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REVIEW

Putting the Theory into Practice—Maximizing Real-Life Blood Pressure Control for Hypertensive Patients by Improving Adherence to Therapy

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Abstract: The prevention and treatment of hypertension is a public health challenge, in part because most patients treated for hypertension do not achieve adequate blood pressure (BP) control. Noncompliance is a common cause, influenced by factors such as tolerability, tablet load, complexity, efficacy, and cost. Additionally, patients may question the need for lifetime treatment of an asymptomatic condition with medications that often reduce their quality of life. Clinical inertia, underdosing, and limited use of combination and new treatments also contribute. Strategies to improve BP control include the use of highly effective, long-acting, and well-tolerated antihypertensives that encourage adherence, with efficacy that extends beyond the 24-hour dosing period to provide lasting protection and mitigation against the effects of missed doses. Angiotensin receptor blockers (ARBs) encourage higher adherence than other antihypertensives, and the ARB telmisartan offers 24-hour BP reductions. Ultimately, successful management of hypertension requires the physician to help the patient understand the seriousness of their condition, the implications of noncompliance, and the need for lifetime treatment.

Keywords: hypertension, cardiovascular disease, adherence, tolerability, angiotensin receptor blockers

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Introduction

Hypertension is a major risk factor for fatal myocardial infarction (MI) and an important risk factor for nonfatal stroke: a long-term 7 mm of Hg increase in diastolic blood pressure (BP) is associated with a doubling in stroke risk.[1] Stroke remains one of the most common hypertension-induced diseases worldwide. In a recent population study of stroke mortality in elderly primary care patients across Spain, poor BP control was shown to account for 66% of the variance in stroke mortality.[2] For patients with heart failure secondary to MI, prognosis is as poor as it is for some cancers, and morbidity is high.

One of the difficulties with managing hypertension is that, like raised cholesterol, it is asymptomatic. Consequently, hypertension often remains undiagnosed until patients visit their general practitioner for another reason and their BP is checked as a routine procedure or, worse still, after a patient is admitted to the hospital having suffered a hypertension-induced event. Data from the recent National Health and Nutrition Examination Surveys (NHANES) suggest that, between 1988 and 2000, the prevalence of undiagnosed hypertension remained constant at around 30%.[3]

Hypertension is estimated to affect over one billion individuals worldwide and, with the population aging, prevalence is predicted to increase by around 30% by 2025.[3,4] Yet, despite worldwide initiatives to increase awareness of the benefits of reducing BP to within recognized limits, and significant advances in antihypertensive treatments, hypertension remains poorly controlled.[3,5–9] This paper discusses the factors that can contribute to lack of BP control in the hypertensive population, including noncompliance, and explores how BP control rates can be improved through the use of longer-acting, more tolerable antihypertensive agents and improved patient understanding.

Benefits of BP Control

The importance of hypertension treatment is undisputed, with the total cost of high BP in the United States for 2010 estimated at $76.7 billion,[10] yet physicians often face resistance from patients to long-term treatment (a misunderstanding of the hazard may lead to a form of nihilism—"I've got to die of something, doctor"). But the consequences of poor BP control are not just increased risk of cardiovascular (CV) death. The consequences of surviving a CV event must also be considered. Stroke prevention is particularly important because of the life-long consequences of stroke survival.[2] With one-third of stroke victims being left dependent or moderately disabled,[10] and eight million working days lost each year in the UK due to stroke,[11] the morbidity associated with stroke has major implications for the wider economy as well as for individual patients.

It is vital that physicians encourage patient acceptance of the concept of adequate BP control, especially in those elderly patients where hypertension presents a significant threat. By treating BP adequately, it is estimated that coronary events could be reduced by 20%–25%, stroke could be reduced by 35%–40%, and the incidence of heart failure could be reduced by >50%.[3,12,13] Effective BP management could avoid around 7 million premature deaths worldwide.[14]

Rates of BP Control in the Hypertensive Population

In addition to lifestyle modifications, clinical guidelines recommend BP control rates of ≤140/90 mm of Hg.[3,12,14] However, evidence suggests these levels are rarely achieved and BP control rates remain low globally, with little improvement seen during the past 20 years. Data from the 2003–2006 NHANES United Stages survey[15] show that BP control was achieved in just 44.1% of hypertensive patients—a small increase from the 34% control rate recorded in 1999–2000 (Fig. 1).[3,15] Europe fares no better: findings from the recent European Action on Secondary Prevention by Intervention to Reduce Events (EUROASPIRE) survey report that between 2006 and 2007, only 44% of patients examined 6 months after a coronary event achieved BP control to within recommended levels.[16] This rate has remained relatively unchanged since the first EUROASPIRE survey was conducted in 1995.[5,6]

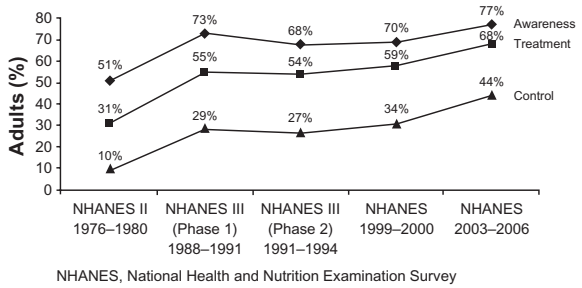

Figure 1. Hypertension awareness, treatment and control: United States, 1976–2000.[3]

The importance of BP control is greater in high-risk patients, including the elderly, diabetics, and those patients with a history of dyslipidemia, heart disease, stroke, or renal disease.[3,8,12,14] Clinical guidelines recommend more stringent BP control levels in these patients, yet hypertension in high-risk populations remains considerably undermanaged.[9,10] In a 1989–1990 study of hypertension prevalence and management in diabetic patients from 16 European countries, only 11% of patients with hypertension had BP below the 130/85 mm of Hg target, and just 17% were <140/90 mm of Hg.[8] More recently, an observational study of >12,700 hypertensive patients in Italy showed that, in treated patients with diabetes, BP control <130/80 mm of Hg was achieved in just 3% of patients.[7]

Systolic BP Control as Predictors of Events

BP control may be less common for systolic BP (SBP) than for diastolic BP (DBP).[17–19] In a post hoc analysis of BP values of hypertensive patients from the Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) study,[20] SBP control was shown to be significantly less prevalent than DBP control.[18] This was the case for office, home, and 24-hour ambulatory BP measurements; therefore, the authors could not attribute this observation to a "white-coat" effect.[18]

The management of SBP control has important clinical implications, since it is argued that SBP may be a better predictor of CV risk than DBP.[12,21–23] For example, a study found that patient treated for hypertension had a two-fold increase in CV mortality as compared with age- and gender-matched untreated subjects from the general population; SBP control was found to be positively correlated with CV mortality whereas DBP was negatively correlated with CV mortality.[23] The relationship between SBP and DBP is further confounded because SBP increases with age, whereas DBP has been shown to peak at around 50–60 years in men and at 60–70 years in women, then declines thereafter.[12,24,25] Thus, SBP control is of particular importance in elderly hypertensive patients.

Reasons for lack of BP control

There are numerous factors that contribute to the uncontrolled BP control seen in many patients. In some cases, BP may be affected by the lifestyle of the patient themselves (eg, being overweight, smoking, drinking excessive alcohol), and simple changes can make a big difference.[26,27] However, these lifestyle changes are not always easy to implement and motivation can be an issue. In some cases, the physician may carry some responsibility if they are not testing their patients and therefore not aware of the problem, or if they do not educate their patients or manage their medication correctly. However, if lifestyle changes have been implemented and if both the patient and physician are in agreement with the need for medication, the medication itself may be the cause of the poor control (eg, high cost, intolerable side-effects, or complex treatment regimen with many medications). Finally, other factors, such as the use of home blood pressure measurements or a therapeutic team-based approach, with the inclusion of pharmacists, may help some patients to achieve BP control.[28–30]

The reasons for poor BP control are multifactorial, but one factor we are able to address and should prioritize is that of patient compliance by utilizing the most appropriate treatment regimen.

Patient Compliance

Antihypertensive therapy can only be effective if the patient is motivated to take their prescribed medication, and has a thorough understanding of the seriousness of their condition and the need for continued treatment. We know that, for short-term treatment, compliance is relatively good; but patients are often asked to take drugs over a long number of years. For many, the use of antihypertensive medications that compromise their quality of life (QoL) is more troubling than having symptomless elevated BP. A patient frightened as a result of a hypertension-related event will initially be highly motivated to comply with their prescribed medication. But once discharged, this determination often fades and patients start to question why they should continue taking multiple medications for many years that, at best, make them feel no better at all and, at worst, can have discomforting or inconvenient side effects.

Poor compliance with antihypertensive treatments remains a common and significant cause of inadequate BP control. Recently, a longitudinal database study of 4,783 patients prescribed once-daily antihypertensive treatments during 1989 through 2006 reported that half had stopped taking their prescribed treatments

within 1 year.[31] While a small proportion of this drop in adherence was attributed to poor execution of the dosing regimen, discontinuation of treatment accounted for most nonadherence.[31]

Patient misunderstanding or denial of their condition, lack of involvement in their treatment plan, medication side effects, and complex treatment regimens all contribute to noncompliance. In countries where patients pay for their drugs, cost can also significantly influence whether they will persist with treatment.

There are also difficulties associated with physician behavior, including failure to inform and motivate patients, infrequent monitoring, clinical inertia, underdosing, and failure to initiate better and/or simpler-to-use antihypertensive regimens. The majority of hypertensive patients require two or more antihypertensive drugs to achieve BP goals; clinical guidelines recommend the use of multidrug therapy, specifically in patients with BP levels >20/10 mm of Hg above normal.[3,12] Yet within clinical practice, physicians typically prefer sequential monotherapy regimens that rarely achieve effective BP control, thus increasing noncompliance.[9,12,17,32] In a cohort study of >445,000 patients newly prescribed antihypertensive monotherapy between 1999 and 2002 in Italy, initial monotherapy was maintained in only 38% of patients at 6 months, declining to just 6% after 5 years.[32] Over 30% of patients discontinued treatment after 6 months, rather than switching to or combining with another class of antihypertensive; this increased to 50% after 5 years.[32]

Misleading BP measurements can result in treatment discontinuation. Many hypertensive patients (especially those prescribed diuretics) take a single dose in the morning and measure their BP later in the day, by which time it is likely to be under control and affected by normal diurnal variations. These skewed readings can give patients and physicians a false sense of security, diminishing motivation to continue treatment. Ambulatory BP monitoring may be a more reliable approach, but is not always feasible, especially given its cost and complexity.

Overall, however, tolerability is extremely important: the patient's experience with a drug determines their willingness to continue treatment. Drug effects on QoL vary among individuals and among antihypertensives.[33] A recent study[32] found that treatment discontinuation correlated with drug class. Using patients prescribed angiotensin-converting enzyme (ACE) inhibitors as a reference, discontinuation rate was shown to be lower in patients starting treatment with an angiotensin II receptor blocker (ARB), higher with calcium channel blockers (CCBs), and highest of all in patients prescribed diuretics or β-blockers at initiation of treatment.[32] These results correlate with other, longer-term, studies evaluating the effect of initial drug choice on persistence with treatment.[34,35] In a database study of >22,000 newly diagnosed hypertensive patients, lowest persistence after 6 months and 4.5 years of observation was seen in patients initially prescribed diuretics, followed by patients prescribed β-blockers or CCBs.[34] Patients prescribed an ACE inhibitor were most likely to persist with treatment.[34] A cohort study of 15,175 patients receiving antihypertensive therapy showed a similar picture: persistence in the ARB class was statistically greater than all other drug classes at 1, 2, and 3 years, and was maintained versus CCBs, β-blockers, and diuretics after 4 years, with a trend for superiority over ACE inhibitors.[35] Around half of the patients in the β-blocker and diuretic class were not receiving any antihypertensive therapy by 4 years.[35]

In a pharmaco-epidemiologic survey of primary care physicians, secondary care specialists, and hypertensive patients in Italy during 1996, physicians attributed discontinuations or drug switching to inadequate BP control in 51.2% of patients, and to treatment side effects in 34.5% of patients, with the greatest incidence of side effects being observed with CCBs.[9] Rather interestingly, patients themselves most commonly gave "drug side effects", rather than inadequate BP control (53.3% versus 34.1%, respectively) as the reason for switching medication (Fig. 2).[9] Side effects are clearly a complex issue, as their symptoms

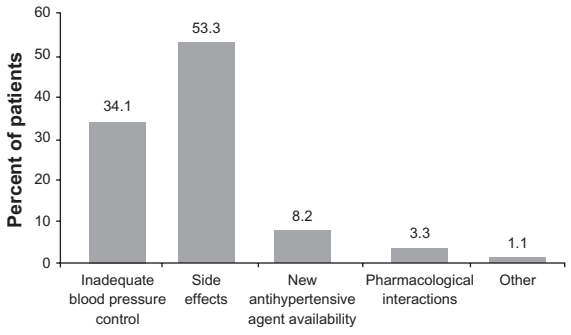

Figure 2. Patients' reasons for switching antihypertensive therapy. Reprinted with permission.[9]

and impact are subjective. Nevertheless, given their importance in patient compliance, minimizing side effects should be a key factor in treatment choice.

Improving Patient Compliance and BP Control

Longer-acting antihypertensives, with effects that extend beyond the 24-hour dosing period, are useful in mitigating the effects of noncompliance (such as the impact of missed doses). Evidence suggests that few patients take their prescribed medication on a regular basis; a 2008 study found that 95% of hypertensive patients missed a single dose at least once a year; 48% took at least one drug holiday (>78 hours) a year; and half missed a day's dose once a month.[31] Missed doses have a significant impact on BP control, putting patients at increased risk of events—notably during the risky early-morning period, when BP is known to surge. Thus, there is a need for agents that can provide sustained BP control even if a dose is missed.

The once-daily CCB, amlodipine, has demonstrated effective antihypertensive control throughout the dosing interval;[36] a number of studies found that, during short periods of noncompliance, its antihypertensive efficacy is more reliable than the older CCB, nifedepine.[37–39] Among the ARBs (considered the best-tolerated class of antihypertensive), telmisartan has the longest plasma half-life, which translates into potent BP reductions and long-lasting effects.[40–45] The Micardis® Missed Dose (MICADO®) trials compared the effects of telmisartan (80 mg) with high-dose valsartan (160 mg) on BP control during the last 6 hours of the dosing interval when occurrences of BP-related complications are at their highest, and also during the 24 hours following a missed dose.[42] Telmisartan was shown to produce a significant reduction in ambulatory 24-hour SBP and DBP compared to valsartan during the last 6 hours of the dosing interval, and provided significantly better BP control following a missed dose.[42] Two studies have also demonstrated the sustained antihypertensive effects of candesartan (16 mg) following a missed dose.[46,47] The comparator in both studies was losartan (100 mg), which demonstrated a reduction in efficacy. The newest class of antihypertensive is the direct renin inhibitor, of which aliskiren is the only currently available. Aliskiren has a half life approaching 40 hours, thus provides a long-lasting dosing effect. Available studies indicate that aliskiren (150 mg) has similar effects to ARBs in terms of efficacy and safety, and may be another useful treatment option.[48]

Newer drug classes of antihypertensives have generally had better tolerability than the older classes, such as diuretics, β-blockers, and CCBs. ACE inhibitors remain a popular choice of therapy, although the introduction of ARBs (having a similar efficacy to ACE inhibitors, but with improved tolerability) has increased the therapeutic options. In the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET®), fewer permanent discontinuations were reported in patients treated with telmisartan than in patients treated with the ACE inhibitor, ramipril, during a 2-year follow-up—despite patients being screened for ACE inhibitor tolerance and active efforts to maintain adherence throughout the study (Fig. 3).[49] ACE inhibitors are commonly associated with adverse effects (notably cough), and it is estimated that ~20% of patients (particularly women and Asians) are unable to tolerate their use.[50,51] In the Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND®), fewer patients in the telmisartan group permanently discontinued treatment than patients receiving placebo.[50] Since patients in the placebo arm received numerous antihypertensives to achieve BP control (including β-blockers, CCBs, and diuretics), this result is consistent with superior tolerability of telmisartan, compared with other antihypertensive classes of medication. For patients intolerant of ACE inhibitors, or achieving inadequate BP control, telmisartan is an effective treatment option. Potent 24-hour BP reductions and excellent tolerability can encourage greater patient adherence, which may translate into more effective long-term CV protection.

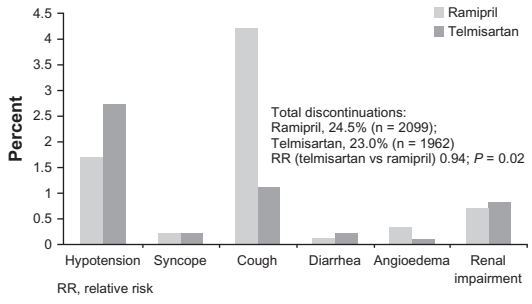

Figure 3. Discontinuations from the ONTARGET study.[49]

Conclusion

Hypertension remains persistently under managed, despite its public health impact and treatment potential. Poor patient compliance, as well as physicians' reluctance to employ simple to use treatment regimens (eg, multidrug combination products), and poor patient communication, all contribute to the low levels of BP control targets being achieved worldwide. Evidence-based management of hypertension requires interventions that not only lower BP effectively and reduce CV risk, but are also well tolerated. The newer agents, such as telmisartan, which combines demonstrated CV risk reduction with a long duration of action and placebo-like levels of tolerability, have an important place in the future management of hypertensive patients. Ultimately, however, choice of treatment will be dependent on patient and physician preference. The least cost-effective drug is the one that stays in the medicine cabinet. Treatment for life requires a well-tolerated drug, but also requires the patient to understand the seriousness of their condition and the need to take drugs, perhaps even for life. If we are to avoid a continued increase in the incidence of hypertension-induced morbidity and mortality, physicians must work with patients to help them achieve this understanding and adhere to their prescribed treatment.

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