

Blood pressure targets for haemodialysis patients: aspirational or practical ?

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Abstract

Whereas there is strong relationship between high blood pressure and increased overall and cardiovascular mortality for the general population, observational studies in haemodialysis patients have reported a "U" shaped relationship between pre-haemodialysis blood pressure recordings and patient survival. Previous attempts to introduce pre and post-haemodialysis blood pressure targets were associated with an increased the frequency of intra-dialytic hypotension, itself an independent risk factor for mortality. On the other hand meta-analyses of trials of antihypertensive medications in haemodialysis patients, reported survival benefit for those prescribed medication. More recently, further meta-analyses have suggested a reduced risk for cardiovascular mortality benefit with r systolic blood pressures of less than

140 mmHg, the absolute benefit, in terms of risk reduction was greatest in those with the highest vascular disease burden. Even though data from current observational studies and studies of antihypertensive medications would suggest that patient survival would be greater with pre-dialysis systolic blood pressure should be less than 160 mmHg, there is no current data to propose specific blood pressure targets.

Defining blood pressure targets can only be answered by adequately powered prospective randomised controlled trials comparing different targets. As the benefits of lowering blood pressure appear to be greatest for those with most vascular disease, then blood pressure targets may have to be adjusted on an individual risk basis, and future trials should therefore stratify patients according to vascular morbidity and have different targets for patients with differing degrees of pre-existing cardiovascular disease.

Introduction

In the general population there is strong inverse relationship between increasing blood pressure and survival [1]. A recent meta-analysis of 34 randomised clinical trials of blood pressure control showed that hypertensive patients randomised to more intense blood pressure lowering had significantly reduced risk of stroke [relative risk (RR) 0.71 (0.60-0.84)], coronary events [0.80 (0.68-0.95)], major cardiovascular events [0.75 (0.68-0.85)] and cardiovascular mortality [0.79 (0.63-0.97)], but not heart failure and all-cause death [2]. Stratification of these trials using three systolic blood pressure (SBP) cut offs (150, 140 and 130mmHg) showed that a SBP/diastolic blood pressure (DBP) difference of -10/-5mmHg across each cut off significantly reduced the risk for all outcomes. All major outcomes were reduced by lowering SBP a few mmHg below vs. above 130mmHg, but the lower the starting SBP then the absolute risk reduction was lower, suggesting that patients with lower starting SBP were at a lower level for cardiovascular risk.

Although this meta-analysis of clinical trials would suggest tighter SBP is an advantage, and patients should have a target SBP of 130 mmHg, there have been concerns that these lower blood pressure targets are not protective and may actually cause harm in high risk patients, such as those with pre-existing cardiovascular disease, chronic kidney disease, or diabetes [3]. So whereas previous guidelines recommended target blood pressure levels of around 130/85 mm Hg for patients with cerebrovascular disease, coronary heart disease, renal disease, and diabetes, more recent versions of these clinical guidelines now recommend higher target levels of 140/90 mm Hg in these higher risk patients [4-6].

Blood Pressure targets for patients with chronic kidney disease

As there have been concerns that patients with greater cardiovascular risk should have different blood pressure targets compared to those with lower cardiovascular risk factors, a recent meta-analysis reported 19 trials of blood

pressure control in these higher risk patients, with a mean blood pressure of 133/76 mm Hg in the intensive blood pressure control cohort compared to 140/81 mm Hg in the less intensive treatment group, reported that those patients in the intensive blood pressure lowering cohort achieved relative reductions for major cardiovascular events (14% [95% CI 4-22]), myocardial infarction (13% [0-24]), stroke (22% [10-32]), albuminuria (10% [3-16]), and progression of retinopathy in diabetic patients (19% [0-34]) [7]. However, there was no significant benefit of lower blood pressures for heart failure (15% [95% CI -11 to 34]), cardiovascular death (9% [-11 to 26]), overall mortality (9% [-3 to 19]), or progression to end-stage kidney disease (10% [-6 to 23]) [7]. The absolute benefits of these lower blood pressure targets were greatest in those trials which enrolled patients with vascular disease, chronic kidney disease (CKD), or diabetes. On the other hand patients randomised to the more intensive blood pressure lowering cohort were more likely to suffer severe hypotension (relative risk 2.68 [1.21-5.89], $p=0.015$), although the absolute excess was small (0.3% vs 0.1% per person-year), and there was no statistical difference in the 6 trials which reported severe adverse event rates (1.2 vs 0.9% per year).

Blood pressure in haemodialysis patients

Whereas there is a diurnal variation in blood pressure in healthy subjects, there are also additional changes in blood pressure profiles for haemodialysis (HD) patients during the cycle of the dialysis week [8], with most patients having a fall in blood pressure during the dialysis session, followed by a gradual increase in blood pressure between dialysis sessions, which may then increase exponentially in the few hours prior to the next session [8-11].

Based on the data supporting blood pressure control in the general population, some clinical guideline groups issued blood pressure targets for both pre and post haemodialysis blood pressures [12]. However observational studies reported that those dialysis centres which had a greater proportion of patients achieving these targets also had a greater incidence of intra-dialytic hypotension [13].

Blood pressure in any individual haemodialysis patient depends upon the complex interplay between sodium balance [14,15,16] and extracellular volume overload [17] on one hand, and vasoconstriction caused by neuro-humoral mechanisms [18], and arterial stiffness [19] on the other. These mechanisms lead to vascular and cardiac dysfunction and may be important in the observation of the "U-shaped" mortality curve reported in observational studies of pre-dialysis blood pressure measurements in dialysis patients [20,21].

Although the concept of pre-dialysis hypertension being associated with greater patient survival compared to those who are normotensive appears somewhat counterintuitive, one possibility is that patients with normal cardiovascular function respond to the inter-dialytic sodium gains and volume expansion by increasing blood pressure, whereas those with cardiac failure are unable to respond appropriately, and as such these patients have a higher risk of early mortality [22]. This would be keeping with the previous UK National

Institute for Clinical Excellence (NICE) CKD 1-4 guidance [3] which suggested that low blood pressures (<120/60) are associated with adverse outcomes. Intra-dialytic hypotension remains the commonest complication of haemodialysis treatments [23], and the heart depends on the diastolic pressure for its own perfusion, and as such many studies have reported myocardial stunning occurring during dialysis in patients with known cardiovascular disease [24]. As such several studies have reported that mortality is increased for patients with intra-dialytic hypotension [25,26], and also for those with greatest variability in blood pressure, ie pre-dialysis hypertension coupled with intra-dialytic hypotension [27].

Blood pressure measurement in haemodialysis patients

It is well recognised in the general population that blood pressure varies, and that equipment used to measure blood pressure should be regularly calibrated to ensure accuracy [6], and similarly blood pressure measurements have been shown to differ from when patients first arrive at the dialysis centre to starting dialysis [8]. Coupled with dialysis centre practices, of whether anti-hypertensive medications are taken or omitted prior to dialysis, or the prescription of anti-hypertensive medications which are cleared during dialysis mean that the convenient, but often poorly standardised, practice of measuring blood pressure just before and just after dialysis sessions may be profoundly misleading of the inter-dialytic blood pressure [8,28]. Clinical guidelines for recording blood pressure recommend that blood pressure should ideally be measured after five minutes rest in a chair, after at least 30 minutes of abstention from drugs which may affect blood pressure, including caffeine, theophylline (coffee and tea) or nicotine, with the patient seated comfortably, and with the arm supported at heart level, and a minimum of two measurements taken, several minutes apart, to allow for the alerting response to blood pressure measurement [29]. If the second measurement is significantly lower than the first, a third measurement should then be taken, with further repeats if there is a further fall in measured blood pressure. The mean of these later measurements should then be taken as the result [29]. Not surprisingly, blood pressure measured as recommended above is somewhat lower than that taken during routine clinical practice [30]. Thus, home or ambulatory blood pressure recordings have been recommended to confirm or refute unexpected high or low blood pressure readings [29], and ambulatory blood pressure studies in haemodialysis patients have reported that ambulatory blood pressure readings more closely mirror left ventricular hypertrophy than routine pre and post-dialysis recordings [28].

Blood pressure targets for haemodialysis patients

There are observational reports that pre-dialysis systolic blood pressures of >150-160 mmHg in haemodialysis patients are associated with increased mortality risk [31,32], and that mortality is lowest with home systolic blood

pressure recordings between 120-130 mmHg and ambulatory systolic blood pressures in the range of 110-120 mmHg [33]. Ambulatory blood pressure recordings show that blood pressure tends to increase during the inter-dialytic period, particularly prior to the next dialysis session and with the longer inter-dialytic interval with increased weight gain, so timing of the ambulatory blood pressure recordings in relationship to the inter-dialytic period will influence outcomes [34,35]. Indeed some investigators advocate 44 hour monitoring rather than 24 hour monitoring, however many patients find these measurements intrusive, and analysis of recordings may show many periods of absent recordings, suggesting either technical problems with recording measurements, or that patients have temporarily removed the device.

Unfortunately there are no adequately powered prospective randomised controlled trials to compare one blood pressure target with another in haemodialysis patients. There have been a limited number of interventional controlled trials using particular individual antihypertensive medications, without necessarily achieving pre-specified blood pressure targets, some reporting improved outcomes[36,37], whereas one trial with blood pressure targets reported no specific benefit for an angiotensin receptor blocker [38]. Meta-analysis of trials of antihypertensive medications in haemodialysis patients reported similar reductions in blood pressure compared to progressive ultrafiltration and resetting of post-dialysis target weight [39,40]. However, interventional studies designed to reduce post-dialysis weight in a step wise fashion have reported increased intradialytic hypotension [40], and concerns have been raised that lowering blood pressure may also increase the risk of intradialytic hypotension [13], which is an independent predictor of mortality [25-27]. Although patients with lower pre-dialysis blood pressure are at increased risk of mortality [20,21], observational studies have reported a beneficial effect on survival for the prescription of beta blockers and angiotensin converting enzyme inhibitors in haemodialysis patients [41]. However it needs to be recognised that these observational trials have a number of potential confounders, and results report an association and do not necessarily prove benefit.

Summary

There remains considerable debate both about how and when to measure blood pressure and the whether there should be blood pressure targets for haemodialysis patients. Although ambulatory blood pressure recordings are considered the gold standard, prolonged inter-dialytic recordings are generally disliked by patients, and many records have missing data points reducing reliability. Home blood pressure readings offer an alternative, but these can be falsified, or not taken in the recommended manner, and many home blood pressure machines are not as frequently serviced and recalibrated as hospital equipment (table 2). Thus for practical purposes pre and post haemodialysis blood pressure recordings remain the mainstay in clinical practice. However

there is room for improvement by introducing standardised operating procedures as to how and when to take blood pressure, and the number of measurements to be made. In some dialysis centres practices have become lax; taking measurements with the cuff placed over outer clothing, failing to use the appropriate cuff size, and failure to recalibrate blood pressure modules integrated into the modern day haemodialysis machine.

As to actual blood pressure targets, these can only be answered by adequately powered prospective randomised controlled trials comparing different targets. Although there is currently not enough data to suggest absolute blood pressure targets, mounting evidence from observational studies that haemodialysis patients would benefit from having a systolic blood pressure < 160 mmHg, and for those with greater underlying vascular disease, then lower pre-dialysis systolic blood pressures of 140 mmHg or less may provide greater benefit. As such the benefits of lowering blood pressure should be considered on an individual cardiovascular risk basis, and future trials should stratify patients according to vascular morbidity and have different targets for different cohorts. On the other hand actively lowering systolic blood pressure to below 130 mmHg does not appear to add benefit, and may potentially increase risk.

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Table 1. UK National Institute for Clinical Excellence (NICE) clinical guidelines for blood pressure control in patients with chronic kidney disease (CKD) stages 1-4. Proteinuria defined as an albumin/creatinine ratio of >70 mg/mmol, or a protein creatinine ratio > 100 mg/mmol [3].

Chronic kidney disease	Upper target	Target range
Systolic blood pressure mmHg	140	129 - 139
Diastolic blood pressure mmHg	< 90	
CKD and diabetes or proteinuria		
Systolic blood pressure mmHg	130	120 - 129
Diastolic blood pressure mmHg	< 80	

Table 2. Quality improvement program to increase reliability of pre and post blood pressure recordings in haemodialysis patients.

Reliability of equipment	maintenance
	recalibration
Technical use of equipment	chose correct blood cuff size
	correct placement of arm cuff
	correct positioning of arm
	blood pressure monitor at level of heart
Measurement	patient rested in sitting or lying posture
	repeat measurement
	repeated measurement if 2 not similar to 1
	report averaged measurement