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Cost-Effectiveness of Enhancing Adherence to Therapy with Blood Pressure–Lowering Drugs in the Setting of Primary Cardiovascular Prevention

Lorenza Scotti, PhD[1], Gianluca Baio, PhD[1], Luca Merlino, MD[2], Giancarlo Cesana, MD[3], Giuseppe Mancia, MD[3,4], Giovanni Corrao, PhD[1,]*

[1]*Department of Statistics and Quantitative Methods, Unit of Biostatistics, Epidemiology and Public Health, University of Milano-Bicocca, Milan, Italy;* [2]*Operative Unit of Territorial Health Services, Lombardia Regional Council, Milan, Italy;* [3]*Department of Clinical and Preventive Medicine, University of Milano-Bicocca, Milan, Italy;* [4]*Clinica Medica, Ospedale S. Gerardo, Monza, Italy*

ABSTRACT

Objective: To estimate the cost-effectiveness of enhancing adherence to blood pressure (BP)-lowering drug therapy in a large population without signs of preexisting cardiovascular (CV) disease. **Methods:** A cohort of 209,650 patients aged 40 to 79 years resident in the Italian Region of Lombardia and newly treated with BP-lowering drugs during 2000 to 2001 was followed from index prescription to 2007. During the follow-up, the 10,688 patients who experienced a hospitalization for a coronary or cerebrovascular event were identified (outcome). Adherence was measured by the proportion of days covered by the therapy with BP-lowering drugs. The cost-effectiveness of enhancing adherence was measured through the incremental cost-effectiveness ratio. **Results:** Enhancing adherence from 52% (baseline) to 60% and 80% led to a reduced rate for CV outcomes (from 85 to 83 and 77 events every 10,000 person-year, respectively) and increased the cost for drug therapy (from €1,325k to €1,507k and €1,934k every 10,000 person-year, respectively). The resulting incremental cost-effectiveness ratio decreased from €76k (95% confidence interval €74k–€77k) to €74k (95% confidence interval €72k–€75k) for each CV event avoided by enhancing adherence from baseline to 60% and 80%, respectively. **Conclusions:** Enhancing adherence to BP-lowering medications in the setting of primary CV prevention might offer important benefits in reducing the risk of CV outcome, but at a substantial cost.

Keywords: adherence, administrative database, blood pressure–lowering drugs, cardiovascular events, cost-effectiveness.

Introduction

Randomized clinical trials have consistently shown that hypertension is a reversible risk factor; that is, a reduction in elevated blood pressure (BP) induced by pharmacological treatments reduces the risk of fatal and nonfatal cardiovascular (CV) events [1]. It is also well known, however, that effective BP reduction is rare in the hypertensive population [2–5], and in individuals with uncontrolled BP, the incidence of CV events is higher than among patients who have achieved BP control [6]. Evidence shows 1) very low adherence to BP-lowering medication in the setting of daily clinical practice [7,8], 2) that poor adherence to antihypertensive medication is related to lack of BP control [9], and 3) that there is a relationship between adherence to BP-lowering drugs and the risk of CV outcomes [10–15].

These findings suggest that interventions aimed at increasing adherence to BP-lowering agents would be effective in achieving full benefits from drug treatment [16]. However, interventions of this type necessarily lead to an increment in the overall costs because of increased drug use. This is particularly important from the public health perspective because the economic resources available are limited and it is important to allocate them in the best way to maximize the level of population health [17]. It is, therefore, suitable to jointly evaluate cost and effectiveness of the treatment to quantify the additional cost needed to increase the effectiveness of treatment-related enhanced adherence. To the best of our knowledge, no such evaluation has been carried out in the setting of primary prevention of CV outcomes and using BP-lowering drug therapy.

We estimated the cost-effectiveness of enhancing adherence to BP-lowering drug therapy in a large population without signs of preexisting CV disease in the setting of primary CV prevention. Costs and effectiveness were estimated from a population-based cohort study. Data were derived from an administrative database monitoring the use of health services of the population residing in the Lombardia region (Italy).

* *Address correspondence to:* Giovanni Corrao, Department of Statistics, Unit of Biostatistics and Epidemiology, University of Milano-Bicocca, Via Bicocca degli Arcimboldi, 8, 20126 Milan, Italy.

E-mail: giovanni.corrao@unimib.it.

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Methods

Setting

The data used for the present study were retrieved from the health care service databases of Lombardia, a region of Italy that accounts for about 16% (9 million) of its population. In Italy, health care is provided by the National Health Service (NHS). In Lombardia, this has been associated since 1997 with an automated system of databases to collect a variety of data, including: 1) an archive of residents who receive NHS assistance (effectively the whole resident population), including demographic and administrative data; 2) a hospital discharge database providing data on diagnoses recorded for each admission in a public or private hospital of the region; and 3) a database of outpatient drug prescriptions reimbursable by the NHS; this includes data on Anatomical Therapeutic Chemical (ATC) code and the corresponding amount of active drug for each prescription dispensed by a pharmacy of the region.

For each patient we linked the above databases by using a single identification code. To preserve privacy, each identification code was automatically converted to an anonymous code. The inverse process was prevented by the deletion of the conversion table. Full details of the procedure have been reported elsewhere [18].

Study Cohort and Follow-Up

The Lombardia residents who were beneficiaries of the NHS and were aged 40 to 79 years represented the target population. According to the 2001 Italian Census, this population comprised 4,341,438 individuals. Among them, we identified those who received at least one BP-lowering drug prescription at any time from January 1, 2000, to December 31, 2001. The first drug prescription was defined as the index prescription. The drugs considered belonged to all the available BP-lowering drug classes, that is, agents acting on alpha-adrenergic receptors (ATC code C02), diuretics (ATC code C03), beta-blockers (ATC code C07), calcium channel blockers (ATC code C08), and agents acting on the renin-angiotensin system (ATC code C09), dispensed either as monotherapy or as a fixed-dose or extemporaneous combination of two or more drugs.

To make the data as relevant as possible to the study aim, four categories of patients were excluded from data analysis: 1) patients who had received at least one BP-lowering drug prescription within 3 years before the index prescription, to ensure the inclusion of newly treated individuals only; 2) patients who had been hospitalized for CV disease or who had received a prescription of drugs used for coronary heart disease or heart failure (e.g., digitalis and organic nitrates) in the 3 years preceding the index prescription, to focus the data on primary CV prevention; 3) patients who did not reach at least 1 year of follow-up, to ensure at least 1 year of potential exposure to the drugs of interest; and 4) patients who had received only one BP-lowering drug prescription during the first year after the date of index prescription, based on the assumption that continuous drug treatment might not have been indicated for these patients.

Each member of the cohort accumulated person-years (PY) of follow-up from the date of index prescription until the first-ever hospital admission for CV disease or the end of the study period (December 31, 2007). Individuals who transferred out of the region or died during follow-up were censored.

Assessment of Adherence to BP-Lowering Drug Therapy

All prescriptions dispensed to each cohort member during the follow-up were used to measure the cumulative exposure to BP-lowering drugs. Starting from the index prescription, the number of days with drug available was calculated by dividing the total amount of active drug dispensed at each prescription by the recommended defined daily dose. In this way, each day in the follow-up period was labeled as "covered" or "not covered" by drug availability, regardless of whether availability concerned single or combined prescriptions. Adherence was measured by dividing the cumulative number of covered days by the number of days of follow-up, a measure denoted as *proportion of days covered* (PDC) [19,20]. PDC was categorized into the following four levels: very low ($\leq$25%), low (26%–50%), intermediate (51%–75%), and high adherence ($>$75%).

Outcome

Data on hospital discharge were used to identify cohort members who experienced a hospitalization for coronary or cerebrovascular (major CV) event during the follow-up. The WHO-MONICA criteria for the ascertainment of coronary and cerebrovascular events were followed [21,22]. Coronary events included those related to acute myocardial infarction, acute or subacute types of ischemic heart disease, and interventions of coronary revascularization. Cerebrovascular events included those related to subarachnoid hemorrhage, intracerebral hemorrhage, unspecified intracranial hemorrhage, occlusion of cerebral arteries, acute cerebrovascular disease, and surgical interventions on intra- or extracranial head or neck vessels. The occurrence of at least one of these events was sufficient for a patient to be considered as experiencing the outcome; the earliest date of hospital admission recording one of these events was considered as the time of the outcome onset.

Other Factors

The type of drug regimen at the index date (monotherapy or a combination of two or more drugs as first-line BP-lowering therapy) and the number of BP-lowering classes used during the follow-up were recorded. Drugs used for heart failure or coronary heart disease (i.e., digitalis glycosides and organic nitrates), lipid-lowering agents, other CV drugs, and antidiabetic medications dispensed to each cohort member during the follow-up were also recorded. In addition, the Charlson comorbidity index [23] was calculated by using diagnostic information from inpatient visits in the 3 years prior to and 1 year after the index date. The index was summarized by using two categories (i.e., 0 or 1, respectively, suggesting the absence or presence of at least one comorbidity factor).

Estimating the Relationship between Adherence and Outcome

A time-to-event analysis was undertaken by using the Cox proportional hazards model to estimate the hazard ratio (HR), and the corresponding 95% confidence interval (CI), for the association between adherence to BP-lowering drug therapy and the time of outcome occurrence. The predictor variables of interest were the dummy factors constructed according to the categories of PDC, using very low adherence as the reference category. Estimates were adjusted for factors measured at baseline (such as age, gender, antihypertensive drug regimen, and Charlson comorbidity index) as well as during follow-up (i.e., number of BP-lowering classes and cotreatments with CV and antidiabetic drugs during follow-up). Because adherence, as well as all the other factors measured during follow-up, can change over time, the assessment of their effects requires properly accounting for the time-varying nature of these variables. This was done by fitting a Cox model that includes these factors as time-dependent covariates [24]. For instance, by considering the predictor variables of interest (i.e., the dummy factors of PDC), each subject's cumulative adherence is recalculated from the