



NEW THERAPEUTIC PARADIGMS AND CLINICAL-FINANCIAL MANAGEMENT OF HYPERTENSION. A NARRATIVE REVIEW

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Abstract: Hypertension (HT) is a major cardiovascular risk factor which has a major global burden on society as revealed by the World Bank in 1990s. The disability adjusted life year (DALY) is an indicator which quantifies mortality, morbidity and the burden associated with hypertension. All of this data is highlighted in the context in which global public health is undergoing a paradigm shift, through the transition from “evidence-based medicine” (EBM) to “value-based medicine” (VBM). The advantages of interventions on HT are the reduction of the risk of cardiovascular disease, death and disability rates, as well as the reduction of costs due to acute and chronic (preventable) HT complications. At the cost of increasing the psychological burden and interference with the quality of life, once the diagnosis of HT is established, a need to make lifestyle changes develops and the risk of exposure to antihypertensive medication’s adverse effects ensues. At the same time, this diagnosis increases the health system burden, with direct and indirect management costs, such as: antihypertensive drugs, treatment adherence costs, HT-treatment resistant costs, informal costs (informal care). There is a need for a formal integration of cost analysis when putting together HT guidelines, while also considering factors such as opportunity cost, efficiency, benefits, and the cost-effectiveness incremental rapport.

INTRODUCTION

Hypertension (HT) has been recognised as a major cardiovascular risk factor at the Framingham Heart Study (FHS), the first prospective, cohort observational study addressed to the epidemiology of cardiovascular disease.(1)

The first results of the study included an increase in the incidence of atherosclerotic heart disease among participants with blood pressure (WT) > 160/95 mmHg, as well as the link between cerebrovascular and HT diseases.(1,2) By defining the concept of cardiovascular risk factors and identifying them, the Framingham study has generated the premises for the development of public health analyses and policies aimed at reducing the societal impact of cardiovascular diseases (CVD).

The impact or the global burden of disease (GBD) on society was later assessed by the homonymous study GBD Study, ordered by the World Bank in the early 1990s. The quantification of the burden of a disease is achieved through the DALY (disability adjusted life year) indicator. It represents a year of healthy life lost and it sums up the number of years of life lost (YLL) due to a premature death with the number of years lived with disability of known severity and duration (YLD).(3) GBD analysis from 2010-2019 identified high systolic wall tension (SWL) as the main cause of DALY, attributed to risk factors, globally, responsible for 10.8 million deaths in 2019 alone.(4)

Quantifying mortality, morbidity and the burden associated with hypertension through DALY presents a fragmentary perspective of the impact it has on society. To

these, there are added the substantial economic burden resulting from the direct medical costs in connection with the prevention, diagnosis, treatment and follow-up of the hypertensive patient, the management of acute and chronic complications caused by poor adherence to treatment, as well as from the indirect costs caused by the loss of productivity through premature death or disability.

2017 American Heart Association (AHA) statistics show that between 2012 and 2013 the costs associated with HT management itself amounted to USD 51.2 billion, representing over 16% of the total USD 316.1 billion used annually for the entire sphere of cardiovascular pathologies. The same analysis estimates that by 2030 the direct costs related to CVD will triple, and the indirect costs will suffer an increase of up to 58%. HT spending projections show the amount of USD 225 million per year in 2025 and an increase of up to USD 274 million in 2030.(5)

All of this data is highlighted in the context in which global public health is undergoing a paradigm shift, through the transition from “evidence-based medicine” (EBM) to “value-based medicine” (VBM). The EBM assumes that medical decisions are justified by medical evidence from clinical trials, plus the preference of the patient and the health care provider. VBM starts from the same principles of EBM, the application of which will be modulated according to the value perceived by the patient in connection with an intervention.(6)

The evaluation and explicit quantification, in economic terms, of the use of the resources allocated to the

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clinical management of the HT is the first step towards achieving the goal of providing the best possible medical care, based on evidence, in accordance with the patient's preferences, and cost-effectiveness.(7,8)

In conclusion, the conceptual definitions of HT are susceptible to the permanent changes, depending on the results of the on-going clinical trials, and are relevant through the actions or inactions they generate at the level of public health policies. The advantages of interventions on HT are the reduction of the risk of CVD, of death and disability rates, as well as the reduction of costs due to acute and chronic, preventable HT complications, at the cost of increasing the psychological burden and interference with the quality of life once the diagnosis of HT is established, the need to change lifestyle, exposure to the risks and adverse effects of antihypertensive therapies, as well as increasing health system costs.(9)

AIM

The present paper aims to analyse the costs regarding the therapeutic interventions that be done in hypertensive patients and the means to make them more efficient.

MATERIALS AND METHODS

The current paper is a narrative short review which was brought about by doing database searches such as Google Scholar and Web of Science, with the use of such keywords as: hypertension, global burden, cardiovascular risk, management costs, cardiovascular disease.

RESULTS AND DISCUSSIONS

In 2010, HT was the leading cause of death and DALY globally, and in the United States of America (USA) it was responsible for more deaths from CVD than any other modifiable cardiovascular risk factor. HT ranks second, after smoking, among the causes of preventable mortality of all causes.(7) The current situation at national level is appreciated by extrapolating data from the SEPHAR III study. Their analysis shows a prevalence of 45.1% of HT in Romania, with variations between 15.4% for the age group 18-24 years and over 66% for respondents over 65 years of age. In urban areas, the prevalence of HT in males is statistically significantly higher than in female individuals. In both rural and urban areas, the same gender gap is maintained for cases of newly diagnosed HT.(10)

Although the awareness rate of the diagnosis of HT was almost 81%, according to SEPHAR III, and more than 72% of hypertensive respondents said they had been receiving antihypertensive drug treatment for at least 2 weeks at the time of enrolment in the study, the control rate of the blood pressure values was only 30.8%. In other words, about 1 in 5 hypertensive Romanians do not know that they suffer from HT, and 7 out of 10 Romanians diagnosed with HT do not have an optimal control of the condition. With the advancement in age, the control rate decreases from 63.3% for the group 18-24 years to 17.8% for the group > 65 years, differences that remain statistically significant after the adjustment for sex and environment of origin.(10)

Costs associated with the clinical management of HT

Historically, society's reporting to public health has undergone a number of paradigm shifts. In the aftermath of the Second World War, the establishment of the British National Health Service (NHS) generated the premise that access to free health services is a right of every citizen.(11) In 1972, Archibald Cochrane produced a first paradigm shift with the establishment of the foundations of epidemiology and evidence-based medicine and the formulation of the need for health care to be

effective, not only free.

In the early 1990s, with the development of economies and health systems in most of the world's countries, it was concluded that directing investment in health requires cost-effectiveness, a concept particularly promoted by the British institute NICE (National Institute for Clinical Excellence).(11) Subsequently, in the early 2000s, two reference studies are published, one related to the discrepancies between the potential and the real quality of medical care, and the second in relation to medical errors and patient safety.(12) At that time, the new paradigm was based on the idea that effective and cost-effective health care should be provided at a high level of quality and safety.

Shortly after, the impact of the global economic crisis was evident also at the level of health systems, determining a new approach based on the concept of value, which is the "triple value paradigm", without denying the previous principles. Specifically, the three values are allocative value, technical value, and personalised value. Thus, value is the criterion by which the health system is assessed both by the population that finances it and by each individual who benefits from health care.(11).

The increasing trend of the care requirement associated with HT and its complications has been reiterated in the recent work of the WHO (World Health Organization) and national and international societies in the field.(12) In 2014, one year after the development of the second-to-last American management guide to HT, AHA and ACC (American College of Cardiology) presented a joint paper proposing the formal integration of the analysis of the costs of implementing HT recommendations in the formulation of guidelines. On this occasion, the concept of value associated with an intervention was brought to attention, defined as the demonstrated positive effect of its implementation on the favourable outcome, patient safety and satisfaction, with a reasonable and accessible cost. Value is partly overlapping to the idea of efficiency and has been conceived as an additional attribute of the reasoning for applying an evidence-based intervention, complementing the class of recommendation (COR) system and the level of evidence (LOE). Small interventions shall be considered to be those which do not contribute sufficiently to the favourable development, safety or satisfaction of the patient or require disproportionately high costs.(8)

Some principles of economics, the understanding of which are useful at this point are:

Opportunity cost - Scarcity refers to the inability of resources, given by their insufficiency, to be able to cover unlimited subjective needs or desires. At the level of the society, the directions of apportionment of the resources will be decided. Choices will be in favour of, respectively, the detriment of one or more options, and the benefit lost by sacrificing an option defines the opportunity cost.

Efficiency – Starting from the idea that the objective of public health policies is to improve the well-being of the population, the elements of the health economy will provide the data necessary for informed decision-making to achieve this objective. Cost-benefit and cost-effectiveness analyses are tools to quantify the efficiency of different policies by relating the incremental costs of producing a good or service to the incremental benefits obtained.

Efficiency can be considered as a measure of the value of an intervention. From an economic point of view, cost-benefit analysis is preferred by economists as it assesses the benefits of an action in monetary terms and can be summarised by the simple reasoning that a policy should be adopted if the benefit exceeds the costs from a financial point of view. The nuance between cost-benefit and cost-effectiveness refers to the

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difference in the unit of measurement used in terms of health benefits, which will be assessed in the impact on survival or quality of survival.

Benefit – The beneficial effect of a medical intervention will be expressed in QALY (quality-adjusted life year) - years of life gained, adjusted to quality of life, using a utility scale between 0 (equivalent to death) and 1 (equivalent to perfect health), which allows patients to assign similar values to interventions that generate similar increases in QALY, whether they are aimed at increasing survival or improving the quality of life.

Incremental cost-effectiveness ratio – The analysis of an intervention in incremental terms, compared to the relevant alternatives, determined the formulation of the incremental cost-effectiveness ratio (ICER), defined as the difference between the costs of two interventions in relation to the difference between their effects, measured in QALY.(8)

Direct costs of the clinical management of HT

Direct costs are all those medical expenses in connection with the prevention, diagnosis and treatment of HT and its complications.

Costs with primary prevention of HT

The primary prevention of HT aims to promote a healthy lifestyle, with the aim of delaying the appearance of HT or risk factors for WT and other CVD, among the general, healthy population, as well as the screening of the general population for the identification and correction of risk factors, prior to the diagnosis of HT. A systematic review of the literature on the economic impact of interventions on HT carried out in the community highlighted the cost-effectiveness of implementing education programs for lifestyle changes and interventions of tensional self-monitoring at home.(13) A study on screening of American adolescents at risk of developing HT concluded that the association between screening measures associated with initiating antihypertensive treatment was particularly cost-effective for male adolescents aged ≥ 15 years (lifetime ICER estimated at \$21,734/QALY).(13)

Antihypertensive treatment costs

The cost-effectiveness of the implementation of the antihypertensive treatment according to the indications of the guidelines of the profile companies was analysed using as reference the AHA guide from 2014, which defined the HT similar to the European guide in force, namely $SWT > 140$ mmHg. Investigators have proposed to simulate the impact of this intervention for the period 2014-2024. The study showed that about 860,000 Americans between the ages of 35 and 74 were eligible for antihypertensive treatment as directed by the 2014 guidelines. It has been estimated that the treatment used until the wall tension target is reached, could prevent approximately 16,000 CV events and 6,000 annual deaths from CVD. Achieving the recommended targets by treating about 8.6 million people with HT as primary CVD prevention could prevent about 41,000 CV events and 7000 deaths annually. In this study, the cost-effectiveness of an intervention was defined as the allocation of $< 50,000$ USD/QALY.(14) The study also showed that the treatment of patients with HT of any stage accompanied by CVD or those with stage 2 HT is cost-effective for men between 35 and 74 years of age and for women between 45 and 74 years of age, as well as maintaining the cost-effectiveness of the treatment of these categories of patients, even in the conditions of doubling the costs of treatment by expenses with measures to increase adherence to treatment. As regards the HT treatment stage 1, the intervention proved to be justified for people of both sexes aged between 45 and 74 years, but not for women with HT stage 1, without CVD, between 35 and 44 years.(14)

The AHA guide from 2017 reduces the target of

antihypertensive treatment from $< 140/90$ mmHg to $< 130/80$ mmHg and proposes to approach the hypertensive patient in the team (TBC- team based care). The study that aimed to assess the economic impact of these two measures demonstrated the cost-effectiveness of them both. To achieve the $< 130/80$ mmHg vs. $< 140/90$ mmHg tension target, ICER has been calculated at approximately 47,000 USD/QALY.(15)

Antihypertensive drug treatment can prevent MI and stroke, both in primary and secondary prevention, regardless of the initial value of HT, as the results of the recently presented BPLTTC (Blood Pressure Lowering Treatment Trialists' Collaboration) study show.(16)

Costs to improve treatment adherence

Lack of adherence to antihypertensive treatment is a well-known cause of poor control of tension values in hypertensive patients and it includes inconsistency in administration, postponement of initiation or interruption on its own initiative of the administration of prescribed medication.

Explanations for poor adherence come from complex interactions between demographic, economic, social, treatment-related, patient and medical team factors.

A study carried out in five European countries concluded that by increasing treatment adherence among hypertensive patients to 70% more than 80,000 cardiovascular events annually could be avoided, saving approximately EUR 332 million.(17)

Adherence to antihypertensive pharmacotherapy is reported to $< 50\%$, one year after the establishment, it is associated with increased overall CV risk, negatively influenced by the complexity of treatment and it decreases by about 10% for each pill that is added to treatment. In order to improve adherence, it is recommended to use single-pill combination (SPC).(17-20)

The lack of treatment adherence is a significant economic burden, as well as the efforts to improve adherence can prove to be cost-effective for health systems. It is estimated that 10% of hospitalizations of older adults are due to non-adherence to treatment; the typical non-adherent patient requires on average 3 additional hospitalizations annually. Moreover, it is estimated that costs of around EUR 1.25 billion are attributable annually to the lack of adherence to treatments of substance at European level.(21)

Costs with resistant HT

Resistant HT has been defined as an HT that does not respond to an antihypertensive treatment based on three classes of drugs, one of which is diuretic, administered at the maximum doses recommended or maximum tolerated by the patient. RH also includes patients who have reached the target blood pressure values through the concomitant use of at least four hypotensive substances.(18)

It is estimated that 10% of all hypertensive patients in Europe suffer from RH. An analysis of the situation in 5 western European states included 9.4 million people with WT higher than the target value, despite treatment with at least 3 antihypertensive substances. Patients with RH are 47% more likely to have an unfavourable evolution in terms of CV events, as well as a higher risk of developing CKD compared to hypertensive patients without HR. A number of comorbidities have been associated with HR: obesity, LVH, albuminuria, DM, sleep apnoea syndrome, CKD, all of which augment the overall cardiovascular risk of the hypertensive patient.(22)

The direct medical costs of RH treatment were estimated at €3.9 billion in 2013 in the 5 countries mentioned before. RH will contribute to 188,000 cases of CAD, 57,400 cases of stroke, 31,500 cases of IC, 1,400 cases of CKD and 30,000 deaths annually.(23)

Indirect costs of the clinical management of HT

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Indirect costs are a form of opportunity cost and they express productivity losses through morbidity and premature mortality. Unlike direct costs, which focus on expenditure related to health systems, indirect costs refer to revenues that could be saved by preventing events that lead to days of “absenteeism” (unplanned absence from work) or “presenteeism” (presence at work but with reduced productivity).

A recent study published in the European Journal of Preventive Cardiology assessed the impact that the prevention of a new case of coronary heart disease has on the years of life and productivity among the Australian population aged 15-69 for the period 2020-2029, introducing a new indicator: PALY (productivity-adjusted life year). It is defined as a year of productivity lost due to illness, so that a PALY was assigned the financial value given by the gross domestic product achieved by a worker in one year.(21)

The authors of the study estimated that preventing all 290,000 predicted coronary events over the next 10 years would avoid more than 4000 deaths, save over 8000 years of life, and save 104,000 PALY, equivalent to a gain of AUD 21.8 billion.(24)

Reports on indirect costs caused by the HT itself are inconsistent in the literature dedicated to the economic impact of HT; the indirect costs due to HT complications such as stroke or acute HF are significant globally, but quantifying the exact proportion of the HT's effect on them is difficult to objectify and it requires further research.

Informal costs of the clinical management of HT

Hypertensive patients suffering complications of HT such as HF or stroke may experience manifestations of addiction for which they require “informal caregiving”. The concept of “informal care” refers to personal assistance activities carried out by unpaid people, most commonly family members, outside an organized/institutional setting, in order to facilitate the basic activities of daily living (ADL) or instrumental activities of daily living (IADL).

The estimated value of informal care emerges from the quantification of the number of hours spent with ADL and IADL that replaces potential formally remunerated activities. Specifically, informal costs will be the product of the number of hours and the value of the average hourly wage of a worker performing similar duties in the field of social services provision.(25)

A comparative analysis of two groups: one of them with subjects who will have suffered stroke and require assistance with ADL and IADL, and the second with subjects who require assistance with ADL and IADL without having suffered stroke, highlighted a difference of 8.5 hours / week attributable to stroke-related care. Multiplying the 8.5 hours by an average of \$9.84/h (the average hourly wage of a personal assistant in the U.S. in 2008), the annual informal costs attributable to stroke amounted to over \$4,000/year/patient. The estimated range of additional informal costs attributable to the stroke is between 11.1 and 20.1 billion USD/year.(22) A similar analysis of the costs of informal care required by patients with HF showed that in 2010 they totalled about USD 3 billion.(26)

The overall burden of HT is increasing and represents substantial morbidity and mortality, and diet and physical inactivity contribute to this burden. Regular physical activity is associated with a decrease in WT and a reduced cardiovascular risk.(27)

CONCLUSIONS

“Value-based medicine” (instead if the old “evidence-based medicine”) comes as a paradigm change in the therapeutical management of high blood pressure

(hypertension/HBP) given the growth of both costs and the incidence of this condition, with estimates saying the number of diagnosed patients will triple by 2030.

The costs of HBP management include direct costs (related to prevention, diagnosis, and treatment), indirect costs (including those connected to HBP complications) and informal costs (the activity provided by unpaid personal assistants, in most cases them being family members).

The global economic crisis led to a shift towards the value concept named “the Triple Aim paradigm” (including the distributive, technical and personal values). This the reason why there is a need for a formal integration of cost analysis when putting together HBP guidelines, while also considering factors such as opportunity cost, efficiency, benefits, and the cost-effectiveness incremental rapport.

The future goal is to optimize the HBP treatment by developing new therapeutical agents and innovative medical devices which can guarantee the optimal progression of this pathology, with the lowest possible number of comorbidities and the most reduced usage of medical resources.

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