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RESEARCH ARTICLE

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Diffusion of a new drug among ambulatory physicians—The impact of patient pathways

Ronja Flemming[1] | **Franziska Frölich**[2] | **Norbert Donner-Banzhoff**[3] | **Leonie Sundmacher**[1]

[1]Technical University of Munich, Munich, Germany

[2]AOK PLUS SHI in Thuringia and Saxony, Dresden, Germany

[3]Department of General Practice, Preventive and Rehabilitation Medicine, University of Marburg, Marburg, Germany

Correspondence
Ronja Flemming, Technical University of Munich, Georg-Brauchle-Ring 60, 80992 Munich, Germany.
Email: ronja.flemming@tum.de

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Abstract

When drugs enter the market, physicians' prescribing behavior plays a crucial role in the diffusion process. Although regulations to foster economically efficient prescribing exist, physicians have some degree of freedom in choosing medication and are subject to various influencing factors. The aim of the present analysis is to investigate how interaction among patients and physicians affects the diffusion. We look at two different ways that patient pathways might influence physicians and examine these effects for Sacubitril/Valsartan (S/V), a new drug for patients with heart failure. Using administrative data from Germany, we identify physicians who prescribed S/V in the first 2 years of its availability. We apply survival models to estimate the impact of the patient-physician interaction on the physicians' adoption time. To this end, we determine whether individual physicians treated patients that had been prescribed S/V, and how many other physicians already prescribing S/V were connected in patient-sharing networks. Our main findings are that patients with a previous prescription seem to induce adoption by demanding repeat prescriptions. Moreover, patients establish connections between physicians that may lead to prescriptions for new patients. Our results therefore suggest that patient pathways play a significant role in the diffusion of a new drug.

KEYWORDS
diffusion of new drugs, network analysis, patient pathways, routine data, survival model

1 | INTRODUCTION

Health care expenditure in developed countries continues to rise unabatedly. This is driven not only by demographic change, leading to increased morbidity, but also by new waves of health care innovation, especially in the area of medical devices and pharmaceuticals (Okunade & Murthy, 2002). For example, expenditure on drugs by statutory health insurance funds in Germany increased from 19.4 billion euros in 2000 to 37.7 billion euros in 2017 (Gesundheitsberichterstattung des Bundes, 2019), with the share of total expenditure rising from 15% to 17% over the same period (Gesundheitsberichterstattung des Bundes, 2019).

In order to contain the increasing expenditure on new pharmaceuticals, regulatory instruments exist at different stages in the product life cycle of a new drug. At the stage of market entry, first, an authorization must be obtained (e.g., from the

European Medicine Agency), which ensures the safety, quality and efficacy of the new drug (European Medicines Agency [EMA], 2019). The decision about a drug's reimbursement by the SHI and its price is based on a benefit assessment. At the stage of market diffusion, physicians play an essential role as prescribers and are therefore required by law to prescribe efficiently. These regulatory instruments are intended to ensure the cost-effective prescribing of pharmaceuticals. However, they coexist with evidence-based guidelines and the freedom of physicians to determine, within bounds, the appropriate therapy for their patients.

1.1 | Background

The diffusion of new drugs and their adoption by physicians has been studied from a variety of perspectives. Several important influencing factors have previously been identified (Lublóy, 2014). Contextual factors such as the social environment, marketing activities of pharmaceutical companies, patients, and regulations were found to impact upon the diffusion process. A physician's decision to prescribe a new drug instead of established treatments depends to a great extent on his or her personal appraisal of appropriateness and on professional judgment. It also depends to some extent on the patient's disease severity, age and comorbidities (Greving et al., 2006; Liu et al., 2011; Ohlsson et al., 2009). Although patient characteristics have been considered in some studies, as described above, the various ways in which they influence their physician's decision to adopt have not yet been analyzed in detail. In addition to the known, medically determined patient effect, our study seeks to analyze two possible mechanisms that might explain how patients influence their ambulatory physician's adoption of a new drug.

First, patients with a previous prescription of a new drug could induce prescriptions by demanding a repeat prescription from a different physician. It has been shown that the adoption of a new drug accelerates when it is directly requested by patients (Liu & Gupta, 2012). This effect is an example of the "demand-induced supply" of medical services (Shih & Tai-Seale, 2011), which has been studied in the context of prescription drugs. The authors define "demand-induced supply" as "the phenomenon that patients move the demand curve out due to a change in their knowledge or taste" (Shih & Tai-Seale, 2011). McKinlay et al. (2014) investigated the prescription of oxycodone and Celebrex, finding that physicians prescribed both drugs significantly more often to patients who directly requested it, compared to patients who did not. It is assumed that patients are knowledgeable and that their demand for a specific drug influences physicians' prescription decisions independently of their professional judgment (Shih & Tai-Seale, 2011).

This might also explain a comparable but more indirect effect which was observed in an intersectoral context, namely that patients' follow-up medication in ambulatory care was affected by hospital stays (Lund et al., 2015; Müller-Bühl et al., 2009) and more frequently included new on-patent and more expensive drug prescriptions (Grimmsmann et al., 2007). We therefore assume that patients' pre-existing medication also affects physicians' adoption of new drugs in ambulatory care. Patients with chronic diseases who receive, for example, their initial medication from a specialist might get a repeat prescription from their general practitioner (GP). This sequence of prescriptions in the context of new pharmaceuticals would correspond to a kind of demand-induced adoption by the GP through their patients demanding a repeat prescription.

Second, as patients in Germany may choose which physicians to consult, they establish connections between physicians. Within the resulting patient-sharing networks, information transfer may take place. This transfer of information can occur either through treating patients who are already prescribed the new drug and thereby transfer information regarding this treatment from one physician to another or through a professional information exchange about newly available drugs between connected physicians. Both effects can thereby accelerate the diffusion of the new drug.

The concept of patient-sharing networks uses information about common patients to identify connections between physicians (Barnett et al., 2011). Donohue et al. (2018) applied this approach to analyze social contagion effects among physicians. Social contagion describes the influence of the opinion of colleagues about an innovation on the adoption decision and is caused, for example, by information transfer or normative pressure (van den Bulte & Lilien, 2001). The effect of social contagion in different types of physician networks has been established in several studies, some of which used survey data to identify friendship, discussion or professional networks among physicians (Coleman et al., 1966; Iyengar et al., 2011). Other studies have used geographic or professional proximity to approximate social influence (Lin et al., 2011; Liu & Gupta, 2012; Manchanda et al., 2008). Arnold et al. (2021) have found that the likelihood of a physician prescribing a new drug depends on the degree of connection to other physicians who prescribe the same drug in a patient-sharing network. All these studies found that social contagion has a positive effect on the diffusion of a new drug in networks.

1.2 | Study objectives

The present study investigates the two described mechanisms for the influence that patients may have on the diffusion of a new drug. To this end, we analyze the diffusion of the drug *Sacubitril/Valsartan (Entresto®)* (S/V) among ambulatory physicians in Germany. The drug was approved in January 2016 for the treatment of heart failure patients and was shown to provide a considerable additional benefit compared to standard therapy. However, it was given the lowest of three defined quality of evidence categories and was not approved for heart failure patients with diabetes mellitus, for whom only a minor additional benefit was found with the lowest quality of evidence rating. The annual therapy costs at entry were about 50 times higher than the costs for the comparative therapy with the angiotensin converting enzyme inhibitor (ACE inhibitor) *Enalapril* (Beschluss über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Sacubitril/Valsartan, 2016).

The German medical guideline (NVL) for heart failure patients was updated in August 2017. It recommends that only patients with heart failure of severity NYHA II to NYHA IV (New York Heart Association [NYHA], 2019) with persistent symptoms despite treatment with ACE inhibitors should receive S/V. The authors of the guideline cite quality concerns with the study (PARDIGM-HF) (Bundesärztekammer [BÄK] et al., 2017) for their decision. The generalizability of the findings, and thus the application of S/V to a larger population of heart failure patients, remains under discussion (Yandrapalli et al., 2017).

Our objectives are to investigate the role patients play in the diffusion process of a new drug. We hypothesize that patients can accelerate the diffusion of S/V by demanding repeat prescriptions and thus inducing adoption. Additionally, we assume that, due to social contagion and information transfer, physicians who share any patients with physicians who are already prescribing the new drug are more likely to adopt the new drug. Given the properties of the analyzed drug and the recommendations in the NVL, we are furthermore interested in whether the guideline modified the effect of patient flow. We assume that factors related to patient pathways have a stronger impact on the prescription of the drug to patients for whom it is not recommended than for patients for whom it is recommended.

The study at hand contributes to the literature by investigating the role of patients in the diffusion of new drugs. To this end, patient pathways are modeled and incorporated in four different survival analyses estimated based on routine data.

2 | MATERIALS AND METHODS

2.1 | Data source and population

The dataset was derived from the routine data of three regional health care funds belonging to the AOK group of statutory health insurers, covering four German federal states (Thuringia, Saxony, Hesse and Bavaria). In Germany, about 90% of the population is insured with a statutory health insurance and the AOK is one of the largest, covering about 42% of the population in the four federal states. The population insured with the AOK only differs slightly in terms of age and gender from the German population (Jaunzeme et al., 2013).

The analyzed data comprises information about ambulatory and hospital care as well as drug prescriptions and patient metadata from the years 2015–2017. Physicians are included in the analysis of adoption time if they prescribed S/V (ATC C09DX04) to one or more patients insured by these funds during the observation period. For the patients with at least one prescription of S/V, we were provided with a record of all reimbursed services in the ambulatory and hospital sector together with related diagnoses, procedures, and drug prescriptions. The patients receiving S/V were complemented by patients with a prescription from a select list of other drugs between 2013 and 2017 (see Appendix A). Compiling the covariates (see section on Explanatory variables) necessitated this extended patient population, which consists of approximately 14% of all those insured by the cooperating regional funds of the AOK. Additional information about regional characteristics at a district level were obtained from the Federal Institute for Research on Building, Urban Affairs and Spatial Development (BBSR) (Indikatoren und Karten zur Raum- und Stadtentwicklung [INKAR], 2020a, 2020b).

2.2 | Samples

In order to investigate the two stated effects of patient influence on the diffusion of S/V and the impact of the guideline recommendation on these effects, we consider four different samples of ambulatory physicians. Our observation period covers the 2 years after market admission (January 2016 to December 2017). We generally differentiate between two types of adoption: A physician might adopt the new drug either by prescribing a repeat prescription to a patient or by initiating therapy with the

new drug to a patient. In Sample 1 we include all adopting physicians irrespective of the type of adoption, whereas in Sample 2 we focus on physicians who adopted by initiating a medication. In Samples 3 and 4 we further subdivide the physicians who adopted by initiating a medication according to whether this first prescription was consistent with the NVL recommendations (Sample 3) or a potentially not recommended therapy (Sample 4). The Samples can be summarized as follows:

Sample 1: In the first sample ("all prescribers"), we include all physicians who prescribed S/V at least once during the observation period and consider the time of first prescription to be the time of adoption. This set describes the complete population of adopters in our dataset. The regression results enable conclusions about the effect of patients demanding repeat prescriptions.

Sample 2: In the "initial prescriptions" sample we include only those physicians who initiated a medication with S/V for at least one patient and define this month of first prescription as the time of adoption. By excluding physicians who only prescribe repeat prescriptions and focusing on the time of the initial prescription, we seek to provide insight into whether patients affect a physician's decision to initiate a medication with S/V by establishing connections among physicians.

Sample 3: In the "recommended initial prescriptions" sample we take from the population of Sample 2 those physicians whose first S/V prescription was consistent with the recommendations of the NVL, operationalized as patients being prescribed long-term medication of ACE-inhibitors.[1]

Sample 4: The last sample, the "not recommended initial prescriptions" sample comprises physicians whose initial S/V prescription was seemingly in conflict with the NVL guidance.

2.2.1 | Outcome variable

In order to analyze the diffusion of the new drug and in line with existing studies (Iyengar et al., 2011; Liu & Gupta, 2012; Manchanda et al., 2008; van den Bulte & Lilien, 2001; Zhang et al., 2019), we use the month of first prescription or initial prescription, as the time of adoption for each individual physician.

2.2.2 | Explanatory variables

We include the same set of covariates in all four samples, differentiating between *time-constant* and *time-varying* covariates.

Physician specialization, identified through the last two digits of the physician ID, is a *time-constant variable* and allows differentiation between cardiologists, internists, GPs, and other specialist areas. A further time-constant variable describes whether a physician operates in a solo practice, in a group practice or in several different practices. Physicians' characteristics have previously been found to influence the time of adoption. For example, specialists might adopt new drugs earlier than GPs (Liu & Gupta, 2012; Tamblyn et al., 2003). The reported effects of practice type (solo or group practice) on the time of adoption is inconsistent in the literature (Lublóy, 2014).

Two regional variables are added to the analyses to control for external influences, which might affect the physicians' adoption decision. From earlier studies it is known that hospital stays can influence a medication plan in the ambulatory setting (Feely et al., 1999; Gallini et al., 2012; Müller-Bühl et al., 2009), so we include the number of hospital beds per head of population in each district as a variable to control for this effect. Additionally, we add a dummy for whether a physician is operating in an urban or rural area, because previous studies have shown that a physicians' location may affect the time of adoption (Lublóy, 2014) in both directions. For instance, Bourke and Roper (2012) have shown that physicians from rural locations adopt new drugs later than physicians from urban areas whereas Greving et al. (2006) found that GPs from rural areas were more likely to prescribe new drugs than their colleagues from urban areas.

The *time-varying variables* are calculated on a monthly basis and are included in the model with a time lag of 1 month to enable inferences from the regression results and to ensure the covariate is not influenced by the outcome it is intended to predict.

In order to examine the effect of patients demanding repeat prescriptions, one covariate controls for whether a physician treated a patient with a prescription for S/V the month before. We distinguish between patients who received the prescription from a physician of the same practice and from a physician from another practice, in order to better differentiate between the patient's influence and possible practice effects.

Coleman et al. (1966) and Iyengar et al. (2011) used information on self-reported social networks of physicians to investigate the influence of social contagion. Diverging from this approach and following the idea of Donohue et al. (2018), we define

connections between two physicians based on the number of patients[2] they have in common. The number of shared patients is used to weight the strength of connection between two physicians, assuming that the strength of the connection increases with the number of patients they share (Barnett et al., 2011).

For each physician we examine a monthly weighted ego-network, which includes all physicians connected through shared patients in the extended patient population. In order to include only relevant ambulatory physicians in the ego-networks, we focused on physicians who prescribed a medication from the ATC "C09" group (agents acting on the renin–angiotensin system) at least six times during the observation period and at least once in 2016. The covariate of *number of neighbors*, which is defined as the number of physicians connected through at least one shared patient, approximates the monthly connectivity of each physician.

An *exposure value* is calculated in order to approximate the strength of the social contagion effect within the physicians' ego-networks. To derive the personal exposure values, the physicians' ego-network matrices are multiplied with the monthly computed vectors of connected adopters (Valente, 2005): The higher the proportion of connected adopters, the higher the physicians' exposure values, weighted by the strength of connection (in our case the number of shared patients). See Figure 1 for an example of an ego-network for a physician ***A*** who is connected to three other physicians, of whom one had adopted the drug in case (Figure 1a), two in (Figure 1b) and all in (Figure 1c). The resulting exposure values are presented as E_A. In the regression analyses we differentiate between five categorical groups of exposure values, to enable a better interpretation of results: I: 0%; II: (0%; 25%]; III: (25%; 50%]; IV: (50%; 75%] and V: (75%; 100%].

If physicians are part of a group practice, the prescribing behavior of colleagues within the same practice might influence their own prescribing behavior either by indirect mechanisms through exchange of expertize or directly by writing repeat prescriptions for commonly treated patients. We therefore include a covariate indicating whether a physician from the same practice had prescribed S/V in the month before.

2.3 | Statistical method

In order to identify accelerating factors in the diffusion process of S/V, we apply a survival model to our dataset. Survival analysis is applied when the aim is to examine the time at which an event of interest occurs. There exists a broad range of models that can be used to analyze these event history data and the model selection depends on the time structure of the dependent and independent variables.

In our case, the independent variable and thus the event of interest is the time at which each physician first prescribed S/V. As described before, the time of adoption is measured on a monthly basis, even though the real time of adoption for each physician might occur on different days within this interval. We thus have a time-interval-censored data structure, in which adoption time is aggregated per month and measured since market admission.

Additionally, we aim to include time-varying independent variables, as we know that the physicians' patient pool changes every month and so do their patient-sharing networks and the covariate of patients with a prior S/V therapy. We also assume

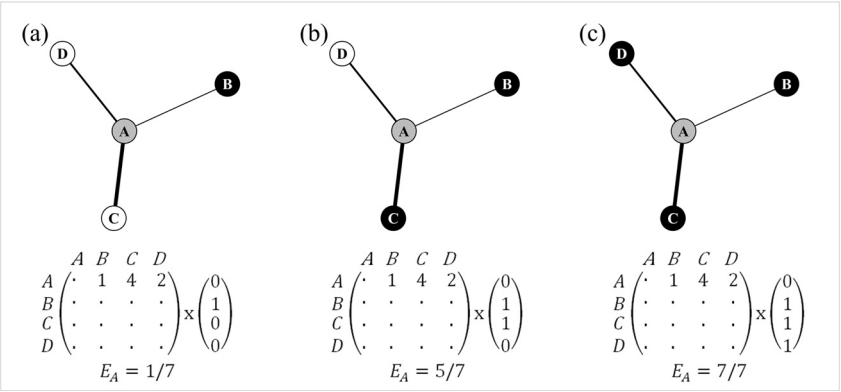

FIGURE 1 Examples for weighted exposure values. Vertices depict physicians and edges the shared patients. The matrix comprise the numbers of shared patients between two physicians. The black vertices are physicians who adopted until the period $t-1$. We calculate the exposure values for physician ***A*** in three different scenarios: (a) Physician ***B*** has adopted, (b) Physicians ***B*** and ***C*** have adopted and (c) Physicians ***B***, ***C*** and ***D*** have adopted. E_A is the resulting weighted exposure value for physician *A* in the three scenarios.

and know by estimating our model that some effects of covariates are not constant over time. Models that assume proportional hazards for the whole observation period, as for example, the Cox proportional hazard model does, are therefore not applicable.

Since our dataset of physicians comprise all prescriptions since market admission, the data has no left-censoring, whereby individuals would be excluded who may have experienced the event before the observation began. Right-censoring means that there are individuals in the dataset who do not experience the event during the observation period but who might do in the future. As prescribing S/V at least once is an inclusion criterion, our data are not right-censored either. We may therefore apply a generalized linear model (GLM), with the monthly reported binary response of adoption as the outcome variable and a complementary log-log link function. The advantage of this link function is that the exponentiated estimated regression coefficients can be interpreted as hazard ratios (HR) (Austin, 2017; Tutz & Schmid, 2016).

For the estimation of the selected model and the included independent variables, the dataset needs to be organized in a physician-month format, which means that each physician has one row for each month until he or she adopts.[3]

The result of interest obtained from the survival model is the hazard rate for the occurrence of an event at a specific time point, given that it has not occurred until then, and how this hazard is affected by the covariates. Formally, the hazard rate is given by:

$$h_{it} = \text{prob}(T_i = t | T_i \geq t; X_{it}) \tag{1}$$

in which h_{it} defines the hazard rate of physician i in month t.

The regression equation of the complementary log-log link function is then given by:

$$\log\left[-\log(1 - h_{i,t})\right] = \beta_0 + \beta_1 x_{1,it} + \ldots + \beta_n(x_{n,it}) + e_{it} \tag{2}$$

In Equation (2) the betas are the coefficients to be estimated, e describes the error term and the vector X comprises all covariates for each physician, some of them being constant and others varying over time.

In order to control for a possible nonlinear time trend, we included a smooth function for time measured in months since market admission. The smooth functions have the advantage that one doesn't have to specify the functional relationship between time and hazard rate and the function is more flexible than assuming, for example, a polynomial association. The generalized additive model (GAM) framework allows to estimate these associations between dependent and independent variables in flexible manner, without assuming a linear relationship (Hastie & Tibshirani, 1986). We applied the function *gam* from the R package *mgcv* (Wood, 2020) and used thin plate regression splines for the smooth functions (Wood, 2017).

The regression equation of the GLM in Equation (2) in terms of a GAM looks as follows:

$$\begin{aligned}\log\left[-\log(1 - h_{i,t})\right] = \beta_0 + f_0(t) + f_1(t)x_{1,it} + \beta_1 x_{1,it} + \ldots \\ + f_m(t)x_{m,it} + \beta_n x_{n,it} + e_{it}\end{aligned} \tag{3}$$

in which $f_0(t)$ is the smooth function for time, the *betas* are still the coefficients to be estimated and the vector X comprise the remaining covariates. As we assume time varying effects for selected covariates, we estimate a smooth function for time per covariate by including a "smooth-factor" interaction for each of these variables (Wood, 2017). They are represented by the $f_1(t)x_{1,it} + \ldots + f_m(t)x_{m,it}$ part of the regression function (3). For the following covariates we expected a time varying effect and respectively include a "smooth-factor" interaction: exposure value, patient effect, practice type and specialization.

As a sensitivity analysis, we also applied the GLM to the data and found comparable results with respect to our main variables. We therefore focus on presenting the GAM results and report the results of the GLM in Appendices F and G.

3 | RESULTS

In total, 7533 physicians prescribed at least once S/V and 9585 patients received the drug during the observation period. Figure 2 presents for each of the four samples the number of new adopters in each month.[4]

Sixty five percent of all prescribing physicians ($n = 4878$) initiated medication with S/V for at least one patient during the observation period, of which 2825 (58%) were identified as initial prescriptions that seem to be consistent with the guidelines of the NVL.

The number of new S/V prescribers per month rises in the first 6 months after market admission in January 2016 to reach a peak of 400 new adopters in June 2016 (Sample 1). The number then falls to approximately 325 new adopters in September 2016 before stabilizing at a level between 300 and 350. The number of physicians who initiate S/V therapy for the first time

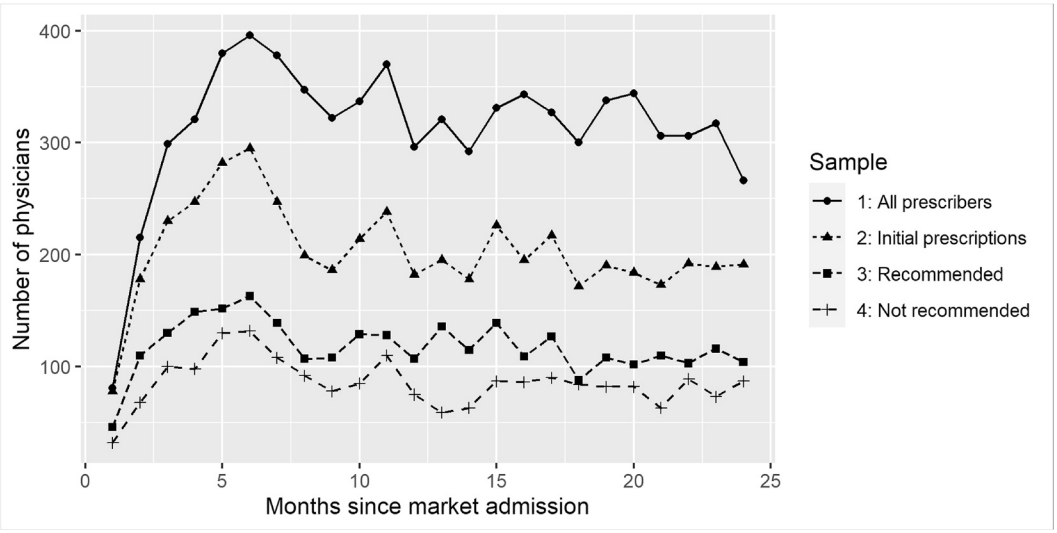

FIGURE 2 Number of adopters per month. The figure summarizes the number of adopters of S/V per month: Sample 1 includes all physicians who prescribed S/V at least once and the month of adoption is the month of first prescription; sample 2 includes physicians who initiated a medication with S/V for at least one patient; sample 3 includes physicians who initiated a "recommended" medication with S/V; sample 4 includes physicians who initiated a "not recommended" medication.

(Sample 2) follows a similar pattern, with about 100 fewer physicians per month in comparison with the full model. The number of adopters with initial prescription seemingly consistent with the guideline recommendation (Sample 3) and seemingly not consistent (Sample 4) are similar in size, with a slightly higher number of physicians initiating a recommended S/V therapy.

For the regression analyses, we excluded 335 physicians who could not be assigned to a district due to missing data. The summary statistics of the four samples are presented in Table 1. In the upper part of the table, summaries of the time-constant variables are shown. It can be seen that the proportions of covariates do not differ substantially between the four samples. Small differences occur, for example, in the distribution of physicians' specializations (e.g., 87% of physicians in Sample 4 [not recommended prescriptions] are GPs versus 83% in Sample 3 [recommended prescriptions]).

The time-varying covariates are summarized in the lower part of the table. The composition of the covariates differs only slightly between the samples with, for example, 24% of physician-months with 0% connected adopters in the sample with all prescribers compared to 22% of physician-months in the other samples. The proportion of physician-months for which a physician had not treated a patient with a prescription of S/V the month before adoption is constant at about 95%. For Sample 3 (recommended prescriptions), 1.76% of patients received their prior S/V therapy from a colleague in the same practice, compared with 1.30% for Sample 4 (not recommended prescriptions).

The regression results are depicted in Table 2 and comprise the estimated HR for the included covariates along with their *p*-values. HR indicate the ratio of hazard rates for two individuals who differ only with respect to the covariate under investigation, all other covariates being equal.

The HRs for the exposure values are significant in all four samples. In Sample 1, including both types of adoption, the effect increases with the proportion of adopters in the physician's network. This sample sees the largest effect size, with a HR of 2.8 for physicians with more than 75% of adopters in their ego-network, as compared to physicians with zero adopters. The smallest effect of the exposure values in all categories occurs in Sample 3, which includes physicians who adopted by initiating medication with S/V to patients for whom it was seemingly recommended by the guideline.

The effect of patients demanding a repeat prescription is strongly positive and significant in Sample 1. A physician who treated a patient with prior S/V therapy has a HR of 3.4 as compared to a physician who has not treated a patient with prior S/V therapy. The effect is estimated to be stronger if a colleague from the same practice prescribed S/V than when a physician from another practice issued the prescription. The treatment of a patient with prior S/V therapy from a colleague has a smaller estimated impact on the time of adoption when focusing on adoptions through initial prescriptions (Samples 2–4). The treatment of patients with prior S/V therapy from a physician from a different practice has no significant effect on the adoption time in these samples (Samples 2–4).

Physicians working in group practices are estimated to have a smaller hazard rate to adopt than do physicians in solo practices. This effect is significant in all four samples. Working in several different practice locations does not significantly influence the hazard to adopt.

TABLE 1 Descriptive results

	Sample 1 (all prescribers)		Sample 2 (initial prescriptions)		Sample 3 (recommended prescriptions)		Sample 4 (not recommended prescriptions)	
	Mean [min; max] absolute (%)		Mean [min; max] absolute (%)		Mean [min; max] absolute (%)		Mean [min; max] absolute (%)	
Number of adopting physicians	***n* = 7198**		***n* = 4689**		***n* = 2718**		***n* = 1980**	
Month of adoption	12.72	[1; 24]	12.26	[1; 24]	12.24	[1; 24]	12.27	[1; 24]
Practice type								
Solo practice	1823	(25.33%)	1349	(28.71%)	760	(27.96%)	589	(29.75%)
Several practices	60	(0.83%)	36	(0.77%)	14	(0.52%)	22	(1.11%)
Group practice	5315	(73.84%)	3313	(70.52%)	1944	(71.52%)	1369	(69.14%)
Medical specialization								
General practitioners	6217	(86.37%)	3989	(84.91%)	2260	(83.15%)	1729	(87.32%)
Internal medicine	197	(2.74%)	136	(2.89%)	77	(2.83%)	59	(2.98%)
Cardiology	613	(8.52%)	485	(10.32%)	330	(12.14%)	155	(7.83%)
Other	171	(2.38%)	88	(1.87%)	51	(1.88%)	37	(1.87%)
Urban area	3163	(43.94%)	1947	(41.44%)	1119	(41.17%)	828	(41.82%)
Rural area	4035	(56.06%)	2751	(58.56%)	1599	(58.83%)	1152	(58.18%)
Hospital beds (per 100,000 pop.)	627.75	[0; 2986]	627.67	[0; 2986]	627.69	[0; 2986]	627.65	[0; 2986]
Number of physician-months (rows)	**91,593**		**57,580**		**33,278**		**24,302**	
Exposure value[a]								
0%	22,170	(24.20%)	12,888	(22.38%)	7426	(22.32%)	5462	(22.48%)
≤25%	40,092	(43.77%)	24,846	(43.15%)	14,587	(43.83%)	10,259	(42.21%)
≤50%	16,479	(17.99%)	10,837	(18.82%)	6256	(18.80%)	4581	(18.85%)
≤75%	9697	(10.59%)	6916	(12.01%)	3908	(11.74%)	3008	(12.38%)
≤100%	3155	(3.44%)	2093	(3.63%)	1101	(3.31%)	992	(4.08%)
Number of neighbors[b]	16.42	[0; 261]	17.39	[0; 261]	17.75	[0; 184]	16.90	[0; 261]
Patient with prior S/V therapy[c]								
None	87,173	(95.17%)	54,983	(95.49%)	31,651	(95.11%)	23,332	(96.01%)
From the same practice	1568	(1.71%)	901	(1.56%)	585	(1.76%)	316	(1.30%)
From another practice	2852	(3.11%)	1696	(2.95%)	1042	(3.13%)	654	(2.69%)
Prescription of a colleague[d]								
No	50,989	(55.67%)	33,022	(57.35%)	18,771	(56.41%)	14,251	(58.64%)
Yes	40,604	(44.33%)	24,558	(42.65%)	14,507	(43.59%)	10,051	(41.36%)

[a]Exposure value is the proportion of physicians who are connected through shared patients and who have already prescribed S/V.

[b]Number of neighbors is the number of physicians who are connected through shared patients.

[c]This variable indicates whether the physician treated a patient with prior S/V therapy the month before prescribing S/V.

[d]Colleague refers to a physician from the same practice.

The peer effect of a colleague from the same practice who has prescribed S/V in the previous month is positive in all four samples but only significant in Sample 1, which includes both types of adoptions, and Sample 4, which includes only those adoptions that seemingly did not follow guideline recommendations.

Physicians in rural areas are estimated to have a slightly higher hazard rate to adopt than physicians in urban areas, with HRs ranging between 1.08 for Sample 1 and 1.10 for Sample 4.

Finally, the effects of the selected covariates vary with time, as, for example, the estimated smooth functions are significant for the exposure value categories 1 and 2 in Sample 1 (see Appendix D). Because of the nonlinear link function, the estimated effects of the smooth functions cannot be summed up easily in order to get a total effect for specific time points. We therefore report the complete list of estimated smooth functions in Appendix D.

TABLE 2 Regression results with spline function for time and "smooth-factor" interactions

	Sample 1 (all prescribers) $n = 7198$		Sample 2 (initial prescriptions) $n = 4698$		Sample 3 (recommended prescriptions) $n = 2718$		Sample 4 (not recommended prescriptions) $n = 1980$	
	HR	***p*-value**	**HR**	***p*-value**	**HR**	***p*-value**	**HR**	***p*-value**
Exposure value (ref. 0%)[a]								
≤25%	1.593	0.000	1.298	0.000	1.190	0.006	1.452	0.000
≤50%	2.043	0.000	1.343	0.000	1.263	0.002	1.450	0.000
≤75%	2.736	0.000	1.436	0.000	1.335	0.001	1.619	0.000
≤100%	2.755	0.000	1.261	0.054	1.224	0.222	1.325	0.111
Number of neighbors[b]	1.002	0.007	1.003	0.005	1.003	0.036	1.003	0.069
Patient with prior S/V therapy (ref. none)[c]								
From the same practice	3.351	0.000	1.511	0.003	1.438	0.047	1.436	0.079
From another practice	2.760	0.000	1.127	0.238	1.108	0.410	1.102	0.578
Practice type (ref. solo practice)								
Several practices	0.906	0.547	1.131	0.504	0.841	0.603	1.373	0.162
Group practice	0.881	0.001	0.875	0.003	0.874	0.022	0.878	0.060
Prescription of a colleague[d]	1.176	0.000	1.068	0.100	1.013	0.809	1.135	0.039
Medical specialization (ref. GP)								
Internal medicine	1.178	0.049	1.172	0.101	1.192	0.171	1.103	0.515
Cardiology	1.641	0.000	1.468	0.000	1.530	0.000	1.354	0.002
Other	0.901	0.306	0.982	0.888	0.989	0.948	0.931	0.728
Rural area (ref. urban)	1.081	0.002	1.090	0.005	1.086	0.043	1.100	0.046
Number of hospital beds	1.000	0.662	1.000	0.533	1.000	0.632	1.000	0.767
Intercept	0.032	0.000	0.053	0.000	0.056	0.000	0.047	0.000
Smooth terms								
Time (in months)	Yes		Yes		Yes		Yes	
Time per exposure Value	Partly		Partly		No		Partly	
Time per patient with prior S/V therapy	Partly		No		No		No	
Time per practice type	Partly		Partly		Partly		No	
Time per medical specialization	Partly		Partly		Partly		Partly	

Note: The complete table of regression result is available in Appendix D. The indication for significance of the smooth terms in this table (yes, partly, no) refers to the significance level of 10%.

[a]Exposure value is the proportion of physicians who are connected through shared patients and who have already prescribed S/V.

[b]Number of neighbors is the number of physicians who are connected through shared patients.

[c]This variable indicates whether the physician treated a patient with prior S/V therapy the month before prescribing S/V.

[d]Colleague refers to a physician from the same practice.

4 | DISCUSSION

The present study investigates the effect of patient pathways on the diffusion of new drugs in the ambulatory care sector. We were particularly interested in how patients accelerated the adoption of *Sacubitril/Valsartan* among ambulatory care physicians via two different mechanisms, and how these effects were related to guideline recommendations.

The regression results of Sample 1 confirm a significant effect of a patient's pre-existing S/V therapy on the physicians' time of adoption. This effect was observed independently of whether the patient had previously received the S/V prescription from a colleague in the same practice or from a physician in another practice. Thus, patients seem to influence the adoption of S/V by physicians. This is consistent with the assumption of demand-induced repeat prescriptions, although this effect might not be the result of a direct request for a specific drug, as was observed in the United States by McKinlay et al. (2014). In particular, it is important to note that in Germany, in contrast to the United States, no direct-to-consumer advertising is allowed for

prescription drugs. However, we do find evidence that patients induce physicians to start prescribing the new drug through repeat prescriptions.

In order to disentangle the effect of patients demanding repeat prescriptions and the effect of social contagion, Sample 2 considers only those adoptions that resulted from initial patient prescriptions. Focusing on this type of adoption allows to examine the effect of contagion among physicians on the physician's choice for a new drug compared to standard therapy. The results of Sample 2 confirm the assumed effect of contagion within patient-sharing physician networks because the estimated coefficients of the exposure values are positive and significant. Being connected to many physicians who are already prescribing S/V increases the probability that a physician initiates the S/V prescription for another patient. This finding is in line with the results of Arnold et al. (2021) who analyzed the effect of being connected to other physicians prescribing S/V on the probability to prescribe S/V in another German federal state.

It is important to note that the cause of the observed contagion effect cannot be conclusively be determined as either resulting from professional exchange among physicians or through information transfer along patient pathways. Patients who receive a prescription for S/V from a physician in the first instance and then subsequently get a repeat prescription from another physician automatically build a connection between the two physicians in the network. On the basis of the available data, it is not possible to determine whether a physician decides to prescribe S/V to another patient because he or she learned about the new drug's availability and effectiveness through the patient with a previous prescription of the drug, or through professional exchange with colleagues within patient-sharing networks. However, the connections within the ego-networks also comprise a large number of patients without any prescription for S/V, such that the patients with prior S/V therapy represent only a small proportion of the shared patients. Connections among physicians might also be established that contain no patients with prior S/V therapy. The significant effect for treating patients with prior S/V therapy and for the exposure values in the initial prescription sample (Sample 2) point to the coexistence of a diffusion effect through information transfer and an effect of social contagion among physicians.

Regarding our interest in whether the patient effects for recommended and potentially not recommended initial prescriptions are different, it is remarkable that the estimated HRs of the exposure values in Sample 4 (not recommended prescriptions) are systematically higher than those in Sample 3 (recommended prescriptions). This result suggests that contagion within patient-sharing networks has a slightly stronger influence in cases where the physician's first prescription was seemingly not guideline adherent.

A previous prescription by a colleague, which could be interpreted as a peer effect, is only significant in Sample 1 (when adoption via repeat prescriptions is considered) and Sample 4 (with potentially non-guideline adherent prescriptions). The size of peer effect is smaller in Sample 4 than in Sample 1 and it is important to note that it might be contained within the contagion effect in patient-sharing networks, assuming that physicians from the same practice also share a reasonable number of patients.

In order to better differentiate between network and practice effects, we conducted additional sensitivity analyses, with the exposure values calculated under the exclusion of physicians from the same practice (see Appendix E for the regression results). The estimated HRs for the exposure values in these sensitivity analyses are systematically smaller compared to the initial samples. Furthermore, the effect of a colleague from the same practice prescribing S/V in the previous month has a small but significant positive effect in Samples 1, 2 and 4. This finding suggests that a contagion effect among colleagues exists even if we exclude physicians adopting through repeat prescriptions, and that it plays only a subsidiary role when analyzing initial prescriptions in concordance with the NVL (Sample 3).

The effect of specialists' prescriptions on the prescribing behavior of GPs has been discussed in the literature (Florentinus et al., 2009; Garjón et al., 2012; Glass et al., 2004; Huskamp et al., 2013; Iyengar et al., 2011; Lin et al., 2011; Liu & Gupta, 2012; Lo-Ciganic et al., 2016; Ruof et al., 2002; Zullig et al., 2019) and was not the focus of our study. However, our results indicate that specialists (i.e., cardiologists and internists) have higher hazard rates for S/V adoption than do GPs, with a significant change over time for the cardiologists.

Our study has several important limitations, which must be taken into account when interpreting our results. First, our data lack information that has been shown to influence diffusion processes. These are mainly physician characteristics (e.g., age, gender, nationality) (Bourke & Roper, 2012; Huskamp et al., 2013; Steffensen et al., 1999; Tamblyn et al., 2003; Zhang et al., 2019) and information about the marketing activities and payed incentives of pharmaceutical firms (Carey et al., 2021; Liu & Gupta, 2012; Manchanda et al., 2008; van den Bulte & Lilien, 2001). The effect of payments by pharmaceutical firms has been found to affect physicians' peers in social networks and their decision to prescribe drugs (Agha & Zeltzer, 2019). Marketing activities are known to accelerate diffusion of new drugs and were shown to decrease social contagion effects (van den Bulte & Lilien, 2001). Even though we tried to control for regional varying marketing activities in rural and urban areas, our findings of social contagion could be overestimated. In addition, unknown confounding variables might exist, which were not considered in our analyses and might therefore bias the estimated effects of our covariates.

Second, even though our dataset includes patients from the largest SHI insurance companies per federal state, we may lack information on physicians who have prescribed S/V to other patients. Similarly, we might have missed some connections

between physicians who only share either patients from other insurances companies or patients not included in our dataset. Both facts might have biased our results in underestimating an existing contagion effect or by missing potential earlier adopters.

Third, routine data are collected for billing purposes and quarterly fixed payments often cover consultations on multiple days. For this reason, while information about the exact treatment day is available in the dataset, the billing data does not necessarily comprise all physician visits. As a result, we might have an incorrect or incomplete chronological sequence of physician visits, which could have underestimated the exposure values or the treatment of patients with prior S/V therapy. Additionally, routine data does not include information about prescriptions issued during a hospital stay, thus we might have missed information about patients being prescribed with S/V in hospital.

Finally, we tried to approximate the recommended S/V therapy with 365 daily-defined doses of ACE inhibitors and/or ARB-therapy over the previous year. Additionally, due to the often unspecific nature of diagnoses coded in the ambulatory care sector, we did not consider patients' NYHA class, which might have led to some patients with NYHA class I being falsely classified as having guideline-consistent S/V therapy. In a real-world setting, these criteria may not correspond to a relevant difference with respect to guideline consistency. However, this definition allowed us to distinguish between the effects due to patients with recommended and potentially not recommended prescriptions.

5 | CONCLUSIONS

Our study investigated two different ways in which patients influence physicians' prescribing behavior and thereby influence the diffusion of new drugs among ambulatory physicians. We showed that patients with prior prescription of a new drug induce its adoption by more physicians through repeat prescriptions. Additionally, we find evidence for a contagion effect within networks of physicians that are established through patient pathways. The effect is stronger when physicians do not strictly follow medical guidelines. The findings therefore suggest that patient pathways play a significant role in the diffusion of a new drug in ambulatory care.

Thus, physicians may need more guidance on what to consider when patients demand new drugs, in case of repeat prescribing and when they share responsibility for the same patient population. It might be helpful to address these situations in medical guidelines. In addition, routine analyses of prescribing behavior in networks may support good practice in prescribing by providing physicians and stakeholders with important information.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the three cooperating statutory health insurances (AOK PLUS, AOK Bavaria and AOK Hesse). Restrictions apply to the availability of these data, which were used under license for this study (Innovation Fund project “WirtMed study”). Data are available from the corresponding author upon reasonable request and with permission of the statutory health insurances and their supervisory authorities.

ETHICS STATEMENT

The present study was a secondary data analysis and therefore did not need an ethics approval. The following Ministries in their role as supervisory authorities of the statutory health insurances approved the utilization of the data: Bavarian State Ministry for Health and Care, Hessian Ministry for Social Affairs and Integration and Saxon State Ministry for Social Affairs and Consumer Protection. The legal basis for the processing was given by the Section 75 of Book X of the German Code of Social Law.

ORCID

Ronja Flemming https://orcid.org/0000-0003-3123-1808

ENDNOTES

[1] In order to define a set of patients who would potentially profit from taking S/V we controlled for their medication in the year before and defined those prescriptions as medically recommended, which were prescribed to patients who had received at least 365 daily doses ACE inhibitors and/or ARB-therapy (ATC C09A/B/C/D).

[2] Patients refer to all included patients in the dataset. See section Data source and population for the description.

[3] Appendix B summarizes the included explaining variables and gives an example of three physicians, who adopted in the third month (physicians A and B) and the first month (physician C).

[4] The Kaplan-Meier curves of adoption are available in Appendix C.

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