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Practical application of the ATOM study

Treatment efficacy of antihypertensive drugs in monotherapy or combination (ATOM metaanalysis according to PRISMA statement); tables for the use of antihypertensive drugs in monotherapy or combination

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Abstract

Background: The response to antihypertensive drugs is predictable. The absence of precise prescription recommendations to treat arterial hypertension (HT) lead to use drugs unable to reduce blood pressure (BP) to target values.

We published ATOM study, in which we found significant differences in the ability to reduce BP between the different drugs.

The objective of the study was to determine the expected decrease in blood pressure with the use of commercialized doses of the drugs commonly used in the treatment of HT in clinical practice, to avoid the use of drugs or combinations that even with the best response, are unable to obtain the necessary BP decrease to reach the goal.

Methods: The analysis was based on the results of the ATOM study. To convert the mean doses of the different drugs and combinations in commercialized doses, the conclusions of the study by Law et al have been applied.

Results: Based on the results, two tables were drawn, one for systolic BP and the other for diastolic BP, where the doses of the different drugs and combinations are classified according to the BP decrease that can be expected from them. In order to favor the use of the tables in clinical practice, the different drugs have been grouped in intervals of 10 millimeters of mercury (mmHg) for the decrease of the systolic BP and of 5 mmHg for the diastolic BP.

Conclusions: Recommendations for the use of antihypertensive treatments should not be limited to pharmacological families. They should also consider differences between drugs or specific combinations. From the data of the ATOM study we have implemented tables that express the effect of the drugs commonly used in clinical practice and that should allow the clinicians to choose with care the treatment to use.

Abbreviations: ARB = angiotensin receptor blocker, BMI = body mass index, BP = blood pressure, HCTZ = hydrochlorothiazide, HT = hypertension, mm Hg = millimeters of mercury.

Keywords: antihypertensive agent, ATOM study, hypertension, hypertension treatment, tables to select antihypertensive treatment

1. Introduction

The main benefit of treating arterial hypertension (HT) is obtained with an adequate control of blood pressure (BP), regardless of the treatment used.[1] Although at present the target values of BP are under discussion, especially following the publication of the SPRINT[2] study, the management guidelines for HT have brought different recommendations based on the clinical characteristics of the patients.

Most international guidelines make recommendations for specific antihypertensive families based on age and ethnicity. These recommendations assume that all classes of antihypertensive are equipotent and that there are no differences between the different active principles of each family. The European guidelines[1] leave the treatment to be used at the discretion of the practitioner without distinguishing between the different pharmacological classes. None of the guidelines establish differences between drugs, even though their antihypertensive potency cannot be considered equivalent.[1,3]

The absence of precise prescription recommendations may lead in many cases to use drugs that, even with the best response, are unable to reduce BP to target values. This could result in an increased cardiovascular risk.

We recently published the results of the ATOM[4] study, a meta-analysis of 208 clinical trials, with 94,305 patients included.[4] In this study, we found significant differences in the ability to reduce BP between the different drugs used in monotherapy and, more significantly, between the different pharmacological combinations. However, in this study, the drugs and combinations are expressed in mean doses resulting from the studies analyzed, making it difficult to apply them in practice.

Achieving the equivalence of the results of the ATOM study with the commercialized doses of the different drugs would allow the elaboration of tables in which the capacity of each drug in the reduction of the BP was determined, thus helping the clinician to make the right choice of the treatment to be used to achieve the target BP values. To that end, the results of the study by Law et al[5] can be used. The study determined the effect of doubling or halving the dose of the various drugs on the decrease of the BP. It also established the expected percentage of variation of that effect on the systolic and diastolic BP with the dose change, thus making it easy to convert the mean doses of the ATOM study into the usual doses.

The objectives of this study are to apply the Law et al[5] equation to the results previously determined in the ATOM study to adapt them to the doses of drugs commonly used in clinical practice and to design tables that allow the clinician to choose the drug according to the decrease in BP necessary to reach the target.

2. Methods

The analysis was based on the results of the ATOM[4] study. Briefly, a Bayesian meta-regression of clinical trials whose main objective was to assess the efficacy of the drugs in the reduction of BP was conducted in this study.

To convert the mean doses of the different drugs and combinations in commercialized doses, the conclusions of the study by Law et al[5] have been applied. In that study it was determined that doubling or halving a dose of any drug modifies the response to it by approximately 20% for both systolic BP and diastolic BP. In the case of combinations, the effect is estimated as the sum of the efficacy of each drug separately, as reported by the aforementioned authors.

Based on the mean doses reported in the ATOM study, the Law equation was applied in each of the drugs, to transform them into the "real" doses that are commonly used in clinical practice. When the "real" dose is greater than the mean dose calculated in ATOM, an increase in the response of 19.78% for systolic BP and 18.18% for diastolic BP has been applied. Otherwise, when the "real" dose is lower, a reduction of 21.98% and 20.00%, respectively, has been applied. In the Law study, there were little differences between the variations of BP observed in the category of drugs analyzed (betablockers, thiazides, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker [ARB] and calcium channel blockers). These differences were very small and we applied the average reported.

In the case of combinations, as previously stated, each drug was calculated separately, expressing the effect of the combination as the sum of each of the components separately.

2.1. Ethical considerations

The variables recorded come from clinical trials that do not contain any personal data. For this reason, the approval of an ethics committee was not considered necessary.

Table 1

Characteristics of the patients included in the ATOM study.

	N= 94.305
Age, y	54.5 ± 1.9
Sex: women, %	45.2
Type 2 diabetes, %	10.6
Caucasians, %	82.9
Afro-Americans or Afro-Caribbeans, %	17.1
Systolic BP, mm Hg	155.2 ± 5.7
Diastolic BP, mm Hg	99.3 ± 1.8

3. Results

The profile of the patients included in the ATOM study is detailed in Table 1. Its characteristics allow to apply of the conclusions to a large group of hypertensive patients, regardless of their age and their baseline BP, as detailed in the original study.

The results, in the reduction of systolic and diastolic BP, of the different drugs used in monotherapy after applying the Law equation are expressed in supplemental content 1, http://links.lww.com/MD/C914, whereas the different combinations are shown in supplemental content 2, http://links.lww.com/MD/C914 (see supplemental content that illustrates the effect of combinations on systolic and diastolic BP, after applying the Law equation to the mean doses calculated in the ATOM study, http://links.lww.com/MD/C914).

Based on the results obtained, 2 tables were drawn, one for systolic BP (Table 2) and the other for diastolic BP (Table 3), where the doses of the different drugs and combinations are classified according to the decrease of BP that can be expected from them.
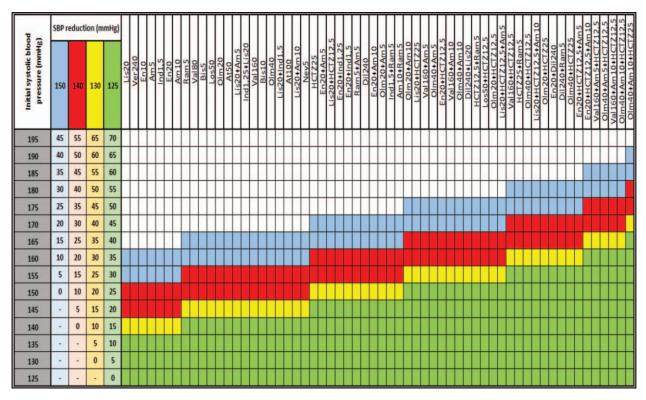
To favor the use of the tables in clinical practice, the different drugs have been grouped in intervals of 10 mm Hg for the decrease of the systolic BP and of 5 mm Hg for the diastolic BP, which is specified in supplemental content 3 and 4, http://links.lww.com/MD/C914 (see supplemental content, http://links.lww.com/MD/C914, that illustrates the interval grouping in the reduction of the systolic BP of the different drugs and combinations and Table 4, supplemental content, http://links.lww.com/MD/C914, that illustrates the grouping intervals in the reduction of the diastolic BP of the different drugs and combinations). In this way, the tables express the initial BP of the patient and the BP that will be obtained with the use of the different drugs or combinations. Knowing the objective BP, the clinician can choose the treatment he considers.

Thus, for example, a patient with a systolic BP of 165 mm Hg, in which the target BP is <140 mm Hg, allows the use of different combinations to achieve the desired decrease, as shown in Table 4. For practical use, the patient's initial BP is determined (reflected as A in the table), the target BP (B in the table) is chosen and the drugs and/or combinations capable of obtaining the decrease of PA (C in the table) are identified, which in the present case would range from the double combination of olmesartan 20 and amlodipine 10 to the triple association of enalapril 20, hydrochlorothiazide (HCTZ) 12.5 and amlodipine 5.

As noted in the ATOM study, and as shown after applying the Law equation, no monotherapy drug achieves a reduction of systolic BP >20 mm Hg, whereas only high doses of olmesartan, nebivolol, and diltiazem are capable of producing a decrease in diastolic BP >10 mm Hg. On the contrary, most combinations guarantee a decrease of systolic BP >20 mm Hg and of diastolic

Table 2

Effect of different doses of drugs and combinations on systolic BP.

Initial systolic blood pressure (mmHg)	SBP reduction (mmHg) 150	140	130	125
195	45	55	65	70
190	40	50	60	65
185	35	45	55	60
180	30	40	50	55
175	25	35	45	50
170	20	30	40	45
165	15	25	35	40
160	10	20	30	35
155	5	15	25	30
150	0	10	20	25
145	-	5	15	20
140	-	0	10	15
135	-	-	5	10
130	-	-	0	5
125	-	-	-	0

Drug/combination column headers: Lis20, Ver240, En10, Am5, Ind1.5, En20, Am10, Ram5, Val80, Bis5, Los50, Olm20, At50, Lis20+Am5, Ind1.25+Lis20, Val160, Bis10, Olm40, Lis20+Ind1.5, Lis20+Am10, At100, Nev5, HCTZ25, En20+Am10, Lis20+HCTZ12.5, En20+Ind1.25, En20+Ind1.5, Ram5+Am5, Dil240, En20+Am10, Olm20+Am5, Ind1.5+Ram5, Am10+Ram5, Olm20+Am10, Lis20+HCTZ25, Val160+Am5, Olm40+Am5, En20+HCTZ12.5, Val160+Am10, Olm40+Am10, Dil240+Lis20, HCTZ12.5+Ram5, Los50+HCTZ12.5, Olm20+HCTZ12.5, Lis20+HCTZ12.5+Am5, Val160+HCTZ12.5, HCTZ25+Ram5, Olm40+HCTZ12.5, Lis20+HCTZ12.5+Am10, Olm20+HCTZ25, En20+Dil240, Dil240+Ram5, Olm40+HCTZ25, En20+HCTZ12.5+Am5, En20+HCTZ12.5+Am10, Val160+Am5+HCTZ12.5, Olm40+Am5+HCTZ12.5, Val160+Am10+HCTZ12.5, Olm40+Am10+HCTZ12.5, Olm40+Am10+HCTZ25

Knowing the systolic blood pressure of the patient (left side) and the blood pressure objective (150 mm Hg = blue color, 140 mm Hg = red color, 130 mm Hg = yellow color, or 125 mm Hg = green color), the table provides the appropriate therapeutic alternatives at the top.

Women show a better response to thiazide diuretics (4%), ARB (4%), and combinations (6%).

Obese patients show a better response to ARB (5%) and combinations (6%) for each unit over 25 kg/m^2

Afro-American/Afro-Caribbean patients show a worse response to beta-blockers (−8%).

Abbreviations (the number corresponds to the daily dose of drug in mg).

Lis = lisinopril; Ver = verapamil; Am = amlodipine; Ind = indapamide; En = enalapril; Ram = ramipril; Vals = Valsartan; Bis = bisoprolol; Los = losartan; Olm = olmesartan; At = Atenolol; Nev = Nevibolol; HCTZ = hydrochlorothiazide; Dil = diltiazem.

BP >15 mm Hg. The combination with the highest potency in the decrease of BP is the combination of high doses of olmesartan, amlodipine, and HCTZ, which is the only one able to achieve a reduction of systolic BP of 40 mm Hg.

4. Discussion

Our study allows a practical clinical application of the results of the ATOM study, converting the mean doses of antihypertensive drugs determined in the ATOM study, into commercialized and commonly used doses. As already mentioned, the characteristics of the analyzed population allow the results to be applied to a large population of hypertensive patients, unlike other previously published[6,7] and questioned[8] meta-analysis because they were not adjusted according to variables that modify the response, such as age, sex, body mass index (BMI), or ethnicity. This prevents its practical application to a broad population of patients with HT.

Although, as already mentioned in the ATOM study, no significant differences in efficacy were found between the different pharmacological classes considered as a whole, there are differences between specific drugs and, especially, between combinations. This fact is not included in the different managemen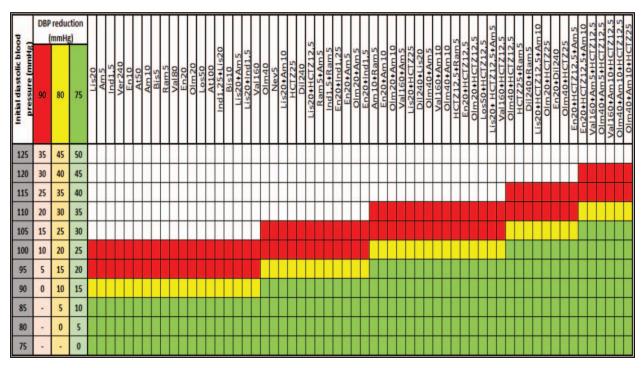t guidelines for HT[1,3,9,10] whose recommendations are summarized in pharmacological classes without addressing the differences between specific drugs.

However, the careful use of antihypertensive drugs as well as the achievement of therapeutic goals as quickly as possible is relevant for several reasons. First, a decrease in morbidity and mortality due to HT has been reported in patients whose control goal is achieved early.[11] In addition, obtaining the therapeutic target before 6 months after starting treatment improves adherence to it,[12] whereas treatment changes have the opposite effect. Finally, successive medication changes, sometimes with the use of drugs which even with the best response cannot achieve the objectives, can have a greater economic cost and therefore be harmful from a pharmacoeconomic point of view.

The tables developed in our study should allow the clinician to make informed choices about the treatment to be used to achieve the proposed objective. Knowing the BP of the patient and the objective BP, the tables express the appropriate therapeutic alternatives the physician can choose taking into account other aspects such as clinical benefits beyond BP control demonstrated by different drugs, comorbidities, side effects, pharmacoeconomic considerations, or phenotypic aspects that can predict a better or worse response. This was demonstrated by the ATOM study and its importance had already been invoked by other publications.[13–17]

Table 3

Effect of different doses of drugs and combinations on diastolic BP.

Knowing the diastolic blood pressure of the patient (left side) and the blood pressure objective (90 mm Hg = red color, 80 mm Hg = yellow color or 75 mm Hg = green color), the table provides the appropriate therapeutic alternatives at the top. Women show a better response to thiazide diuretics, ARB, and combinations.
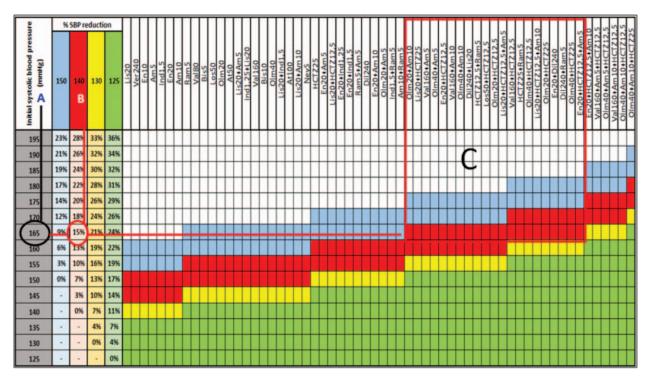
Obese patients show a better response to ARB and combinations.

Afro-American/Afro-Caribbean patients show a worse response to beta-blockers.

For abbreviations, see Table 2.

Table 4

Practical example of the use of the tables.

A: Initial blood pressure. B: Target of BP. C: Drugs and/or combinations capable of obtaining the decrease of PA.

In this example, the interval (C) would range from the double combination of olmesartan 20 and amlodipine 10 to the triple association of enalapril 20, hydrochlorothiazide (HCTZ) 12.5 and amlodipine 5.

For abbreviations, see Table 2.

The tables show other interesting aspects. As noted in the ATOM study, no monotherapy drug achieves a reduction of systolic BP >20 mm Hg, whereas only high doses of olmesartan, nebivolol, and diltiazem are able to produce a decrease of diastolic BP >10 mm Hg. In view of the need for BP declines of this magnitude, we recommend the use of combinations, which, in general, guarantee responses of that intensity.

The study has limitations: as noted in ATOM study, only in subgroups with 7 or more studies was possible the meta-regression. Drugs or combinations with not enough studies are not included in the tables. Therefore, some interesting drugs, such as chlorthalidone or nifedipine, were not included in the tables. However, all pharmacological families of antihypertensive drugs are represented by more than one drug.

The adjusted results presented in this work can be helpful in choosing the treatment and the dose of the appropriate antihypertensive agent(s) to achieve BP control, but the final choice of antihypertensive treatment should take into account the patient's clinical situation (renal or liver disease, type 2 diabetes, risk of orthostatism, etc.), the specific indications for each situation (stable coronary disease, heart failure, ischemic or haemorrhagic stroke, chronic kidney disease, cognitive decline, etc.), the concomitant morbidity, the respective treatments and their possible interactions (i.e., potassium-sparing diuretics and ACEI in heart failure), and the cost and accessibility of the treatment.[1,3] However, in the tables, with the exception of those patients who require high BP drops, all antihypertensive families are represented in each interval of BP reduction, and that should allow the clinicians to choose carefully the treatment to use.

In addition, although our results are adjusted for age, sex, ethnicity, body mass index, baseline BP, type 2 diabetes and cardiovascular disease, the clinicians should take into account for their decision the patient's phenotype, as well as the risk factors associated with HT.

In summary, the effect of antihypertensive drugs is predictable. We have made tables that are intended to be a useful tool for practitioners to choose the treatment to be used wisely and to avoid the use of drugs or combinations that, even with the best response, are unable to obtain the necessary BP decrease to reach the goal.

5. Conclusion

Recommendations for the use of antihypertensive treatments should not be limited to pharmacological families. They should also consider differences between drugs or specific combinations. Such differences are important enough to determine whether or not to achieve therapeutic goals.

From the data of the ATOM study, we have implemented tables that express the effect of the drugs commonly used in clinical practice and that should allow the clinicians to choose with care the treatment to use.

Author contributions

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