Individualization of Antihypertensive Drug Treatment

Giuseppe Mancia, md[1]
Guido Grassi, md[2,3]

Antihypertensive drug classes are usually classified as 1st, 2nd, 3rd, and 4th or 5th choice to help physicians select the drug most suitable for treatment initiation among the very many classes available to lower blood pressure (BP) in patients with a BP elevation. However, this approach was appropriate decades ago when several drugs had inconveniences that made their use in monotherapy inadvisable. An example was the then widely used vasodilator hydralazine whose sodium-retaining and tachycardic effects made its administration recommendable only with a diuretic or a β-blocker, with, thus, a classification as a 2nd- or 3rd-choice drug (1). This is no longer the case because several current antihypertensive drug classes are characterized by a similar BP-lowering effect (2), a good tolerability profile (2), and evidence of cardiovascular protection in prospective randomized trials (3,4). As recently argued in a document of the European Society of Hypertension (5), this implies that rather than classifying drugs as 1st, 2nd, 3rd, and further choice, it might be more appropriate to help physicians select the drug (or drug combination) that might be preferred for treatment initiation in a given patient or a given clinical condition. This article will discuss the factors that may help physicians move toward this more individualized treatment approach.

Demographic factors

Evidence is available that antihypertensive treatment is protective in either hypertensive males or hypertensive females and that for a similar decrease in BP the reduction of cardiovascular risk is proportionally similar in both sexes (6). Thus, sex does not represent a factor to consider in the choice of antihypertensive treatment except for the need to avoid blockers of the renin-angiotensin system (ACE inhibitors, angiotensin receptor antagonists, and renin inhibitors) in pregnant women because of the suspicion, from animal studies, of teratogenic effects (7).

Although the British guidelines have long maintained that antihypertensive treatment should be different in young and elderly patients (8), there is no substantial basis for an age-related choice of antihypertensive drugs (5). Diuretics, ACE inhibitors, angiotensin receptor antagonists, calcium antagonists, and β-blockers have been shown to have a similar protective effect in patients younger and older than 65 years in a meta-analysis from a large number of randomized trials, with an overall similar ability also to lower an elevated BP (3). An exception might be hypertensive individuals aged ≥80 years. Because in these patients protection against cardiovascular and all-cause death has thus far been documented in only one trial (9), it might be prudent to preferentially use the antihypertensive drugs that this trial adopted, i.e., a diuretic with the addition of an ACE inhibitor, if needed to achieve BP control.

Finally, although reducing an elevated BP is beneficial in all ethnic groups, ACE inhibitors and angiotensin receptor antagonists have been shown to have a limited BP-lowering effect in African Americans (10). Thus, in these patients, and in general in blacks, diuretics or calcium channel blockers are the monotherapy of choice, and the two drugs together represent the preferred combination.

Biochemical markers

Decades ago, the suggestion was made to select antihypertensive treatment by the levels of plasma renin activity and thus by the different degree of activation of the renin-angiotensin system (11). However, plasma renin levels are heavily influenced by the current sodium intake and exhibit a marked increase in patients undergoing treatment with commonly used drugs such as ACE inhibitors and angiotensin receptor antagonists, which means that their assessment requires, to be valid, a washout period under stable conditions—a procedure hardly feasible in clinical practice. Furthermore, although blockers of the renin-angiotensin system may have a somewhat greater BP-lowering effect than other drugs in hypertensive patients with high renin levels (12), in normal– and low–renin level individuals (i.e., the majority of the hypertensive population) no substantial between-drug difference has been consistently reported (13). This explains why after an initial popularity, this procedure was abandoned and is now regarded as obsolete.

Although hypertensive patients are often characterized by sympathetic activation (14), there is also no advantage in selecting treatment based on the level of sympathetic influences on the cardiovascular system because 1) acceptable quantification of sympathetic activity, such as via plasma norepinephrine levels, is hardly possible in the clinical setting and the most modern and precise methods (e.g., microneurography) are only limited to research; 2) simple methods,

such as measuring heart rate, are fallible because absolute heart rate values and changes heavily depend also on the vagal influences on the sinus node and because the degree of cardiac sympathetic activation may not go pari passu with the vascular one (15); and 3) drugs that most effectively counteract sympathetic cardiovascular influences, i.e., α-blockers and α- and β-blockers, although capable of effectively reducing BP, have never been tested against placebo in event-based trials and have lost in confrontation with diuretic treatment in the only comparison trial thus far available (16). It should be mentioned, however, that widely used 1st-choice drugs such as blockers of the renin-angiotensin system all have a moderating influence on sympathetic cardiovascular influences because of removal of the stimulating effect of angiotensin II at sympathetic central and peripheral sites (17,18). This is the case also for β-blockers, although their sympatho-moderating effect is mostly evident for the heart. Easier-to-use methods of direct or indirect sympathetic drive quantification (e.g., plasma brain natriuretic peptide levels) may change this negative perspective in the future.

Cardiovascular risk factors
Hypertension is frequently associated with alterations in blood glucose and lipid profile (19), and prevalence of prediabetes, diabetes, dyslipidemias, and metabolic syndrome is much greater in subjects with high than in those with normal BP (20,21). In a recent meta-analysis of Italian observational studies in >52,000 hypertensive patients, diabetes was found in almost 20% and an increased serum cholesterol in >60% of the studied population (22). A quantitative association of plasma lipid and glucose variables with in- and out-of-office BP has also been reported (23). β-Blockers and diuretics have been shown to adversely affect, albeit to a modest degree, serum cholesterol, HDL cholesterol, and triglycerides (24,25). Thus, they should not be considered the preferred drugs in patients with lipid abnormalities unless several agents are required to control BP, as it may not infrequently happen in hypertensives with an unfavorable cardiovascular risk profile (26).

Diuretics and β-blockers have also been found to increase the risk of new-onset diabetes (27,28). On the contrary, although in a randomized trial in individuals with glucose intolerance the ACE inhibitor ramipril did not significantly reduce the development of diabetes compared with placebo (29), a meta-analysis of a large number of studies for a total of ~150,000 patients has shown this drug class, as well as the angiotensin receptor antagonists, to be associated with less new-onset diabetes, particularly compared with treatments based on diuretics and β-blockers (28). Furthermore, compared with diuretics and β-blockers, these drugs have been shown to reduce insulin resistance (30)—a well-known precursor of diabetes (31). This justifies the recommendation of guidelines to avoid isolated or combined administration of diuretics or β-blockers in patients predisposed to diabetes such as those with metabolic syndrome (19) or a blood glucose in the glucose intolerance range, i.e., between 100 and 125 mg/dL (10,13). In these patients, blockers of the renin-angiotensin system should be regarded as the first treatment approach, followed, if needed, by the addition of a calcium channel blocker, which has no adverse effect on glucose metabolism.

This does not mean, however, that in these circumstances diuretics and β-blockers are contraindicated. First, diuretics are frequently needed to control BP, and its diabetogenic influence can be minimized at low doses (27). Second, less or no diabetogenic influence has been reported for vasodilator β-blockers (32). Third, the prognostic impact of new-onset antihypertensive drug-related diabetes, whether it adversely affects outcome like native diabetes or, rather, represents a blood glucose increase of a more cosmetic nature, is still under debate (27,33).

Asymptomatic organ damage
For a similar BP reduction, antihypertensive drugs have been found to have different effects on several asymptomatic organ damages. ACE inhibitors, angiotensin receptor antagonists, and calcium antagonists favor regression of echocardiographic or electrocardiographic left ventricular hypertrophy more effectively than diuretics and β-blockers (34). ACE inhibitors and angiotensin receptor antagonists much more effectively reduce urinary protein excretion than other antihypertensive drugs (35). Blockers of the renin-angiotensin system and calcium channel blockers more effectively regress arteriolar remodeling (i.e., the modification of arteriolar wall structure that increases wall thickness at the expense of the lumen) than other drugs (36). Thus, these drugs should be preferentially used in the presence of these markers of cardiac, renal, and vascular damage, which are all associated with an increased cardiovascular risk (37–39). This is particularly the case for left ventricular hypertrophy and micro- or macroalbuminuria, which can be easily identified and for which there is also evidence, albeit not consistent in all studies (40), that their changes may reflect the effect of treatment on cardiovascular morbid and fatal events (41–43), thus offering an important tool to determine the achieved degree of patients' protection by treatment.

No conclusive evidence is currently available on whether antihypertensive drugs differ for their ability to favorably affect other markers of cardiac, vascular, or renal damage of prognostic significance (diastolic dysfunction, pulse wave velocity, left atrium dimension, white matter lesions, etc.), with the exception of carotid atherosclerosis, which has been found to be more effectively delayed by calcium channel blockers than by other drugs (44). The advantage of this greater antiatherogenic effect is not so clear, however, because both in hypertension and in other conditions in need of cardiovascular drug treatment the prognostic significance of treatment-related changes in carotid intima-media thickness and plaque number has not been clearly documented (45,46).

Clinical conditions
Evidence is available that in type 2 diabetes diuretics, β-blockers, ACE inhibitors, angiotensin receptor antagonists, and calcium channel blockers have a similar protective effect on the cardiovascular system, presumably because in this condition cardiovascular protection is largely due to BP lowering per se (47). Thus, in diabetic patients physicians can make use of all the above drugs to achieve an effective BP control, i.e., a reduction <140/90 mmHg (5,47,48).

However, because they unfavorably modify insulin resistance (30), diuretics and β-blockers increase the number/doses of hypoglycemic drugs necessary to achieve an adequate blood glucose control (49). Furthermore, β-blockers may blunt the signs and symptoms of hypoglycemia, thereby favoring its potentially harmful consequences. Finally, and most importantly, ACE inhibitors and angiotensin receptor antagonists not only

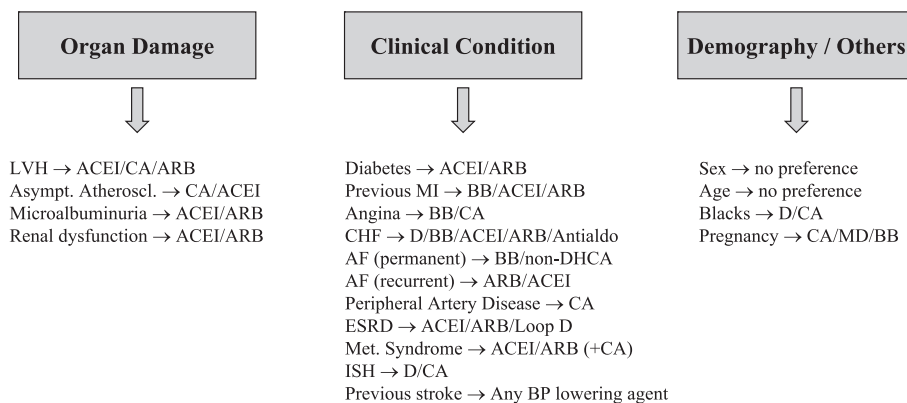**Table 1—Major contraindications to antihypertensive drugs**

	Compelling	Possible
Thiazide diuretics	Gout	Metabolic syndrome, glucose intolerance, pregnancy, hypokalemia
β-Blockers	Asthma A-V block (grade 2 or 3)	Peripheral artery disease Metabolic syndrome, glucose intolerance, athletes and physically active patients, chronic obstructive pulmonary disease
Calcium antagonists (dihydropiridines)	A-V block (grade 2 or 3)	Tachyarrhythmias, heart failure
Calcium antagonists (verapamil, diltiazem)	Heart failure	
ACE inhibitors	Pregnancy Angioneurotic edema Hyperkalemia Bilateral renal artery stenosis	Women at risk of pregnancy
Angiotensin receptor antagonists	Pregnancy Hyperkalemia Bilateral renal artery stenosis	Women at risk of pregnancy
Diuretics (antialdosterone agents)	Renal failure Hyperkalemia	

reduce cardiovascular risk (50,51) but also decrease urinary protein excretion, delay appearance of micro- or macroalbuminuria, and slow down progression of renal damage to end-stage renal disease (5,52–54). This nephroprotective effect makes these drugs a mandatory component in the management of this condition both to maximize renal protection and to avoid the increase of cardiovascular risk that occurs when diabetic nephropathy becomes clinically manifest (55). Of note, evidence on the protective properties of blockers of the renin-angiotensin system in diabetes does not extend to renin inhibitors, i.e., aliskiren. Indeed, in diabetic patients administration of this drug on the background of an ACE inhibitor or an angiotensin receptor antagonist has recently been shown to have unfavorable therapeutic effects (56).

The following evidence also exists. In hypertensive patients with a history of heart failure, treatment should avoid calcium channel blockers and include ACE inhibitors, angiotensin receptor antagonists, or diuretics, with those of the loop being necessary if heart failure is clinically manifest or renal function is impaired (10,13). β-Blockers are also drugs of choice in this clinical condition, with those with vasodilating properties (57,58) offering the additional advantage of reducing the marked vasoconstriction characterizing individuals with an inadequate cardiac output. Heart failure also favors the administration of antialdosterone drugs, which in patients with an impaired cardiac function exert a protective effect (59) possibly because of the ability to reduce the elevated aldosterone levels much more effectively than blockers of the renin angiotensin system (60). Antialdosterone drugs should also be considered in resistant hypertension, i.e., when BP fails to be controlled under a three-drug regimen that includes a diuretic, a blocker of the renin-angiotensin system, and a calcium channel blocker, all at effective doses (61). β-Blockers should be preferred in patients with a history of myocardial infarction (in whom they exert a better protection against recurrence of myocardial necrosis and sudden death [10,13]), while β-blockers or calcium channel blockers should be given to patients affected by angina pectoris for their symptomatic benefit. Despite claims to the contrary, there is, on the other hand, no undisputable evidence that some antihypertensive drugs exert a greater prevention of stroke than others and should therefore be preferably used when the risk of stroke is particularly high, as in patients with a history of cerebrovascular disease (4). It is likely that the lesser protective effect against stroke by β-blockers versus calcium channel blockers reported in some meta-analyses (4,62) is accounted for by somewhat lower BP values achieved by patients treated with the latter drugs in a number of studies (63,64). It appears that, given the steep relationship between stroke and BP, strategies to prevent this event should focus on BP control more than on drug selection. Preference to some drugs versus others has been advocated also for control of rate frequency in permanent atrial fibrillation (β-blockers) and for preventing recurrences in paroxysmal atrial fibrillation (blockers of the renin-angiotensin

Organ Damage	**Clinical Condition**	**Demography / Others**
⇩	⇩	⇩

LVH → ACEI/CA/ARB Asympt. Atheroscl. → CA/ACEI Microalbuminuria → ACEI/ARB Renal dysfunction → ACEI/ARB	Diabetes → ACEI/ARB Previous MI → BB/ACEI/ARB Angina → BB/CA CHF → D/BB/ACEI/ARB/Antialdo AF (permanent) → BB/non-DHCA AF (recurrent) → ARB/ACEI Peripheral Artery Disease → CA ESRD → ACEI/ARB/Loop D Met. Syndrome → ACEI/ARB (+CA) ISH → D/CA Previous stroke → Any BP lowering agent	Sex → no preference Age → no preference Blacks → D/CA Pregnancy → CA/MD/BB

Figure 1—*Some criteria for selecting drugs for antihypertensive treatment. ACEI, ACE inhibitors; AF, atrial fibrillation; Antialdo, antialdosterone drugs; ARB, angiotensin II receptor blockers; Asymp. Atheroscl., asymptomatic atherosclerosis; BB, β-blockers; CA, calcium antagonists; CHF, congestive heart failure; D, diuretic; DH, dihydropyridine; ESRD, end-stage renal disease; ISH, isolated systolic hypertension; LVH, left ventricular hypertrophy; MD, methyldopa; Met., metabolic; MI, myocardial infarction.*

system). Evidence is available for either condition, although the advantages of using blockers of the renin-angiotensin system in paroxysmal atrial fibrillation, supported as it is by pathophysiological data (favorable remodeling of left atrium value and wall structure) and post hoc analyses of randomized trials, have not been confirmed by randomized issue-specific trials (5).

Other criteria of choice

As mentioned by the 2007 European Society of Hypertension–European Society of Cardiology guidelines (13), other criteria that may help selection of appropriate drug treatment are represented by *1*) the duration of the BP-lowering effect because drugs that cover the 24-h time interval and thus can be given on a once-a-day basis provide a simplified form of management that helps adherence to the therapeutic regimen (65), *2*) the cost of treatment, *3*) the contraindications to different drugs as summarized by the European guidelines (Table 1), and *4*) the previous experience of the patient with the BP-lowering ability and side effects of a given drug class. Continuing attention to development of side effects is particularly important because treatment-related side effects are the main cause of treatment discontinuation (66), which is accompanied by a marked increase in hypertension-related complications (67).

Conclusions

Although BP control remains the fundamental goal of antihypertensive treatment, drugs to be used to achieve this purpose can be selected to better suit the individual patient based on demographic and anthropometric characteristics, concomitant cardiovascular risk factors, asymptomatic organ damage, and clinical conditions (Fig. 1). This allows management of hypertension to be differentiated in many patients, although a central core remains in which no clue exists as to the use of one drug (or drug combination) or another. The trend toward individualization of antihypertensive treatment, however, will unquestionably continue in the future as research will more and more frequently discover differences between different drugs and treatment strategies in different patients and diseases. Hope lies also in genetic studies that could identify, by simple and inexpensive blood tests, polymorphisms associated with the magnitude of the BP response to a given drug

as well as the chance of developing side effects.

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