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EDITOR'S COMMENTS

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The important African American Study of Kidney Disease (AASK) was designed to compare the impact of lowering blood pressure to two different blood pressure goals defined as “usual” (a mean arterial pressure [MAP] of 102-107 mm Hg) or “low” (a MAP of <92 mm Hg). In addition, using a 3x2 factorial design, 3 different antihypertensive drug classes were compared as first line therapy: an ACE inhibitor (ramipril), a dihydropyridine calcium antagonist (amlodipine), and a β -blocker (metoprolol). Importantly, the protocol specified three primary comparisons: “low” versus “usual” blood pressure goal and two specific treatment comparisons: ramipril versus metoprolol and amlodipine versus metoprolol. It was surprising, therefore, that an interim publication appeared in JAMA in June 2001 reporting a comparison between ramipril and amlodipine ahead of completion of the trial, culminating in the conclusion that the amlodipine arm should be discontinued. By the authors’ own admission, when planning the study, the ramipril versus amlodipine comparison was thought likely to be complicated by the initial acute divergence of proteinuria and glomerular filtration rate (GFR) soon after initiation of treatment. As such, this was designated a secondary—not primary—comparison.

The interim report in JAMA also introduces the post-hoc decision of the investigators to separate the data into those with and without overt baseline proteinuria (defined arbitrarily but reasonably as

a urinary protein:creatinine ratio of >0.22, equating to a urinary protein excretion of ~300 mg/day). The justification given for these criteria for analysis is that data had emerged suggesting beneficial effects of ACE inhibition in protecting against progressive renal disease—especially in patients with overt proteinuria.

The interim study report on the discontinuation of amlodipine in AASK concluded that, amongst participants with a urinary protein excretion above the threshold specified above, randomisation to ramipril was associated with a 36% slower mean rate of decline of GFR (primary end point of the study) over 3 years when compared to those randomised to amlodipine and a 48% reduction in a composite of prespecified clinical end points. This “proteinuric” cohort that forms the basis of the interim report comprises about a third of those patients randomised to ramipril or amlodipine. However, when the entire cohort is analysed (the original intention of the study), there was no difference between ramipril and amlodipine in the rate of decline of GFR over 3 years. On the contrary, the total mean GFR decline to 3 years was almost 1 mL/min/yr faster in the ramipril group than in the amlodipine group in those with a GFR of at least 40 mL/min/1.73 m². In real terms, this equates to a GFR loss rate of 1.53 mL/min/yr in the ramipril group and only 0.55 mL/min/yr in the amlodipine group. This is, in part, accounted for by the acute rise in GFR observed in the amlodipine treated group but received a lack of emphasis in the report or the subsequent discussion. When urinary protein excretion was elevated into the proteinuric range and/or GFR was below 40 mL/min, the situation was reversed, with those randomised to ramipril exhibiting a lower rate of decline of GFR than those randomised to amlodipine. This raises some interesting questions. For the majority of the randomised patients who had a urinary protein:creatinine ratio <0.22 and a baseline GFR greater than 40 mL/min, there was no difference in the primary end point; in fact, there was a smaller loss of GFR over 3 years in the amlodipine group! Only in the group with overt proteinuria and more advanced renal impairment did ramipril appear to convey an advantage over amlodipine. Unfortunately, this key differentiation and the imperfections, indeed dangers, of post-hoc and nonprespecified analyses was lost in the publicity that preceded publication of the data and discussion that followed in the interim report.

The decision to stop the amlodipine arm of this trial has inevitably reinforced, for some, the simplistic notion that ACE inhibition is good and calcium channel blockade is bad, but for most patients and their physicians, who mainly treat patients without proteinuria or renal impairment, it has caused confusion, concern, and dismay.

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EDITOR'S COMMENTS

In this issue Poulter and Williams discuss the recent decision to end the amlodipine arm of the AASK trial, an important ongoing study in African-American hypertensives with renal disease. Several important issues are raised which are relevant to many previous and current outcome trials. Indeed the issue of interim analyses and secondary endpoints has been a concern in several recent studies. The finding in the AASK trial that amlodipine seems to have a better effect on renal function than ramipril or metoprolol among the group with the best baseline renal function is similar to the observations with captopril in the study of type I diabetics in which only those with baseline serum creatinine >1-1.5 mg/dL showed a decreased rate of progression of renal impairment. The “bottom line” message seems to be the caveat to reserve judgement about the implications of the AASK trial until the study is completed. Unfortunately, judgement regarding any potential beneficial effect of amlodipine, particularly as an agent to lower blood pressure aggressively, may be lost in view of the termination of that portion of the study. Also in this issue, Ram and Fenves provide practical insight into an unusual and often perplexing problem in their discussion of refractory hypertension. Their suggestions provide a helpful checklist for understanding and dealing with this challenge.

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Editor-in-Chief

A further problem is that many physicians now think that AASK was a study comparing ramipril with amlodipine and that it has finished! The final results may well be overshadowed by these interim results and be largely ignored, much in the same way that the final and, to some extent, contradictory results of the ABCD trial, were eclipsed.

Many will have lost sight of the fact that AASK is a study of patients with hypertensive nephrosclerosis in a poorly studied patient population. All trials of renoprotection so far have emphasized that the most effective protective strategy is to ensure that blood pressure is controlled. A key question remains; how low should blood pressure be lowered for optimal renoprotection? AASK was uniquely designed to address this key question. Additional benefits unique to a drug class have received much emphasis but they are likely to be, at best, additive and complementary to blood pressure control. Nobody will get renoprotection with ramipril if the systolic blood pressure is 180 mm Hg. Moreover, no single antihypertensive agent alone will likely control blood pressure, especially an ACE inhibitor in an African American population. All such patients with nephrosclerosis will require a cocktail of antihypertensive therapy. Indeed, in AASK on average more than 1.5 other antihypertensive drugs were added to each group—details of which we have been spared to date. In patients with proteinuria (microalbuminuria to overt proteinuria), blockade of the renin angiotensin system should form part of that treatment cocktail. Calcium channel blockers (CCBs) are so effective at lowering blood pressure, especially in African Americans, that it would be a tragedy if, on the basis of misinterpretation of the AASK interim report, the message was conveyed that such patients should not receive a CCB as part of their antihypertensive therapy. There is no evidence, even in patients with overt proteinuria, that the addition of a CCB to an ACE inhibitor or an angiotensin II receptor antagonist will blunt the renoprotective effects of these latter two drug classes. Moreover, the African American population is at especially high risk of stroke, more so than renal disease, and the evidence for stroke protection with CCBs is strong.

Finally, given that a key objective of the AASK study is to evaluate whether a lower blood pressure is better than usual blood pressure control, the AASK investigators present only “mean arterial pressure” data. This is not a clinical parameter that most clinicians are familiar with in routine clinical practice. Systolic and diastolic values need to be presented in the final report if the significance of the main outcome of this important study is not to be lost in clinical practice, where its findings will need to be implemented.

Randomised controlled trials are acknowledged as the gold standard study design. They are massively expensive and difficult to carry out and should therefore not be initiated without great care and consideration. Similarly, since biased or misinterpreted trials may do more harm than good, the decision to terminate trials early—particularly for post-hoc secondary endpoints—should only be made on the hardest of evidence. Surely this is not a lot to AASK? ■

Summary

Refractory hypertension is a term clinically used to characterize hypertension that fails to respond to an adequate regimen of at least 3 antihypertensive drugs in combination.

Failure to normalize the blood pressure can be due to a number of factors—patient related and doctor related. Refractory hypertension is perhaps more frequently encountered in hypertension specialty clinics rather than in a general setting because of the referral patterns. It is necessary to identify and manage refractory hypertension properly; otherwise patients with uncontrolled hypertension are at a greater risk of vascular complications. Patients with refractory hypertension are more likely to have end-organ damage such as left ventricular hypertrophy, renal insufficiency, and vascular disease.

The diagnosis of refractory hypertension should only be made after the patient’s compliance to a prescribed drug treatment is established. Once it is apparent that the patient truly has refractory hypertension, appropriate evaluation should be undertaken on the basis of history, physical examination, and laboratory findings. Therapeutic changes in the dosages and drugs must be attempted to control the blood pressure effectively. Under certain circumstances, an investigation should be undertaken to establish or exclude a secondary form of hypertension. A methodical approach is, as discussed in this article, to help manage refractory hypertension in a rational manner.

Refractory Hypertension

True refractory hypertension is somewhat unusual in the current management of hypertensive disorders. A majority of patients with uncomplicated primary hypertension respond to one or two drugs. Definitions have varied, but hypertension is considered refractory if the blood pressure cannot be reduced below 140/90 mm Hg in patients who are compliant with an appropriate triple-drug regimen that includes a diuretic, with all the components prescribed in near maximal or tolerated doses. For patients with isolated systolic hypertension, refractoriness has been traditionally defined as a failure of an adequate triple-drug regimen to reduce systolic blood pressure below 160 mm Hg. However, recent observations strongly suggest that the target level for systolic blood pressure should be <140 mm Hg.

Whereas refractory hypertension may be still encountered in specialized centers, its prevalence in the general population of hypertensive patients is quite low. As indicated in the introductory paragraph, most patients with chronic uncomplicated hypertension should respond to appropriate therapy.

Etiology

The major causes of refractory hypertension are listed in Table 1. When a hypertensive patient demonstrates resistance to standard or conventional therapy, proper management often requires the

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Table 1 Causes of Refractory Hypertension

<p>Pseudoresistance</p> <ul style="list-style-type: none"> • “White-coat hypertension” or office elevations • Pseudohypertension in older patients • Use of small cuff on very obese arm <p>Nonadherence to Therapy</p> <p>Volume Overload</p> <p>Drug-related Causes</p> <ul style="list-style-type: none"> • Doses too low • Wrong type of diuretic • Inappropriate combinations • Drug actions and interactions <ul style="list-style-type: none"> • Sympathomimetics • Nasal decongestants • Appetite suppressants • Cocaine • Caffeine • Oral contraceptives • Adrenal steroids • Licorice (as may be found in chewing tobacco) • Cyclosporine, tacrolimus • Erythropoietin • Antidepressants • Nonsteroidal antiinflammatory drugs <p>Concomitant Conditions</p> <ul style="list-style-type: none"> • Obesity • Sleep apnea • Ethanol intake of more than 1 oz (30 mL) per day • Anxiety, hyperventilation <p>Secondary causes of hypertension (e.g., renovascular hypertension, adrenal causes, and renal disease)</p>

identification of a possible cause. Before making dramatic therapeutic changes, certain questions should come to the physician’s mind: Does the patient truly have refractory hypertension? Are there any host/environmental factors? Does the patient have pseudoresistance? Are there drug reactions? Does the patient have a secondary form of hypertension such as renovascular hypertension? Are there any mechanisms (pressor) that are responsible for elevating the arterial blood pressure?

Pseudoresistance

It is not uncommon to see a patient whose clinic/office visit blood pressure measurements are higher than the levels obtained outside the office setting. This is referred to as “white-coat” hypertension. Although white-coat hypertension is often considered in the context of mild hypertension (stage I or II), in some cases refractory hypertension may reflect white-coat hypertension. Patients who have refractory white-coat hypertension do not demonstrate evidence of target organ damage despite very high blood pressure readings in the office/clinic. The disparity between the degree of hypertension and the lack of target organ damage can be supported by the measurement of home blood pressures, and or by obtaining ambulatory blood pressure recordings with an automatic device.¹

Another possible source of erroneous blood pressure measurement is pseudohypertension, found mostly in elderly individuals. Persistently high readings in the absence of target organ damage or

dysfunction may indicate pseudohypertension. This condition is due to the fact that the hardened and sclerotic artery is not compressible so that falsely elevated pressures are recorded—the Osler’s phenomenon.² Because of thickened arteries, a greater apparent pressure is required to compress the sclerotic vessel than the intra-arterial blood pressure requires. There is little doubt that pseudohypertension does occur in older individuals, yet its exact prevalence is not known. While some have advocated the use of intra-arterial blood pressure determination as a means of accurately making the diagnosis of this aberration, we believe this is usually not practical and unnecessary.

A far more common example of pseudoresistance is the measurement artifact, which occurs when the blood pressure is taken with an inappropriately small cuff in people with large arm circumference. With the patient in the seated position and the arm supported at heart level, the blood pressure should be taken with an appropriate cuff size to ensure accurate determination. The bladder within the cuff should encircle at least 80% of the arm. One has to be cautious, however, before dismissing an elevated reading as a measurement artifact, since patients with refractory hypertension experience a high rate of cardiovascular and other complications.

Noncompliance

Failure to follow a prescribed regimen is perhaps the most frequent cause of refractory hypertension. There may be legitimate reasons for patients’ noncompliance such as side effects, costs, complexity of the drug regimen, and lack of understanding. Social and personal factors may also play some roles in noncompliance. Noncompliance can be verified by periodic pill counts and also by inquiring about side effects.

Volume Overload

Volume overload from any mechanism³ may not only increase the blood pressure but also can offset the blood pressure lowering effects of many medications. Excessive salt intake causes resistance to antihypertensive drugs and can actually raise the blood pressure in salt-sensitive patients. The elderly and the African-American patients are particularly sensitive to fluid overload, as are patients with renal insufficiency and congestive heart failure. Many antihypertensive drugs such as direct vasodilators, anti-adrenergic agents, and most of the nondiuretic antihypertensive drugs cause plasma and extracellular fluid expansion, thus attenuating the antihypertensive effects. Of all the nondiuretic antihypertensive drugs, ACE inhibitors, angiotensin II antagonists, and calcium channel blockers (CCB) are least likely to cause fluid retention. The ankle edema seen with dihydropyridine CCBs is not due to volume overload, but is due to selective precapillary dilation of the blood vessels in the foot. Antihypertensive responsiveness can be reclaimed by restricting the sodium intake, adding or increasing the dose of a diuretic and, in some cases, switching to a loop diuretic from thiazides.

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Drug-related Causes

Hypertension may be seemingly refractory if the drugs are used in subtherapeutic doses or when an inappropriate diuretic is used, e.g., using a thiazide-type diuretic as opposed to a loop diuretic in patients with significant renal insufficiency, congestive heart failure, or in those on potent vasodilators such as minoxidil or hydralazine. Inappropriate combinations can also limit their therapeutic potential. Adverse drug interactions can raise the blood pressure in normotensive as well as in hypertensive patients. Such adverse interactions (Table 2) can occur as a result of alterations in drug absorption, metabolism, or in the pharmacodynamics of concomitant drugs administered for different indications. One example of unfavorable drug interaction is that between indomethacin and β -blockers, diuretics, and ACE inhibitors. Tricyclic antidepressants (no longer widely used) have a significant interaction with sympathetic blocking agents. Hypertension associated with renal insufficiency is often difficult to treat; hypertensive patients with reduced renal function generally require concomitant therapy with a loop diuretic such as furosemide, since thiazide diuretics do not work effectively in this clinical setting.

Table 2 Drug Interactions That May Lead to Resistant Hypertension

Antihypertensive Agents	Interacting Drugs
Hydrochlorothiazide	Cholestyramine
Propranolol	Rifampin
Guanethidine	Tricyclics
ACE Inhibitors	Indomethacin
Diuretics	Indomethacin
All Drugs	Cocaine, Tricyclics
All Drugs	Phenylpropanolamine

Of all the drugs listed in Table 1, the nonsteroidal antiinflammatory drugs (NSAIDs) are particularly important because of their treatment use by the public; these drugs attenuate the vasodilatory actions of (intrarenal) prostaglandins, thus inhibiting natriuresis and causing volume expansion, resulting in blood pressure elevation.⁴ Therefore, in patients with refractory hypertension, NSAIDs should be discontinued if possible. Recent observations suggest that cyclooxygenase-2 (COX-2) inhibitors might also exert adverse effects on kidney function and on blood pressure levels.⁵⁻⁸ Hence, the possible consequence of COX-2 inhibitors should be considered in the evaluation of patients with hypertension. It is important to inquire about NSAID use in patients as many of them may not list these among their prescription medications. Estrogens as a component of oral contraceptive preparations may also raise the blood pressure,⁹ but hormonal replacement therapy has no adverse effect on blood pressure and may even be beneficial for cardiovascular protection.

Concomitant Conditions

It is claimed that cigarette smoking can interfere with blood pressure mechanisms.¹⁰ Obesity often is a factor in the occurrence of

refractory hypertension. Obstructive sleep apnea is being increasingly recognized as a possible factor in the development of resistant hypertension. Excessive alcohol consumption (more than 1 oz or 30 mL) clearly raises the systemic blood pressure, sometimes to dangerously high levels.¹¹ We have occasionally witnessed panic attacks and hyperventilation as etiologic factors in some patients with refractory hypertension. Similarly, chronic pain may be associated with marked hypertension.

Secondary Causes of Hypertension

In some of the patients with refractory hypertension, the underlying cause may be a secondary form of hypertension such as renovascular hypertension¹² or other identifiable etiologies (Table 3). Conversely, patients with a secondary form of hypertension may simply present with resistant hypertension. The sudden loss of effectiveness of a previously stable antihypertensive regimen should raise the suspicion of renovascular disease or other secondary forms of hypertension. In a broader context, certain hemodynamic and/or humeral mechanisms can also result in severe/resistant hypertension that should be corrected.

Table 3 Selected Examples of Secondary Forms of Hypertension That May be Resistant to Antihypertensive Therapy

- Renovascular Hypertension
- Primary Aldosteronism
- Pheochromocytoma
- Hypothyroidism
- Hyperthyroidism
- Hyperparathyroidism
- Aortic Coarctation
- Renal Disease

Management of Refractory Hypertension

Proper management of refractory hypertension entails a systematic approach based on the considerations described in the preceding sections. It should be emphasized that, since uncontrolled hypertension can cause significant morbidity and mortality, haphazard changes in the treatment plan should be avoided. An overall management approach should be based on careful evaluation and rational therapy.

Evaluation and Assessment

When a patient's blood pressure does not respond satisfactorily, at the outset, one has to consider whether the patient has pseudoresistance due to white-coat hypertension, pseudohypertension in the elderly, or measurement artifact. In some individuals it is appropriate to obtain home blood pressure readings and/or 24-hour ambulatory blood pressure recordings in order to document the degree of hypertension outside the office/clinic setting. In obese individuals, blood pressure should be measured with a large cuff or taken in the forearm if a large cuff is not available. Once the validity of the blood pressure measurement is confirmed, it is critical to ascertain the patient's compliance to a prescribed regimen; nonadherence to treatment must be ruled out before further

evaluation is undertaken. Factor(s) responsible for noncompliance should be identified and corrected, if possible. The treatment should be simplified to encourage patient participation. Often a sympathetic, yet firm dialogue with the patient can reveal whether or not compliance is the cause. With a good rapport with the patient, it will be unnecessary to measure the drug level in the blood to determine a patient's compliance.

Correction of volume overload is one of the most successful interventions in managing resistant hypertension. Excessive salt intake must be curtailed. Adequate diuretic therapy should be implemented based upon clinical circumstances. The dosage and the choice of the diuretic should be appropriately modified. Patients with concomitant congestive heart failure or renal insufficiency require optimal volume control to achieve adequate blood pressure regulation. The dosages of antihypertensive drugs should be titrated systematically to determine whether or not the patient is responding to the treatment. Drug interactions^{13,14} should be considered and eliminated in the treatment of hypertension. A thorough inventory should be made of drugs that could increase the blood pressure such as steroids, oral contraceptives, sympathomimetics, nasal decongestants, cocaine and appetite suppressants, etc. Patients should be counseled about alcohol consumption, weight control, salt intake, and regular physical activity. Conditions such as obstructive sleep apnea or chronic pain should be addressed.

Secondary causes of hypertension such as those listed in Table 3 should be considered in the evaluation of patients with resistant hypertension. Based upon the clinical hallmarks, renovascular hypertension should be pursued in patients with truly refractory hypertension. Other causes such as primary hyperaldosteronism, pheochromocytoma, Cushing's syndrome, coarctation of the aorta, and renal disease should be considered based on the clinical course and laboratory findings. If an underlying cause is found, it should be corrected (if possible) to permit better blood pressure control.

Drug Treatment of Refractory Hypertension

When an identifiable cause is not found, patients with refractory hypertension merit aggressive drug therapy to control the blood pressure. The first step is to optimize the existing therapy either by increasing the dosages or by changing to different combinations and observing the patient for a few weeks. If the blood pressure still remains uncontrolled, effective and optimal diuretic therapy should be implemented.^{15,16} Assuming that the patient has failed to respond to conventional therapies, consideration should be given to the use of hydralazine or minoxidil (in conjunction with a β -blocker and a diuretic).¹⁷⁻¹⁹ Because direct vasodilators cause significant reflex activation of sympathetic nervous system and fluid retention, their use should be accompanied by co-administration of a β -blocker and a diuretic (usually a loop diuretic). We often give a trial of hydralazine therapy before trying minoxidil therapy. Occasionally, further reductions in the blood pressure can be secured by adding a fourth agent such as clonidine. In patients

with marked renal impairment, the initiation of dialysis might be required for adequate control of blood pressure.

In most patients with chronic primary hypertension, blood pressure can be controlled with changes in lifestyle and with one or two drugs. In a small percentage of patients, however, the blood pressure remains uncontrolled, even on a three-drug regimen. These patients have refractory or resistant hypertension. In the management of refractory hypertension, it is essential to determine the cause(s) that could be responsible for the failure of the patient or the blood pressure to respond to an appropriate regimen. If an identifiable cause is not found or cannot be corrected, suitable changes should be made in the treatment plan, including effective diuretic therapy and proper application of potent classes of antihypertensive drugs such as the direct vasodilators. With the pathophysiologic and therapeutic concepts discussed above, we can approach the problem of refractory hypertension in a systematic fashion and on a rational basis. ■

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