blood pressure as a significant risk factor was due to the fact that a single clinical measurement was used rather than ABPM. While that may well be true, the point was that when analysed in a pool of risk factors and biomarkers, blood pressure may have limited impact. This point is illustrated by trials of ABPM in CKD, where the significance of ABPM on outcomes is lost when other parameters are entered into multivariate analyses [3].

Although home monitoring was not part of the original debate it provides a useful common ground—providing additional information on interdialytic blood pressures and empowering the patient in the management of their own disease. Dr Agarwal did not cover the practical issues of establishing ABPM monitoring in a dialysis setting, such as the frequency of measurements and targets, and the logistics of providing a service beyond a research-focussed clinical setting. In contrast, home monitoring offers a more practical, readily implemented system, with the possible advantage that ‘out-of-hospital’ BP readings may be a better prognostic target [4].

Ultimately, I am sure that Dr Agarwal and I agree that the CV outcomes on maintenance haemodialysis are unacceptably poor, and that more detailed information on BP control would be useful, as would lung ultrasound, echocardiography, and other measures of fluid balance and cardiac function. Home monitoring does more to empower and engage the patients than ABPM, which is yet more mechanized, remote monitoring in an already machine-dominated life. However, the subject of the debate was whether ABPM should be a routine part of our current management of haemodialysis patients, providing added value to the management of individual patients. To my mind, there is insufficient evidence to support this view, in the management of complex haemodialysis patients, with limited resources, at least until an intervention based on ABPM is shown to alter outcomes for the better.

REFERENCES


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Con: Ambulatory blood pressure measurement in patients receiving haemodialysis: a sore arm and a waste of time?

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ABSTRACT

Ambulatory blood pressure monitoring (ABPM) has become popular in the investigation and management of patients with essential hypertension. In patients receiving haemodialysis, ABPM identifies patients who may fare worse in the long term. However, the available studies are small, and when conventional risk factors are included, there is no added value to ABPM over conventional BP measurements. In haemodialysis, ABPM remains an experimental investigation, and in the absence of specific, evidence-based targets for blood pressure in this population, it would be better to invest in large-scale trials to provide specific blood pressure targets and strategies, rather than concentrating on an alternative technique for blood pressure measurement.

Keywords: ambulatory monitoring, cardiovascular risk, haemodialysis, hypertension
INTRODUCTION

The purpose of this paper is to present a polar view; a view that challenges the assumption that ambulatory blood pressure measurements (ABPM) are an important, or necessary, part of the cardiovascular (CV) assessment of patients with end-stage kidney disease (ESKD) treated by haemodialysis. The adoption of such a view is challenging, since it is generally possible to find a situation where ABPM (or any clinical measurement) might be useful. However, although I regularly use ABPM to assess patients with hypertension, I have not—with the exception of patients in clinical trials [1–3]—ever requested ABPM in a patient receiving haemodialysis.

When requesting a clinical test—such as ABPM—it is essential to identify the added value that the test will provide, with respect to diagnoses and quantification of risk, and balance this against any potential risk to the patient. This should be set in the context of other tests and information that are available, the disease process and the impact of remediable risk factors. In the management of patients with essential hypertension (EH), standard BP monitoring involves isolated clinic measurements according to protocol: the average of successive measurements, taken in the non-dominant arm, after a period of rest. Such guidelines are seldom followed correctly in clinical practice, and ABPM offers a series of repeated measurements taken during various states of activity, including sleep—which provide averaged data with much less variability than clinic measurements. It is recognized that measurements of BP made using ABPM allow reduced numbers of patients in interventional trials, increasing statistical power and reducing sample size. In individual patients, ABPM is useful in identifying patients with ‘white coat’ syndrome (WCS)—whose ‘real’ BP is lower than that taken at the clinic, and who have low underlying CV risk and ‘masked’ hypertension, where clinic readings suggest lower levels of blood pressure. In practice, WCS is the principal indication, and the identification of patients whose blood pressure does not dip at night—‘non-dippers’—who are at increased CV risk [4, 5].

In patients with EH, hypertension is the major risk factor for stroke, whilst hyperlipidaemia and cigarette smoking are the major modifiable risk factors for coronary heart disease (CHD). Left ventricular hypertrophy (LVH) and proteinuria (albeit to a lower degree in Caucasian patients) are markers of severe hypertension and associated with increased risk, where they act as surrogates and intermediate therapeutic targets. In studies of patients with EH, the use of ABPM gained traction as the values obtained are stronger determinants of the long-term risk of CV events than clinic readings, and are strongly associated with LVH; with the added value to individuals that they identify patients with WCS, saving them for inappropriate initiation or escalation of therapy. These factors have led to the adoption of ABPM in guidelines for the management of patients with EH [4, 5]. Thus, there is a strong argument for the use of ABPM in essential hypertension to assess individual risk and individualize treatment.

Patients with mild CKD share a similar pattern of CVD to the general population and patients with EH. It may seem logical that ABPM will have a similar place in the management of hypertension in this population [6]. However, we are increasingly aware that the pattern of CVD changes as CKD progresses and is very different in advanced and end stage kidney disease. The key difference, as CKD progresses, is the shift from CHD to sudden cardiac death and heart failure, as the most common events [7–10]. Non-CHD events are most strongly influenced by the development of uraemic cardiomyopathy and its most common form—LVH. Various studies have looked at the role of ABPM in CKD. In a recent large study of 489 hypertensive CKD patients followed for 9 years [6] failure to reach clinic target BP was associated with poor cardiovascular and renal outcomes, as expected. The main finding was that patients who achieved clinical but not ambulatory targets had a worse outcome than patients who achieved targets. This confirms that elevated blood pressure is bad in this population, regardless of how it is measured, and questions the relationship between clinical and ABPM targets, rather than proving the superiority of the latter measurement. Furthermore, although ABPM may be more strongly associated with LVH and with CV outcomes in patients with CKD, this is limited when proteinuria and LVH are included in the model [6], suggesting that ABPM may have limited added value.

This brings us to the point of this debate: the use of ABPM in patients with ESKD treated by haemodialysis. This patient group has a pattern of CVD that is very different from the general population or patients with EH. The overall CV mortality is an order of magnitude, or more, greater than the general population [7–10], and the pattern of CV disease is unique. CHD is a relatively minor component of the overall CV burden, whilst heart failure and sudden (presumed arrhythmic) death are the predominant events. The pathogenesis, risk factors and risk management also differ from the general population. In a post hoc analysis of the AURORA study, which failed to show a benefit of Rosuvastatin therapy in 2800 haemodialysis patients [10], we examined risk factors for CVD. Blood pressure parameters were not significantly associated with CV events; although there was a positive relationship with SBP and a negative relationship with DBP, and CV events, reflecting the importance of vascular stiffness and calcification—the derivative pulse pressure being most strongly associated with outcomes. The strongest, potentially remediable risk factors were markers of inflammation (CRP, albumen) and phosphate levels; trailing behind the irremovable—diabetes and age. The pathophysiological link to sudden death and heart failure is uraemic cardiomyopathy—specifically extreme LVH (with fibrosis)—providing the substrate for conduction abnormalities and systolic and diastolic dysfunction [10, 11]. Studies that have examined the determinants (and potential therapeutic targets) for LVH have shown that blood pressure is an important determinant, regardless of the measurement involved [1–3]. However, vascular stiffness, and markers of vascular calcification—such as calcium, phosphate, pulse pressure and pulse-wave velocity, volume overload and duration of dialysis [1]—are more important determinants, and in this population blood pressure (regardless of how it is measured) is likely to follow changes in intravascular volume rather than being the primary pathophysiological mechanism [3].

Is there evidence that ABPM provides a better marker than clinic BP, for CV outcomes in patients with ESKD treated by
Blood pressure is not linearly related to CV outcomes [12]. In ESKD, in patients treated by HD, the situation is different. More reliable information that allows one to tailor therapy. In and antihypertensive therapy is unproven [20]. BP is dependent on cardiac output [3] and its determinants—anaemia, fluid overload, systolic function, dialysis ‘dose’; factors which are independently associated with CV outcomes in this population. Moreover, correction of volume overload, or anaemia, or increasing the dose of dialysis has been associated with correction of blood pressure. These parameters have much better surrogate measures than BP or ABPM, including ‘lung comets’, echocardiographic parameters and circulating neurohormones [21–24]. Perhaps the most compelling reason against the routine use of ABPM is that we do not have evidence-based targets for ABPM in ESKD; not least because we do not have evidence-based targets for any BP measurement in ESKD [20]. Given that BP and LVH (which is a much stronger and more established marker of CV outcome in HD patients) are dependent on volume status, CaxPO₄ product, dialysis dose and other factors that have established impact on adverse outcome—I would prefer to target therapy based on markers of volume status and overload (e.g. BNP, lung ultrasound, bioimpedence or structural cardiac assessment; [21–24]). Moreover, strategies to address these targets such as daily dialysis or bioimpedence targeted dialysis are associated with improved BP and LVMI. There is no evidence that treatment based on ABPM has benefit.

Finally, the main reason I have not routinely used ABPM in ESKD is that patients do not like it. Whilst ABPM may be relatively straightforward in EH, it may be painful (especially in patients with high pressures) and not tolerated. Patients treated by haemodialysis are at particular risk, as higher cuff inflation pressures and unsuccessful measurements are more common where pressures are high and difficult to measure. Patients with ESKD are at increased risk of bleeding and bruising, especially if anticoagulated. Moreover, the upper limb vasculature is often abnormal—a consequence of current, prior or failed vascular access procedures; or the reason that vascular access procedures are impossible. In my limited experience of ABPM, it is less well tolerated in ESKD.

Although I do not argue that ABPM has no role in the investigation of the large majority of patients with hypertension, including those with early CKD, in ESKD I can live without it. BP is dependent on volume overload, and cardiac function, for which there are much better surrogates, with established adverse impact, on which to target therapy. Blood pressure has a complex relationship with outcomes in this population. There are no evidence-based studies to support existing targets in ESKD—either clinical measurements or ABPM—or indeed therapeutic strategies or agents. Overall, I would have to agree with Dr Agarwal’s published view on ambulatory monitoring: ‘ABPM remains a research tool in haemodialysis patients’ and that to establish its role, if any, a large scale trial is required [13].

**CONFLICT OF INTEREST STATEMENT**

None declared.

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trolled data, we often cling on to our belief that association is causative in nature. As an example, in the AURORA study, C-reactive protein was associated with poor outcomes [2].

However, this study among haemodialysis patients was instrumental in burning the inflammation hypothesis. Despite sub-
stantial lowering of CRP with rosuvastatin it did not reduce cardiovascular morbidity or mortality [3]. Thus, CRP is not causally related to the cardiovascular outcomes measured in this trial [2]. In the same study, blood pressure was not asso-
ciated with outcomes [2]. This is not surprising. First of all, these were dialysis unit measurements, not ambulatory, and se-
cond this was not a randomized trial testing a goal blood pressure; therefore observational studies like this do not support or refute BP being a cardiovascular risk factor in dialysis patients. One reason why ambulatory BP is not thought to be appro-
riate for use in haemodialysis patients is because there are little

REFERENCES

1. Patel RK, Oliver S, Mark PB et al. Determinants of left ventricular mass and hypertrophy in haemodialysis patients assessed by cardiac magnetic reson-
2. Stewart GA, Mark P, Johnstone N et al. Determinants of hypertension and left ventricular function in end stage renal failure: a pilot study using cardio-
vascular magnetic resonance imaging. Clin Physiol Funct Imaging 2004; 24: 387–393
3. Mancia G, Verdecchia P. Clinical value of ambulatory blood pressure: evi-
4. Niiranen TJ, Mäki J, Puukka P et al. Determinants of cardiovascular risk markers and limit left ventricular hypertrophy in thrice daily and night/day ratio in nondiabetic, cardio-
6. Zoccali C, Mallamaci F, Tripepi G et al. Prediction of left ventricular geom-
etry by clinic, pre-dialysis and 24-h ambulatory BP monitoring in hemodi-
alysis patients. J Hypertens 1999; 17: 1751–1758
7. Wheelan DC, Becker GJ. Summary of KDIGO guideline. What do we really
events and mortality in ESRD. J Am Soc Nephrol 2013; 24: 1–8
10. Schneider A, Jardine AG, Schneider MP et al. Determinants of cardiovas-
11. Mark PB, Johnston N, Groenning BA et al. Redefinition of uremic cardio-
myopathy by contrast-enhanced cardiac magnetic resonance imaging. Kidney Int 2006; 69: 1839–1845

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Opponent’s comments

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The field of nephrology is rich in observational studies but poor in randomized controlled trials [1]. Despite randomized con-
trolled data, we often cling on to our belief that association is causative in nature. As an example, in the AURORA study, C-reactive protein was associated with poor outcomes [2]. However, this study among haemodialysis patients was instrumental in burning the inflammation hypothesis. Despite sub-
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