

ARTICOLI ORIGINALI

Penultimate Pulse Wave Velocity Prognosticates Mortality in ESRD patients



Macaulay Onuigbo^{1,2}, Nnonyelum Onuigbo³, Antonio Bellasi⁴, Domenico Russo⁵, Biagio Raffaele Di Iorio⁶

(1) College of Medicine, Mayo Clinic, Rochester, MN, USA

(2) Department of Nephrology, Mayo Clinic Health System, Eau Claire, WI, USA

(3) NTEC Solution LLC, Eau Claire, WI, USA

(4) Nefrologia, "S. Anna" Hospital, Como, Italia

(5) Nefrologia, Università "Federico II", Napoli, Italia

(6) Nefrologia, Ospedale "A. Landolfi", Solofra (AV), Italia

Per un disguido tecnico non è ancora disponibile la versione in italiano.
Appena disponibile l'articolo verrà aggiornato.

Abstract

Background: Cardiac disease remains the major cause of death among ESRD patients. Indeed, the risk of cardiovascular events in ESRD is reported to be at least 3.4 fold higher than that of the general population. Moreover, annual mortality rates among ESRD patients on hemodialysis approximate 20%, with cardiovascular disease accounting for almost half of this mortality profile. Despite this knowledge, so far we have been unable to identify treatable pathogenetic factors among ESRD patients to help reverse these poor cardiovascular outcomes. The difficulty to prognosticate cardiovascular mortality in ESRD remains elusive. However, in 2011, our group, for the first time, had demonstrated that cyclic variations of arterial stiffness as measured by pulse wave velocity (PWV) before and after hemodialysis determined mortality differences within an ESRD cohort. We have therefore examined the impact of individual patient-level translational PWV changes over time on mortality outcomes in an Italian ESRD cohort.

Study design and setting: Prospective observational study, 2007–2010, in an Italian ESRD cohort who underwent in-center outpatient conventional thrice weekly hemodialysis.

Methods: PWV was measured by the foot-to-foot method and repeated after six months. Coronary artery calcification (CAC) was measured at 0, 12 and 24 months. Routine clinical data and patient demographics were recorded and mortality outcomes were analyzed.

Results: Between 2007 and 2010, 466 Italian ESRD patients, 229 males and 237 females, age 19–97 (65.6) years, were followed up for 28.9 months. 128 patients (74M:54F) died. The major causes of death were acute myocardial infarction (AMI) in 47 (37%) patients (age 70, 26M:21F) and sudden death (SD) in 29 (23%) patients (age 72, 19M:10F). Paired PWV data was available in 308 surviving patients and in 106 patients who died. Baseline PWV was lower in surviving vs dead patients – 8.46 +/- 1.8 vs 9.43 +/- 3.75 (p=0.0005). Repeat PWV values were unchanged in the 308 survivors (8.46 +/- 1.8 vs 8.53 +/- 1.85, p=0.5, NS). Repeat PWV values increased in the 106 patients who died from 9.43 +/- 3.75 to 12.11 +/- 4.18 (p<0.0001). Of the 29 patients who died from SD, death occurred <12 hours after the last dialysis (ATLD) in 7, >24 hours ATLD in 20 and >48 hours ATLD in 17. Of the 47 patients who died from AMI, 6 died <12 hours ATLD, 35 died >24 hours ATLD and 23 died >48 hours ATLD. Of the 14 ESRD patients in the cohort that died from hyperkalemia, 3 died <12 hours ATLD, 11 died >24 hours ATLD, and 7 died >48 hours ATLD. CAC data scatter did

not allow for adequate statistical subgroup analysis but overall, baseline CAC values were higher in the AMI/SD dead patients vs surviving patients.

Conclusions: This is the first report to show a scalable and direct relationship between translational follow up PWV changes after six months versus observed cardiovascular mortality in an ESRD cohort. We have shown, for the first time, that penultimate PWV, better than baseline PWV, predicted cardiovascular mortality in this ESRD cohort. Moreover, higher proportions of the ESRD deaths from AMI, SD and hyperkalemia occurred during the long inter-dialytic (weekend) period when ESRD patients went for 3 days without hemodialysis. We propose that PWV be monitored among all new ESRD patients, and be repeated after six months of initiation of chronic hemodialysis. Our group had earlier demonstrated in 2012 that daily dialysis reduced PWV in chronic hemodialysis patients. From these study findings, we have proposed that ESRD patients who exhibit elevated initial PWV values, or more so, ESRD patients who demonstrate accelerated PWV values after six months on maintenance chronic hemodialysis should be converted to daily hemodialysis protocol. Furthermore, such patients may require more intense cardiovascular analysis by cardiologists. Further research into new preventative or therapeutic options in this area of ESRD care is warranted.

Key words: ESRD

Introduction

It is commonly acknowledged that the risk of cardiovascular events in ESRD patients is at least 3.4 fold higher than that of the general population [1] (full text). Besides, annual mortality rates among ESRD patients on hemodialysis approximate 20%, with cardiovascular disease accounting for almost half of this increased mortality risk [2], [3], [4], [5], [6], [7]. What's more, patients with ESRD have a 10- to 20-fold increased risk of CV events as compared to age-matched subjects with normal renal function [2], [4], [5]. Indeed, this excess cardiovascular mortality risk among ESRD patients is even higher when left ventricular hypertrophy is present [3]. Despite this common knowledge, so far we as physicians in general and nephrologists in particular, have been unable to identify any treatable pathogenetic factors among ESRD patients to help reverse these unfortunate cardiovascular outcomes [8]. The difficulty to prognosticate cardiovascular outcomes in ESRD appears elusive and calls for more research [8].

Nevertheless, in 2011, our group had demonstrated, for the first time, that cyclic pulse wave velocity (PWV) variations, a measure of arterial stiffness, recorded before and after dialysis, predicted mortality differences in patients with ESRD who received conventional intermittent thrice weekly maintenance hemodialysis [9]. Furthermore, our group had also demonstrated in 2012 that daily dialysis reduced PWV in chronic hemodialysis patients [10].

We therefore completed a prospective mortality outcomes analysis of the impact of translational changes of PWV measured at 0 and 6 months after initiation of chronic hemodialysis, as well as the impacts of changes in coronary artery calcification (CAC) measured at 0, 12 and 24 months, in an Italian ESRD cohort, who dialyzed three hemodialysis sessions of 4 hours per week.

Study design and setting

Prospective observational study, 2007-2010, in an Italian ESRD cohort who underwent in-center outpatient conventional intermittent thrice weekly hemodialysis.

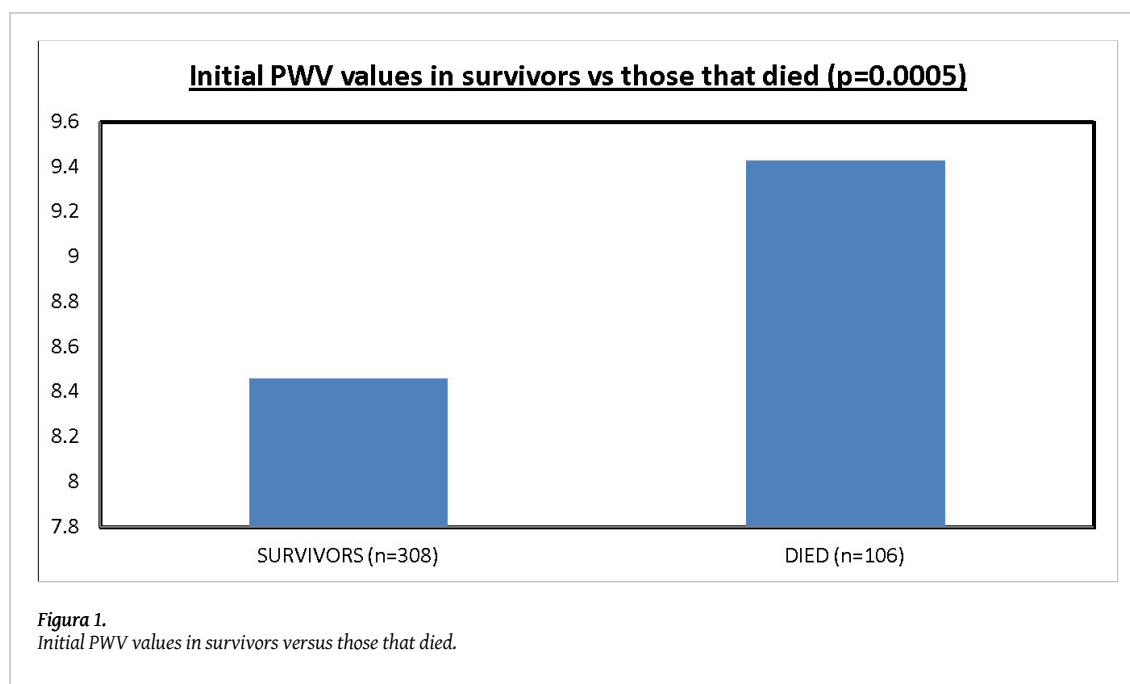
Methods

PWV was measured by the foot-to-foot method and repeated after six months. Coronary artery calcification (CAC) was measured at 0, 12 and 24 months. Routine clinical data and patient demographics were recorded and mortality outcomes were analyzed.

Results

Between 2007 and 2010, 466 Italian ESRD patients, 229 males and 237 females, age 19-97 (65.6) years, were followed up for 28.9 months. 128 patients (74M:54F) died during this period of observation. The major causes of death were acute myocardial infarction (AMI) in 47 (37%) patients (age 70, 26M:21F) and sudden death (SD) in 29 (23%) patients (age 72, 19M:10F). Other causes of death included stroke in 14 patients, hyperkalemia in another 14 patients, malignancy in 7 patients, cachexia in 5 patients, acute lung disease in 2 patients, and arrhythmia in 1 patient. Paired PWV data was available in 308 surviving patients and in 106 patients who died. Baseline PWV was lower in surviving vs dead patients – 8.46 +/- 1.8 vs 9.43 +/- 3.75 (p=0.0005) (Figura 1). Repeat PWV values were unchanged in 308 survivors (8.46 +/- 1.8 vs 8.53 +/- 1.85, p=0.5, NS) (Figura 2). Repeat PWV values increased in the 106 patients who died from 9.43 +/- 3.75 to 12.11 +/- 4.18 (p<0.0001) (Figura 2). Of the 29 patients who died from SD, death occurred <12 hours after the last dialysis in 7 patients, >24 hours after the last dialysis in 20 patients and >48 hours after the last dialysis in 17 patients (Figura 3). Of the 47 ESRD patients who died from acute myocardial infarction, 6 died <12 hours after the last dialysis, 35 died >24 hours after the last dialysis, and 23 died >48 hours after the last dialysis (Figura 4). Of the 14 ESRD patients in the cohort that died from hyperkalemia, 3 died <12 hours after the last dialysis, 11 died >24 hours after the last dialysis, and 7 died >48 hours after the last dialysis (Figura 5). Coronary artery calcification data scatter did not allow for adequate statistical analysis but baseline coronary artery calcification values were higher in the acute myocardial infarction and sudden death patients versus the other surviving patients.

Discussion



In this prospective observational study of this large Italian ESRD cohort, followed for over two years, we have demonstrated a scalable and direct relationship between translational follow up changes in PWV, as repeated after six months versus observed cardiovascular mortality in an Italian ESRD cohort of 466 patients. We have shown, for the first time, that penultimate PWV, better than baseline PWV, predicted cardiovascular mortality in this ESRD cohort. Moreover, a higher proportion of the ESRD deaths that resulted from acute myocardial infarction, sudden death and from hyperkalemia, all increasingly occurred during the long inter-dialytic (weekend) period when patients went for about 3 days without hemodialysis treatment.

Foley et al studied 32,065 participants in the End-Stage Renal Disease Clinical Performance Measures Project, a nationally representative sample of U.S. patients receiving hemodialysis three times weekly, at the end of calendar years 2004 through 2007 [11] (full text). Foley et al demonstrated that the long inter-dialytic interval on weekends experienced by ESRD patients who carry out in-center outpatient conventional thrice weekly chronic hemodia-

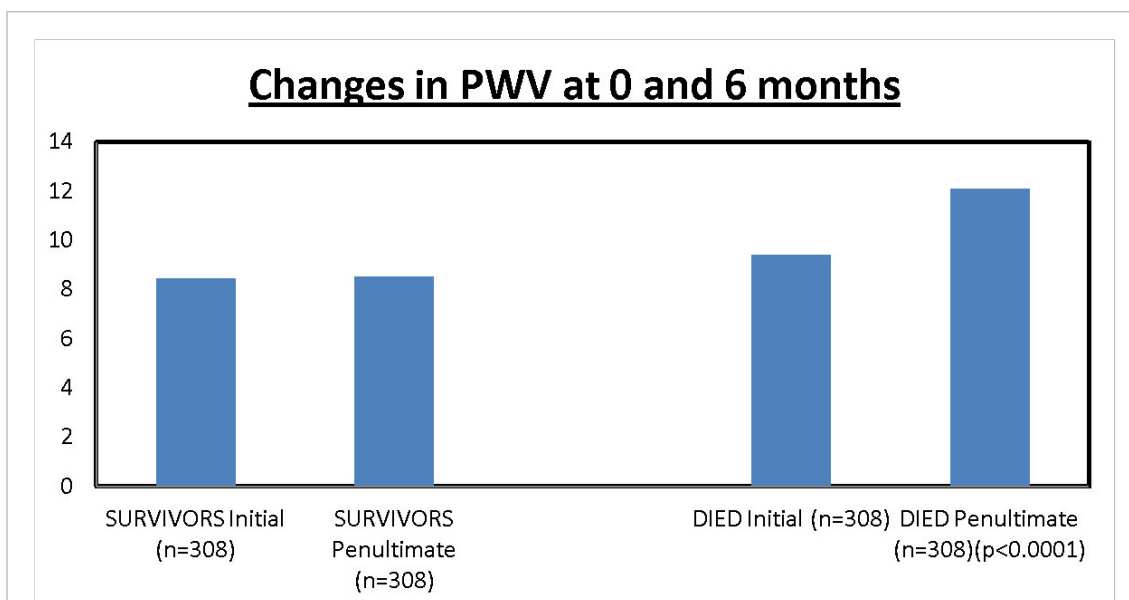


Figura 2.
Translational changes in PWV at 0 and 6 months among survivors and those that died.

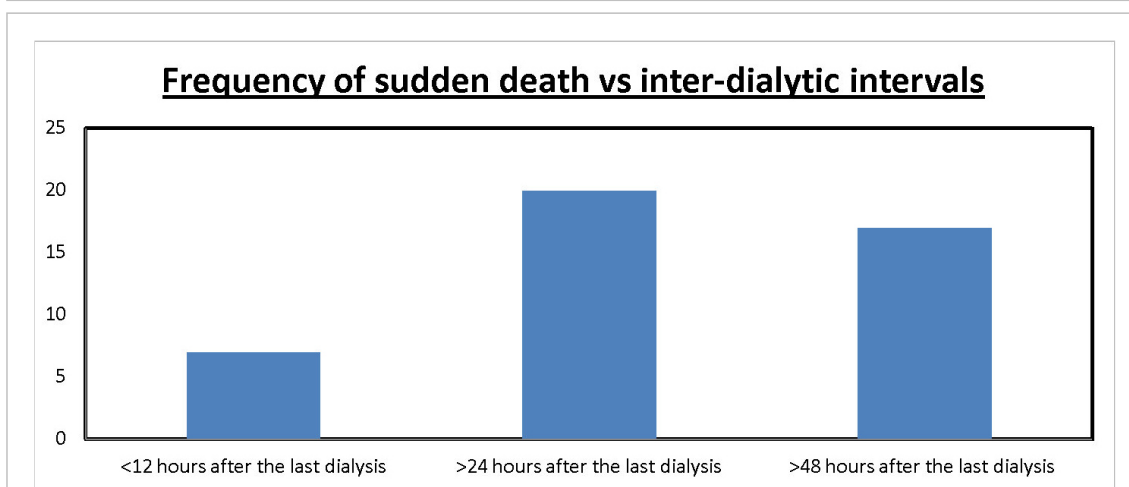
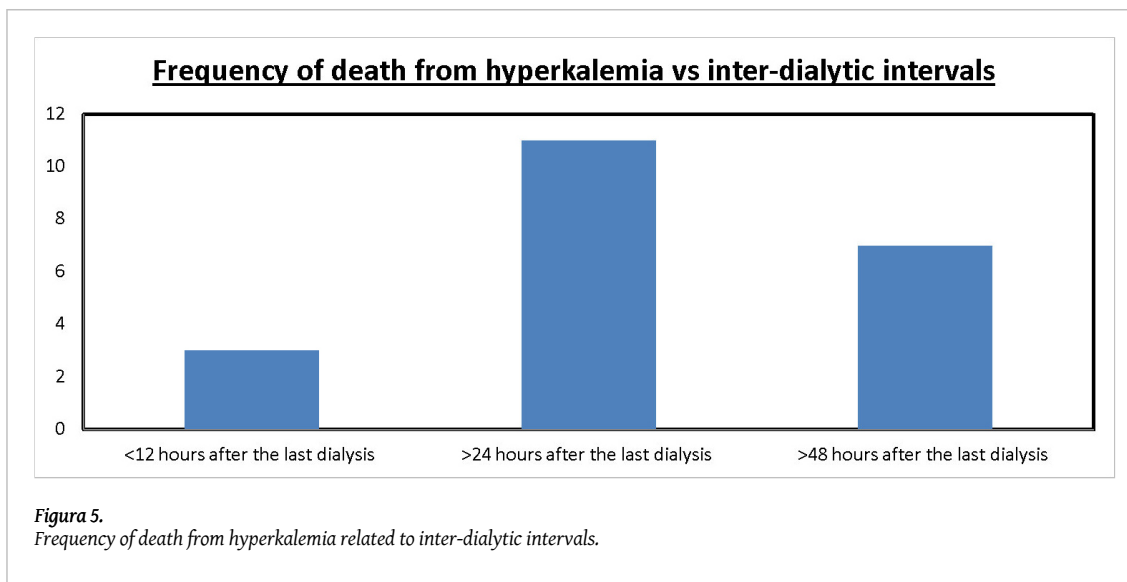
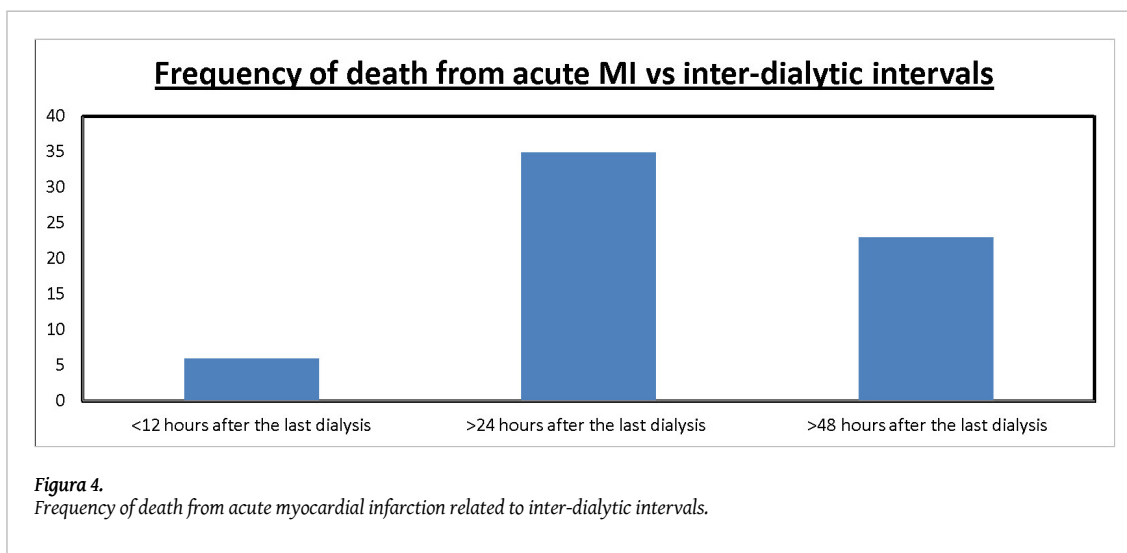


Figura 3.
Frequency of death from sudden death related to inter-dialytic intervals.

lysis is associated with increased all-cause mortality, higher mortality from cardiac causes, higher hospital admission rates, increased stroke incidence and dysrhythmia [11] (full text). The results of our study which showed a correlation between longer inter-dialytic intervals and ESRD deaths from acute myocardial infarction, sudden death and hyperkalemia only further strengthen these observations (Figures 3,4,5). As a result, we hypothesize that as a general principle, daily or near-daily renal replacement therapy arguably would end up producing better cardiovascular and other outcomes among ESRD patients [11] (full text), [12], [13] (full text), [14] (full text).

Our group, Di Iorio et al, had previously demonstrated that cyclic pulse wave velocity (PWV) variations, a measure of arterial stiffness, measured before and after dialysis for individual ESRD patients, predicted mortality differences in patients with ESRD on conventional thrice weekly maintenance hemodialysis [9], [15]. Furthermore, the same group had subsequently demonstrated in 2012 that daily dialysis reduced PWV in chronic hemodialysis patients [10]. It therefore stands to reason for us to propose that, according to the results of this new translational changes in PWV study, that ESRD patients who exhibit elevated initial PWV values, or more so, ESRD patients who demonstrate accelerated PWV values repeated after six months while on maintenance thrice weekly chronic hemodialysis, should be converted to a daily hemodialysis protocol. This switch from intermittent to daily RRT may



ameliorate the poor cardiovascular mortality outcomes associated with ESRD patients. Also, such ESRD patients with high initial PWV values and those with accelerated PWV values after six months demand to be more critically evaluated by cardiologists. It remains unclear what other preventative or therapeutic options will be available to the cardiologists to further improve cardiovascular outcomes in this very vulnerable patient group [8].

In a recent review of the ESRD literature on mortality outcomes and therapeutic options, we had concluded that there was no quick simple solution to the high cardiovascular mortality among hemodialysis patients [8]. Cardiovascular mortality among ESRD patients, clearly very high, is under the influence of just too many confounding factors and variables [8]. Therefore, only through a concerted multifaceted approach, targeting all the plausible variables, and most importantly, with significant flexibility to individualize and tailor therapies as they are applicable and tolerated by each individual ESRD patient, would we even begin to dent the high cardiovascular mortality among hemodialysis patients [8].

Finally, we submit, from our study findings, that a switch to some daily or near-daily renal replacement therapy modality for selected ESRD patients with elevated initial PWV values and more so for ESRD patients with rapidly accelerating PWV values after six months of starting hemodialysis may help reduce cardiovascular mortality [11] (full text), [12], [13] (full text), [14] (full text). The daily or near-daily therapies would include home peritoneal dialysis, home hemodialysis, or in-center frequent daily or nocturnal dialysis therapies [11] (full text), [12], [13] (full text), [14] (full text). Clearly, more studies of this our hypothesis are urgently warranted as there are newer studies that dispute the findings of improved patient survival with daily dialysis among ESRD patients [16], [17].

Epilogue

Maduell et al, on behalf of the for the On-Line Hemodiafiltration Survival Study, or Estudio de Supervivencia de Hemodiafiltración On-Line (ESHOL) Study Group just recently published the results of a multicenter, open-label, randomized controlled trial in which assigned 906 chronic hemodialysis patients either to continue conventional hemodialysis (n=450) or to switch to high-efficiency post-dilution On-Line Hemodiafiltration (OL-HDF) (n=456) [18]. The mean follow-up was 1.9161.10 years (median 2.08 years; interquartile range [IQR], 0.86–3.00) [18]. Compared with patients who continued on hemodialysis, those assigned to OL-HDF had a 30% lower risk of all-cause mortality (hazard ratio [HR], 0.70; 95% confidence interval [95% CI], 0.53–0.92; P=0.01), a 33% lower risk of cardiovascular mortality (HR, 0.67; 95% CI, 0.44–1.02; P=0.06), and a 55% lower risk of infection-related mortality (HR, 0.45; 95% CI, 0.21–0.96; P=0.03) [18]. The estimated number needed to treat suggested that switching eight patients from hemodialysis to OL-HDF may prevent one annual death [18]. The incidence rates of dialysis sessions complicated by hypotension and of all-cause hospitalization were lower in patients assigned to OL-HDF [18]. The ESHOL study had concluded that high-efficiency post-dilution OL-HDF reduces all-cause mortality compared with conventional hemodialysis.

Given these impressive findings on mortality reduction with high-efficiency post-dilution OL-HDF, we have posited that ESRD patients who demonstrate rapidly increasing 6-month follow up repeat PWV evaluations represent a high CV-risk group and, where the modality is available, should then be switched from conventional thrice weekly intermittent HD to the online-HDF modality.

There are no conflicts of interests to be declared for all the authors.

Bibliografia

- [1] Go AS, Chertow GM, Fan D et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *The New England journal of medicine* 2004 Sep 23;351(13):1296-305 (full text)
- [2] Brown JH, Hunt LP, Vites NP et al. Comparative mortality from cardiovascular disease in patients with chronic renal failure. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association* 1994;9(8):1136-42
- [3] Lopez-Gomez JM, Verde E, Perez-Garcia R et al. Blood pressure, left ventricular hypertrophy and long-term prognosis in hemodialysis patients. *Kidney international. Supplement* 1998 Dec;68:S92-8
- [4] Wright RS, Reeder GS, Herzog CA et al. Acute myocardial infarction and renal dysfunction: a high-risk combination. *Annals of internal medicine* 2002 Oct 1;137(7):563-70
- [5] Gupta R, Birnbaum Y, Uretsky BF et al. The renal patient with coronary artery disease: current concepts and dilemmas. *Journal of the American College of Cardiology* 2004 Oct 6;44(7):1343-53
- [6] U.S. Renal Data System. *USRDS 2010 annual data report: atlas of chronic kidney disease and end-stage renal disease in the United States*. Bethesda, MD: National Institutes of Health NIDDK; 2010.
- [7] Cravedi P, Remuzzi G, Ruggenti P et al. Targeting the renin angiotensin system in dialysis patients. *Seminars in dialysis* 2011 May-Jun;24(3):290-7
- [8] Onuigbo MAC. Is combined angiotensin-converting enzyme inhibition and angiotensin receptor blockade associated with increased risk of cardiovascular death in hemodialysis patients? *Current Hypertension Reviews*; 2012; 8 (4): 256-266 (eBook).
- [9] Torraca S, Sirico ML, Guastaferro P et al. Variability of pulse wave velocity and mortality in chronic hemodialysis patients. *Hemodialysis international. International Symposium on Home Hemodialysis* 2011 Jul;15(3):326-33
- [10] Di Micco L, Torraca S, Sirico ML et al. Daily dialysis reduces pulse wave velocity in chronic hemodialysis patients. *Hypertension research : official journal of the Japanese Society of Hypertension* 2012 May;35(5):518-22
- [11] Foley RN, Gilbertson DT, Murray T et al. Long interdialytic interval and mortality among patients receiving hemodialysis. *The New England journal of medicine* 2011 Sep 22;365(12):1099-107 (full text)
- [12] Onuigbo MA Long inter-dialytic interval and mortality among patients receiving maintenance haemodialysis for end-stage renal disease - a call for more studies on the right amount or frequency of maintenance haemodialysis for end-stage renal disease. *International journal of clinical practice* 2012 Mar;66(3):327
- [13] Jefferies HJ, Virk B, Schiller B et al. Frequent hemodialysis schedules are associated with reduced levels of dialysis-induced cardiac injury (myocardial stunning). *Clinical journal of the American Society of Nephrology : CJASN* 2011 Jun;6(6):1326-32 (full text)
- [14] Culleton BF, Asola MR The impact of short daily and nocturnal hemodialysis on quality of life, cardiovascular risk and survival. *Journal of nephrology* 2011 Jul-Aug;24(4):405-15 (full text)
- [15] Bellasi A, Salvi P, Papagni S, Ferramosca E, Ratti C, Russo D, Di Iorio B. Arterial stiffness, pulse wave analysis: What can't blood pressure tell you in chronic kidney disease. *Current Hypertension reviews*. 2012;8:244-249.
- [16] Suri RS, Lindsay RM, Bieber BA et al. A multinational cohort study of in-center daily hemodialysis and patient survival. *Kidney international* 2013 Feb;83(2):300-7
- [17] Mehrotra R, Himmelfarb J Dialysis in 2012: Could longer and more frequent haemodialysis improve outcomes? *Nature reviews. Nephrology* 2013 Feb;9(2):74-5
- [18] Maduell F, Moreso F, Pons M et al. High-efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. *Journal of the American Society of Nephrology : JASN* 2013 Feb;24(3):487-97