

The corporate bias and the molding of prescription practices: the case of hypertension

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Drug management of hypertension has been a noticeable example of the influence of the pharmaceutical industry on prescription practices. The worldwide leading brands of blood pressure-lowering agents are angiotensin receptor-blocking agents, although they are considered to be simply substitutes of angiotensin-converting enzyme (ACE) inhibitors. Commercial strategies have been based on the results of clinical trials sponsored by drug companies. Most of them presented distortions in their planning, presentation or interpretation that favored the drugs from the sponsor, i.e., corporate bias. Atenolol, an ineffective blood pressure agent in elderly individuals, was the comparator drug in several trials. In a re-analysis of the INSIGHT trial, deaths appeared to have been counted twice. The LIFE trial appears in the title of more than 120 reproductions of the main and flawed trial, as a massive strategy of scientific marketing. Most guidelines have incorporated the corporate bias from the original studies, and the evidence from better designed studies, such as the ALLHAT trial, have been largely ignored. In trials published recently corporate influences have touched on ethical limits. In the ADVANCE trial, elderly patients with type 2 diabetes and cardiovascular disease or risk factors, allocated to placebo, were not allowed to use diuretic and full doses of an ACE inhibitor, despite the sound evidence of benefit demonstrated in previous trials. As a consequence, they had a 14% higher mortality rate than the participants allocated to the active treatment arm. This reality should be modified immediately, and a greater independence of the academy from the pharmaceutical industry is necessary.

Key words: Hypertension; Blood pressure agents; Clinical trials; Ethics; Corporate bias

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Hypertension, a major risk factor for cardiovascular disease, may be controlled by numerous effective pharmacological and non-pharmacological therapies. Since almost all individuals are or will be hypertensive if they live enough (1), the management of hypertension represents a huge source of profits for the pharmaceutical industry. As a result of this commercial interest, the marketing strategies of the pharmaceutical industry have noticeably influenced the prescription of blood pressure-lowering agents. Five of the 10 leading brands of blood pressure-lowering drugs were angiotensin-receptor antagonists (ARB) in the US in 2006 (2), even though these drugs are considered to

be only substitutes for angiotensin-converting enzyme (ACE) inhibitors. Commercial strategies, mostly based on the results of clinical trials sponsored by drug companies, have led doctors to believe that new agents are superior to old ones. In letters and commentaries, I and others have identified the influence of the pharmaceutical industry on the planning, presentation and interpretation of clinical trials that resulted in the distortion of the evidence in favor of their products, i.e., the corporate bias. Letters, however, are considered to be a neglected genre of writing, and have been mostly ignored in the shaping of clinical knowledge (3).

Most, if not all, corporate-funded trials of blood pressure drugs had at least one component of the corporate bias. For instance, several trials employed atenolol and other β -blockers as comparator drugs in elderly patients, ignoring the results of the MRC trial with elderly participants, which showed that atenolol was inert as first option in this age group (4). The CAPPP, NORDIL, and STOP-2 trials were the first to incur such planning bias (5). In a meta-analysis of these and other trials (6), β -blockers and diuretics were merged into an "old strategy" group, ignoring the different efficacy of these groups of blood pressure-lowering agents (7). More recently, the LIFE (8) and ASCOT (9) trials again employed atenolol as the comparator drug in elderly patients, incurring once more in the planning component of the corporate bias (10,11). The advantage of losartan in the LIFE trial (8) could also be explained by the more frequent use of diuretics by patients treated with losartan (12). Despite these major shortcomings, the LIFE trial has been the basis of a massive strategy for the commercial promotion of losartan, resulting in more than 120 reports with LIFE trial or LIFE study in the title, a case of multiple publications of the same study never seen before (13). In the ASCOT-BPLA study (9), the decline in blood pressure was greater and faster with the amlodipine-based regimen, explaining the lower incidence of cardiovascular outcomes in patients allocated to this arm of the trial (11).

Even in better designed trials, the corporate bias appeared in the interpretation of findings. In the INSIGHT trial, patients treated with the nifedipine gastrointestinal therapeutic system (GITS) in comparison with a combination of hydrochlorothiazide and amiloride had a higher incidence of myocardial infarction and heart failure (14). Results of secondary outcomes, such as the marginal difference of effect on lipids and glucose, were presented with greater emphasis than the main outcomes. Discussion was very confusing and never highlighted the clear trend of a higher incidence of unfavorable outcomes and lower compliance in patients treated with nifedipine GITS. In a report restricted to patients with diabetes (15), the INSIGHT investigators used ill-defined outcomes, leading to the assumption that they had counted the deaths twice (16). The real outcomes employed in the analyses (worsening of angina, for instance) were presented only in the reply letter. The original report should have been formally withdrawn from the literature since none of the outcomes really employed in the analyses were even cited in the manuscript.

In the VALUE study (17), the incidence of myocardial infarction and stroke was higher among participants allocated to a valsartan-based treatment than to an amlodipine-

based treatment. In patients with blood pressure matched for the attained systolic pressure, the incidence of stroke and myocardial infarction was similar in both groups (18). Since the incidence in the whole sample was higher in patients treated with valsartan, and similar in patients with blood pressure matched for the attained systolic pressure, it is evident that the incidence of stroke and myocardial infarction was much higher in patients on valsartan having too high systolic pressure to allow matching. These findings could give origin to a third paper based on the VALUE trial data, which was surely not prepared and submitted. The VALUE trial (17) is a major example of the distortion of the evidence by the presentation and interpretation components of the corporate bias, since valsartan, the less effective blood pressure-lowering agent in the trial, has been the leader in profits in many countries, including Brazil.

The shortcomings of these trials could be explained in part by the state of art at the time of their planning, when the lower efficacy of β -blockers in elderly individuals had not become fully evident, and when the expectations about the existence of additional pleiotropic effects of blood pressure agents were higher. The NIH-funded ALLHAT trial was specifically designed to compare the efficacy of 4 groups of blood pressure-lowering agents as first option to prevent major cardiovascular events (19). Chlorthalidone, the diuretic, was more effective than doxazosin (an α -blocker), lisinopril (an ACE inhibitor) and amlodipine (a calcium channel blocker) in the prevention of several major cardiovascular outcomes. The ALLHAT trial had more patients in each comparison arm than all patients of most corporate-funded trials. Moreover, the ALLHAT trial was double-blind, while most trials funded by the industry employed the "Probe design", which is just another name for an open trial. Among various specific comparisons, the ALLHAT trial (19) was the first to compare the efficacy of these drugs in preventing renal impairment by hypertension. In diabetic patients with moderate baseline loss of glomerular filtration rate (60 to 90 mL/min), the incidence of end-stage renal failure was more than 70% higher in patients treated with amlodipine or lisinopril than in patients treated with chlorthalidone (20). The superiority of chlorthalidone was also demonstrated in patients with diabetes and in patients who developed diabetes during the follow-up (21). This finding is of particular interest since it demonstrates that the higher frequency of diabetes in patients treated with chlorthalidone does not result in a worse prognosis. Taken together, the findings of the ALLHAT trial demonstrated that the pleiotropic effects of blood pressure-lowering agents, if they existed, were fully surpassed by the more effective blood pressure-lowering

efficacy of chlorthalidone.

With the exception of the US guidelines for hypertension, which recommend diuretics as the first option for most patients with hypertension (22), most international guidelines for hypertension management have absorbed the corporate bias of the original studies. For instance, an updated version of the United Kingdom guideline on hypertension (23) recommended ACE inhibitors (or an ARB agent if an ACE inhibitor was not tolerated) as initial therapy for patients less than 55 years of age. The foundation for such recommendation is paradoxical, as can be seen by this statement included literally in the guideline (23): "there are data suggesting that the blood pressure-lowering response in older patients is greatest when initial therapy is with a CCB or a thiazide-type diuretic. However, there are more limited data examining blood pressure-lowering efficacy in younger patients. This evidence suggests that initial therapy with a β -blocker or an ACE inhibitor (or angiotensin-II receptor antagonist) may provide superior initial blood pressure lowering when compared with a CCB or thiazide-type diuretic". This interpretation may be a unique case of reversed scholasticism. In another example, the 2007 European Society of Hypertension guideline recommended diuretics for black and elderly patients (24), and ARB agents or ACE inhibitors for a long series of clinical conditions, such as left ventricular hypertrophy, microalbuminuria, renal dysfunction, previous myocardial infarction, heart failure, recurrent atrial fibrillation, end-stage renal disease, metabolic syndrome, and diabetes mellitus. These recommendations were based on the results of the biased studies commented upon before, or even on the absolute absence of evidence, such as atrial fibrillation, and against the evidence, as in the case of the metabolic syndrome. For instance, a recent analysis of the ALLHAT trial (25) showed the superiority of chlorthalidone over amlodipine and lisinopril in the prevention of major cardiovascular outcomes in patients with metabolic syndrome.

In recently published trials the corporate influences have gone too far, threatening the ethics of science. The interpretation that the efficacy of blood pressure drugs derives mostly from their blood pressure-lowering effect is almost consensual. The exposure of large numbers of patients (particularly if for long periods) to placebo is not ethical. Despite this, placebo-controlled trials continued to be published (26). The ADVANCE trial (27) is a major example of such unethical studies. This trial compared a fixed combination of perindopril and indapamide with placebo of both drugs in patients with type 2 diabetes and cardiovascular disease or major risk factors. It was, in fact, a withdrawal trial, since the participants in the placebo

group, who were mostly enrolled while taking diuretics and ACE inhibitors, were not allowed to be treated with diuretics and full doses of ACE inhibitors during the trial. These agents had already been declared to be first option to treat patients with diabetes and hypertension by guidelines in effect at the time of the trial planning, and 63% of the participants had hypertension. The MICRO-HOPE trial had already shown the beneficial effects of an ACE inhibitor in patients with diabetes, irrespective of their baseline blood pressure (28). As a result of this major deviation from good research practices, participants allocated to the placebo group in the ADVANCE trial (27) had a 14% higher mortality rate than those treated effectively, as a consequence of the increase in blood pressure after having their effective treatments withdrawn. How could patients with type 2 diabetes, major cardiovascular disease or other risk factors for cardiovascular disease, and an average blood pressure of 145/81 mmHg, not be treated with full doses of ACE inhibitors and diuretics (29)?

Other recently reported trials involved the same deviation from ethics in human research at this point in time, i.e., to compare blood pressure agents with placebo in high-risk patients. For instance, two corporate-funded trials compared telmisartan with placebo in patients recovered from stroke (30) and in patients with diabetes at higher risk of cardiovascular events (31). The PROGRESS trial had already demonstrated that the combination of a diuretic and an ACE inhibitor reduced the recurrence of stroke by more than 40%, irrespective of the baseline blood pressure (32). In patients with diabetes at higher risk of cardiovascular events an ACE inhibitor had already been effective in preventing several cardiovascular outcomes (28). Therefore, telmisartan should have been compared with an ACE inhibitor in patients recovered from stroke and with another blood pressure drug in patients with diabetes, since the participants in this trial were intolerant to an ACE inhibitor. The small decrease in blood pressure in both trials (30,31) did not result in clinically relevant reduction of outcomes, adding another piece of evidence against the existence of pleiotropic effects of ARB agents.

Clinical trials influenced by the corporate bias have been the basis for a massive strategy of promotion of blood pressure drugs that resulted in the shaping of prescription practices departing from the best evidence. The collaboration between scientists from Universities and the pharmaceutical industry is welcome for the joint development of science and technology. In this case, however, we are facing a crisis that has touched on ethical limits. Instead of being involved in biased clinical trials sponsored by the pharmaceutical companies, scientists should be focusing on other relevant hypertension-related issues, such as the

vexing rates of high blood pressure control worldwide. A higher independence of the academy from the pharma-

ceutical industry to set the research agenda in hypertension is urgently required.

References

1. Moreira LB, Fuchs SC, Wiehe M, Gus M, Moraes RS, Fuchs FD. Incidence of hypertension in Porto Alegre, Brazil: a population-based study. *J Hum Hypertens* 2008; 22: 48-50.
2. Smith RE, Ashiya M. Antihypertensive therapies. *Nat Rev Drug Discov* 2007; 6: 597-598.
3. Horton R. Postpublication criticism and the shaping of clinical knowledge. *JAMA* 2002; 287: 2843-2847.
4. MRC Working Party. Medical Research Council trial of treatment of hypertension in older adults: principal results. *Br Med J* 1992; 304: 405-412.
5. Fuchs FD. What does STOP-2 tell us about management of hypertension? *Lancet* 2000; 355: 651.
6. Turnbull F. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet* 2003; 362: 1527-1535.
7. Fuchs FD. Effects of different blood-pressure-lowering regimens on major cardiac events. *Lancet* 2004; 363: 332.
8. Dahlof B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002; 359: 995-1003.
9. Dahlof B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* 2005; 366: 895-906.
10. Fuchs FD. Losartan for cardiovascular disease in patient's with and without diabetes in the LIFE study. *Lancet* 2002; 359: 2203-2204.
11. Fuchs FD, Gus M, Ribeiro JP. ASCOT-BPLA. *Lancet* 2006; 367: 205-208.
12. Kato J, Eto T. Diuretics in the LIFE study. *Lancet* 2004; 364: 413-414.
13. Melander H, Ahlqvist-Rastad J, Meijer G, Beermann B. Evidence b(i)ased medicine - selective reporting from studies sponsored by pharmaceutical industry: review of studies in new drug applications. *BMJ* 2003; 326: 1171-1173.
14. Brown MJ, Palmer CR, Castaigne A, de Leeuw PW, Mancia G, Rosenthal T, et al. Morbidity and mortality in patients randomised to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT). *Lancet* 2000; 356: 366-372.
15. Mancia G, Brown M, Castaigne A, de Leeuw P, Palmer CR, Rosenthal T, et al. Outcomes with nifedipine GITS or Coamilofide in hypertensive diabetics and nondiabetics in Intervention as a Goal in Hypertension (INSIGHT). *Hypertension* 2003; 41: 431-436.
16. Fuchs FD. May we die twice? *Hypertension* 2003; 42: e8.
17. Julius S, Kjeldsen SE, Weber M, Brunner HR, Ekman S, Hansson L, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet* 2004; 363: 2022-2031.
18. Weber MA, Julius S, Kjeldsen SE, Brunner HR, Ekman S, Hansson L, et al. Blood pressure dependent and independent effects of antihypertensive treatment on clinical events in the VALUE Trial. *Lancet* 2004; 363: 2049-2051.
19. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; 288: 2981-2997.
20. Rahman M, Pressel S, Davis BR, Nwachuku C, Wright JT Jr, Whelton PK, et al. Renal outcomes in high-risk hypertensive patients treated with an angiotensin-converting enzyme inhibitor or a calcium channel blocker vs a diuretic: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Arch Intern Med* 2005; 165: 936-946.
21. Barzilay JI, Davis BR, Cutler JA, Pressel SL, Whelton PK, Basile J, et al. Fasting glucose levels and incident diabetes mellitus in older nondiabetic adults randomized to receive 3 different classes of antihypertensive treatment: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Arch Intern Med* 2006; 166: 2191-2201.
22. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003; 289: 2560-2572.
23. National Collaborating Centre for Chronic Conditions. *Hypertension: management of hypertension: in adults in primary care partial update*. London: Royal College of Physicians; 2006.
24. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al. 2007 ESH-ESC Practice Guidelines for the Management of Arterial Hypertension: ESH-ESC Task Force on the Management of Arterial Hypertension. *J Hypertens* 2007; 25: 1751-1762.
25. Wright JT Jr, Harris-Haywood S, Pressel S, Barzilay J, Baimbridge C, Bareis CJ, et al. Clinical outcomes by race in hypertensive patients with and without the metabolic syndrome: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Arch Intern Med* 2008; 168: 207-217.
26. Fuchs FD. It is time to stop comparing blood pressure-lowering drugs with placebo. *Arch Intern Med* 2006; 166:

- 1786-1787.
27. Patel A, MacMahon S, Chalmers J, Neal B, Woodward M, Billot L, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet* 2007; 370: 829-840.
 28. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. *Lancet* 2000; 355: 253-259.
 29. Fuchs FD. The ADVANCE trial. *Lancet* 2008; 371: 25.
 30. Yusuf S, Diener HC, Sacco RL, Cotton D, Ounpuu S, Lawton WA, et al. Telmisartan to prevent recurrent stroke and cardiovascular events. *N Engl J Med* 2008; 359: 1225-1237.
 31. Yusuf S, Teo K, Anderson C, Pogue J, Dyal L, Copland I, et al. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. *Lancet* 2008; 372: 1174-1183.
 32. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet* 2001; 358: 1033-1041.