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VALUE IN HEALTH

The Impact of Drug Vintage on Patient Survival: A Patient-Level Analysis Using Quebec's Provincial Health Plan Data

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ABSTRACT

Objectives: There is some debate about the value received for the money spent on prescription drugs. Some argue that most drug spending is on "me-too" drugs—drugs that provide only marginal health gains. Others suggest that the opposite is true—new drugs offer good value for money and are well worth the cost. To provide evidence on this issue, we evaluated the impact of drug innovation on the longevity of Canadians.

Methods: We analyzed patient-level claims data from Quebec's provincial health plan. We selected elderly patients with continuous health coverage dispensed at least one drug prescription in each year of the study period, 1997 to 2006. Drug vintage was defined as the active ingredient's earliest marketed date. We estimated the impact of drug vintage on patient survival using a time-varying Cox proportional hazards model that controlled for year indicator variables, patient age, sex, region of residence, low income status, medical services use, concomitant drug use, and comorbidities.

Results: Of the 102,743 subjects in the study population, 14,154 (14%) died during the study period. Mean patient age was 68 years; 59% were women. Our survival models indicated that the use of newer medications was associated with a statistically significant mortality risk reduction (hazard ratio: 0.522; 95% confidence interval: 0.476 to 0.572, $P < 0.0001$), relative to older medications. Other covariates associated with an increased risk of mortality included age, sex (male), low guaranteed income supplement status, hospitalization, and number of comorbidities.

Conclusion: This analysis showed that recent drug innovation has had a significant beneficial impact on the longevity of elderly patients.

Keywords: Canada, drug innovation, longevity, pharmaceuticals, survival.

Introduction

There is some debate about the value received for the money spent on prescription drugs. Most drug expenditure growth in Canada is due to substitution of newer for older medications. Some argue that most drug spending is on "me-too" drugs—medications that provide only marginal health gains [1]. Canada's Patented Medicine Prices Review Board classified 89% of the new active substances introduced over the period 2001 to 2006 as offering only limited or no therapeutic advantages over existing drugs [1]. Others suggest that the opposite is true—spending on new drugs has contributed to the 11-year gain in life expectancy in Canada during the last 50 years [2] and thus represents good value for money [3,4]. For instance, recent innovation in cancer therapy has had considerable impact, not only in cancer care and survival, but also in quality of life improvement for cancer patients [5–7]. Similar findings were also reported in other disease areas, such as human immunodeficiency virus (HIV) and cardiovascular disease (CVD). For instance, Lichtenberg showed that new drugs played a key role in a sharp decline in the number of US deaths caused by HIV from 1995 to 1998 [8,9]. With respect to CVD, Cutler et al. reported that the use of new drugs to manage hypertension and hyperlipidemia and to dissolve blood clots have markedly reduced CVD morbidity and mortality [10]. More recently, it was estimated that average blood pressures in the US for 1999 to 2000 would have been 10% to 13% higher without the use of antihypertensive drugs [11]. The authors also reported that 86,000 excess premature deaths from CVD would have occurred in 2001 if these drugs were not on the market [11]. New treatments also have the potential to reduce costly hospitalization admissions [12–14].

Some of the methods and particularly the aggregate nature of the data used in the literature of drug innovation have been criticized [15]. As far as we know, detailed individual-level data, allowing to control for other determinants of patient health outcomes and nondrug health-care costs that could be correlated with the use of newer treatments, have not been used yet to document potential gains from drug innovation in Canada. Studies using individual patient-level survival data yield compelling estimates of the impact of drug innovation on longevity for several reasons. First, these data allow researchers to better control for other determinants of longevity that might be correlated with drug innovation, such as age, sex, medical resources utilization, and comorbidities. Second, these data lend themselves to more precise measurement of drug consumption. Finally, analyses of individual-level data are less liable to various statistical problems, such as nonstationarity. The problem of nonstationarity in aggregate time series occurs when there is no long-run mean to which the longitudinal data returns. Because the standard econometric theory is derived under the assumption that variables of concern are stationary and the error term has zero expected value, standard techniques are invalid in the presence of nonstationary data. The level of gross domestic product is an example of nonstationary time series, as its mean value constantly increases over time.

This study therefore used patient-level survival data to estimate the impact of drug innovation on longevity. We modeled the

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survival of senior residents of the province of Quebec, from several birth cohorts who were afflicted with a variety of health problems. Survival hazards were modeled semiparametrically as a function of the vintage of the prescription drugs used (following Lichtenberg 2004) [16] as well as controls for a variety of factors unique to the patient (age, sex, indicator of low income, region of residence, disease status) and their use of other health services (hospitalization and physicians services). Briefly, we found evidence that drug vintage has a marked effect on survival, with newer drugs leading to increased longevity, especially for the treatment of asthma and CVD.

Patients and Methods

Hazard Model

The impact of drug innovation on longevity, conditional on time-varying patient demographic characteristics, use of medical services, and the nature and complexity of disease was estimated using a semiparametric hazard model. This technique models the hazard or the instantaneous probability of dying at any point in time among those who are still alive at that time. Such model allowed us to handle censored observations and appropriately model the dependent variable (survival), which is usually non-normally distributed. Although there are no assumptions made about the shape of the underlying hazard function, this approach assumes a multiplicative relationship between the probability of dying and the log-linear function of the covariates, also referred to as the "proportionality" assumption. In practical terms, this model assumes that given two observations with different values for the covariates of interest, the ratio of the hazard functions for those two observations does not depend on time.

Data Source

Medical and pharmacy claims data from Quebec's provincial health plan, *Régie de l'assurance maladie du Québec* (RAMQ), from January 1997 to December 2006 were used in this analysis. Data elements were drawn from four RAMQ databases: 1) *Information personne assurée*, patient demographic characteristics; 2) *Périodes d'admissibilité*, patient eligibility and type of coverage; 3) *Services pharmaceutiques*, outpatient prescription drug dispensing; and 4) *Services médicaux*, medical services billed. The four RAMQ databases are linked via a unique and encrypted patient identifier and allow longitudinal follow-up of patients. Information on the vintage of drug ingredients was drawn from the Health Canada *Drug Product Database* (available at: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php).

Drug Vintage Definition

We elected to define drug vintage as the earliest date of sale reported for each ingredient contained in the drug. Hence, if the drug was a combination of ingredients (e.g., hydrochlorothiazide, a combination of angiotensin-converting enzyme inhibitor and diuretic in the control of hypertension), each ingredient contained in the drug was separately considered as a prescription with its own drug vintage. The Health Canada *Drug Product Database* contains the marketed date of each active ingredient for each drug product. This marketed date is reported by pharmaceutical companies (notification is mandatory) to Health Canada.

Following the approach proposed by Lichtenberg [16], we generated the following drug vintage variables to assess the impact of drug innovation in the analysis:

- Pre-1970: the proportion of a patient's drug prescriptions made of active ingredients dated before 1970;
- Post-1970: the proportion of a patient's drug prescriptions made of active ingredients dated after 1970;
- Post-1980: the proportion of a patient's drug prescriptions made of active ingredients dated after 1980;
- Post-1990: the proportion of a patient's drug prescriptions made of active ingredients dated after 1990.

The "Pre-1970" period was the reference category in the regression analysis. In this context, because we used a cumulative distribution approach to formulate the drug vintage covariate, the parameter estimate associated with the variable "Post-1970" may be interpreted as the "marginal benefit" associated with the consumption of only 1970s versus Pre-1970 medications; the coefficient associated with the variable "Post-1980" may be interpreted as the "marginal benefit" associated with the consumption of only 1980s versus 1970s medications; and the coefficient associated with the variable "Post-1990" may be interpreted as the "marginal benefit" associated with the consumption of only Post-1990 versus 1980s medications. The cumulative impact on the hazard of dying of all Post-1970 medications relative to only Pre-1970 ingredients can be determined by adding the three coefficients (i.e., $\beta_{\text{Post-1970}} + \beta_{\text{Post-1980}} + \beta_{\text{Post-1990}}$).

Other Determinants of Survival

The other covariates used for adjustment in the regression model were year indicator variables and patient-specific demographic characteristics (age, sex, and region of residence), government guaranteed income supplement (GIS) status (an indicator of low income), medical resources utilization, drug utilization, and comorbidities.

The variables controlling for medical services use were stratified by inpatient and outpatient services. For the inpatient setting, we included two covariates in the model: a variable indicating the number of inpatient admissions for each calendar year and a variable indicating the total hospital length of stay (days) during the calendar year. For the outpatient setting, we controlled for the number of outpatient consultations to any physician and for the occurrence of consultations to a specialist (yes/no) during the calendar year. With respect to drug use, we controlled for the number of pharmacy claims observed during the calendar year, after adjusting the prescription length to 28 days per prescription.

Lastly, following the approach proposed by Lichtenberg [16], we inserted two categorical covariates to control for the nature of the person's illnesses in our model. First, we used the International Classification of Diseases, Ninth revision (ICD-9) diagnosis codes reported in all medical claims to calculate the fraction of each person's diagnoses (i.e., DISEASE_SHARE) that were in each of the following broad disease categories: 1) *Infectious and parasitic diseases* (ICD-9 codes: 001–139); 2) *Neoplasms* (ICD-9 codes: 140–239); 3) *Endocrine, nutritional, metabolic, immunity disorders* (ICD-9 codes: 240–279); 4) *Diseases of the blood and blood-forming organs* (ICD-9 codes: 280–289); 5) *Mental disorders* (ICD-9 codes: 290–319); 6) *Diseases of the nervous system and sense organs* (ICD-9 codes: 320–389); 7) *Diseases of the circulatory system* (ICD-9 codes: 390–459); 8) *Diseases of the respiratory system* (ICD-9 codes: 460–519); 9) *Diseases of the digestive system* (ICD-9 codes: 520–579); 10) *Diseases of the genitourinary system* (ICD-9 codes: 580–629); 11) *Skin and subcutaneous tissue disorders* (ICD-9 codes: 680–709); 12) *Musculoskeletal system and connective tissue disorders* (ICD-9 codes: 710–739); 13) *Congenital anomalies* (ICD-9 codes: 740–759);