Chapter 15
Selecting Optimum Antihypertensive Therapy

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Introduction

The selection of optimum antihypertensive therapy for a particular patient represents a challenge, which the treating physician managing patients with arterial hypertension confronts every day. The choice involves not only the initial selection of antihypertensive drugs, but also the right dual, triple, or multiple combination therapy for the particular patient, since antihypertensive drugs as monotherapy are efficacious in the minority of cases (30–40 %) and blood pressure response is unpredictable. Therefore, the choice affects all hypertensive patients and is neither simple nor careless.

Undoubtedly, essential hypertension is not due to one cause and certainly there is no therapy that fits all. Arterial hypertension is a multi-factorial disease with several mechanisms implicated in blood pressure elevation. Each class of antihypertensive drugs targets one or more mechanisms but leaves unaffected or even has an adverse impact on the other mechanisms. Therefore, the selection of optimum therapy requires the identification of the specific mechanism(s) contributing to blood pressure elevation in each individual.

The aim of this chapter is to present the therapeutic strategies for the management of arterial hypertension (stepped-care, sequential monotherapy, individualized,

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renin-based, hemodynamic), and critically discuss each approach highlighting its advantages and disadvantages. Moreover, several practical recommendations are provided on the build-up of optimum antihypertensive therapy in individual patients.

Therapeutic Strategies for the Management of Arterial Hypertension

The main therapeutic strategies for the management of arterial hypertension are depicted in Table 15.1. There are three main therapeutic approaches: (a) the stepped-care approach, (b) the sequential monotherapy approach, and (c) the individualized, patient-centered approach.

Last but not least, special emphasis needs to be placed in two particular approaches: (a) the renin approach, and (b) the hemodynamic approach. Although both approaches could be considered as part of the individualized approach, they merit discussion separately, since each one represents a complete particular concept with its own advantages and disadvantages, strengths and weaknesses.

The Stepped-Care Approach

The traditional stepped-care approach dominated the hypertension field at the beginning of antihypertensive drug therapy. According to this approach, when the first antihypertensive drug (titrated to maximum dose) fails to achieve blood pressure control, then a second drug is added and titrated to maximum dose, and so on, until successful blood pressure control occurs.

The efficacy of the stepped care approach in blood pressure reduction and the subsequent benefits in cardiovascular morbidity and mortality have been demonstrated very early in the antihypertensive era, with the first large clinical studies, such as the VA trials, the USPHS trial, the Australian trial, and the Oslo trial [1–5]. Moreover, the superiority of the stepped care approach over usual care has been confirmed in the HDFP trial [6].

The stepped care approach was designed as a simple algorithm that was found very effective, resulting in significant blood pressure reduction (mean 10/5 mmHg; maximum 20/10 mmHg, in patients with mild to moderate hypertension) [7]. The

Table 15.1 Therapeutic strategies for the management of arterial hypertension

Stepped-care approach
Sequential monotherapy
Individualized approach
Renin-based approach
Hemodynamic approach

stepped care approach was embraced by the Joint National Committee which issued the US guidelines for the management of arterial hypertension in 1977, 1980, 1984, and 1988 [8–10].

As every approach, the stepped care approach has its own advantages and disadvantages. It is easy to understand and thus can be widely implemented, it highlights the selection of drugs from different classes to attain synergistic actions, and it includes a gradual dose titration to identify the maximum tolerated dose of a drug. On the other hand, the stepped care approach ignores the different pathogenetic mechanisms contributing in blood pressure elevation in different patients, the hemodynamic and hormonal variability in hypertension, i.e., the heterogeneity in hypertension pathogenesis. Moreover, the stepped care approach does not take into account several factors, such as target organ damage, cardiovascular disease, cardiovascular risk factors, other comorbidities, concomitant medication, drug adverse effects, and adverse metabolic actions of antihypertensive drugs.

The stepped care approach was not the result of rigorous and extensive scientific clinical testing, but rather an expert opinion aiming to provide a standard management plan, appropriate for implementation in large populations in everyday clinical practice. Nevertheless it was simple enough, easy to follow and help in the wide spread of blood pressure treatment and control in the US and around the world.

Sequential Monotherapy

As the years passed by, however, it was realized that: (a) the various antihypertensive drug classes result in blood pressure control (<140/90 mmHg) in a limited percentage of hypertensive patients (30–40 %), and (b) not all patients respond the same way to each antihypertensive drug category, i.e., an individual patient may respond to one class of drugs, be totally unresponsive to another class, and experience a partial response to a third class. Therefore, the concept of sequential monotherapy has emerged, a classic interpretation of the 'trial and error' method. According to this approach, antihypertensive drug classes are consecutively tested in all hypertensive patients in order to discover effective drugs and uncover ineffective drugs for the individual patient. The rationale beneath this concept is solid and attractive, since antihypertensive therapy is life-long and it is therefore of utmost importance and clinically meaningful to detect the efficacy of each drug class for the individual patient. Like every concept however, sequential monotherapy has its own disadvantages. The main disadvantage is that the time required to test the efficacy of each class is long and at times unacceptable. In particular, drugs have to be administered for several weeks, at least 4–6 weeks and even longer for diuretics, to evaluate appropriately the full effect of each drug category. In addition a wash-out period of 3–4 weeks has to follow each drug-testing period to avoid the carry-over effect. Thus, it was soon realized that a very long period of 1–1.5 years is required to test the efficacy of the four main antihypertensive drug classes (diuretics, beta blockers, calcium antagonists, ACE-inhibitors), and an

even longer period required if dose escalation or second line drugs (alpha blockers, centrally acting, direct vasodilators, mineralocorticoid receptor antagonists) are being tested as well.

The time consuming sequential monotherapy approach carries significant consequences. First, the patients get tired, may consider themselves 'testing objects', and thus exhibit poor adherence rates and high discontinuation rates. Then, the cost of medical visits (direct and indirect) both for the patient and the insurance system is high, and there is no guarantee (reassurance) that the response pattern to each drug will be maintained the same over the time. Moreover, this approach raises safety flags for several patient populations, especially high-risk patients with either established cardiovascular disease or a cluster of cardiovascular risk factors. In addition, available data suggests that the earlier the blood pressure control the better. For example, in the VALUE trial, it was found that cardiovascular event rates were lower in patients achieving early blood pressure control (during the first 6 months of the study) compared to patients with initially uncontrolled blood pressure, irrespective of the administered antihypertensive drug [11]. It is obvious that sequential monotherapy does not offer rapid, prompt and early blood pressure control. Finally, the efficacy of sequential monotherapy is questionable in more advanced stages of hypertension, since it is highly unlikely that blood pressure will be controlled with monotherapy in patients with severe hypertension, and rather unlikely in patients with moderate hypertension.

The Personalized Approach

It is therefore of no surprise that recent therapeutic strategies have moved towards individualized therapy for the reduction of elevated blood pressure in hypertensive patients. Indeed, individualized therapy represents the key element of the last European guidelines for the management of arterial hypertension [12–15]. According to this approach, the selection of an antihypertensive drug for each individual is based on: (a) several individual's baseline demographic characteristics (age, gender, race, and body mass index) and the heart rate, (b) the presence and the type of target organ damage, (c) the presence and the type of established cardiovascular disease, and (d) the presence and the type of other comorbidities.

In addition, the selection of optimum antihypertensive therapy is influenced by the specific characteristics of each antihypertensive drug and concomitant medications (pharmacokinetics, pharmacodynamics, adverse events, metabolic effects). Finally, the selection of optimum therapy has to take into account several other very significant factors, such as individual's prior experience with antihypertensive drugs (efficacy and safety), the quality of life with special emphasis on sexual function, adherence to antihypertensive therapy and discontinuation rates, the blood pressure pattern (isolated systolic hypertension, non-dippers), lifestyle factors (salt intake, exercise), and the cost (direct and indirect), especially in these times of financial constraints worldwide and recession in many parts of the world.

Another very important aspect is to evaluate whether the profile of the selected drug match the needs and the preferences of the specific individual. For example, a diuretic might not be the best choice for a young and highly active executive in a multi-national company; a beta blocker might not be the best choice for someone who is involved in intense physical activities [16].

Of major importance, the individualization of antihypertensive therapy has to fulfill several requirements: (a) to be effective, (b) to be safe and well tolerated, (c) to reduce the risk for cardiovascular morbidity and mortality, (d) to improve or at least attenuate target organ damage, and (e) to exert beneficial or at least neutral effects on traditional cardiovascular risk factors and/or other comorbidities.

A detailed analysis of the factors influencing the choice of antihypertensive therapy according to the individualized approach will be presented later in this chapter, after the presentation of the renin-based and the hemodynamic approach.

The Renin-Based Approach

Renin was identified at the very end of the nineteenth century by Tigerstedt, a Scandinavian physiologist, who extracted from rabbit kidneys a substance with pressor properties [17]. Its role however in blood pressure control was not established until more than three decades later, when Goldblatt performed his landmark experiments in one-clip and two-clip hypertension, and proposed the theory that renal ischemia (through clamping of renal artery) results in the production of a strong pressor molecule from the kidneys (renin), which is capable of producing blood pressure elevation [18]. It took almost two more decades to describe the renin-angiotensin system (RAS) [19] and realize the role of this system as a servo-control with crucial role in blood pressure, water, sodium, and potassium regulation [20–24]. In parallel, Jerome Conn has identified primary hyperaldosteronism and described its main characteristics [25, 26], long before aldosterone and renin could be actually measured, since the first clinical assays appeared in 1964 (10 years after Conn's first description).

The role the RAS was thus established in secondary hypertension (renovascular hypertension, primary hyperaldosteronism); however, its role in essential hypertension remained controversial. It is the life-time, persistent work of the late John Laragh, which highlighted the importance of renin in essential hypertension, and even proposed the renin-based management of hypertensive patients (Table 15.2). The renin approach is based in two simple assumptions: (a) hypertensive patients can be divided according to renin status in high and low renin groups, and (b) antihypertensive drugs are mainly effective in ore or the other category.

Plasma renin activity (PRA) is broadly distributed in hypertensive patients. About one third of hypertensive patients have low PRA levels, suggesting a functional renal response to elevated blood pressure and sodium overload. The remaining two thirds of hypertensive patients have inappropriately elevated renin for the blood pressure and sodium status, indicating a relative over-activation of the RAS

Table 15.2 The renin-based approach

Low renin levels	*High & normal renin levels*
PRA < 0.65 ngAI/ml/h	PRA > 0.65 ngAI/ml/h
Volume overload	RAS overactivation
More effective drugs	More effective drugs
Thiazides	ACE-inhibitors
Calcium antagonists	Angiotensin receptor blockers
Spironolactone	Beta blockers

both in patients with high PRA values (about 15 % of patients) or normal PRA values (about 50 % of patients) [27–29]. To sum up, one out of three hypertensive patients have low renin hypertension which is salt-mediated, while the other two out of three patients have inappropriately high renin levels (either normal or high in absolute values), and blood pressure elevation is due to RAS over-activation.

The second assumption regards the efficacy of antihypertensive drugs in these two patient subgroups. Hypertensive patients with high and normal PRA values tend to respond to drugs affecting the RAS, such as beta blockers and centrally acting drugs (directly affecting renin secretion), ACE-inhibitors, angiotensin receptor blockers, and direct renin inhibitors. In contrast, hypertensive patients with low PRA levels tend to respond to natriuretic drugs and subsequent volume depletion (diuretics, alpha blockers, calcium antagonists).

The efficacy of the renin approach has been tested and verified mainly by the Laragh group in New York. The selective efficacy of antihypertensive drugs according to baseline renin levels, with beta blockers being preferentially effective in normal and high renin patients, and diuretics being preferentially effective in low renin patients, have been shown in numerous studies during the 1970s [30–42]. An even more important set of data comes from two studies suggesting that diuretics in fact raise blood pressure in patients with elevated renin levels, and vice versa, beta blockers may raise blood pressure in patients with low renin levels [43, 44].

Another significant characteristic of the renin approach is that it can be applied not only to naïve (previously untreated) patients, but also to patients with uncontrolled blood pressure while on therapy with antihypertensive drugs. In the original small clinical study of 73 patients with uncontrolled blood pressure despite administration of at least one antihypertensive drug, it was found that a renin-based therapeutic strategy resulted in a significant blood pressure reduction, an additional reduction in the number of antihypertensive medications used by study participants, and even cost benefits [45].

More recently, the renin-based approach was compared with clinical hypertension specialist care in another small clinical study of 84 patients with treatment resistant hypertension [46]. It was found that blood pressure reduction was similar with both approaches, while the renin-based approach was superior to specialist care regarding the removal of antihypertensive drugs and dose reductions of some antihypertensive agents, in addition to a non-significant trend towards better blood pressure control. Therefore, the renin-based therapeutic strategy seems to be as effective as specialist care, and therefore represents an attractive alternative for primary care practice.

This year, the PATHWAY-2 trial provided also some evidence supporting the renin-based strategy. In this placebo-controlled, randomized, cross-over study, spironolactone was compared to alpha- and beta-blockers in a large number of patients with resistant hypertension [47]. It was found that the blood pressure response was strongly affected by baseline renin levels, with spironolactone being very effective and superior to comparator drugs in patients with low and normal renin levels, while beta blockers were more effective in patients with high renin levels, achieving the efficacy of spironolactone.

The renin approach has not been widely applied in the management of arterial hypertension for several reasons [48, 49]. PRA determination requires a well-equipped and specialized laboratory, is time consuming and not practical in everyday clinical practice. Moreover, the results may be inaccurate, present interpretation difficulties, and most importantly have reproducibility problems. [50–52] Indeed, one out of four patients classified in one renin group (high, normal, or low) is actually re-classified in another group on repeat testing [48]. In addition, PRA values have to be adjusted for age, gender, race, and several other parameters, in order to ensure the accuracy of each laboratory [48, 50, 51]. Moreover, PRA presents great variations according to sodium intake, potassium levels, posture and its duration, and timing of the sampling during the day. Of equal importance, renin concentrations are highly affected by antihypertensive drugs, which either reduce significantly renin levels (beta blockers, centrally acting drugs) or result in significant elevation of renin levels (diuretics). Of note, other drugs might also affect renin determination, such as non-steroidal anti-inflammatory drugs and fludrocortisone, while the effects of commonly used psychotropic drugs (such as anxiolytics and antidepressants) on renin levels have not been adequately clarified, despite the fact that such drugs may inhibit sympathetic activity and subsequently renin levels. Another very significant and clinically meaningful limitation of the renin approach regards the poor correlation (about 50 %) between renin categorization and subsequent blood pressure response to indicated drugs [51, 53].

The Hemodynamic Approach

Blood pressure equals the product of cardiac output (CO) and systemic vascular resistance (SVR). Aging is accompanied by significant hemodynamic changes in hypertensive patients. At the early stages of hypertension in young patients, the CO is increased due to sympathetic overactivity and the subsequent tachycardia (CO is the product of heart rate and stroke volume), while SVR is inappropriately high (relatively increased) [54–57]. Later on, when hypertension is established, the CO is usually slightly reduced by 10–15 %, whereas SVR is slightly increased by 15–20 % [54, 58, 59]. At the late stages of hypertension in the elderly, the CO is further decreased up to 25 %, while SVR is further increased up to 25–30 % [54, 58, 59]. Therefore, SVR is elevated in hypertensive patients and this represents the primary hemodynamic abnormality.

From the hemodynamic point of view, it seems rational to reduce blood pressure through the reduction of SVR, while maintaining the CO unaffected, in order to ensure adequate renal blood flow and the perfusion of vital organs. Ideally, these alterations should not be accompanied by compensatory changes, such as water and salt retention, reflex tachycardia, and vasoconstriction.

The hemodynamic effects of antihypertensive drugs (Table 15.3) can be divided in five groups according to their effects in SVR, CO, organ perfusion and arterial compliance [60–72]. RAS inhibitors (ACE-inhibitors, ARBs, and direct renin inhibitors), calcium antagonists, and vasodilatory beta blockers reduce SVR, while preserving CO and improving organ perfusion and arterial compliance. Alpha blockers and centrally acting agents reduce SVR and preserve CO and perfusion, while their effects on arterial compliance are not yet adequately clarified. Direct vasodilators and beta blockers with intrinsic sympathomimetic activity reduce SVR, preserve CO and organ perfusion, while worsening arterial compliance. Diuretics and ganglionic blocking agents reduce SVR, CO, and organ perfusion, whereas arterial compliance is worsened. Finally, traditional beta blockers (without intrinsic sympathomimetic activity or vasodilatory properties) increase SVR and reduce CO, organ perfusion, and worsen arterial compliance.

Table 15.3 Hemodynamic effects of antihypertensive drugs

Group A
SVR reduction, CO unaffected, organ perfusion & arterial compliance improved
RAS inhibitors (ACE-inhibitors, angiotensin receptor blockers)
Calcium antagonists
Vasodilatory beta blockers
Group B
SVR reduction, CO & organ perfusion unaffected, arterial compliance unclarified
Alpha blockers
Centrally acting agents
Group C
SVR reduction, CO & organ perfusion unaffected, arterial compliance worsened
Vasodilators (Hydralazine, minoxidil)
Beta blockers with intrinsic sympathomimetic activity
Group D
SVR & CO & organ perfusion reduction, arterial compliance worsened
Diuretics
Ganglionic blocking agents
Group E
SVR increased, CO & organ perfusion reduction, arterial compliance worsened
Traditional beta blockers

Some points regarding the hemodynamic effects of antihypertensive drugs need to be highlighted. First, the most favorable hemodynamic profile is expressed by RAS inhibitors and calcium antagonists. In contrast, diuretics and especially beta blockers seem to exhibit the most detrimental hemodynamic profile. Second, the hemodynamic effects of diuretics are time-dependent. During the first weeks, diuretic use is accompanied by sodium and water excretion and subsequent shrinkage of intravascular volume, a slight reduction of CO (by approximately 5 %) and renal perfusion with subsequent decrease of renal blood flow and glomerular filtration rate, and a slight increase of heart rate [62–65, 67, 73]. However, after some weeks of treatment (usually 8 up to 12 weeks), SVR is reduced, the CO tends to return in pre-treatment values, and the intravascular volume is slightly expanded (reduced by 5 % compared to pre-treatment values) [62–64, 66].

The determination of the hemodynamic status of a hypertensive patient provides valuable information, which in turn might guide the selection of antihypertensive therapy, based on the above-mentioned hemodynamic effects of antihypertensive drugs. However, the hemodynamic evaluation is invasive, carries some risks, and it is not applicable in everyday clinical practice, limiting its use only in experimental studies. Recent technologic advances however permitted for the development of devices that provide significant information about the hemodynamic status of patients, by using the thoracic bio-impedance [74]. Therefore, the hemodynamic profile of an individual patient can be evaluated using a non-invasive, accurate, cheap, and reproducible method, which can be widely applied in everyday clinical practice [75–79].

The non-invasive hemodynamic approach was introduced by the Mayo Clinic group (Sandra Taler and Stephen Textor) and adopted by Carlos Ferrario and others. Up to now, three small, single-center clinical studies have been performed using this approach. In the first study, 104 patients with resistant hypertension were randomized to hemodynamic-guided therapy or specialist care [80]. It was found that the hemodynamic approach was associated with lower blood pressure values and higher control rates compared to specialist care. Intensification of diuretic therapy and greater reductions in SVR seem to mediate the superiority of the hemodynamic approach over specialist care in this pilot study [80]. The second study included 164 patients with uncontrolled blood pressure while on three antihypertensive drugs [81]. Once again, the hemodynamic approach was associated with lower blood pressure values, better control rates (77 % vs 57 %; $p < 0.01$), and lower SVR. The third study randomly assigned 128 patients with uncontrolled blood pressure (either untreated or taking up to two antihypertensive drugs) to hemodynamic-guided therapy or standard empiric care [82]. Similarly to the other studies, blood pressure values were lower with the hemodynamic approach both by office and ambulatory blood pressure measurements. A recent meta-analysis revealed a benefit for the hemodynamic approach with combined odds ratio of 2.4, and 67 % control rates in randomized studies, while a similar blood pressure control rate (68 %) was observed in single-arm studies [83].

The Individualized Approach

Attempts have been made to identify genes or SNPs that predict blood pressure response and/or outcomes, but the yield was rather poor. In the GenHat for example, more than 42,000 patients were genotyped and SNPs were identified that predicted better BP response to ACE inhibitors, diuretics and beta blockers. Certain genotypes also predicted better outcomes with certain drug therapies [84]. When the results however were corrected for cofounders the association was minimized. Thus gene guided treatment of hypertension still remains problematic.

Demographic factors, such as age, gender, race, and adiposity may provide useful information, which will help the orientation about the mechanisms involved in the pathogenesis of elevated blood pressure and subsequently help in the prediction of blood pressure response to a given therapy. It needs to be emphasized however that their contribution is soft and not very helpful in individual patients. Before treatment initiation (monotherapy or combination therapy) the cardiovascular status should be carefully assessed. In conjunction with blood pressure control, cardiovascular risk reduction necessitates the management of other cardiovascular risk factors as well.

The European guidelines for the management of arterial hypertension place significant emphasis on individualized (Table 15.4) antihypertensive therapy [12–15]. A lot of patients fail to achieve blood pressure goals due to inadequate blood pressure response to certain drugs, due to known variability in response with all currently available antihypertensive drugs. Therefore, a personalized approach to antihypertensive therapy seems particularly prudent for the astute physician.

Age

The pathophysiology of hypertension is highly age-dependent. In brief, younger patients tend to present hyperdynamic circulation, characterized by increased CO (increased heart rate and stroke volume), sympathetic and RAS over-activation, while SVR is usually normal. With increasing age, SVR tends to increase, whereas CO tends to return towards normal [85–87]. On the other hand, older hypertensive patients have elevated arterial stiffness, increased SVR, lower CO [88], and plasma renin levels tend to decrease with advancing age [53, 87, 89–91]. Whether these pathophysiological changes can predict blood pressure response to antihypertensive drugs remains a matter of debate.

Data support a favorable effect of diuretics and calcium antagonists in older hypertensive patients and a favorable effect of beta blockers and ACE-inhibitors in younger patients with hypertension. Indeed, diuretics seem to be particularly effective in older patients [37, 92, 93]. Similar effects have been reported for calcium antagonists as well [90, 91]. On the other hand, several studies indicate that beta blockers are very effective in younger patients [90, 91, 93–95], while older hypertensive patients show a poor blood pressure response to beta blockers, and

Table 15.4 Factors influencing the choice of antihypertensive therapy according to the individualized approach

1. Demographic
Age, *race*, *gender*, *adiposity*
2. Heart rate
3. Blood pressure pattern
Isolated systolic hypertension, *non-dipping*
4. Target organ damage
Left ventricular hypertrophy, *arterial stiffness*, *albuminuria*, *carotid IMT*
5. Comorbidities
Diabetes mellitus, *metabolic syndrome*, *stroke*, *coronary artery disease*, *heart failure*, *atrial fibrillation*, *peripheral artery disease*, *chronic kidney disease*
6. Concomitant medications
Drug interactions
7. Antihypertensive drug characteristics
Indications, *contra-indications*, *adverse events*, *metabolic effects*
8. Adherence to therapy
9. Lifestyle
Exercise, *sodium intake*
10. Quality of life
Especially sexual function
11. Cost
Direct and indirect
12. Patient's preference
13. Genetics, genomics

only 20 % of them achieve blood pressure goals [96]. In fact, the age-dependent efficacy of beta blockers seems gradual and remarkable: in one study diastolic blood pressure control was achieved in 80 % of younger patients (<40 years), 50 % in middle-aged patients (40–60 years), and only 20 % in older patients (>60 years) [94]. Finally, ACE-inhibitors seem also to be more effective in younger patients [90, 95, 97]. Further credence to the above-mentioned findings of small clinical studies comes from a post-hoc analysis of the MRC trial reporting that diuretics were more effective than beta blockers in older patients (>45 years) [93].

The findings of these older studies, performed in the 1970s and 1980s were verified in more recent studies performed by the Cambridge study group in UK. A double-blind, randomized, cross-over study of 56 young hypertensive patients evaluated the response rates to monotherapy with the four main categories of antihypertensive drugs (ACE-inhibitors, beta blockers, calcium antagonists, and diuretics) [98]. A marked variability in blood pressure response to the tested drugs was observed. However, significant correlations were reported in the blood pressure response between the ACE-inhibitors and beta blockers in one hand, and between the calcium antagonists and diuretics in the other hand. Another study of 34 young hypertensive patients of identical design with the previous study evaluated the effects of the five main categories (ACE-inhibitors, beta blockers, calcium

antagonists, diuretics, and alpha blockers) compared to placebo [99]. This study replicated the results of the previous study. In addition, it was found that the majority of participating patients (two thirds of participants) responded best to a drug inhibiting the RAS (ACE-inhibitor or beta blocker).

More recently, the Identification of the Determinants of the Efficacy of Arterial blood pressure Lowering drugs (IDEAL) trial evaluated the effect of age and gender on blood pressure response to a diuretic (indapamide) and an ACE-inhibitor (perindopril). This randomized, double-blind, placebo-controlled, cross-over study included 112 untreated, middle aged hypertensive patients [100]. It was found that age and gender were important determinants of blood pressure response to these two drugs since: (a) the systolic blood pressure response to indapamide increased by 3 mmHg every 10 years of age gradient in women, and (b) the systolic blood pressure response to perindopril decreased by 2 mmHg every 10 years of age gradient in both sexes [100].

The group of Morris Brown in Cambridge has proposed a modified version of the renin concept [101], which was adopted by the British guidelines for the management of arterial hypertension [102]. Based on the differences in PRA levels according to age and race, the British version uses age and race as surrogates for renin, in order to overcome existing difficulties with renin determination. The basic assumption is that renin levels are more likely to be elevated in patients younger than 55 years of age, while renin levels are more likely to be low in older patients and patients of black race. Therefore, similar to the renin approach, antihypertensive drugs inhibiting the RAS are preferred in younger patients, while diuretics and calcium antagonists are preferred in older patients and blacks. The AB/CD algorithm (from the initials of ACE-inhibitors or ARBs, beta blockers, calcium antagonists, and diuretics) was recently modified to the A/CD algorithm, and the beta blockers are no longer considered as first line agents [102]. This modification was based on the results of the LIFE and the ASCOT studies that used atenolol as the comparator. Several meta-analyses suggest that beta blockers (primarily atenolol) are less effective than the other first line agents in cardiovascular protection [103–106].

This approach has strength in its simplicity. It's very easy to remember this algorithm and thus more likely to implement it in everyday clinical practice. This is very important if one takes into account that the vast majority of hypertensive patients are treated by primary care physicians and not by hypertension specialists. Therefore, a simple algorithm is of utmost importance. On the other hand, the British approach has disadvantages; it does not take into account any patient characteristic apart from age and race. Therefore, target organ damage and other comorbidities are left unaccounted by the British algorithm, a simple but mechanistic approach, in contrast to the European guidelines that promote a more sophisticated individualized approach.

Another significant concern is raised about the age categorization. Although renin levels are usually low in the elderly, it is not unusual to find high renin levels in older hypertensive patients. Diuretics have been found to be preferentially effective in elderly patients with low PRA levels, while beta blockers were more efficacious in elderly hypertensives with high PRA levels [107, 108]. Caution should be

used however when diuretic therapy is administered as they can easily get dehydrated. Low doses are preferred [87].

Large randomized clinical trials suggest that most antihypertensive drugs work in the elderly. Evidence proving the beneficial effects of antihypertensive therapy in older hypertensive patients exists not only for diuretics [109–113] and calcium antagonists [114–116], but also for beta blockers [111, 117], ACE-inhibitors [116] and ARBs [118]. Of even greater importance, a large meta-analysis evaluating the effects of antihypertensive drug categories according to age revealed that there is no evidence supporting the concept that the various drug categories are differently effective in patients younger or older than 65 years of age [119]. The recently published SPRINT study showed greater benefit in patients >75 years with intensive BP control [120].

Race

The pathophysiology of hypertension presents some differences between African American and Caucasian patients. PRA is lower in African Americans, even after adjustments for sodium excretion and plasma volume, or after stimulation with orthostasis or diuresis [121–124]. In addition, plasma volume is relatively expanded in African American compared to Caucasian hypertensives [121, 125], suggesting an enhanced salt sensitivity in African Americans [121]. In summary, almost 50 % of African Americans with arterial hypertension have low PRA levels and volume-dependent hypertension, while low PRA levels are found in only 10–15 % hypertensive patients of Caucasian origin [121, 126–128].

The pathophysiology of hypertension in African Americans seems to affect blood pressure response to antihypertensive therapy. Beta blockers seem to be rather ineffective in African Americans and are consistently less effective compared to Caucasian patients [129–134]. Several studies revealed a poor blood pressure response to beta blockers compared with diuretics or other drugs in African Americans [41, 130, 133, 135–138]. Blood pressure response to beta blockers was found extremely poor in African Americans, even similar to placebo in one study [137] or of marginal benefit in another study (4 % response rates in low renin hypertensives) [135]. In another study using renin profiling, blood pressure control with beta blockers was achieved only in 2 % of African Americans who had either low or normal PRA values [139]. In the VA trial the mean blood pressure reduction was significantly less with propranolol (8/9 mmHg) compared to hydrochlorothiazide (20/13 mmHg) in the 643 African American study participants [130]. Thus, diastolic blood pressure control in African Americans was achieved more often with diuretics (71 %) than with beta blockers (53 %), while the beta blockers failed to reduce blood pressure to less than 160/100 mmHg in 18 % of African Americans [130].

An analogous lack of efficacy in African Americans was observed with ACE-inhibitors, while diuretics were more effective than ACE-inhibitors in African

Americans, and ACE-inhibitors were more effective in Caucasians [140–142]. On the other hand, calcium antagonists seemed to be more effective than beta blockers with similar efficacy to diuretics in African Americans [125, 143–145]. In summary, African Americans have a better blood pressure response to diuretics and calcium antagonists compared with RAS inhibitors and beta blockers [146].

Gender

Life expectancy is longer in females than in males; moreover, cardiovascular events are less frequent and occur later in life in females [147]. Several differences exist between genders regarding prevalence, awareness, treatment, and control of hypertension, and the observed differences are age-dependent [148]. The pathophysiology of hypertension seems to be different in females and males [149]. Estrogens seem to exert beneficial effects on blood pressure and the cardiovascular system, including vasorelaxation, sympathetic inhibition and subsequent attenuation of the RAS [150]. Along with the hormonal differences, the mechanical properties of the arteries differ as well, since more pronounced increments at older age are observed in females than in males [151]. Moreover, several differences between the two genders have been reported in target organ damage, comorbidities, and cardiovascular risk [149].

Data from small clinical studies suggested that the blood pressure response to antihypertensive therapy might be different in females than in males [152–154]. Furthermore, post-hoc analyses from some large trials (ALLHAT and VALUE, but not in others) suggested that either the blood pressure reduction with some drugs differed according to gender [155, 156] or the cardiovascular outcomes might be different between the two genders (Heart Attack trial, Hypertension Care Computing Project, Second ANBP) [157–159].

However, there is yet no firm evidence that a particular drug class is better suited than another for treating arterial hypertension according to gender. In fact, a recent meta-analysis of large clinical trials with antihypertensive drugs according to gender did not find any significant differences in blood pressure reduction and cardiovascular outcomes between males and females [160]. Moreover, no evidence was found that the different antihypertensive drug classes are more effective in one gender than the other [160].

Adiposity

The pathophysiological mechanisms underlying blood pressure elevation in lean and obese patients have significant differences [161, 162]. Therefore, the probability for different optimum antihypertensive therapy according to adiposity might be a credible assumption.

Very recently, the Blood Pressure Lowering Treatment Trialists Collaboration performed a meta-regression analysis to evaluate the cardiovascular effects of antihypertensive drugs according to baseline adiposity categories [163]. The authors analyzed the data of more than 135,000 patients participating in 22 trials and divided participants in obese, overweight, and lean according to baseline body mass index values. The categorical analysis of the outcome did not show any special protection from cardiovascular events across the three adiposity categories. In contrast, the analysis of the comparisons as continuous variables revealed that ACE-inhibitors provided greater protection from cardiovascular events over other drugs (calcium antagonists and diuretics) for each 5 kg/m^2 increase in baseline body mass index levels. The combined findings of continuous and categorical analyses led the Collaboration to conclude that the superiority of ACE inhibitors over other drugs in obese versus lean patients is probably a false-positive finding, and therefore the findings of previous clinical trials might be a play of chance [163].

On the other hand, a sub-analysis of the ACCOMPLISH trial revealed that the combination of a calcium antagonist with an ACE-inhibitor had similar outcome benefits across the baseline adiposity status (lean, overweight, and obese). In contrast, the combination of a diuretic with an ACE-inhibitor was associated with significantly greater benefits in obese patients than in overweight and especially in lean patients, suggesting that the diuretic combination might be less effective in lean hypertensive patients when compared with a calcium antagonist combination [164].

The findings of the ACCOMPLISH study are in line with the results of the Systolic Hypertension in the Elderly Programme (SHEP). In a post-hoc analysis of the SHEP study, chlorthalidone (a thiazide-like diuretic) was less effective in cardiovascular protection (stroke) and mortality reduction in lean elderly hypertensive patients, especially in women [165]. In contrast, no difference in cardiovascular events and mortality was observed between lean and obese patients randomized to placebo.

Left Ventricular Hypertrophy

Left ventricular hypertrophy is a strong and independent cardiovascular risk factor. Several observational studies have shown that the reversal of left ventricular hypertrophy is associated with significant reductions in cardiovascular morbidity and mortality, as well as all-cause mortality [166–168]. Recent findings from large clinical trials confirmed that: (a) regression of left ventricular hypertrophy with antihypertensive therapy can occur, but it takes up to 2–3 years to reach maximum left ventricular mass reduction and then remains stable [169, 170], and (b) reversal or regression of left ventricular hypertrophy is associated with significant cardiovascular benefits [171].

Antihypertensive drugs seem to exert different effects on left ventricular mass, with RAS inhibitors and calcium antagonist having the greatest efficacy and beta blockers the lowest. [172–180] The findings of these studies should be taken with a

grain of salt, since some studies were not adequately blinded (operator reading bias), the sample size was usually small, the study duration short, and blood pressure differences between comparator drugs were not always reported. However, the large echocardiography sub-study of the LIFE trial with 960 hypertensive patients with left ventricular hypertrophy was devoid of the abovementioned problems, and revealed a significant superiority of angiotensin receptor blocker over the beta blocker on left ventricular hypertrophy reduction [170].

Arterial Stiffening

Large arteries stiffen with age, and arterial hypertension is a major contributor of enhanced stiffening along with other factors. Therefore, antihypertensive therapy results in improvement of arterial compliance through the reduction of blood pressure *per se* [181–183]. Whether differences between antihypertensive drug classes on their effect on arterial stiffness exist remains unknown. Although some studies suggested superiority of RAS inhibitors over the other antihypertensive drugs in reducing arterial stiffness [184–186], other high quality studies –such as the EXPLOR- failed to confirm it [187]. Of note, significant within-class differences seem to exist for beta blockers regarding their effects on arterial stiffness; however the clinical significance remains unclarified [188].

Diabetes Mellitus

Diabetes mellitus usually coexists with hypertension. Blood pressure control is more difficult to be attained in patients with diabetes mellitus, and the vast majority of diabetic patients require combination therapy to achieve target blood pressure [189]. Therefore, it seems meaningless to spend time in finding appropriate monotherapy since most patients will require two or more medications. From existing data it seems reasonable to start with a RAAS blocker with or without a diuretic depending on the level of baseline BP. ACE inhibitors or ARBs are particularly indicated in the presence of macro or micro-albuminuria [190]. Despite concerns about using beta blockers in diabetic patients, mainly due to the impairment of insulin sensitivity, beta blockers have been shown to be equally effective with ACE inhibitors in the UKPDS trial [191]. Overall, all antihypertensive drugs have a place in the treatment of patients with diabetes mellitus and can be used for effective BP control [192] but a RAAS blocker should be the first or second agent.

. Three studies that addressed combination therapy among diabetics produced variable results. The ONTARGET and ALTITUDE trials, found no benefit with the combinations of two RAAS inhibitors, while an increased risk of adverse events

was reported [193, 194]. In the ACCOMPLISH study, the combination of an ACE inhibitor with a calcium antagonist was significantly superior to the combination with a diuretic in the whole study population, as well as in diabetics and in high-risk diabetic patients [195]. Therefore, the combination of two RAS inhibitors is contraindicated, while the combination of a RAS inhibitor with calcium antagonists seems to be more beneficial than the combination with diuretics but this is still debated. In the ACCORD trial combinations of RAAS blockers with diuretics did not seem to be inferior to other combinations.

Metabolic Syndrome

The metabolic syndrome is a disputable clinical entity, which represents a clustering of cardiovascular risk factors (obesity, hypertension, dyslipidemia, and glucose abnormalities) [196–198]. Patients with metabolic syndrome are at increased risk to develop diabetes mellitus. It appears therefore reasonable to try to avoid antihypertensive agents that increase insulin resistance in such patients. Consequently, RAS inhibitors and calcium antagonists are preferred instead of diuretics and beta blockers, and especially their combination. When the latter categories are used, it seems prudent: (a) to prefer vasodilatory beta blockers that do not share the adverse metabolic actions of traditional beta blockers, (b) to combine the diuretic with a potassium-sparing drug, since hypokalemia enhances glucose intolerance, and (c) to select low doses of these drugs, since their metabolic actions are dose-dependent [199–202].

Stroke

All antihypertensive agents are effective for primary stroke prevention, since arterial hypertension is a major risk factor for cerebrovascular disease and blood pressure reduction results in significant benefits [203]. Calcium antagonists seem to be more protective from stroke than the other antihypertensive drug classes, as shown in several meta-analyses and meta-regression analyses [204–206]. However, this does not hold true for the totality of CV complication protection and treatment should be individualized. Until accurate predictors of future cardiovascular events are identified, the relative superiority of one class over the other for a specific outcome remains meaningless.

Secondary stroke prevention has not been adequately studied [207]. Significant benefits with antihypertensive medication have been observed in two studies, one using a diuretic and the other an ACE inhibitor combined with a diuretic [208, 209]. In addition, better cerebrovascular protection with ARBs than with other antihypertensive agents has been also observed [210, 211].

Myocardial Infarction

Antihypertensive therapy has resulted in significant reduction of cardiovascular morbidity and mortality. However, the benefits on myocardial infarction risk reduction are less impressive as compared to the benefits on stroke reduction, a finding observed first in the VA trials and confirmed later in several large randomized trials [1, 5, 12]. This disparity in risk reduction may be due to the fact that hypertension plays a less important role in the pathogenesis of coronary artery disease. The INTERHEART study for example showed that only 25 % of the risk for myocardial infarction could be attributed to hypertension [212].

Beta blockers and RAS inhibitors have demonstrated significant benefits in many studies, in patients who suffered a recent myocardial infarction [204, 213, 214]. Later on, agents from every antihypertensive drug class can be used and exert similar benefits [204]. In hypertensive patients with symptomatic coronary artery disease, beta blockers and calcium antagonists should be preferred agents at least for symptom relief.

Heart Failure

Arterial hypertension is the major risk factor for heart failure and antihypertensive therapy has resulted in pronounced reduction of heart failure development [12]. Calcium antagonists seem to be inferior to other antihypertensive drugs in heart failure prevention [205], diuretics were more effective than ACE-inhibitors in ALLHAT [155], and ARBs were even less effective in some studies (ONTARGET, TRANSCEND, PROFESS) [194, 215, 216]. As mentioned above however, the relative benefits of one class over the other regarding a specific benefit remain without clinical significance, since prediction of a specific outcome in an individual is currently impossible.

Beta blockers, RAS inhibitors (ACE inhibitors and ARBs), and mineralocorticoid receptor antagonists (spironolactone and eplerenone) have all shown significant survival benefits in patients with heart failure and reduced ejection fraction. Therefore, these agents are recommended for the management of heart failure patients, independent of blood pressure level even in patients with low BP as long as they can be tolerated. Loop diuretics are used primarily for decongestion and symptom relief [12]. Calcium antagonists do not seem to have a place in the management of systolic heart failure unless needed for blood pressure control. In patients with heart failure and preserved ejection fraction, an entity with high prevalence of hypertension and left ventricular hypertrophy, optimal control of hypertension is the ultimate goal. Specific use antihypertensive drugs failed to show added benefit [12, 217].

Atrial Fibrillation

Hypertension is frequently encountered in patients with atrial fibrillation, and in fact hypertension may contribute to the development and maintenance of atrial fibrillation. In these patients ventricular rate is usually high [218, 219]. Therefore, antihypertensive agents reducing heart rate, such as beta blockers and non-dihydropyridine calcium antagonists (verapamil and diltiazem), are frequently used for rate control in this patient population.

From the clinical point of view, the prevention of incident atrial fibrillation or the attenuation of recurrences is of paramount importance. Several lines of evidence coming from post-hoc analyses of large clinical trials suggested that ARBs were superior to calcium antagonists and beta blockers for the prevention of incident atrial fibrillation [220–224], which however was not observed in other trials [215, 216]. Studies specifically addressing the effect of ARBs on atrial fibrillation failed to show either prevention of recurrences in paroxysmal and persistent atrial fibrillation or prevention of cardiovascular events in patients with established atrial fibrillation [225–229]. Finally, incident atrial fibrillation was prevented by beta blockers and mineralocorticoid receptor antagonists in patients with heart failure and reduced ejection fraction [230, 231].

In Summary

Selection of optimal antihypertensive therapy should have the following three generic goals in mind:

1. Control blood pressure with least intrusive means
2. Take into consideration co-morbidities and how to optimize symptom control
3. Contribute to improvement of health outcomes and life expectancy.

It is well known that most patients with hypertension will need more than one medication to achieve blood pressure control. Monotherapy is only adequate in 20–25 % of patients with hypertension. Achieving blood pressure control is probably much more important than what drug combination has been used. Although current guidelines allow for acceptable BP control a systolic up to 150 mmHg, the recently published SPRINT study demonstrated to all of us in an undisputed way that lower is better and goals of systolic BP <120 mmHg provide improvement in morbidity and mortality. The SPRINT study was not a drug focuses study; it was rather a blood pressure level focused study and yet surprised us all with impressive improvement in health outcomes with the intensive lowering of blood pressure.

Focusing on co-morbidities is important and will make patients feel better and live longer. For example, patients with high heart rate, angina and/or atrial fibrillation

will benefit from beta blockers or heart rate lowering calcium antagonists. Rate control will make patients feel better and probably live longer. Similarly patients with heart failure will benefit from beta blockers, ACE-i/ARBs and MRAs and certainly most of them need diuretics for symptom control.

Since the early studies from the Veterans Administration that demonstrated marked improvement in health outcomes with blood pressure control, we came a long way in our understanding of optimal choice of antihypertensive therapy. Taking into consideration co-morbidities we can not only prolong life, but can pretty much eliminate symptoms and minimize complications of hypertension.

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