. Interventions aiming at reducing cardiovascular mortality, especially SCD, in dialysis patients are therefore extremely important and clinically highly relevant. The purpose of this review is to give an outline of the epidemiology of SCD in dialysis patients and to provide a comprehensive overview of several interventional strategies (medical therapies, changing dialysis modality, and revascularization). Furthermore, it will discuss the current knowledge regarding the value of preventive implantable cardioverter defibrillator implantation and address future implications of the interventional strategies mentioned

INTRODUCTION

Currently, ~350 000 people are treated with dialysis in the USA. It is estimated that this number will increase to >500 000 by the year 2020.[1] In Europe, the number of dialysis patients is also increasing annually.[2,3] The mortality in dialysis patients is very high with a mean death rate of ~23% per year. This rate is mainly influenced by age, with a yearly mortality of 4% in patients younger than 20 years rising to 35% in patients older than 65 years.[1] In dialysis patients, sudden cardiac death (SCD) is the major cause of death, accounting for ~25% of all-cause mortality.[4] The risk of SCD in dialysis patients is also strongly associated with patient age, with a 3-year probability of developing cardiac arrest of ~12% in patients younger than 20 years rising to ~34% in patients older than 75 years.[4] Because the increase in number of patients treated with dialysis for end-stage renal disease (ESRD) can mainly be attributed to older patients, the total burden of SCD is rapidly increasing.[1]

Given the high event rate of SCD in dialysis patients, identification of risk factors and finding preventive interventions seem highly desirable. The objective of this review is (i) to provide an outline of the epidemiology of SCD in this patient group and furthermore (ii) to provide a comprehensive overview regarding several preventive interventions aiming at reducing cardiovascular mortality. We will especially focus on SCD, since this is the single largest cause of death in this highly vulnerable patient group.

Epidemiology of sudden cardiac death in dialysis patients

Incidence

Approximately 60% of all cardiac deaths and 25% of all-cause mortality in patients on dialysis are due to SCD.[4] In several large survival trials with dialysis patients, such as the Hemodialysis (HEMO) study and the German Diabetes and Dialysis (4D) study, similar incidences for SCD were found.[5,6] These studies will be discussed in more detail later on. This high incidence may even be an underestimation as was demonstrated by Bleyer et al.[7] They reviewed death notification forms from 1995 to 2003, obtained from five US dialysis centres. According to an accepted definition of SCD, they found that in total 88 of 228 deaths (39%) could be classified as sudden. The patient's primary nephrologist had only classified 59 of these 88 deaths as sudden, i.e. 26% of all deaths. The remaining 29 sudden deaths were initially not classified as sudden, but as acute myocardial infarction (6 patients), atherosclerotic heart disease (4 patients), cardiomyopathy (3 patients), pulmonary oedema (2 patients), other (2 patients), valvular heart disease (1 patient), and unknown (11 patients).

Factors relating to sudden cardiac death

The mechanisms that underlie SCD in dialysis patients are complex and many factors are involved. In addition to the traditional risk factors associated with SCD in the general

population, such as ischaemic heart disease, there are several more specific factors and circumstances in dialysis patients which may contribute to the risk of SCD. These factors include: left ventricular hypertrophy (LVH), rapid electrolyte and fluid shifts in haemodialysis (HD) patients, and abnormalities in myocardial ultrastructure and function, including endothelial dysfunction, interstitial fibrosis and sympathetic overactivity.[8–12]

Peritoneal dialysis vs. haemodialysis

A recent study compared the survival of Dutch HD and peritoneal dialysis (PD) patients. A survival advantage for PD compared with HD was documented which decreased over time, with age and in the presence of diabetes mellitus as primary disease.[13] The initial advantage of PD compared with HD may be explained by the fact that PD patients have lower co-morbidity at initiation of dialysis therapy[14] and a better preservation of the remaining kidney function.[15] With regard to SCD, there is no apparent difference between PD and HD.[4]

Medical interventions

β-Blocker therapy

It has been documented that dialysis patients exhibit sustained activation of the sympathetic nervous system (SNS) and that the diseased kidneys themselves are the trigger of this overactivity.[16,17] This sympathetic nerve overactivity is associated with mortality and worse cardiovascular outcomes,[18] and it is likely that SCD in dialysis patients is associated with the overactivation of the SNS.[19]

β-Blocker therapy interferes with the deleterious actions of the SNS on cardiac endpoints[20] and is a well-established and evidence-based intervention in hypertension[21] and after myocardial infarcation.[22] In the general population, much of the benefit conferred by β-blocker therapy can be attributed to the prevention of SCD.[19,23]

A large observational study by Foley et al.[24] indicates that β-blocker therapy has a robust association with survival in dialysis patients. Despite this observation, only a few trials regarding β-blocker therapy in dialysis patients have been conducted so far. In a recent placebo-controlled trial in HD patients with dilated cardiomyopathy, Cice et al.[25] showed that carvedilol gave a significant reduction (52 vs. 73%) in mortality. With regard to SCD in dialysis patients, it has been documented that in HD patients, β-blocker use at the time of a cardiac arrest is associated with higher survival.[26]

Nevertheless, although a potential benefit of β-blocker therapy has been indicated, it has been documented that β-blocker therapy is used in <30% of patients on HD.[27] Furgeson and Chonchol[19] suggest four major reasons for this low utilization: (i) therapeutic nihilism for these chronically ill patients, (ii) the unconventional epidemiology of cardiovascular disease in this population, (iii) the paucity of efficacy data in patients with serum creatinine >177 μmol/mL (2 mg/dL), and (iv) the potential for higher rates of adverse effects, including hypotension, hyperkalaemia and glycaemic abnormalities. In their review, they conclude

that risks of dangerous side effects appear to be rare and manageable and that long-term clinical trials are desperately needed to evaluate the safety and efficacy of β-blockers in chronic dialysis patients.

When defining the role of β-blockers as a preventive intervention for SCD, it should also be considered that in several high-risk patient groups, prophylactic implantable cardioverter defibrillator (ICD) implantation has proven to be superior compared with β-blocker therapy.[28–32]

Statin therapy

Statin therapy safely reduces the 5-year incidence of major coronary events, coronary revascularization, and stroke in a wide range of individuals by reducing LDL cholesterol.[33] However, until recently, with regard to dialysis patients, only limited prospective data on the effectiveness of statin therapy were available. In 2005, the results of the German 4D study were published. The 4D study was the first prospective trial to evaluate the effectiveness of statins in 1255 patients receiving chronic HD with type II diabetes mellitus. This study showed that atorvastatin, despite its ability to lower LDL cholesterol, had no beneficial effect on cardiovascular death, non-fatal myocardial infarction, and stroke. It was, therefore, speculated by the investigators that the pathogenesis of vascular events in patients with diabetes mellitus who are receiving HD may, at least in part, be different from that in patients without ESRD.[6]

A recently published meta-analysis by Strippoli et al.[34] demonstrated that statins significantly reduce lipid concentrations and cardiovascular endpoints in patients with chronic kidney disease. A significant reduction of ~20% in the risk of cardiovascular mortality was documented, and in addition to this, compared with placebo, statin therapy also significantly decreased the risk of non-fatal cardiovascular events by ~20%. However, this meta-analysis also showed no benefit on all-cause mortality.

The specific effect of statins on SCD remains doubtful as the mechanisms involved may be less amenable to cholesterol lowering. This is confirmed by the fact that statin therapy had no effect on SCD in the 4D study[6] and in other statin trials in non-dialysis patient groups, such as in heart failure patients in the CORONA study.[35]

Erythropoietin therapy

A relationship between anaemia and the development of LVH in ESRD patients has been demonstrated.[36] Left ventricular hypertrophy is associated with a lower survival in ESRD patients[37] and especially the worsening of LVH, independent of left ventricular (LV) mass, is a strong predictor of SCD in this patient group.[38] Considering the relationship between LVH and anaemia and the strikingly high prevalence of LVH in dialysis patients,[39] a strong beneficial effect of restoring anaemia with erythropoietin could be anticipated. However, the optimal level of haemoglobin (Hb) correction with erythropoietin remains uncertain. Although several studies showed that complete correction of anaemia improved

several cardiovascular prognosis parameters in dialysis patients,[40] at this moment there is insufficient published literature to generalize the risks or benefits of Hb levels >7.2 mmol/L (120 g/L).[41,42]

It should also be taken in account that correction of anaemia with erythropoietin to higher Hb-levels may increase blood pressure, the risk of vascular access thrombosis, and may lead to an increased number of adverse cardiovascular events,[42] thus counterbalancing the potential positive effects. Considering the above, more information about the ideal Hb target level is needed and therefore only partial correction of anaemia by erythropoietin is nowadays recommended.[43]

Changing dialysis modality

Dialysis therapy itself is probably an important risk factor for SCD. For instance, it has been observed that SCD is temporally related to the HD procedure[7] and several treatment-related factors, such as dialysis dose and the size of molecules that are removed, are implicated in mortality and morbidity among patients undergoing HD.[44,45] The fact that dialysis should be considered pro-arrhythmic is supported to a certain extent by the significant decline of SCD rate after renal transplantation.[4] Considering these observations, interventions aiming at altering the dialysis therapy may prove to be useful in reducing all-cause and cardiovascular mortality. In the last decade, many studies have been conducted in order to evaluate the effect of different alterations in dialysis therapy on mortality and cardiovascular morbidity. With regard to these alterations in dialysis therapy, changing dialysis dose, haemodiafiltration, and increasing dialysis frequency will be discussed below.

Changing the dialysis dose

Several observational studies reported significant mortality reductions in patients treated with a higher dialysis dose compared with a control group receiving standard dialysis dose.[46,47] The HEMO study was the first randomized controlled trial designed to evaluate the effect of the dialysis dose on all-cause mortality and cardiovascular mortality. In this study, 1846 patients were randomized to receive either a standard dose (urea eKt/V 1.05) or high dose (urea eKt/V 1.45) and either a low-flux or high-flux dialyzer in a 2 × 2 factorial design with equal allocation. The results of the low- vs. high-flux dialyzer will be discussed in the next paragraph. No significant difference was observed between the standard dose vs. the high-dose group in all-cause or cardiovascular mortality.[5] More recent observational data consisting of large study cohorts (n > 4000), however, indicate that dialysis dose and session length are associated with mortality risk.[48,49] Therefore, the debate regarding the optimal dialysis dose and session length remains ongoing.

Haemodiafiltration

Haemodiafiltration and high-flux HD, which is considered a form of haemodiafiltration, are

treatment modalities which not only remove small molecules (<5 kDa) but are also capable of obtaining considerable clearance of middle molecular weight substances (5–50 kDa).[50] Middle molecular weight molecules include markers of inflammation, complement factor D, and other molecules that might be relevant in the pathogenesis of cardiovascular morbidity and mortality.[51]

Although large observational data indicate a significant reduction in mortality when comparing haemodiafiltration with low-flux HD,[52] until now this has not been confirmed by randomized controlled trials. The earlier mentioned HEMO study, which also compared low-flux HD with high-flux HD, showed that in the high-flux group, there was an 8% reduction of all-cause mortality. This was, however, not statistically significant. Also a 20% reduction in cardiac death was documented, which was not statistically significant after adjustment for the multiple comparisons performed. It is therefore concluded that the overall pattern is consistent with a possible benefit for high-flux dialysis, which was too small to be detected given the power of the study.[53] At this moment, several trials are ongoing which will further evaluate the value of haemodiafiltration with mortality and cardiovascular morbidity and mortality as primary or secondary outcome.[54]

Increasing dialysis frequency

Already in 1969, it was documented that daily dialysis improved several clinical outcome parameters in a selected patient group.[55] However, at this moment, the majority of the HD patients depend on two to three dialysis sessions a week. Considering the potential benefit of a higher frequency, several possibilities have been proposed to increase the frequency of dialysis therapy. These include frequent nocturnal HD and short daily HD.

A recently published trial that compared the effects of frequent nocturnal HD vs. conventional HD on change in LV mass and health-related quality of life over 6 months showed promising results. Fifty-two patients were randomized in a 1:1 fashion to nocturnal HD or conventional HD. There was a regression in LV mass in the treatment group, whereas there was an increase in LV mass in the control group. This difference was statistically significant. Also a statistically significant improvement in some measures of mineral metabolism and selected measures of quality of life in the treatment group was documented.[56]

Promising results have also been reported regarding short daily HD. A recently published observational study showed that survival in 416 patients (52 ± 15 years) on short daily HD (frequency 5.8 ± 0.5 times weekly, duration 136 ± 35 min) was two to three times better than that of matched three times weekly HD patients reported by the United States Renal Data System (USRDS). The 5-year cumulative survival was 68 ± 4.1%.[57]

Although the results for both nocturnal HD and short daily HD are indeed promising, prospective data on significant changes in all-cause and/or cardiovascular mortality are lacking at this moment. Adequately powered trials with hard endpoints are therefore warranted to define the role of these treatment modalities.

Revascularization

In the general population, coronary artery disease (CAD) is present in ~80% of the patients suffering from SCD.[58] The HEMO investigators pointed out that CAD was the largest contributor to SCD also in dialysis patients.[59,60] The prevalence of CAD in dialysis patients is ~40%.[61] However, despite the high prevalence of CAD in this highly vulnerable patient group, the utilization of invasive cardiac procedures in dialysis patients is clearly underused. For instance, the use of both diagnostic angiography and revascularization after MI is significantly lower in dialysis patients compared with patients with normal renal function.[62] The underutilization of these therapies may be a reflection of 'therapeutic nihilism'. Another explanation is the lack of evidence of benefit in this patient group due to the exclusion of dialysis patients in most clinical trials.

In a recent observational study, Hemmelgarn et al.[63] compared patients receiving CABG, PCI, or no revascularization after coronary angiography and found that in dialysis patients, survival was significantly higher after CABG or PCI compared with no revascularization. However, in a population of dialysis patients with ischaemic heart disease, treated with optimal surgical coronary revascularization, Herzog et al.[64] found that the probability of all-cause mortality and arrhythmically mediated death was not lower than that reported for the entire US dialysis population. They documented that, in 2002, the 2-year probability of all-cause death was 40% and the probability of SCD was 14% in prevalent US dialysis patients. In US dialysis patients receiving CABG, they found a 2-year all-cause mortality of 43% and a mortality attributed to arrhythmic mechanisms of 14%. These data do not suggest that coronary revascularization in dialysis patients is not efficacious, rather it is proposed that coronary revascularization may be a particularly incomplete therapy for cardiac disease in ESRD patients and that additional treatment strategies targeting the 'non-ischaemic' contributors to SCD may be necessary, as a large untreated hazard of arrhythmic death may remain despite revascularization.

Implantable cardioverter defibrillator therapy

Several trials in multiple patient groups have shown that ICD therapy is superior to medical therapy in primary and secondary prevention for all-cause mortality, almost exclusively by reducing SCD.[28–32] Almost all ICD trials, however, excluded dialysis patients or did not publish subgroup analyses on this group of patients. Thus, only very limited literature is available with regard to ICD therapy in dialysis patients.

The few studies that evaluated the benefit of ICD therapy in dialysis patients, however, seem to indicate a possible benefit: Herzog et al.[65] documented that after aborted cardiac arrest, ICD therapy was associated with a 42% reduction in death risk in dialysis patients, Hreybe et al.[66] found that renal insufficiency is a strong predictor for appropriate ICD shocks and that the incidence of appropriate shocks in HD patients at 1 year is significantly higher

when compared with non-dialysis patients and Robin et al.[67] concluded that ESRD is the greatest predictor for ICD therapies.
Despite these observations, ICD therapy in dialysis patients is probably underutilized. Only 8% of the dialysis patients who survived a cardiac arrest episode receive prophylactic ICD implantation in the USA.[65] This underutilization may be due to several concerns regarding prophylactic ICD implantation in this patient group. An important concern regards the effectiveness of prophylactic ICD implantation. In previous ICD studies, survival was reduced in the ESRD population compared with patients with a normal renal function.[67,68] One explanation is the possibility that, in dialysis patients, ventricular arrhythmias are intermittently refractory to ICD therapies because of metabolic derangements.[68] However, SCD rates in dialysis patients with an ICD have never been assessed. Another explanation is that co-morbidities in ESRD patients meeting current implantation indications may reduce the survival benefit of ICD placements in this population. Also an important concern regarding ICD therapy is that patients with ESRD may have higher rates of cardiac device-related complications, potentially offsetting some benefits of prophylactic ICD therapy. Dasgupta et al.[69] found that dialysis patients indeed had higher complication rates from cardiac device implantation, such as infection and bleeding, but these complications did not result in death.
Considering these possible benefits and risks, further studies are required to assess the potential impact of ICD therapy in dialysis patients. We recently started such a study, the Implantable Cardioverter Defibrillator in Dialysis patients (ICD2) study, which will prospectively evaluate the impact of ICD therapy on SCD in dialysis patients. In addition to that, it will also focus on the feasibility of a larger trial which could evaluate the effect on all-cause mortality.[70]

CONCLUSIONS

The number of prevalent dialysis patients is annually increasing worldwide. Mortality rates among these patients are extremely high, with SCD being the largest contributor to death in this patient group. Interventions aiming at reducing SCD in dialysis patients are therefore very desirable. In the past decade, several interventional methods have been investigated. These methods included medical interventions (β-blockers, statins, and erythropoietin), altering dialysis therapy and revascularization.
Although some observational studies indicate potential survival benefit of the mentioned interventional methods, at this moment prospective data to confirm this benefit are lacking and more adequately powered prospective trials are warranted. With specific regard to their benefit in reducing SCD, the role of these interventional methods remains doubtful. For instance, important trials such as the 4D study did not find a significant reduction in SCD in the treatment arm of their study cohort and it has been observed that after optimal revascularization therapy in dialysis patients with ischaemic heart disease, SCD rates are

similar when compared with the general dialysis population.
Prophylactic ICD implantation has become an important preventive intervention for SCD over the past decades. Because prophylactic ICD implantation is effective for prevention of SCD in several high-risk patient groups, it is hypothesized that this may also be valuable in preventing SCD in dialysis patients. This potential benefit of prophylactic ICD implantation was confirmed by several observational studies. However, this has not yet been evaluated prospectively in dialysis patients and therefore a prospective trial is warranted to define the value of prophylactic ICD implantation in this highly vulnerable patient group. The ICD2 study will be the first prospective randomized study that will evaluate the effects of prophylactic ICD implantation in dialysis patients.

REFERENCE LIST

1. U.S. Renal Data System, USRDS 2007 Annual Data Report: *Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Insitute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD. 2007*.
2. Ansell D., Feehally J., Feest T.G., Tomson C., Williams A.J., Warwick G. UK Renal Registry Report 2007. *UK Renal Registry, Bristol, UK . 2007*.
3. Oppe M, Treur M.J., Barendregt W, de Charro FT. Statistisch Verslag 2007 deel 1. *Stichting RENINE: Rotterdam. 2007*.
4. U.S. Renal Data System, USRDS 2006 Annual Data Report: *Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Insitute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD. 2006*.
5. Eknoyan G, Beck GJ, Cheung AK, Daugirdas JT, Greene T, Kusek JW et al. Effect of dialysis dose and membrane flux in maintenance hemodialysis. *N Engl J Med 2002;347(25):2010-9*.
6. Wanner C, Krane V, Marz W, Olschewski M, Mann JF, Ruf G et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med 2005;353(3):238-48*.
7. 7Bleyer AJ, Hartman J, Brannon PC, Reeves-Daniel A, Satko SG, Russell G. Characteristics of sudden death in hemodialysis patients. *Kidney Int 2006;69(12):2268-73*.
8. Ritz E, Amann K, Tornig J, Schwarz U, Stein G. Some cardiac abnormalities in renal failure. *Adv Nephrol Necker Hosp 1997;27:85-103*.
9. Amann K, Buzello M, Simonaviciene A, Miltenberger-Miltenyi G, Koch A, Nabokov A et al. Capillary/myocyte mismatch in the heart in renal failure--a role for erythropoietin? *Nephrol Dial Transplant 2000;15(7):964-9*.
10. Amann K, Rychlik I, Miltenberger-Milteny G, Ritz E. Left ventricular hypertrophy in renal failure. *Kidney Int Suppl 1998;68:S78-S85*.
11. Amann K, Ritz E. Cardiac disease in chronic uremia: pathophysiology. *Adv Ren Replace Ther 1997;4(3):212-24*.
12. Nishimura M, Tokoro T, Nishida M, Hashimoto T, Kobayashi H, Yamazaki S et al. Sympathetic overactivity and sudden cardiac death among hemodialysis patients with left ventricular hypertrophy. *Int J Cardiol 2009*.
13. Liem YS, Wong JB, Hunink MG, de Charro FT, Winkelmayer WC. Comparison of hemodialysis and peritoneal dialysis survival in The Netherlands. *Kidney Int 2007;71(2):153-8*.
14. Collins AJ, Weinhandl E, Snyder JJ, Chen SC, Gilbertson D. Comparison and survival of hemodialysis and peritoneal dialysis in the elderly. *Semin Dial 2002;15(2):98-102*.
15. Jansen MA, Hart AA, Korevaar JC, Dekker FW, Boeschoten EW, Krediet RT. Predictors of the rate of decline of residual renal function in incident dialysis patients. *Kidney Int 2002;62(3):1046-53*.
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. *N Engl J Med 1992;327(27):1912-8*.
17. Ye S, Gamburd M, Mozayeni P, Koss M, Campese VM. A limited renal injury may cause a permanent form of neurogenic hypertension. *Am J Hypertens 1998;11(6 Pt 1):723-8*.
18. 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(11):1354-9*.
19. Furgeson SB, Chonchol M. Beta-blockade in chronic dialysis patients. Semin Dial 2008;21(1):43-8.
20. Zuanetti G, Maggioni AP, Keane W, Ritz E. Nephrologists neglect administration of betablockers to dialysed diabetic patients. *Nephrol Dial Transplant 1997;12(12):2497-500*.
21. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jr. et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA 2003;289(19):2560-72*.
22. Van de WF, Bax J, Betriu A, Blomstrom-Lundqvist C, Crea F, Falk V et al. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. *Eur Heart J 2008;29(23):2909-45*.
23. Goldstein S, Hjalmarson A. The mortality effect of metoprolol CR/XL in patients with heart failure: results of the MERIT-HF Trial. Clin Cardiol 1999;22 Suppl 5:V30-V35.
24. Foley RN, Herzog CA, Collins AJ. Blood pressure and long-term mortality in United States hemodialysis patients: USRDS Waves 3 and 4 Study. *Kidney Int 2002;62(5):1784-90*.
25. Cice G, Ferrara L, D'Andrea A, D'Isa S, Di BA, Cittadini A et al. Carvedilol increases two-year survivalin dialysis patients with dilated cardiomyopathy: a prospective, placebo-controlled trial. *J Am Coll Cardiol*

2003;41(9):1438-44.
26. Pun PH, Lehrich RW, Smith SR, Middleton JP. Predictors of survival after cardiac arrest in outpatient hemodialysis clinics. *Clin J Am Soc Nephrol 2007;2(3):491-500.*
27. Abbott KC, Trespalacios FC, Agodoa LY, Taylor AJ, Bakris GL. beta-Blocker use in long-term dialysis patients: association with hospitalized heart failure and mortality. *Arch Intern Med 2004;164(22):2465-71.*
28. Connolly SJ, Hallstrom AP, Cappato R, Schron EB, Kuck KH, Zipes DP et al. Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. AVID, CASH and CIDS studies. Antiarrhythmics vs Implantable Defibrillator study. Cardiac Arrest Study Hamburg . Canadian Implantable Defibrillator Study. *Eur Heart J 2000;21(24):2071-8.*
29. Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. *N Engl J Med 1996;335(26):1933-40.*
30. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med 2002;346(12):877-83.*
31. Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G. A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators. *N Engl J Med 1999;341(25):1882-90.*
32. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med 2005;352(3):225-37.*
33. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet 2005;366(9493):1267-78.*
34. Strippoli GF, Navaneethan SD, Johnson DW, Perkovic V, Pellegrini F, Nicolucci A et al. Effects of statins in patients with chronic kidney disease: meta-analysis and meta-regression of randomised controlled trials. *BMJ 2008;336(7645):645-51.*
35. Kjekshus J, Apetrei E, Barrios V, Bohm M, Cleland JG, Cornel JH et al. Rosuvastatin in older patients with systolic heart failure. *N Engl J Med 2007;357(22):2248-61.*
36. Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barre PE. The impact of anemia on cardiomyopathy, morbidity, and and mortality in end-stage renal disease. *Am J Kidney Dis 1996;28(1):53-61.*
37. Silberberg JS, Barre PE, Prichard SS, Sniderman AD. Impact of left ventricular hypertrophy on survival in end-stage renal disease. *Kidney Int 1989;36(2):286-90.*
38. Paoletti E, Specchia C, Di MG, 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. *Nephrol Dial Transplant 2004;19(7):1829-34.*
39. Foley RN, Parfrey PS, Harnett JD, Kent GM, Martin CJ, Murray DC et al. Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. *Kidney Int 1995;47(1):186-92.*
40. Frank H, Heusser K, Hoffken B, Huber P, Schmieder RE, Schobel HP. Effect of erythropoietin on cardiovascular prognosis parameters in hemodialysis patients. *Kidney Int 2004;66(2):832-40.*
41. Volkova N, Arab L. Evidence-based systematic literature review of hemoglobin/hematocrit and all-cause mortality in dialysis patients. *Am J Kidney Dis 2006;47(1):24-36.*
42. Strippoli GF, Navaneethan SD, Craig JC. Haemoglobin and haematocrit targets for the anaemia of chronic kidney disease. *Cochrane Database Syst Rev 2006;(4):CD003967.*
43. KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease. *Am J Kidney Dis 2007;49(2 Suppl 2):S12-154.*
44. Owen WF, Jr., Lew NL, Liu Y, Lowrie EG, Lazarus JM. The urea reduction ratio and serum albumin concentration as predictors of mortality in patients undergoing hemodialysis. *N Engl J Med 1993;329(14):1001-6.*
45. Leypoldt JK, Cheung AK, Carroll CE, Stannard DC, Pereira BJ, Agodoa LY et al. Effect of dialysis membranes and middle molecule removal on chronic hemodialysis patient survival. *Am J Kidney Dis 1999;33(2):349-55.*
46. Port FK, Ashby VB, Dhingra RK, Roys EC, Wolfe RA. Dialysis dose and body mass index are strongly associated with survival in hemodialysis patients. *J Am Soc Nephrol 2002;13(4):1061-6.*
47. Held PJ, Port FK, Wolfe RA, Stannard DC, Carroll CE, Daugirdas JT et al. The dose of hemodialysis and patient mortality. *Kidney Int 1996;50(2):550-6.*
48. Saran R, Bragg-Gresham JL, Levin NW, Twardowski ZJ, Wizemann V, Saito A et al. Longer treatment time and slower ultrafiltration in hemodialysis: associations with reduced mortality in the DOPPS. *Kidney Int 2006;69(7):1222-8.*

49. Marshall MR, Byrne BG, Kerr PG, McDonald SP. Associations of hemodialysis dose and session length with mortality risk in Australian and New Zealand patients. *Kidney Int 2006;69(7):1229-36.*
50. Leypoldt JK. Solute fluxes in different treatment modalities. *Nephrol Dial Transplant 2000;15 Suppl 1:3-9.*
51. Vanholder R, De SR, Glorieux G, Argiles A, Baurmeister U, Brunet P et al. Review on uremic toxins: classification, concentration, and interindividual variability. *Kidney Int 2003;63(5):1934-43.*
52. Canaud B, Bragg-Gresham JL, Marshall MR, Desmeules S, Gillespie BW, Depner T et al. Mortality risk for patients receiving hemodiafiltration versus hemodialysis: European results from the DOPPS. *Kidney Int 2006;69(11):2087-93.*
53. 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. *J Am Soc Nephrol 2003;14(12):3251-63.*
54. van der Weerd NC, Penne EL, van den Dorpel MA, Grooteman MP, Nube MJ, Bots ML et al. Haemodiafiltration: promise for the future? *Nephrol Dial Transplant 2008;23(2):438-43.*
55. DePalma JR, Pecker EA, Gordon A, Maxwell MH. A new compact automatic home hemodialysis system. *Trans Am Soc Artif Intern Organs 1968;14:152-9.*
56. 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(11):1291-9.*
57. Kjellstrand CM, Buoncristiani U, Ting G, Traeger J, Piccoli GB, Sibai-Galland R et al. Short daily haemodialysis: survival in 415 patients treated for 1006 patient-years. *Nephrol Dial Transplant 2008.*
58. Myerburg R.J., Castellanos A. Cardiac arrest and sudden death In: *Braunwald E, ed. Heart Disease: A textbook of Cardiovascular Medicine. Philadelphia, Pa: WB Saunders; 1997:742-779. 1997.*
59. Rocco MV, Yan G, Gassman J, Lewis JB, Ornt D, Weiss B et al. Comparison of causes of death using HEMO Study and HCFA end-stage renal disease death notification classification systems. The National Institutes of Health-funded Hemodialysis. Health Care Financing Administration. *Am J Kidney Dis 2002;39(1):146-53.*
60. 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 Int 2004;65(6):2380-9.*
61. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis 1998;32(5 Suppl 3):S112-S119.*
62. Charytan D, Mauri L, Agarwal A, Servoss S, Scirica B, Kuntz RE. The use of invasive cardiac procedures after acute myocardial infarction in long-term dialysis patients. *Am Heart J 2006;152(3):558-64.*
63. Hemmelgarn BR, Southern D, Culleton BF, Mitchell LB, Knudtson ML, Ghali WA. Survival after coronary revascularization among patients with kidney disease. *Circulation 2004;110(14):1890-5.*
64. 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? *Nephrol Dial Transplant 2008.*
65. 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 Int 2005;68(2):818-25.*
66. Hreybe H, Ezzeddine R, Bedi M, Barrington W, Bazaz R, Ganz LI et al. Renal insufficiency predicts the time to first appropriate defibrillator shock. *Am Heart J 2006;151(4):852-6.*
67. 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(10):1196-201.*
68. Wase A, Basit A, Nazir R, Jamal A, Shah S, Khan T et al. Impact of chronic kidney disease upon survival among implantable cardioverter-defibrillator recipients. *J Interv Card Electrophysiol 2004;11(3):199-204.*
69. 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. *Am J Kidney Dis 2007;49(5):656-63.*
70. 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. *Curr Med Res Opin 2008;24(8):2151-7.*