Ambulatory Blood Pressure Monitoring: An Invaluable Tool Comes of Age for Patients with Chronic Kidney Disease?

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Hypertension is the most common chronic disease in the Western world, with a documented prevalence of 25–30% of adults in developed societies [1], and a major risk factor for cardiovascular events; thus, it is no wonder why it is considered the most important attributable cause of death worldwide [2]. Chronic kidney disease (CKD), on the other hand, is another major public health issue; it is also a potent risk factor for cardiovascular morbidity and mortality, and it has a prevalence of around 10% of adults, with incident end-stage renal disease (ESRD) increasing much faster than expected from CKD growth [3]. Elevated blood pressure (BP) is an established cause, but can also be a consequence of kidney injury [4], and hypertension prevalence rates are >90% in individuals with advanced CKD [5]. Thus, all previous major guidelines in the field have put increased emphasis on the quick diagnosis and aggressive control of BP in CKD patients [2, 4, 6, 7].

Despite substantial efforts from health authorities and effective treatment options being available for decades, BP control rates in the general population remain low in many countries [8] and they are even worse in CKD patients [5]. Of note, reduced hypertension awareness leading to inadequate treatment is proposed as a major factor contributing to poor control, both in the general population and individuals with CKD [5, 8], highlighting the need for proper diagnosis of elevated BP levels. Tra-

ditionally, hypertension diagnosis is based on clinic BP measurements during three separate visits, while other available strategies, such as home measurements and ambulatory BP monitoring (ABPM), the 'gold standard' of diagnosis, are reserved for uncertain cases, including suspicion of 'white-coat' and 'masked' hypertension [2].

A very important recent study [9] compared the cost-effectiveness of the three aforementioned strategies for diagnosis of essential hypertension. The authors performed a Markov-model analysis on a hypothetical primary-care population older than 40 years with a screening BP reading >140/90 mm Hg. They concluded that ABPM was clearly the most cost-effective strategy, producing cost-savings for all gender- and age-stratified groups studied and gains in quality-adjusted life years (QALYs) for older subjects. Clearly, the greater cost-effectiveness of ABPM was due to higher diagnostic accuracy in detecting hypertension [10], leading to effective treatment and associated reductions in cardiovascular events in more hypertensive individuals, and less unnecessary treatment of people without hypertension. Several methodological strengths support the validity of this study's conclusions [9]. The model was run separately for ten gender- and age-stratified groups; the study time horizon was particularly long and a reasonable annual discount rate was applied; periodic rechecking of BP was incorporated to allow for the possibility that peo-

ple not hypertensive at baseline could become hypertensive over time; cost inputs were based on published data and covered all potential sources of cost. Furthermore, gender- and age-specific risks of cardiovascular events were properly calculated, and clinical inputs on sensitivity/specificity of studied diagnostic options and relevant risk reductions with antihypertensive treatment were based on recent, high-quality, meta-analyses [10, 11]. Finally, the issue of uncertainty was extensively investigated in deterministic and further probabilistic sensitivity analyses, supporting the robustness of the results with limited exceptions.

As in all cost-effectiveness analyses, however, a number of unavoidable assumptions relating to potential limitations were also present [9]. The model considered treatment of hypertension as a dichotomous decision, but relevant recommendations suggest this to be based on an integrated approach to total cardiovascular risk [2]. The authors assumed that people with falsely diagnosed hypertension gain no benefit or harm from unnecessary treatment (as there were no data available to quantify relevant effects). Observational evidence suggests that the risks associated with BP are continuous down to 115 mm Hg systolic, but clinical trial data on treatment benefits for patients below current thresholds are controversial [12]. However, disease-labeling and unnecessary treatment almost certainly signifies an (even small) risk of side effects and QALY reductions. Treatment costs were based on most commonly used (and often much cheaper) generic drugs; in practice more expensive drugs are often also prescribed. The analysis only used cost and QALY inputs for first non-fatal cardiovascular events; repeat events were not modeled. Furthermore, the clinical endpoints used referred only to cardiovascular events and excluded other sources of morbidity associated with hypertension, most importantly CKD. Lastly, as in most relevant analyses, cost data were derived from a single country environment, rendering the generalizability of the study findings to other healthcare settings unknown. It is interesting, however, that a hypothetical correction of most of these limitations would rather result in higher lifetime costs associated with hypertension, indicating that cost-savings from correct diagnosis with ABPM could in reality be greater. In other words, most of the above assumptions lead to more conservative estimates and, if absent, would further strengthen the case for ABPM; thus, quite paradoxically, these limitations rather add to the study conclusions.

Without doubt, this study has direct clinical implications for the general population. Although the advan-

tages of ABPM are widely accepted [2], its everyday use is currently rather restricted worldwide in tertiary hypertension centers, with relevant infrastructure and experience; in contrast, this study highlights the need for a major shift in general practice, with ABPM being used in all patients with an elevated clinic reading [9]. Furthermore, the implications of the usefulness and related cost-effectiveness of detecting hypertension with ABPM may be even more important for patients with CKD, for several reasons. Due the high prevalence of hypertension in patients with CKD [4–6], it is perhaps by far the most important risk factor for both kidney and cardiovascular disease progression in such individuals; thus, an accurate diagnosis of the exact BP levels may be much more critical in patients with CKD than in individuals without other co-morbidities. In addition, recent evidence suggests that the BP target to achieve renoprotection may be different within non-diabetic patients with CKD, with BP reduction to <130/80 mm Hg being beneficial for proteinuric CKD patients, but not necessary for those without proteinuria [13]. Given the inherent inaccuracy of clinic BP measurements [10], it may be difficult for the practicing nephrologist to delineate the exact BP in patients with kidney injury presenting with ‘borderline’ BP levels; this further exemplifies the utility of ABPM to secure accurate diagnosis and guide treatment decisions in patients with CKD. Finally, an old problem of the practicing nephrologists is that of adequate diagnosis of hypertension in patients with ESRD undergoing hemodialysis; pre- or post-dialysis BP levels are greatly confounded by numerous issues, including fluid status before, as well as magnitude and speed of fluid removal during a dialysis session, and are known to poorly reflect the true BP during the interdialytic period [14]. As evident by recent data, the use of ABPM over 48 h (i.e. covering both the dialysis and interdialytic period) may be the best way to assess true BP levels and properly diagnose hypertension in these patients [15], thus providing another reason for increased ABPM use in nephrology units.

In addition to the above issue of adequately diagnosing hypertension, ABPM has long been known to have several other advantages, including superior predictive value for both intermediate outcomes of target-organ damage and cardiovascular morbidity and mortality. This is largely attributed to ABPM providing information on factors such as non-dipping status and BP variability, which have been shown to predict target-organ damage, but cannot be captured with clinic BP readings [16]. Current evidence derived from numerous observational

studies in a wide range of populations (such as patients with essential hypertension, type 2 diabetes mellitus, and the elderly) clearly suggests the higher prognostic value of ABPM also for renal outcomes, including progression of albuminuria, decline of estimated glomerular function (eGFR), and incident ESRD, as recently summarized elsewhere [17]. Moreover, with regard to patients with CKD and ESRD, observations for increased frequency of non-dipping status and altered BP variability associated with target-organ injury [18, 19] have progressively evolved to several pieces of evidence, suggesting superiority of ABPM in predicting cardiovascular events and mortality [20, 21]. A recent study on this issue followed 436 patients with CKD (mean eGFR 43 ml/min/m²) for a median of 4.2 years with end-points time to renal death (ESRD or death) and time to fatal and non-fatal cardiovascular events; the results showed a clear stratification of risk with quintiles of daytime and, particularly, nighttime BP levels recorded with ABPM, whereas office BP did not have any prognostic associations [22].

Finally, another major advantage of ABPM is to aid towards improved control of hypertension, which, as discussed above, remains very poor in the general population and even more so in patients with CKD [5, 8]. The notion of inadequate control is confounded by a high prevalence of the 'white-coat' effect within patients with essential hypertension receiving treatment [23]; a similar problem is also suggested in hypertensive individuals

with CKD [20]. Due to the above, use of ABPM to identify the exact levels of BP is currently proposed as a basic step in the investigation of people with poorly controlled or 'resistant' hypertension, many of which also have CKD [23]. Further, due to the aforementioned association of nighttime BP with increased risk in patients with CKD, previous studies have used ABPM to assess the effect of nocturnal dosing of medications on BP [24]. The most recent of them randomized 661 hypertensive patients with various stages of CKD to take all prescribed hypertension medications upon awakening or at least one at bedtime for a median of 5.4 years; the latter group had lower sleep-time BP, better control rate, and an adjusted risk for cardiovascular events that was approximately one-third of that of patients who took all medications upon awakening [25].

Overall, in patients with CKD the use ABPM may confer a number of important benefits, which start from accurate risk stratification and may extend to proper diagnosis of BP levels and assessment of 24-hour BP control. Following recent important evidence on the cost-effectiveness of ABPM in detecting hypertension in the general practice, it would be interesting to see future studies incorporating data on the prognostic value of ABPM in CKD patients to explore the accuracy and the cost-effectiveness of ABPM for assessing hypertension diagnosis and treatment adequacy in CKD.

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