Hypertension Research (2011) 34, 39–40

www.nature.com/hr

COMMENTARY

Going beyond the optimization of pharmacotherapy

Lionel Thevathasan and Peter Bramlage

Hypertension Research (2011) **34,** 39–40; doi:10.1038/hr.2010.207; published online 4 November 2010

Hypertension affects approximately one billion adults worldwide,[1] with control rates hovering around 50% at best,[2,3] urging us to do better. On the other hand, as we strive to better manage our patients and control risk factors, emerging data highlights that our efforts are often still suboptimal. Furthermore, guidelines ask us to treat to ever-lower targets and steer us toward more stringent goals. Concerted efforts have, therefore, been initiated to reduce blood pressure levels at both the individual and the population levels.[4,5]

Pharmacotherapy for hypertension has advanced in recent years with the development of new drug classes, some of which profess to have minimal side effects, and fixed-dose combinations in a variety of cross-class combinations.[6] Thus, by necessity, a great deal of focus has been cast on the intensification of therapy, which is clearly important. However, as stated by Heisler *et al.*,[7] the decision to do so should not be based solely on blood pressure level; it must also address the ability of the patient to adhere.

Compliance or adherence to antihypertensive therapy is a rich area of research, and new strategies are needed to better manage hypertensive patients by multiple approaches. These include reinforcing the patient–doctor relationship, selection of the most appropriate drug regimen, using home blood pressure monitoring as a means of patient empowerment and compliance monitoring, all of which can be implemented by a number of techniques.[8]

WHY DO SO MANY PATIENTS REMAIN POORLY CONTROLLED?

It is our contention that, although there is global recognition that hypertension management requires a multi-level systemic approach, we are reaching the 'ceiling' in controlling blood pressure because we do not necessarily respect the many dimensions required to optimally manage patients, and the progression to resistance or pseudoresistance may be a phenomenon related more to compliance than to true underlying pathology.[9] All the multi-targeted measures employed to reduce blood pressure will be in vain if a patient neither takes the tablet nor adheres to a specific strategy, either intentionally or otherwise.

In this issue of *Hypertension Research*, Ceral *et al.*[10] report on the intentional lack of compliance in hypertensive patients deemed to have resistant hypertension at a single center in the Czech Republic. The investigators employ a technique that is well established in other areas of clinical medicine—measuring serum drug level—but they apply it to a novel use: assessment of antihypertensive medication nonadherence. They found that in patients whose blood pressure remained uncontrolled despite administration of at least three antihypertensive drugs from different classes, approximately two-thirds did not have measurable serum drug levels of at least one of the prescribed drugs, despite patient verification that they had taken their medications. Surprisingly, one-third of patients had none of the drugs detected in their serum, implying complete lack of ingestion of medications.

Although the authors present limited information on the duration of hypertension, appropriateness of the combination of classes of medications or numbers of switches between therapies (a factor known to promote nonadherence, as well as current or previous side effects on medication[10]), this report is valuable for a number of reasons.

First, the authors provide us with another tool by which we can measure the compliance or adherence of patients to their medications. The true added value of this tool may lie more in the time afforded to understanding patient barriers and evaluating the many facets of the patient's life. Such value could help the provider prescribe a more suitable management strategy. However, given that up to 35% of patients (from clinical trial data) may have resistant hypertension, an additive approach such as that described by Ceral *et al.* will be a welcome technique for selected patients.[9]

Second, as the authors report, this technique offers a simple binary outcome of whether certain patients are taking their medications or not. The utility would be reserved for those whose disease is deemed severe and in whom an evaluation of serum drug level is important enough to warrant corrective measures that would otherwise have been substituted by a comprehensive platform of further investigations of other pathological causes for resistant hypertension.

Last, this approach may also be used in clinical trials in resistant hypertension, not only as a screening tool to evaluate those deemed 'resistant', thereby excluding those who are nonadherent, but also as a method to evaluate medication compliance throughout the course of a clinical trial.

Although the identification of these nonadherers is of value, one would need to be sure that the management strategy implemented as a result of this new tool would be clinically efficient and cost effective before this strategy was adopted widely. As there is a constellation of factors contributing to poor compliance, this may help providers identify patients for whom more time, education and sheer effort are required to reduce the risk of cardiovascular events.

CONFLICT OF INTEREST

The author declares no conflict of interest.

Dr L Thevathasan and P Bramlage are at the Institute for Cardiovascular Pharmacology and Epidemiology, Menzelstrasse 21, Mahlow 15831, Germany.
E-mail: lionelthe@me.com

1 Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet* 2005; **365**: 217–223.
2 Egan BM, Zhao Y, Axon RN. US trends in prevalence, awareness, treatment, and control of hypertension, 1988–2008. *JAMA* 2010; **303**: 2043–2050.
3 Sharma AM, Wittchen HU, Kirch W, Pittrow D, Ritz E, Goke B, Lehnert H, Tschope D, Krause P, Hofler M, Pfister H, Bramlage P, Unger T. High prevalence and poor control of hypertension in primary care: cross-sectional study. *J Hypertens* 2004; **22**: 479–486.
4 Bakris G, Hill M, Mancia G, Steyn K, Black HR, Pickering T, De Geest S, Ruilope L, Giles TD, Morgan T, Kjeldsen S, Schiffrin EL, Coenen A, Mulrow P, Loh A, Mensah G. Achieving blood pressure goals globally: five core actions for health-care professionals. A worldwide call to action. *J Hum Hypertens* 2008; **22**: 63–70.
5 Bramlage P, Thoenes M, Kirch W, Lenfant C. Clinical practice and recent recommendations in hypertension management—reporting a gap in a global survey of 1259 primary care physicians in 17 countries. *Curr Med Res Opin* 2007; **23**: 783–791.
6 Bramlage P, Hasford J. Blood pressure reduction, persistence and costs in the evaluation of antihypertensive drug treatment–a review. *Cardiovasc Diabetol* 2009; **8**: 18.
7 Heisler M, Hogan MM, Hofer TP, Schmittdiel JA, Pladevall M, Kerr EA. When more is not better: treatment intensification among hypertensive patients with poor medication adherence. *Circulation* 2008; **117**: 2884–2892.
8 Waeber B, Burnier M, Brunner HR. How to improve adherence with prescribed treatment in hypertensive patients? *J Cardiovasc Pharmacol* 2000; **35**(Suppl 3): S23–S26.
9 Pisoni R, Ahmed MI, Calhoun DA. Characterization and treatment of resistant hypertension. *Curr Cardiol Rep* 2009; **11**: 407–413.
10 Ceral J, Habrdova V, Vorisek V, Bima M, Pelouch R, Solar M. Difficult-to-control arterial hypertension or uncooperative patients? The assessment of serum antihypertensive drug levels to differentiate non-responsiveness from non-adherence to the recommended therapy. *Hypertens Res* 2011; **34**: 87–90.