Examination of Pharmaceutical Innovation Diffusion Using the Cox Model*

Judit Lilla Keresztúri
assistant lecturer
Corvinus University
of Budapest
E-mail: lilla.kereszturi@uni-corvinus.hu

Ágnes Lublóy
associate professor
Corvinus University
of Budapest
E-mail: agnes.lubloy@uni-corvinus.hu

Gábor Benedek
business development director
Thesys SEA Pte Ltd.;
assistant professor
Corvinus University
of Budapest
E-mail:gabor.benedek@thesys.com

The article aims at identifying micro- and meso-level characteristics of the early prescribers of newly marketed innovative drugs. The diffusion of the two most popular, new blood glucose lowering oral antidiabetic drugs (Eucreas and Janumet) is assessed. The process of diffusion is complex – although doctors consider each new drug on its individual merits, some seem more predisposed to adopt them than others do. Therefore, understanding the mechanisms leading to early adoption of new drugs is highly relevant for speeding up the spread of medical innovations, promoting cost-effective prescriptions, developing targeted detailing, and predicting the utilization of new medications. Cox's proportional hazard model is used to examine factors influencing the likelihood of specialists' initial adoption. Belonging to one of the classes of survival models in statistics, the Cox model relates the time passing until new drug uptake to four significant covariates for both Eucreas and Janumet. For these medications the portfolio width of a specialist and the proportion of patients treated with insulin are significant determinants of new drug prescribing. In contrast, working for an academic medical centre and being in a high position do not increase the likelihood of adoption. The authors' results are in line with the findings of similar empirical studies.

KEYWORDS:
Cox model.
New drugs diffusion.

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Innovation and the successful diffusion of new drugs are critical for the financial performance of pharmaceutical companies as well as the health of patients. At macro level, governments are also major influencers, both through regulatory and approval agencies and through budgetary allocations. The diffusion of innovation is thus determined by the strategies of pharmaceutical companies, government policies as well as the behaviour of medical professionals. This article concentrates on the last, through investigating the determinants of prescribing new drugs by specialists.

Understanding the mechanisms leading to prescribers' early adoption of new drugs is important for several reasons (*Lublóy* [2014]). First, it *accelerates diffusion*. Although companies are increasingly innovative and efficient in producing new drugs, the implementation of pharmaceutical innovations is often delayed (*Berwick* [2003]). Where new drugs expand therapeutics in areas of yet unmet clinical need, accelerated adoption benefits both medicine and society, through fast and homogeneous availability. Second, it *promotes cost-efficiency*. Healthcare systems worldwide operate with limited financial resources. When the same pharmacological therapy is available as different brands at different prices, prescribers need to select the new, more expensive brand on medical grounds rather than socioeconomic considerations such as wealthy or demanding patients (for example, *Ohlsson–Chaix–Merlo* [2009]). Third, it *forecasts utilization*. Accurate prediction is important not only for pharmaceutical companies but also for healthcare professionals and policy makers in charge of healthcare budget planning. Fourth, it *develops targeted detailing and continuing medical education*. Distinguishing between doctors who prescribe new drugs early and those who prescribe them late or never enables targeted pharmaceutical company intervention, through relevant, tailored information; economies of both time and money; and appropriate use of new drugs, through prescription of the most efficient/least expensive alternatives.

Doctors have to strike a balance between using new drugs, potentially exposing patients to side effects, and delaying their use, depriving patients of possible benefits. The ensuing diffusion process is complex – although doctors consider new drugs on individual merits, some may be more predisposed to adopt than others do. Several factors are significantly positively associated with early adoption of new drugs (*Lublóy* [2014]): *1*. physicians' interest in particular therapeutic areas, participation in clinical trials, and prescribing volume, either in total or within the therapeutic class of the new drug (for example, *Coleman–Katz–Menzel* [1966], *Glass–Rosenthal* [2004], *Lin–Jan–Kao* [2011], *Liu–Gupta* [2012]); *2*. pharmaceutical companies' marketing efforts (for example, *Kremer et al.* [2008], *Manchanda–Xie–Youn* [2008],

Iyengar–Van Den Bulte–Valente [2011], *Liu–Gupta* [2012]); *3*. social interactions among colleagues, with pharmaceutical sales representatives, and with patients (for example, *Coleman–Katz–Menzel* [1966], *Manchanda–Xie–Youn* [2008], *Iyengar–Van Den Bulte–Valente* [2011], *Lin–Jan–Kao* [2011], *Liu–Gupta* [2012]) – colleagues are indispensable to gaining knowledge and reducing uncertainty about the consequences of new drug adoption (*Peay–Peay* [1994], *McGettigan et al.* [2001], *Prosser–Walley* [2006]); and *4*. physicians with younger patients, patients with higher socioeconomic statuses, and/or patients with poorer health statuses (for example, *Mark et al.* [2002], *Greving et al.* [2006], *Ohlsson–Chaix–Merlo* [2009], *Liu–Kao–Hsieh* [2011]). Some *5*. socio-demographic and *6*. practice-related factors also play important – albeit lesser – roles in the diffusion process.

This article focuses on the diffusion process of new A10Bs[1] for the treatment of T2DM[2]. Pharmaceutical companies are keen to develop such drugs, due to the increasingly high potential market – 347 million people suffer from diabetes worldwide (*Danaei et al.* [2011]), projected to become the seventh cause of death in 2030 (*WHO* [2011]). In Hungary alone, 11 brands were introduced in a subsidized form between April 2008 and April 2010.

In particular, this article assesses the diffusion process of the two most popular, recently introduced, oral anti-diabetic drugs. The Novartis brought Eucreas, having the active substances of metformin and vildaglipin, in November 2008 onto the market. Shortly after introduction, it became the market leader among the new anti-diabetic drugs. Merck Sharp & Dohme launched Janumet, having the active substances of metformin and sitaglipin, in February 2009. As of December 2011 Janumet was the second most successful, newly introduced anti-diabetic drug.

The determinants of new drug diffusion can be best captured by survival models, which examine the factors influencing the time that passes until new drug uptake. Semi-parametric survival models offer substantial advantages over parametric and non-parametric models. A well-known example of a semiparametric survival model is the *Cox* proportional hazard model [1972] that is used in this article as well.

Our study is structured as follows. After introduction, Section 1 describes the survival models briefly, special attention is paid to the Cox's proportional hazard model. Section 2 presents the key characteristics of the studied drugs, the specialists adopting the new oral antidiabetics, and specifies the dependent variables. Section 3 presents the Cox model results (four significant covariates for both studied drugs). Section 4 discusses the results alongside with policy implications. It lists several possible research limitations and suggests directions for future research as well.

[1] A10B: anti-diabetic drug. The World Health Organization' Anatomical Therapeutic Chemical (ATC) classification for blood glucose (HbAc1) lowering drugs other than insulin, based on the organs/systems on which drugs act and/or the therapeutic and chemical characteristics of the drugs.

[2] T2DM: type 2 diabetes mellitus.

1. Survival analysis and Cox's proportional hazard model

Survival analysis is a branch of statistics that deals with the assessment of time duration until one or more particular events happen. It is predominantly applied to irreversible events. For example, once a specialist wrote a prescription for a newly introduced drug, he/she might not be considered as a non-adopter. Survival models might be classified into non-parametric, parametric, and semi-parametric approaches.

Non-parametric survival models focus on the shape of the distribution of the survival times. The most important advantage of non-parametric analysis is that the results do not depend upon distributional assumptions; it lets the data speak for themselves. The non-parametric techniques eventuate in survival and hazard functions that are easy to interpret. In general, they can compare the distribution of the survival times for various patient cohorts or medical therapies. Among them, the *Kaplan–Meier* estimator [1958], also known as the product limit estimator, is the most widely used method for estimating the survival function. The major disadvantage of the non-parametric techniques is that they can only compare a limited number of groups. As a result, it is very difficult to assess the impact of one explanatory variable while controlling for other variables. Additional disadvantages include that they can only deal with qualitative explanatory variables and do not provide a numerical estimate for the relationship between the covariates and the survival time.

Parametric techniques make assumptions both about the functional form of the probability distribution and the way that the covariates influence the survival time. Similarly to regression analyses, for each covariate a coefficient is derived. The most commonly used probability distributions are the exponential, the Weibull, the Gomperz and the lognormal distributions. The main disadvantage of the parametric analysis is that the estimates are influenced by the assumptions about the shape of the survival and hazard functions. There is an intermediate technique whereby only the assumption about the way that the covariates influence the survival time is made – it is called as semi-parametric approach and particularly popular in survival analysis.

Cox's proportional hazard model [1972] is the most widely used semi-parametric survival model. The Cox regression analysis yields an equation for the hazard as a function of several explanatory variables. By definition, the hazard function is the probability that an individual will experience an event (e.g. adoption) within a small time interval given that the individual has survived up to the beginning of the interval. It can therefore be interpreted as the risk of an event occurring at time *t*. In Cox regression, the explanatory variables are named as covariates. The model can easily

handle covariates that are categorical or continuous. Furthermore, the covariates might be time invariant or time varying during observation.

The Cox regression estimates the hazard ratios, exp(β)s; the values of the respective variables differ by one unit, all other covariates are being held constant. Variables with exp(β)s larger than one are associated with increased hazard – the higher the variable, the higher the hazard of the event (*Fox* [2002]).

The Cox model does not require the choice of some particular probability model to represent survival times, and is therefore more robust than parametric methods. Additional advantages of the Cox regression include modelling the effect of covariates on the hazard rate but leaving the baseline hazard rate unspecified. Furthermore, it handles right-censored data appropriately. Right censoring typically occurs when information on time to event is unavailable due to non-occurrence of outcome event before the end of the observation period. In this article, specialists are thus censored in cases where they had not routinely adopted the A10Bs by the end of 2011 (time *t*) (*Garson* [2013], *Klein–Moeschberger* [2005]).

Similarly to many recent diffusion studies (e.g. *Korda–Clements–Dixon* [2011], *Lin–Jan–Kao* [2011]), the present article employs the semi-parametric Cox regression with right-censored data as specified in Equation /1/. The dependent variable is a dummy indicating each month whether the specialist had routinely adopted the newly introduced drug.

$$h(t,\mathbf{x}) = h_0(t,\alpha)\exp\left(\boldsymbol{\beta}^{\mathbf{T}}\mathbf{x}\right) \qquad /1/$$

where $h_0(t,\alpha)$, is the baseline hazard function, t is the time, α is a parameter influencing the baseline value, exp(**β**) is the vector of hazard ratios, and **x** is the vector of the explanatory variables. In Cox's proportional hazard model $h_0(t,\alpha)$ is dependent upon time, but independent of the explanatory variables, whereas $\exp\left(\boldsymbol{\beta}^{\mathbf{T}}\mathbf{x}\right)$ is independent of time, but dependent upon the explanatory variables.

In this article, statistical calculations are performed using SPSS (version 22.0). The covariates are entered into the Cox model in one single step, without checking their significance (forced entry, default option in SPSS). The covariates are time invariant. For multiple highly correlated covariates (with coefficients higher than 0.85), only one variable from the set of intercorrelated variables is used. For testing the overall fit of the Cox model, an omnibus test is performed (*Fox* [2002]). If the null hypothesis is rejected, then the suggested Cox model is not significantly suitable to the data.

2. Data

The main database is managed by DoktorInfo Ltd. and covers prescription information between April 2008 and December 2011. All general practitioners in Hungary are required by law to collect data for NHIFH[3]. Of these, 899 (22%) also feed real-time prescription data into the DoktorInfo database voluntarily. This involves no additional work for general practitioners, who are compensated for providing information such as general practitioner identification number, prescription date, prescribed drug characteristics (brand name, ATC code, and dosage), prescribed drug subsidy, and patient characteristics (age and gender).

2.1. Doctors and drugs

The Doktorinfo database is representative of the entire Hungarian general practitioner population in both age and location (defined by region and population size). Since January 2009, for patients whose care is shared, the identification number of the therapy-initiating specialist is published on the prescription as well. This information enables monitoring the adoption behaviours and prescribing patterns of specialists who share care of T2DM patients.

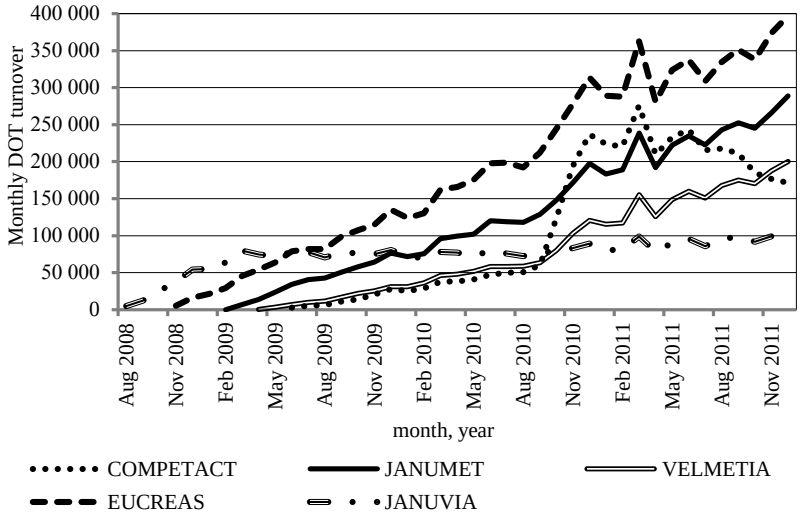
The 318 physicians analysed here account for roughly 80% of the specialists who treated patients with T2DM on a daily basis. It is important to emphasize that not all prescriptions written by specialists are taken into account, only those prescriptions are included in the Doktorinfo database which were initiated by specialists within the shared care scheme. We examine routine, as opposed to just first-time adoption of new A10Bs. Adoption becomes routine when specialists first ask referring general practitioners to prescribe new A10Bs, on grounds of efficacy and efficiency. Intuitively, any such drugs are already part of the specialists' prescribing portfolios, following first-time adoption and follow-up tests. From the 11 recently introduced antidiabetic drugs, the diffusion process of Eucreas and Janumet is analysed in this article in detail.

Figure 1 shows the brand sales of the five most successful, new oral antidiabetic drugs expressed as the number of DOT[4] between January 2008 and December 2011. Novartis introduced Eucreas to the Hungarian market in November 2008. In less than a year it became the market leader among the newly introduced anti-diabetic drugs; this position was hold until the end of the observation period. The daily cost of treatment with Eucreas is HUF 416 – thus it might be considered as a middle-priced first-in class drug (*NHIFH* [2013a]).

[3] NHIFH: National Health Insurance Fund of Hungary.
[4] DOT: days of treatment.

Merck Sharp & Dohme introduced Janumet to the Hungarian market in February 2009. Although its sales have been steadily increasing since then, Janumet never became the market leader. Since July 2011, it has been the second most successful, newly introduced oral anti-diabetic medication. On the day of the rollout, the daily cost of treatment with Janumet was HUF 397 – it is the second cheapest first-in class antidiabetic medication (*NHIFH* [2013a]).

Figure 1. Monthly DOT turnover of the five most successful, newly introduced antidiabetic drugs



Source: Own calculation based on *NHIFH* [2013b].

2.2. Dependent variable

This article has identified 19 determinants that may affect specialists' routine prescribing of new A10Bs. The determinants are grouped into five categories of factors: specialists' socio-demography, workplace, practice, prescribing and patient characteristics.

The another database used in this article is managed by the Office of Health Authorization and Administrative Procedures (*HRTC* [2013]) and covers socio-demographic and practice-related variables as well as physician characteristics.

Socio-demographic characteristics include gender, age of the specialist and number of specialties. The average age of specialists in the sample was 52, the youngest specialist was 32 years old, the oldest one was 78 years old, and 152 specialists (47.8%) were male. On average, specialists had 1.78 specialties.

Workplace characteristics contain the number of workplaces, the position of the specialist, and the type of the institution where the specialist's practice is embedded. On average, specialists worked in 1.46 practices. The position of the specialists was divided into three categories: *1*. high position ((deputy) head of hospital department or outpatient centre); *2*. medium position (chief physician); *3*. low position (associate professor or physician). The institutions where the specialists practice were divided into four groups: *1*. clinic; *2*. university/teaching hospital; *3*. hospital; *4*. outpatient centre and other.

Table 1 summarizes the descriptive statistics of the specialists' socio-demographic and workplace characteristics.

Table 1

Socio-demographic and workplace characteristics of specialists

Variable	Average	Minimum	Maximum	Standard deviation
Gender of the specialist (0 – male; 1 – female)	0.48	0.00	1.00	–
Average age of the specialist (years)	51.92	32.00	78.00	9.94
Number of specialties	1.78	1.00	4.00	0.78
Number of workplaces	1.46	0.00	5.00	0.69
Position of the specialist (1 – head or deputy; 2 – chief physician; 3 – associate professor or physician)	–	1.00	3.00	–
Institution type (1 – clinic; 2 – university/teaching hospital; 3 – hospital; 4 – outpatient centre and other)	–	1.00	4.00	–

Source: Own calculation as of December 2011.

In addition to the socio-demographic and workplace data, information on the specialists' practice, prescribing habits and patient portfolio were collected as well.

Practice characteristics include the number of the specialist's T2DM patients whose care is shared with general practitioners; mean number of consultations per patient resulting in confirmation or change of therapy suggested by the specialist; size of city where the specialist works, proxied by number of inhabitants; prescribing volume; prescribing intensity (mean number of prescriptions per patient); proportion of loyal patients (patients consulting each time the same specialist); number of referring general practitioners (number of general practitioners with whom the specialist share patient care). Table 2 shows the descriptive statistics of specialists' practice characteristics.

Table 2

Practice characteristics of specialists

Variable	Average	Minimum	Maximum	Standard deviation
Number of patients	123.48	14.00	784.00	114.71
Mean number of consultations per patient	1.68	1.00	2.85	0.37
Practice location (1 – Budapest; 2 – large city; 3 – medium-sized city; 4 – small city)	–	1.00	4.00	–
Prescribing volume	1 569.59	315.00	12 262.00	1 618.11
Prescribing intensity (mean number of prescriptions per patient)	12.71	4.63	30.93	3.72
Proportion of loyal patients (%)	70.77	17.54	100.00	19.76
Number of referring general practitioners	21.56	1.00	84.00	15.95

Source: Here and in Tables 3 and 4, own calculation based on data from January 2010 to December 2011.

On average, a typical specialist suggested therapies for 123.48 patients and saw patients 1.68 times. The number of consultations per patient shown in Table 2 is a lower estimate – due to data limitations only those consultations were taken into account that resulted in new prescription initiations by specialists. In shared care systems, specialists hold the exclusive right to start therapies with specialist medications. When specialists initiate certain therapies, general practitioners have to prescribe that medication for a time, usually for one year. To obtain prescribed medication, patients have to visit their general practitioners monthly. Prior research suggests that practice location – rural vs. urban, central vs. peripheral – might also influence new drug uptake (*Lublóy* [2014]). Practice location was categorized by the size of the settlement in which the specialists have their main practices. Using data from *HCSO* [2011], settlements were grouped into four categories: *1*. Budapest; *2*. large city (100 thousands–1 million inhabitants); *3*. medium-sized city (40–100 thousands inhabitants); *4*. small city (under 40 thousands inhabitants). Specialists asked general practitioners to write 1 570 prescriptions – 12.71 prescriptions per patient. Over two thirds of patients (23 671, 70.77%) were loyal to their specialists and did not consult other specialists in the sample. The proportion of loyal patients, variable never assessed in the literature before, might influence new drug uptake as well – presumably specialists are more inclined to prescribe new drugs to patients whom medical history they know better. A typical specialist received referrals from 21.56 general practitioners.

Prescribing characteristics include portfolio width (number of brands prescribed for patients in shared care) and ratio for old A10B (prescriptions for previously introduced A10Bs). Specialists prescribed 4-25 brands to their patients with diabetes.

A typical specialist prescribed almost 17 brands within the therapeutic class. (See Table 3.) The ratio of prescriptions for old oral anti-diabetic drugs might refer to the specialists' general conviction of the proper therapy for diabetes – a therapy being debated in the literature (*Krentz–Bailey* [2005], *Scheen* [2005], *Davis–Abraham* [2011]). The mean ratio of prescriptions for old oral anti-diabetic medications was less than 3%. As a maximum, 33.33% of the prescriptions were for old oral anti-diabetic medications.

Table 3

Prescribing characteristics of specialists

Variable	Average	Minimum	Maximum	Standard deviation
Portfolio width (number of prescriptions)	16.66	4.00	25.00	4.13
Ratio for old oral antidiabetic medication (%)	2.99	0.00	33.33	4.66

Patient characteristics include the mean age of patients, proportion of male patients and mean annual income of patients in the specialist's patient panel and the ratio for insulin (proportion of prescriptions for insulin). The respective descriptive statistics are shown in Table 4.

Table 4

Patient characteristics

Variable	Average	Minimum	Maximum	Standard deviation
Mean age of patients (years)	64.20	44.00	72.87	2.84
Proportion of male patients (%)	47.07	7.02	70.37	7.39
Ratio for insulin (%)	79.10	0.00	100.00	20.84
Mean annual income of patients (thousand HUF)	930.98	380.06	1511.87	179.24

A typical specialist's patient panel was composed of patients with a mean age of 64 years. Forty seven percent of the patients were male. The ratio of prescriptions for insulin might refer to the severity of diabetes. In general, patients are treated with insulin if oral anti-diabetic medications failed. The mean ratio of prescriptions for insulin was 79.1%. The large standard deviation of this ratio reveals large differences in the prescribing habits among specialists. Prior research suggests that high-income patients receive new drugs earlier than others do, not least because of their ability to pay for out-of-pocket treatments (*Lublóy* [2014]). Moreover, expert interviews sug-

gest that in Hungary low-income patients are treated rather with insulin as it is covered by 100% state subsidy. Patient income, that is, the average income of the inhabitants living nearby the general practitioner's office was proxied by either the mean street-level income (settlements over 20 thousand inhabitants) or by the zip code level income (small settlements) based on the zip code/street of the patients' general practitioner office, using the database of *GEOX* [2013]. The average annual income of patients was around HUF 930 thousand, approximately EUR 3100.

2.3. Correlation

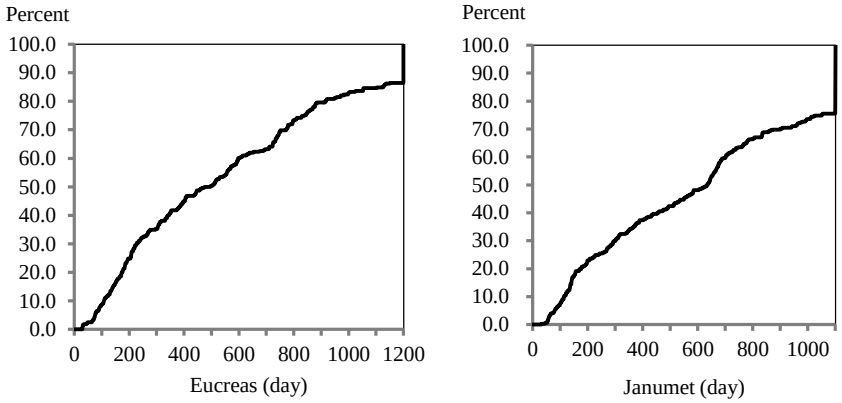
Garson [2013] suggests not inserting covariates correlating higher than 0.85 in Cox regression. For multiple highly correlated covariates (with coefficients higher than 0.85), only one variable from the set of intercorrelated variables is used. The correlation between the number of patients and the number of prescriptions was 0.95 – the number of patients determines the number of prescriptions written by specialists. As a result, the number of prescriptions was excluded from the analysis. Fairly high correlation (0.60-0.65) is found between two other sets of variables (mean number of consultations per patient vs. that of prescriptions per patient, and number of patients vs. portfolio width). Although neither variable from the set of intercorrelated variables is excluded from the model, their influence on the results is discussed later in this article.

3. Results

The proportion of specialists who have adopted the new drug up to the given number of days can be derived, if one minus the survival function is plotted. Eucreas was adopted by 86% of the specialists in 1200 days, whereas Janumet was adopted by 75% of the specialists in 1100 days. As shown in Figure 2, the new drugs were adopted gradually; no jumps or structural breaks can be detected in the diffusion process.

For both Eucreas and Janumet we have assessed the distribution of the survival times. The Q-Q plots (not shown in this article) revealed that none of the widely used distributions (such as the exponential, the log-normal, or the Weibull) fit reasonable to the empirical cumulative probability distribution of the survival times. As a result, this article uses the semi-parametric Cox regression model. This choice requires no assumption on the functional form of the probability distribution.

Figure 2. One minus survival function



Two hundred seventy five of the 318 specialists adopted Eucreas during the observation period. Table 5 shows the regression results for Eucreas – only the significant determinants of adopting this new oral anti-diabetic medication are listed.

Table 5

Significant determinants of adopting Eucreas

Variable	β	Standard error	Wald statistics	Degree of freedom	Significance	Exp(β)
Ratio for insulin (%)	–0.0213	0.0040	28.45	1	0.0000	0.9790
Portfolio width (number of brands)	0.1159	0.0224	26.74	1	0.0000	1.1229
Number of patients	0.0031	0.0008	15.83	1	0.0001	1.0031
Number of consultations per patient	0.8590	0.2486	11.94	1	0.0005	2.3609

Note. The omnibus test of the model suggests that the specified Cox model is suitable to the data at a significance level of 0.000. The parameters of the overall fit of the model are as follows: with 18 degrees of freedom the χ^2 is 154.063, whereas the –2 log likehood is 2654.596.

Source: Own calculation.

According to Table 5, if the number of patients increases ceteris paribus by one, then the probability of the specialist being an early adopter of Eucreas becomes greater by 0.31%. On average, if there is one unit growth in the number of consultations, then the probability of writing a prescription for Eucreas increases by 136.09%. Thus, strong relationship between specialists and patients forwards the idea that specialists – with the aim of finding the most appropriate therapy for their patients – use higher than average number of prescription drugs. Portfolio width is a significant

determinant of new drug adoption as well. If the number of brands prescribed increases by one unit, then the probability of the specialist being an early adopter rises by 12.2%. Moreover, if the ratio of prescriptions for insulin decreases by 1%, then the probability of writing a prescription for Eucreas early ceteris paribus increases by 2.1%. Although in the medical literature the most appropriate therapy for antidiabetic patients is matter of continuous debate, our results reveal that specialists prescribing proportionally less insulin are early adopters of new oral antidiabetic medications with higher probability. In addition to the determinants listed in Table 5, no other factors increase the probability of early adoption of Eucreas significantly.

Table 6

Significant determinants of adopting Janumet

Variable	β	Standard error	Wald statistics	Degree of freedom	Significance	Exp(β)
Portfolio width (number of brands)	0.1879	0.0239	61.63	1	0.0000	1.2068
Ratio for insulin (%)	–0.0271	0.0045	36.94	1	0.0000	0.9732
Proportion of loyal patients (%)	–0.0127	0.0042	9.29	1	0.0023	0.9874
Prescribing intensity (mean number of prescriptions per patient)	0.0784	0.0302	6.74	1	0.0094	1.0815

Note. The omnibus test of the model suggests that the specified Cox model is suitable to the data at a significance level of 0.000. The parameters of the overall fit of the model are as follows: with 18 degrees of freedom the χ^2 is 150.798, whereas the –2 log likehood 2356.785.

Source: Own calculation.

Although portfolio width correlates fairly highly with the number of patients (0.65), both variables increase the probability of early adoption significantly. Even though the number of consultations per patient correlates reasonably highly with the prescribing volume (0.64), in the final model only the former variable is included. When instead of the number of consultations per patient the prescribing volume is added to the Cox model, the prescribing volume becomes a significant predictor of new drug uptake. This finding is in in line with the recent systematic review of *Lublóy* [2014], where physicians with high total prescribing volume (or prescribing volume in the therapeutic class) seemed particularly alert to new drugs.

Two hundred forty of the 318 specialists adopted Janumet during the two-year observation period. Table 6 shows the regression results for Janumet (only the significant determinants of adopting this new oral anti-diabetic medication are listed).

Similarly to Eucreas, portfolio width and ratio of prescription for insulin are significant determinants of adopting Janumet. The influence of portfolio width on the

adoption of Janumet is more pronounced than on Eucreas. Specialists writing higher number of brands adopt follower drugs earlier – most probably due to their previous positive experience with a drug having similar product characteristics. When the ratio of prescription for insulin increases, the probability of prescribing Janumet early decreases to a higher extent for Janumet than for Eucreas. Although for Janumet the number of patients and the number of consultations per patient do not influence the probability of early adoption significantly, the proportion of loyal patients and the prescribing volume are significant predictors of early adoption.

If the proportion of loyal patients ceteris paribus increases by 1%, then the probability of the specialist being an early adopter of Janumet decreases by 1.27%. For loyal patients, due to the efficient specialist-patient collaboration, specialists have already identified the most appropriate therapy even before the relatively late introduction of Janumet. For these loyal patients the most recently introduced oral anti-diabetic medications offer less benefits as compared to the drug already used. If the number of prescriptions per patient ceteris paribus increases by one unit, then the probability adopting Janumet early increases by 8.15%. For Eucreas, instead of the prescribing volume, the number of consultations per patient influenced new drug uptake significantly – however, these variables correlate moderately with each other.

4. Discussion and policy implications

Our results suggest that pharmaceutical companies should target their direct marketing campaigns at specialists with large patient panels. In particular, campaigns should be targeted at specialists who consult with their patients more frequently (Eucreas) or specialists who initiate anti-diabetic therapies for longer than average periods (the number of prescription per patient is high as in the case of Janumet).

The number of brands specialists prescribe is an influential predictor of new drug uptake. For both brands, the wider the prescribing portfolios, the earlier specialists adopt new drugs.

The ratio of prescriptions for insulin is also significantly associated with the rate of adoption for both brands – the higher the ratio of prescriptions for insulin, the later specialists adopt new oral anti-diabetic medications. The four possible explanations for delays in the adoption are as follows. First, the individual specialists may have convictions as to the most appropriate therapy (*Krentz–Bailey* [2005], *Scheen* [2005], *Davis–Abraham* [2011]), which may be related to therapeutic conservatism or to knowledge of and clinical experience with the new oral anti-diabetic medications. Second, patients with long disease histories had already received insulin, thus ex-

cluding new oral anti-diabetic medications as an alternative therapy (*Korytkowski* [2002], *Krentz–Bailey* [2005]). Third, for patients at severe stages of the disease, oral drugs are insufficient for keeping blood glucose levels low. Fourth, low-income patients cannot cover 30% of the drug price, whereas insulin is free of charge due to the state subsidy.

Relying on data mining, pharmaceutical companies might identify early adopting specialists from the database of Doktorinfo Ltd., based on the characteristics of prescribing new drugs early. (Specialists mentioned in this article can all be derived from that database.) To rollout new drugs successfully, data available for subscriptions fee from one single database may be sufficient to identify target specialists and distribute marketing efforts efficiently. Hard-to-obtain data such as specialists' socio-demographic characteristics, scientific orientations and practice characteristics are not necessary.

With the aim of accelerating new drug adoption and stabilizing the health status of patients with diabetes in initial stages, healthcare policy strategists should target their information leaflets and continuous medical education programs at three types of specialists. First, at key opinion leaders of endocrinology – collegial interactions with these opinion-leading physicians seem critical to fast, wide acceptance of pharmaceutical innovations. Second, at specialists with characteristics identified in this article (high number of patients, wide prescribing portfolio) – they accelerate new drug diffusion due to their prescribing and practice characteristics and most probably insert significant influence on their peers. Third, at specialists being less preferred by pharmaceutical companies – they have less patients, their prescribing portfolio is narrow, and treat relatively higher number of their patients with insulin.

Janumet should be preferred over Eucreas if healthcare strategists wish to allocate the limited healthcare budget more efficiently (treat more patients with one of the two recently introduced new oral anti-diabetic medications from the same budget). Assuming 70% state subsidy for both brands, if Janumet is preferred over Eucreas, the daily cost saving is HUF 13, totalling up to HUF 400 on a monthly basis. This policy implication assumes that both drugs reduce the HbAc1 level with close to equal efficiencies and despite distinct modes of action (*EMA* [2014]).

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This article employed Cox's proportional hazard model to identify factors influencing the likelihood of the specialists' initial adoption of the two most successful anti-diabetic drugs (Eucreas, Janumet). The semi-parametric Cox regression does not require the choice of some particular probability model to represent survival times, and is therefore more robust than parametric methods. Furthermore, Cox regression handles right-censored data appropriately – the sample included specialists who have not prescribed the studied drugs until the end of the observation period.

The significant determinants of new drug prescribing are the number of patients, the number of consultations per patient, the portfolio width of a specialist and the proportion of patients treated with insulin for Eucreas, and the variables of prescribing intensity, proportion of loyal patients, portfolio width and proportion of patients treated with insulin for Janumet. Variables identified as significant in this article (number of patients, number of consultations per patient, portfolio width) were associated with the likelihood of initial adoption in similar empirical studies (*Lublóy* [2014]).

This article has several possible limitations. First and foremost, *prescription data are incomplete*. Specialists' prescribing behaviours are monitored through the reported prescription data by general practitioners with whom specialists share patient care. All the sampled general practitioners listed the name/identification number of the therapy-initiating specialists, but only around one fifth of practicing general practitioners were sampled – specialists' routine adoptions of new drugs may therefore occur earlier. However, the sampled general practitioners are geographically representative, and the size of this bias is expected to be constant across specialists and does not undermine the validity of the results. Second, the *influence of professional and social interactions among specialists on new drug diffusion is not studied*. In the literature, interactions appear to be a very important influencing factor, information relayed through direct, personal contacts proving particularly powerful (*Coleman–Katz–Menzel* [1966], *Iyengar–Van Dan Bulte–Valente* [2011], *Manchanda–Xie–Youn* [2008]). Physicians' adopting behaviours are affected by other physicians' knowledge, attitudes, and behaviours, thus reducing safety and efficacy uncertainties. Third, *the marketing efforts of pharmaceutical companies targeted at physicians are not accounted for*. In the pharmaceutical marketing literature, the size and efficiency of marketing efforts targeted at physicians are very powerful predictors of new drug uptake (*Kremer et al.* [2008], *Manchanda–Xie–Youn* [2008], *Iyengar–Van Dan Bulte–Valente* [2011]). Fourth, *conclusions based on only two drugs from the same therapeutic class cannot be generalized*. By incorporating more drugs, future research may examine the determinants of new drug diffusion identified here for consistency by drug characteristics.

Appendix

Table A1

Determinants of adopting Eucreas – variables in decreasing order by significance

Variable	β	Standard error	Wald statistics	Degree of freedom	Signifi-cance	Exp(β)
Ratio for insulin (%)	–0.0213	0.0040	28.45	1	0.0000	0.9790
Portfolio width (number of brands)	0.1159	0.0224	26.74	1	0.0000	1.1229
Number of patients	0.0031	0.0008	15.83	1	0.0001	1.0031
Consultations per patient	0.8590	0.2486	11.94	1	0.0005	2.3609
Number of referring general practitioners	–0.0120	0.0068	3.14	1	0.0766	0.9881
Number of specialties	0.1291	0.0839	2.37	1	0.1238	1.1378
Prescribing intensity (number of prescriptions)	–0.0347	0.0272	1.62	1	0.2034	0.9659
Institution type (1 – clinic; 2 – university/teaching hospital; 3 – hospital; 4 – outpatient centre and other)	–0.1097	0.0882	1.54	1	0.2139	0.8961
Mean annual income of patients (in thousand HUF)	0.0000	0.0000	0.81	1	0.3688	1.0000
Location (1 – Budapest; 2 – large city; 3 – medium-sized city; 4 – small city)	–0.0539	0.0737	0.53	1	0.4648	0.9475
Gender of the specialist (0 – male; 1 – female)	–0.0698	0.1300	0.29	1	0.5913	0.9326
Ratio for old oral anti-diabetic medication (%)	–0.0093	0.0196	0.22	1	0.6360	0.9908
Position of the specialist (1 – head or deputy; 2 – chief physician; 3 – associate professor or physician)	0.0424	0.0980	0.19	1	0.6651	1.0433
Proportion of loyal patients (%)	0.0013	0.0039	0.11	1	0.7357	1.0013
Male patients (%)	0.0024	0.0088	0.07	1	0.7850	1.0024
Age of patients (years)	–0.0059	0.0241	0.06	1	0.8064	0.9941
Number of workplaces	–0.0233	0.0965	0.06	1	0.8094	0.9770
Age of the specialist (years)	–0.0014	0.0083	0.03	1	0.8702	0.9987

Source: Own calculation.

Table A2

Determinants of adopting Janumet – variables in decreasing order by significance

Variable	β	Standard error	Wald statistics	Degree of freedom	Signifi-cance	Exp(β)
Portfolio width (number of brands)	0.1879	0.0239	61.63	1	0.0000	1.2068
Insulin ratio (%)	–0.0271	0.0045	36.94	1	0.0000	0.9732
Proportion of loyal patients (%)	–0.0127	0.0042	9.29	1	0.0023	0.9874
Prescribing intensity (number of prescriptions)	0.0784	0.0302	6.74	1	0.0094	1.0815
Gender of the specialist (0 – male; 1 – female)	–0.2681	0.1391	3.71	1	0.0540	0.7649
Male patients (%)	–0.0183	0.0101	3.33	1	0.0681	0.9818
Number of specialties	0.1503	0.0939	2.56	1	0.1094	1.1621
Institution type (1 – clinic; 2 – university/teaching hospital; 3 – hospital; 4 – outpatient centre and other)	0.1293	0.0902	2.05	1	0.1518	1.1380
Number of patients	0.0010	0.0009	1.25	1	0.2643	1.0010
Ratio for old oral anti-diabetic medication (%)	0.0165	0.0197	0.70	1	0.4015	1.0166
Consultations per patient	–0.2364	0.2901	0.66	1	0.4151	0.7894
Mean annual income of patients (in thousand HUF)	0.0000	0.0000	0.38	1	0.5401	1.0000
Number of referring general practitioners	0.0037	0.0075	0.24	1	0.6253	1.0037
Age of patients (years)	–0.0091	0.0249	0.14	1	0.7131	0.9909
Number of workplaces	0.0244	0.0962	0.06	1	0.7997	1.0247
Location (1 – Budapest; 2 – large city; 3 – medium-sized city; 4 – small city)	–0.0126	0.0780	0.03	1	0.8718	0.9875
Position of the specialist (1 – head or deputy; 2 – chief physician; 3 – associate professor or physician)	–0.0082	0.1012	0.01	1	0.9351	0.9918
Age of the specialist (years)	–0.0007	0.0086	0.01	1	0.9370	0.9993

Source: Own calculation.

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