Invited review

Pharmacoeconomic considerations on the treatment of hypertension

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Abstract

Cardiovascular disease (CVD) is responsible for more deaths worldwide than any other condition, and a large proportion of healthcare budgets in more developed countries is spent on its treatment and prevention. In a period in which monetary resources for health care are limited and continue to be more and more restricted many studies have investigated the cost-benefit ratio of reducing blood pressure by considering patients' characteristics and therapeutic options, to verify if it is possible to improve health outcomes and quality of life at a reasonable cost. Both conventional and newer strategies have been shown to be cost-effective relatively to various other medical interventions, but the latter seem to offer additional long-term benefits. Moreover, the differences in the impact of factors like poor compliance, switching and discontinuation of treatments may significantly affect the overall cost of antihypertensive therapy in clinical practice, and justify a better cost-effectiveness ratio for drugs like ARBs, ACE inhibitors and some CCBs despite their greater retail price. Future research should focus on long-term, real world, longitudinal studies to measure the actual costs and savings associated with increased compliance and persistence, and their impact on positive health outcomes, such as improved blood pressure.

Key words: cardiovascular disease, antihypertensive therapy, cost-effectiveness, quality of life.

Introduction

Cardiovascular disease (CVD) is responsible for more deaths worldwide than any other condition, and a large proportion of healthcare budgets in more developed countries is spent on its treatment and prevention. In the USA, for example, 37% of deaths are caused by CVD, and costs related to the disease are estimated to be $ 401.3 billion for 2006 in this country [1] and € 169 billion annually in the EU [2]. The preventive treatment of CVD aims to control related conditions, such as hypertension, hypercholesterolaemia and diabetes, but since the prevalence of these risk factors, mainly diabetes and hypertension, is expected to rise progressively, the forecasts of health care expenditure both in Europe and the USA indicate a continuous increase at least up to 2030.

There is consistent and robust evidence that hypertension is the most common and powerful cardiovascular risk factor, predisposing to all major atherosclerotic cardiovascular diseases, including stroke, coronary artery

disease, heart failure, peripheral artery disease and end-stage renal disease [3]. In the last decades randomized clinical trials have demonstrated that effective antihypertensive treatment significantly reduces the incidence of these clinical conditions.

Since the awareness of both physicians and patients of the importance of treating hypertension resulted in a tremendous rise in annual prescriptions and costs for anti-hypertensive drugs in the USA and Europe, many studies have investigated the cost-benefit ratio of reducing blood pressure by considering patient characteristics and therapeutic options.

We have to consider in fact that hypertension is a very common disease that needs life-long therapy, so every strategy to improve its awareness and treatment would produce an immediate and enormous increase in social costs, while favourable economic effects, i.e. savings due to corresponding reductions in CVD, will become fully evident only later, especially in low-risk patients. In a period in which monetary resources for health care are limited and continue to be more and more restricted, cost analysis of antihypertensive treatment is necessary to determine whether an intervention provides a sound investment for improving health outcomes and, in particular, quality of life at a reasonable cost.

Economic evaluation of antihypertensive therapy

The evidence of an incomplete benefit by the reduction of blood pressure with drug treatment obtained in earlier clinical trials led to the progressive introduction of new but more expensive anti-hypertensive drugs to the market, which have been summarily considered responsible for the rapid growth in the costs of treatment of hypertension registered in the last two decades.

This raised the question of whether the use of more expensive drugs is economically justified in every hypertensive patient or it should be reserved for a subgroup of particularly high-risk patients.

A correct approach to the economic evaluation of alternative treatments can be performed on the basis of 4 economic models which allow a rather different estimate of outcomes: cost minimization, cost-effectiveness, cost-utility and cost-benefit analysis [4]. The choice of method depends on the question being asked in relation to the clinical situation to be evaluated.

Cost minimization is the most limited type of economic analysis, since it compares only the costs of alternative treatments supposing equal effects. According to the cost-minimization approach the cheaper drugs are considered the more cost-effective, but we have to consider that the wholesale price of the different drugs is not the price of the treatment, as demonstrated by Hilleman et al. [5]. In the **cost-effectiveness analysis** the costs of treatment are compared considering the improvement in health that they produce. The outcomes are expressed in terms of years of life saved and can be detected after an adequate period of follow-up, at least 3-6 years. The calculation of cost-effectiveness ratio indicates the increased cost of a new treatment as compared to an older one and results from the additional cost divided by additional benefit. The **cost-utility** analysis is an even more complex variable, that takes into account the impact of therapy on the "quality-adjusted life years" (QALYs) gained. The cost-benefit analysis is the most difficult form of economic analysis of antihypertensive treatment and requires that all costs and effects of treatment be valued in terms of currency (e.g. dollars, euros) by placing a monetary value on any health benefits gained (Table I). Even if it might have a primary economic impact in the developed countries, which have to decide which price per life-year gained they consider reasonable to pay, the **cost-benefit** analysis of a treatment is not easy to assess and is not frequently used.

In conclusion, the incremental cost-effectiveness ratio represents the most appropriate way to help health policy makers and individual physicians to make the best use of money in order to achieve in every patient the greatest benefit for a given level of expenditure.

From clinical trials to real life

Many cost-effectiveness analyses have been performed mainly on the results of clinical trials providing reliable evaluations. When we consider not only cost of treatment but also costs of hospitalization and of cardiovascular complications even more expensive drugs prove cost-effective or cost-saving in high-risk patients. In particular the results of the HOPE study have demonstrated that ramipril, given at the cumulative dose of 10 mg/day to patients at high risk of CV disease, is more cost-

Table I. Costs of hypertension

Healthcare costs	Non-healthcare costs	Contributors to the cost of drug therapy
Hypertension-related visits	Informal care	Price of drug
Clinical and laboratory evaluation	Productivity loss	Clinical and laboratory costs
Consultations		Compliance
Hospitalizations		Persistence
Cardiovascular complications		
Drug therapy		

effective than placebo, providing a cost-neutral or a cost-saving situation in 90% of cases when costs of hospitalisations, procedures, study drugs and medications are considered together [6]. Recent clinical trials have documented that for an equivalent BP decrease some antihypertensive drugs are more efficacious in preventing CV events than others in high-risk hypertensive patients [7, 8]: angiotensin receptor blocker (ARB), calcium channel blocker (CCB), and angiotensin-converting enzyme inhibitor (ACEI) based therapy reduced the incidence of CV events, mainly stroke, by 20-25% as compared to β-blockers and diuretics. It has been calculated that an ARB reduced the direct stroke-related cost per patient by 1141 euro as compared to diuretic/β-blocker. The net cost per quality-adjusted life years for ARB was 4188 euro, which leads to a definite cost-effective intervention [9].

A further example of cost-effectiveness of treatment in high-risk patients is the use of ARBs in hypertensive patients with concomitant type-2 diabetes and mild renal disease. Palmer et al. performed an economic evaluation of the cost-effectiveness of irbesartan in a Belgian and French cohort of patients based on data from the IDNT study. They not only found that irbesartan delayed the onset of end-stage renal disease (ESRD) by 1.41 and 1.35 years vs. amlodipine and control respectively, but also that this delay improved life expectancy by 0.13 years vs. amlodipine and by 0.26 years vs. control, thereby producing an expected net cost saving in the same period in both France and Belgium [10]. The cost-effectiveness gain was even more consistent when irbesartan treatment was started in the early stage of renal disease (microalbuminuria without overt nephropathy), suggesting again a close relationship between cost-effectiveness of antihypertensive treatment and early management of the diseases, particularly in high-risk patients [11]. These consistent differences in comparative efficacies among antihypertensive drugs have so far been generally considered of value only for high-risk hypertensive patients. The remaining dominant opinion has been that it is the reduction of BP itself that leads to lower CV morbidity and mortality in low-moderate risk hypertensive patients, who represent the majority of the population and the main target of GP. The consequence was that the effectiveness of all anti-hypertensive drugs was considered equivalent and the price of drugs was used as the basis for comparative efficacy in clinical practice. So, in accordance with the assumption that diuretics are the cheapest therapeutic option, the authors of ALLHAT calculated that if the prescription of diuretics had not declined in the United States from 1982 to 1992 then the health care system would have saved 3.1 billion USD in estimated costs for the treatment of hypertension, considering not clinically significant in the long term the metabolic adverse effects induced by diuretics, such as the higher rate of new-onset diabetes [12]. Again we have to bear in mind that for the correct calculation of the global cost of illness in real life it is necessary to consider not only the healthcare costs but also non-healthcare costs, such us informal care and productivity loss, which amount to a great part of total costs [2]. We have also to consider that a large proportion of hypertensive patients all over the world are still untreated or, if treated, they do not achieve adequate blood pressure control. While the hypertensive patients enrolled in clinical trials, more motivated, more controlled and followed by experts for a relatively short period, achieve (with two or more drugs) satisfactory BP control in 70% of cases, this is not true in the general population (Figure 1). A recent review of national surveys in hypertension among hypertensive patients aged 35-64 years showed a treatment level ranging from 25% (England) to 32% (Italy), and even among patients receiving treatment, the rate of successful hypertension control ranged from only 18.2% in Spain to 40% in England [13]. In this scenario the cost of uncontrolled hypertension is responsible for the largest part of the amount of money spent for the health care of patients with high BP, and it should be considered the first target of any project of cost containment.

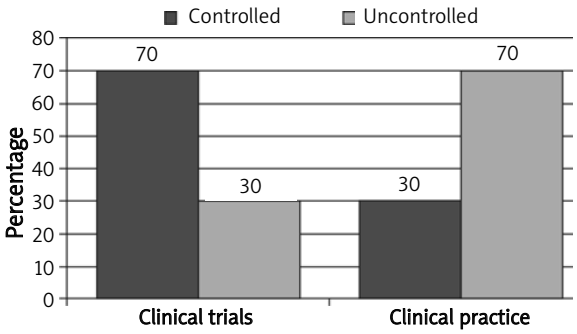

Figure 1. Blood pressure control in hypertensive patients

While pharmacological treatment of hypertension to be effective must be continued sometimes for life despite an absence of any obvious symptoms or benefit to the patient, lack of symptoms in high blood pressure is one of the most common reasons for discontinuing treatment or not taking the prescribed dose at the required intervals, thus leading to decreased effectiveness of treatment while increasing use of healthcare resources and overall expenditure at the same time. In a pharmaco-epidemiological survey conducted in Italy to evaluate the limited achievement of BP control in clinical practice, the rate of discontinuation of treatment or switching to another drug was 66%, with occurrence of drugs' side effects the most frequent cause (53%)

followed by inadequate BP control in 34% [14]. In another study switching from one drug to another has been estimated to increase the annual cost of therapy by 20%, while switching and poor compliance together are responsible of 39% of direct costs of hypertension [15]. It has been estimated that, among patients not reaching target blood pressure, one-half of these failures can be attributed to medication non-adherence [16].

On the other hand, Sokol, in a population-based sample of 137 277 patients under age 65, demonstrated that a high level of compliance (80-100%) with treatment of hypertension was associated with lower non-drug medical costs, mainly due to decrease in the risk of hospitalization [17].

If non-compliance has been recognized as a serious problem with significant economic consequences, including by the World Health Organization, we cannot forget that there is a large body of evidence from the literature that in clinical practice not all antihypertensive drugs are equal in terms of compliance, persistence and percentage of hypertensive patients with BP values at target.

In fact both compliance and persistence appear higher in hypertensive patients receiving ACEIs or ARBs than in those receiving diuretics. In a population-based study the risk of discontinuation of antihypertensive therapy over a 39-month period was 50% lower in patients receiving ARBs as compared to diuretics, and patients initiated on an ARB had a significantly higher likelihood of starting a new course of therapy after the first discontinuation as compared to those initiated on all other antihypertensive drugs [18].

A recent study evaluated the patterns of persistence with antihypertensive drugs in newly diagnosed hypertension in primary care: even if after the first year persistence with antihypertensive medications was extremely low, the continuation rate of patients treated with ARBs was more than double that of those receiving diuretics [19]. Discontinuers represented the least costly group but they accounted for 22.4% of total expenditure without foreseeable clinical benefit. First line treatment with ARBs was associated with an annual increase in cost of 145.2 euro as compared to diuretic treatment but, due to better compliance, it has been possible to calculate in the long term the possible economic advantage for the NHS by using these drugs (Table II) [20]. Corrao et al. recently confirmed not only that in a five-year period at least 50% of hypertensive patients discontinue treatment, but also that the first antihypertensive drug prescription at the index data was not followed by any other prescription in nearly 40% of newly diagnosed hypertensive subjects. In this contest blockers of the renin-angiotensin system were associated with the lowest incidence of treatment discontinuation [21]. Furthermore, in another population study Van Wijk observed that many people who stopped blood-pressure lowering treatment continued to fill prescriptions for other co-medications, suggesting that it may be the combination of an asymptomatic disease together with side-effects of antihypertensive drugs that causes discontinuation of treatment rather than a general behavioural pattern [22].

Another possible economic disadvantage of diuretics is their ability to cause long-term metabolic effects, i.e. higher incidence of new-onset diabetes mellitus with ARBs, ACEs, and CCBs [23].

It has been calculated that the increase of costs caused by the development of diabetes mellitus in hypertensive patients treated with low-dose diuretics balances completely the higher cost of acquisition of ARBs and CCBs. The total cost per patient treated with a diuretic and/or β-blocker was US $ 1105; in those treated with ARBs and/or CCBs US $ 549 [24].

All these studies have documented that in clinical practice there are major differences in efficacy, tolerability and safety of antihypertensive drugs, so the comparative cost of drugs cannot be used as a final discriminator, and diuretics and β-blockers do not represent the most cost-effective treatment of hypertension. A low-dose thiazide diuretic can no longer be considered the first choice drug for most hypertensive patients, both for medical and economic reasons.

Conclusions

In today's healthcare environment, cost considerations have become an increasingly important issue in medical decision making. In particular a correct assessment of the cost-effectiveness of antihypertensive treatment is a key point for the proper allocation of that portion of the National Health System budget designed for the treatment of various diseases, including hypertension. The acquisition costs of drugs are only a small proportion of the total expenditure for the treatment of high blood pressure, and for these reasons they should be considered in the perspective of the capacity of the drugs to prevent CV complications and to not cause troublesome adverse events. Indeed, despite

Table II. Costs of drug treatment and total medical costs according to different class of HTN therapy (Italy, thousands €, 1000 pts/year)

	Drug treatment	NHS costs	Informal care costs	Total costs
ARBS	286,8	644,7	621,4	1552,9
Diuretics	141,6	1101,9	829,4	2072,9
Incremental costs vs. diuretics	A +145,2	–457,2	–208	–520

Table III. Expected economic consequences of delaying first stroke in hypertensives with controlled blood pressure in Italy

Healthcare costs	–13 000 €/stroke
Productivity loss	–37 500 €/stroke
Informal care costs	–6 750 €/stroke
Total savings (184 000 strokes/year)	–10.534 billion €/year

the availability of many effective and well-tolerated drugs, too many hypertensive patients worldwide are still untreated or, if treated, they do not achieve appropriate BP targets: in England the overall cost for hospital and social care of stroke survivors is more than four times the cost of correctly managing all hypertensive patients [25]. The continuous increase in costs of hypertension are largely related to the cost of not treating this disease, costs that do not produce any benefit (under-treatment, discontinuation). The decrease in CV mortality and morbidity caused by early and effective antihypertensive treatment results not only in an increase in life expectancy but in years of life free from CV events. A tremendous reduction of costs of hypertension can be expected from postponing by 1 to 5 years the first CV event (Table III).

The elimination of costs without benefit represents the most effective method for reducing the waste of money in the treatment of hypertension, and the implementation of population strategies should be reinforced in addition to clinical prevention. Both conventional and newer strategies have been shown to be cost-effective relative to various other medical interventions but the latter seem to offer additional long-term benefits. Moreover, the differences in the impact of factors such as poor compliance, switching and discontinuation of treatments may significantly affect the overall cost of antihypertensive therapy in clinical practice and justify a better cost-effectiveness ratio for drugs like ARBs, ACE inhibitors and some CCBs despite their higher retail price.

Again, since the large majority of hypertensive patients require two or more drugs to control their BP, a cost-effectiveness evaluation of drug combinations would be at present more important than that regarding single drugs. Cost-effectiveness of an association may prove to be substantially different from another, depending on type and dose of drugs used and whether they are combined in a single pill or not, and compliance and persistence may be more unpredictable for associations than for single drugs.

Future research should focus on long-term, real world, longitudinal studies to measure the actual costs and savings associated with increased compliance and persistence and their impact on positive health outcomes, such as improved blood pressure.

The future development of a pharmacoeconomic approach more based on cost-utility analysis, which is highly sensitive to even small differences in patients' quality of life due to adverse effects, will certainly increase the possibility to better differentiate between medications with similar clinical efficacy but substantially different tolerability profile. In any case we have to remember that the prevailing strategy cannot be only to reduce the money we spend, but to spend it better.

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