

Haemodialysis, Blood Pressure and Risk: At the Limit of Non-Randomized Evidence.

Sarah Ng¹, Richard Haynes^{1,2}, William G. Herrington^{1,2}

¹ Medical Research Council Population Health Research Unit at the University of Oxford, Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Population Health (NDPH), Oxford, UK

² Oxford Kidney Unit, Churchill Hospital, Headington, Oxford, UK.

Correspondence to: Associate Professor William G. Herrington

Richard Doll Building, Old Road Campus,

Roosevelt Drive, Oxford OX3 7LF, UK

Email: will.herrington@ndph.ox.ac.uk

Phone: +44 1865 743743

Abstract: Not required; Main body: 2444 (limit 2500); References: 29 (limit 30)

Tables/Figures: 2 (max 2)

Keywords (max 5): Blood pressure, dialysis, mortality, epidemiology

Blood pressure and cardiovascular risk

Evidence from non-renal populations

Meta-analysis of individual-level data from 61 prospective observational studies including one million adults and 56,000 cardiovascular deaths has demonstrated a strong log-linear association between blood pressure (BP) and risk of cardiovascular mortality at all ages, without any evidence of a threshold down to at least 115/75mmHg.(1) Meta-analysis of randomized BP lowering trials including 265,000 people and 27,000 major cardiovascular events (i.e. fatal or non-fatal coronary disease, stroke or heart failure) confirmed a one-fifth relative risk reduction for each 10 mmHg reduction in systolic BP (SBP).(2) On a relative scale, these benefits appear to be consistent across the range of SBPs to at least 130 mmHg. Subsequently, the SPRINT trial of intensive versus standard BP control in at risk adults without diabetes was stopped early following confirmation that achieving an average clinic SBP of 121 mmHg, risk of major cardiovascular events was reduced by about one-quarter compared to those allocated to standard BP control (average SBP of 136 mmHg).(3) These results contributed to revised 2017 guidelines from the American College of Cardiology and American Heart Association recommending BP targets of <130/80 mmHg among people at ≥10% 10-year risk of cardiovascular disease, including people with chronic kidney disease (CKD).(4)

Evidence from diseased populations

In contrast to observations from apparently healthy adults, observational studies from more diseased populations have demonstrated “J” or “U”-shaped associations between BP and risk of cardiovascular disease.(5-7) Such non-randomized studies may be affected by reverse causality or other confounding, whereby cardiovascular or other diseases which lower BP and are present at the time of study assessments are incompletely measured or unmeasured. The resultant inability to account for these biases in analyses (however carefully performed) could result in optimal BP (e.g. low-normal levels) apparently being associated with increased risk of cardiovascular events compared to higher SBP. Randomized trials are not affected by such biases, and have shown that lowering BP is effective at reducing cardiovascular risk among people with cardiovascular disease in spite of such populations exhibiting U-shaped observational associations in some studies.(2) Similarly, trials have demonstrated BP lowering is effective in elderly people,(3, 8) in whom some observational studies have also not demonstrated a positive association between BP and risk of cardiovascular disease.(5)

Evidence from renal populations

U-shaped associations between BP and risk of cardiovascular disease risk are also common in advanced CKD cohorts.(9-12) It is challenging to confirm that bias is distorting true associations between BP and cardiovascular risk, as comparatively few people with advanced

CKD having been studied in BP lowering trials. Nevertheless, meta-analysis by the Blood Pressure Lowering Treatment Trialists' collaboration has demonstrated that, among 8500 participants with early-to-moderate CKD, each 5 mmHg SBP reduction lowered risk of major cardiovascular events (n=1150) by about 15%, with similar estimates of relative risk reduction in those with ≥ 60 , $\geq 45 < 60$, and < 45 mL/min/1.73m².⁽¹³⁾ Benefits have also been observed in a separate meta-analysis of trials conducted among people on dialysis (eight RCTs: 495 events in 1679 patients) which showed allocation to antihypertensive therapy lowered risk of major cardiovascular events by nearly 30%. These benefits were achieved with just an average 4.5 mmHg reduction in SBP (although it is not clear when the SBP measurements which constituted this calculation were made relative to dialysis).⁽¹⁴⁾

A plausible source of bias in CKD populations is again reverse causality from pre-existing cardiovascular disease (which may often be subclinical). A study of 2800 peritoneal dialysis patients from the UK Renal Registry found positive associations between BP and mortality that were stronger among those who were listed for transplantation early, or when early follow-up was effectively excluded from analyses (both methodological strategies to control for reverse causality caused by pre-existing disease).⁽¹⁵⁾ Furthermore, in an analysis of 8700 people with moderate-to-advanced CKD, U-shaped associations between SBP and risk of a major cardiovascular event (n=2187) were particularly apparent among those with elevated baseline blood Troponin levels (a marker of increased risk of subclinical cardiac disease). In contrast, BP associations were positive and log-linear among non-dialysis and dialysis-dependent CKD patients who had not reported cardiovascular disease and had a low blood Troponin concentration at recruitment.⁽¹²⁾ These data illustrate that the potential for biases distorting BP associations are particularly strong and difficult to control for in CKD populations. Non-randomized studies in CKD populations should therefore not be used to guide clinical practice, particularly for the selection of BP treatment targets.

There are other methodological challenges for renal epidemiologists studying BP, in addition to those introduced above. Short and medium term within person variability and measurement error can result in a bias referred to as regression-dilution bias.⁽¹⁶⁾ Natural variation in BP is present in all populations and explains the phenomenon of regression to the mean, whereby a second BP measurement is more likely to be closer to the population mean BP than the first. Regression to the mean is more marked in those with an extreme value (i.e. the lowest and highest BP groups: see Figure 1 for further explanation ⁽¹⁷⁾). Such variation is particularly relevant in haemodialysis studies, as in-centre BP readings can be markedly affected by the rapid treatment of volume expansion that is particular to haemodialysis.⁽¹⁸⁾

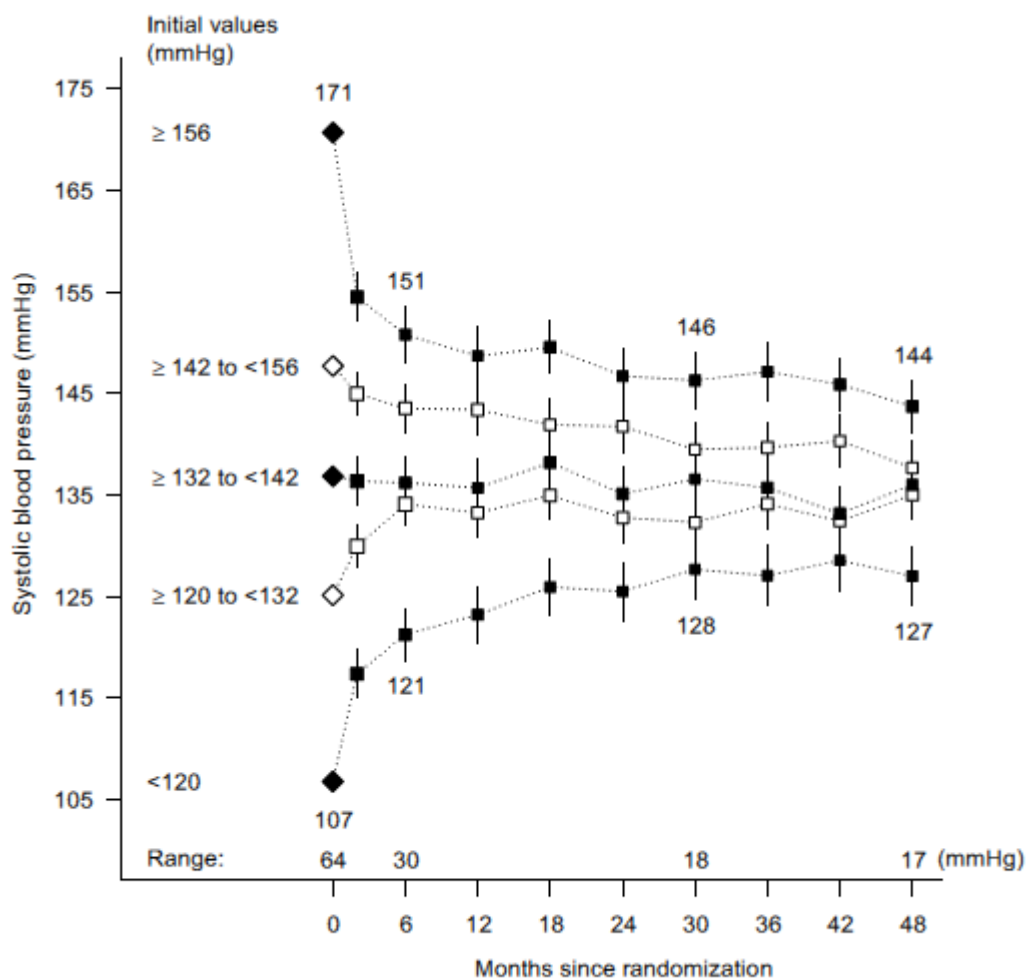


Figure 1: Mean SBP over time for SHARP participants on dialysis in categories defined by fifths of baseline SBP.

Legend: This regression-dilution plot uses the Study of Heart and Renal Protection (SHARP) dialysis patients' single SBP measurements at study visits. The cohort was first divided by fifths of baseline measurement. The mean SBP in the lowest fifth at baseline was 107 mmHg. By 2 months, average SBP in this group had increased to 121 mmHg and by 30 months, it was 128 mmHg. This is the amount by which daily BP fluctuation within individuals may result in patients being miscategorised (adapted from (17)).

If unaccounted for, regression-dilution bias causes underestimations of the strength of BP associations with risk of cardiovascular disease. This phenomenon also needs consideration when stratifying populations and then monitoring BP change over time. For example, as statistical analyses which select a group with low BP will usually observe the subsequent BPs to naturally regress up on re-measurement (Figure 1).

In this issue of Nephrology Dialysis Transplantation, Zhang *et al.*(19) have taken on the challenge of estimating the relevance of pre-dialysis SBP and changes in SBP during dialysis to risk of death. The analyses used US routinely collected haemodialysis centre data from 172,199 patients, among whom 75,329 died during a median of 2.1 years of follow-up. About one-third of the cohort were recorded as having a history of congestive heart failure (CHF) on diagnostic coding. Mean pre-dialysis SBP was 150 (standard deviation [SD] 19) mmHg and mean change in SBP (calculated as post-dialysis minus pre-dialysis SBP and referred to as “peridialytic” SBP change) was -10 mmHg.(14) Seventy three percent of participants’ peridialytic SBP fell, consistent with previous studies (9, 20) and a BP lowering effect of haemodialysis.

The first finding was a J-shaped association between pre-dialysis SBP and risk of death, with a steep negative association at low pre-dialysis SBP. The nadir in risk was around the population mean pre-dialysis SBP of 150 mmHg, and a pre-dialytic SBP of <100 mmHg was associated with at least a 3-times increased risk. This shape of association has been demonstrated in many similar previous studies,(18) and the most likely explanation is confounding by disease(s) as explained above.

The second finding was an unusual and complex non-linear association between peridialytic SBP change and risk. Overall, any peridialytic SBP decline was associated with a modest reduction in mortality compared to no change, but larger peridialytic SBP declines were not associated with further reductions in risk (i.e. there was no exposure-response relationship). This finding differs from similar analyses by Park *et al.* in which small-to-moderate peridialytic SBP changes from zero to -30 mmHg were associated with decreased risk, but larger peridialytic SBP declines were associated with increased mortality (i.e. Park *et al.* reported a U-shaped association between peridialytic SBP change with the risk, with the nadir at about zero to -30 mmHg).(20)

Thirdly, Zhang *et al.* found that pre-dialysis SBP modified associations. Among those with a pre-dialysis SBP of ≥ 110 mmHg mortality risk increased with a peridialytic SBP increase, but among those with low pre-dialysis SBP (<110 mmHg) the association was inverse (i.e. a pre-dialysis SBP <110 mmHg and a post-dialysis SBP increase was associated with lower mortality). At low pre-dialysis SBP, a peridialytic SBP fall was also conversely associated with a poor prognosis. Some of this observation may be accounted for by pre-existing cardiac disease, as this pattern was particularly evident in analyses restricted to the population with baseline CHF (and less clear in those without). The pattern could also partially be explained by misclassification of pre-dialysis SBP at the time of the initial measurement (see Figure 1).

Perhaps less likely is the possibility that these peridialytic SBP changes are a key cause of cardiovascular events.

Disentangling these three explanations is challenging for any study. Zhang *et al.* consider that: “To further our understanding of the underlying pathophysiology specifically designed prospective studies with concurrent biochemical and physiological measurements are warranted”. These studies would necessarily need to be large, include careful assessment for pre-existing cardiovascular disease at baseline, and information on cause-specific mortality. If these medium-term associations between pre-dialysis SBP and peridialytic BP change are causal, it would be expected that associations should be more strongly related to cardiovascular causes of death than other causes. Such would also be useful to incorporate measures of volume expansion (e.g. with bioimpedance measures – see points below).

It is unlikely to surprise a nephrologist that there is high mortality among dialysis patient with a low pre-dialysis SBP, and that this risk increases if SBP declines further during haemodialysis treatment. It may perhaps be less well recognized that those with high pre-dialysis SBP, which increases further on dialysis, are also an important at risk group. In other studies, peridialytic SBP increases have been associated with increased left ventricular mass.(21) Pathophysiologically, Zhang *et al.* hypothesize that the phenomenon could be accounted for by substantial volume expansion, whereby ultrafiltration improves cardiac output and SBP as a patient passes back up the Frank-Starling curve. It is hypothesized that following this initial increase in SBP, further ultrafiltration should result in a drop in SBP.(22, 23) Volume expansion (or “overhydration”) is an independent risk factor for mortality among haemodialysis patients at any level of pre-dialysis SBP (Figure 2).(24) If a peridialytic SBP increase in a “hypertensive” dialysis patient is indeed a marker of volume expansion, then the analyses by Zhang *et al.* suggest dialysis patients with a pre-dialysis SBP of ≥ 160 mmHg who experience a peridialytic SBP increase should be a particular priority for a review of their dry weight.(19)

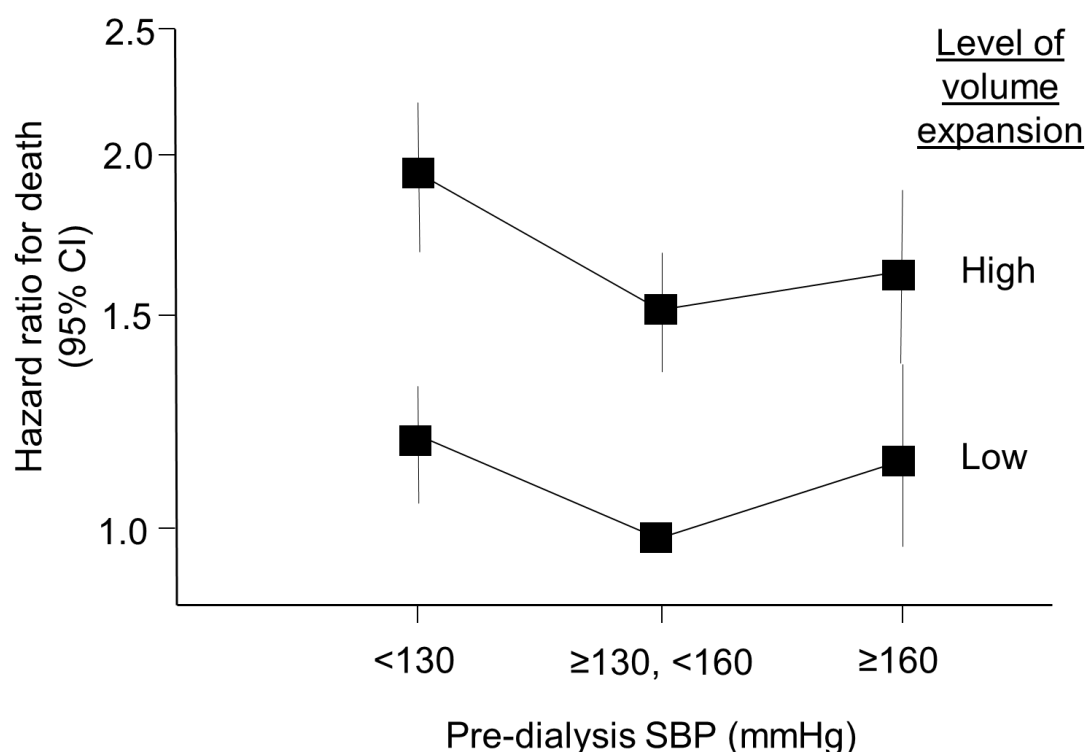


Figure 2: Association between pre-dialysis SBP and risk of death by 1-year cumulative degree of pre-dialysis volume expansion (adapted from (24))

Legend: Data are adjusted hazard ratios and 95% confidence intervals. High volume expansion (also referred to as “overhydration”) defined as ≥ 2.5 L fluid overload, which was estimated from an algorithm incorporating bioimpedance spectroscopy measurements. Those with high volume expansion were on average 4.8 (SD 2.8) L fluid overloaded, and those with low volume expansion, fluid overloaded by 0.9 (1.5) L (adapted from (24)).

The need for a definitive intensive BP lowering trial in dialysis patients

We agree with Zhang *et al.*’s sentiments that: “despite decades of research into the association between BP and outcomes in chronic HD many basic questions have not been resolved”. Identifying the optimal BP targets for people with advanced CKD with randomized evidence is overdue. The recent BP in Dialysis (BID) pilot demonstrated that some nephrologists are willing to randomize patients on dialysis with a pre-dialysis SBP ≥ 155 mmHg, to a standard BP control arm with a “standard” pre-dialysis SBP target of 155-165 mmHg versus intensive control (e.g. pre-dialysis SBP 110-140 mmHg).(25) In this trial, investigators were first asked to review dry weights before starting new antihypertensive agents in order to attain the allocated SBP targets. Nevertheless, there was a paradoxical increase in post-dialysis weight among those allocated intensive control, whilst post-dialysis weight decreased in those on standard control.(25) The consensus is that a definite dry weight should be established through non-pharmacological interventions before altering antihypertensive

regimes,(18) and achieving this before randomization in a trial setting is important methodologically due to inter-dependence of volume control and BP. Other findings from the BID trial have increased the importance of conducting a definitive randomized BP lowering trial in dialysis patients, as intensive control appeared to be associated with not only more cramps on dialysis, but also increased vascular access thrombosis and hospitalizations.

Measurements of SBP in dialysis centres are substantially higher and more variable than home measurements.(26) For example, in a trial of patient-performed home BP monitoring, baseline pre-dialysis SBP was 157 (SD 25) mmHg versus mean baseline 24-hour ambulatory SBP of 144 (SD 14) mmHg.(27) The technical challenge of ambulatory and patient-performed home BP measurements (e.g. twice daily triplicate sets of BP measurements each day for a week) means current observational studies recoding such data are small. Nevertheless, there is growing consensus that the epidemiology of BP is more reliably assessed using SBP measurements mainly recorded away from haemodialysis sessions.(18) Furthermore, an open-label randomized trial found titrating home measured average SBP to $\leq 135/85$ mmHg versus a traditional pre-dialysis SBP target of $<140/90$ mmHg, achieved a weekly average SBP of 144 mmHg versus 154 mmHg.(27) Telemonitoring offers a more convenient method to track SBP and weight measured at home, and can be used to titrate anti-hypertensives between dialysis sessions.(28) Such technology could be combined with systems that have been developed to centrally link up and dialysis centres to collect trial data,(29) thereby facilitating a large-scale definitive trial.

Conclusions

It seems implausible that optimal BP targets to reduce cardiovascular risk would differ substantially from those of general populations, as this would require a strong protective factor unique to dialysis patients which reduces the known effects of high SBP on accelerating cardiovascular diseases. It is much more likely that biases intrinsic to studying BP in diseased populations and the challenges of estimating a haemodialysis patient's long-term average BP are distorting associations in observational studies. Given the extreme cardiovascular risk observed in dialysis populations and the modifiability of BP, reliably establishing the optimal SBP levels in dialysis populations with large randomized studies should remain a top research priority. These studies need to establish volume control before randomizing to an SBP target and consider using telemonitoring and home based BP assessments. For now, the latest observational analyses inform us that high and low pre-dialysis SBP which digress from the mean during dialysis are both associated with highest mortality risk, and such patients deserve careful clinical attention.

References

1. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R, Prospective Studies C. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* (London, England). 2002;360(9349):1903-13.
2. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet*. 2016;387(10022):957-67.
3. Wright JT, Jr., Williamson JD, Whelton PK, Snyder JK, Sink KM, et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *N Engl J Med*. 2015;373(22):2103-16.
4. Whelton PK, Carey RM, Aronow WS, Casey DE, Jr., Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2018;71(19):2199-269.
5. Farnett L, Mulrow CD, Linn WD, Lucey CR, Tuley MR. The J-curve phenomenon and the treatment of hypertension. Is there a point beyond which pressure reduction is dangerous? *JAMA*. 1991;265(4):489-95.
6. Bangalore S, Messerli FH, Wun CC, Zuckerman AL, DeMicco D, Kostis JB, et al. J-curve revisited: An analysis of blood pressure and cardiovascular events in the Treating to New Targets (TNT) Trial. *Eur Heart J*. 2010;31(23):2897-908.
7. Redon J, Mancia G, Sleight P, Schumacher H, Gao P, Pogue J, et al. Safety and efficacy of low blood pressures among patients with diabetes: subgroup analyses from the ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial). *J Am Coll Cardiol*. 2012;59(1):74-83.
8. Blood Pressure Lowering Treatment Trialists Collaboration. Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomised trials. *BMJ*. 2008;336(7653):1121-3.
9. Zager PG, Nikolic J, Brown RH, Campbell MA, Hunt WC, Peterson D, et al. "U" curve association of blood pressure and mortality in hemodialysis patients. Medical Directors of Dialysis Clinic, Inc. *Kidney Int*. 1998;54(2):561-9.
10. Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barre PE. Impact of hypertension on cardiomyopathy, morbidity and mortality in end-stage renal disease. *Kidney international*. 1996;49(5):1379-85.
11. Port FK, Hulbert-Shearon TE, Wolfe RA, Bloembergen WE, Golper TA, Agodoa LY, et al. Predialysis blood pressure and mortality risk in a national sample of maintenance hemodialysis patients. *American journal of kidney diseases : the official journal of the National Kidney Foundation*. 1999;33(3):507-17.
12. Herrington W, Staplin N, Judge PK, Mafham M, Emberson J, Haynes R, et al. Evidence for Reverse Causality in the Association Between Blood Pressure and Cardiovascular Risk in Patients With Chronic Kidney Disease. *Hypertension*. 2017;69(2):314-22.
13. Ninomiya T, Perkovic V, Turnbull F, Neal B, Barzi F, Cass A, et al. Blood pressure lowering and major cardiovascular events in people with and without chronic kidney disease: meta-analysis of randomised controlled trials. *BMJ*. 2013;347:f5680.
14. Heerspink HJ, Ninomiya T, Zoungas S, de Zeeuw D, Grobbee DE, Jardine MJ, et al. Effect of lowering blood pressure on cardiovascular events and mortality in patients on dialysis: a systematic review and meta-analysis of randomised controlled trials. *Lancet*. 2009;373(9668):1009-15.
15. Udayaraj UP, Steenkamp R, Caskey FJ, Rogers C, Nitsch D, Ansell D, et al. Blood pressure and mortality risk on peritoneal dialysis. *Am J Kidney Dis*. 2009;53(1):70-8.

16. Clarke R, Shipley M, Lewington S, Youngman L, Collins R, Marmot M, et al. Underestimation of risk associations due to regression dilution in long-term follow-up of prospective studies. *Am J Epidemiol.* 1999;150(4):341-53.
17. Herrington W, Haynes R, Staplin N, Emberson J, Baigent C, Landray M. Evidence for the prevention and treatment of stroke in dialysis patients. *Semin Dial.* 2015;28(1):35-47.
18. Sarafidis PA, Persu A, Agarwal R, Burnier M, de Leeuw P, Ferro CJ, et al. Hypertension in dialysis patients: a consensus document by the European Renal and Cardiovascular Medicine (EURECA-m) working group of the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) and the Hypertension and the Kidney working group of the European Society of Hypertension (ESH). *Nephrol Dial Transplant.* 2017;32(4):620-40.
19. Zhang H, et al. NDT to insert reference for the paper this editorial accompanies. 2020.
20. Park J, Rhee CM, Sim JJ, Kim YL, Ricks J, Streja E, et al. A comparative effectiveness research study of the change in blood pressure during hemodialysis treatment and survival. *Kidney Int.* 2013;84(4):795-802.
21. Shamir AR, Karembelkar A, Yabes J, Yao Y, Miskulin D, Gassman J, et al. Association of Intradialytic Hypertension with Left Ventricular Mass in Hypertensive Hemodialysis Patients Enrolled in the Blood Pressure in Dialysis (BID) Study. *Kidney Blood Press Res.* 2018;43(3):882-92.
22. Gunal AI, Karaca I, Celiker H, Ilkay E, Duman S. Paradoxical rise in blood pressure during ultrafiltration is caused by increased cardiac output. *J Nephrol.* 2002;15(1):42-7.
23. Agarwal R, Alborzi P, Satyan S, Light RP. Dry-weight reduction in hypertensive hemodialysis patients (DRIP): a randomized, controlled trial. *Hypertension.* 2009;53(3):500-7.
24. Zoccali C, Moissl U, Chazot C, Mallamaci F, Tripepi G, Arkossy O, et al. Chronic Fluid Overload and Mortality in ESRD. *J Am Soc Nephrol.* 2017;28(8):2491-7.
25. Miskulin DC, Gassman J, Schrader R, Gul A, Jhamb M, Ploth DW, et al. BP in Dialysis: Results of a Pilot Study. *J Am Soc Nephrol.* 2018;29(1):307-16.
26. Agarwal R, Peixoto AJ, Santos SF, Zoccali C. Pre- and postdialysis blood pressures are imprecise estimates of interdialytic ambulatory blood pressure. *Clin J Am Soc Nephrol.* 2006;1(3):389-98.
27. da Silva GV, de Barros S, Abensur H, Ortega KC, Mion D, Jr., Cochrane Renal Group Prospective Trial Register CRG. Home blood pressure monitoring in blood pressure control among haemodialysis patients: an open randomized clinical trial. *Nephrol Dial Transplant.* 2009;24(12):3805-11.
28. Warner BE, Velardo C, Salvi D, Lafferty K, Crosbie S, Herrington WG, et al. Feasibility of Telemonitoring Blood Pressure in Patients With Kidney Disease (Oxford Heart and Renal Protection Study-1): Observational Study. *JMIR Cardio.* 2018;2(2).
29. Dember LM, Lacson E, Jr., Brunelli SM, Hsu JY, Cheung AK, Daugirdas JT, et al. The TiME Trial: A Fully Embedded, Cluster-Randomized, Pragmatic Trial of Hemodialysis Session Duration. *J Am Soc Nephrol.* 2019;30(5):890-903.