Use of Electronic Medical Records in the Epidemiological Research

Silvia Dombrowski
Karel Kostev

Cuvillier Verlag Göttingen
Internationaler wissenschaftlicher Fachverlag

Use of Electronic Medical Records in the Epidemiological Research

Use of Electronic Medical Records in the Epidemiological Research

Silvia Dombrowski, Karel Kostev

Bibliographical information held by the German National Library
The German National Library has listed this book in the Deutsche Nationalbibliografie (German national bibliography); detailed bibliographic information is available online at http://dnb.d-nb.de.
1st edition - Göttingen: Cuvillier, 2017

Nonnenstieg 8, 37075 Göttingen, Germany
Telephone: +49 (0)551-54724-0
Telefax: +49 (0)551-54724-21
www.cuvillier.de

1st edition, 2017
This publication is printed on acid-free paper.

ISBN 978-3-7369-9500-0
eISBN 978-3-7369-8500-1

Table of contents

Introduction

Medical record databases are longitudinal patient record databases that are used by health care providers in caring for their patients and that are anonymized for the purpose of research. Data from such retrospective databases allow for investigations into specific subpopulations – e.g., groups with specific diagnoses – thanks to their size and duration of observation. Regarding the quality of such data, it has been proven that carefully planned observational studies can produce results comparable to those of randomized controlled trials.

Patient and health care databases are available in many countries and are often based on routinely collected diagnosis and prescription data. Over time, patient data from such databases have been linked with each other via pseudonyms and then analyzed. In Germany, examples of these databases include not only several statutory health insurance (SHI) databases but also commercial databases like the QuintilesIMS Disease Analyzer database. These databases can be used to evaluate important questions concerning health services, such as whether therapy regimens being applied reflect the current state of scientific knowledge or whether supply shortages, surpluses, or mismatches occur. Using these databases, numerous studies have been conducted to analyze the duration, adverse effects, success, costs, and courses of and compliance with therapies and therapy changes. These studies also play an important role in drug safety and risk prevention. A sufficiently valid database is required in order to be able to guarantee the scientific relevance of epidemiological studies.

Data from German SHI bodies have been identified as an important data source for pharmacoepidemiological studies (Hoffmann, 2009), but so far, only a few German data sources have been presented transparently to the scientific community (Pigeot & Ahrens, 2008). Andersohn and Walker were able to show the good overall agreement between the SHI

database and the German population in terms of morbidity, mortality, and drug usage. The demographic structure of insurants was slightly different than that among the German population, with the database population being younger and with eastern parts of Germany being underrepresented. There was a high persistence of insurants with the database over time, indicating suitability of the data source for longitudinal epidemiological analyses (Andersohn & Walker, 2016).

QuintilesIMS Disease Analyzer is one of the major European patient databases. It contains data from Germany, the UK, and France and allows for anonymous access to a selected panel of physicians' practices and patients. The data are generated directly from the computers in the physicians' practices via standardized interfaces and provide daily routine information regarding patients' diseases and therapies. A practice transmits patient data stored in the physician's computer to IMS on a monthly basis. Before transmission, the data are encrypted for data protection purposes and contain in similar scope and detail the information in the files of patients in the doctor's practice. Patients and practices can be analyzed in a cross-sectional and longitudinal fashion. In Germany, the database contains data from more than 2,000 practices and more than 20 million patients. In addition to data from general practitioners and specialists in internal medicine, data for various specialist groups are also recorded in Germany. The database includes only anonymized data in compliance with the regulations of the applicable data protection laws.

The sampling method for the Disease Analyzer database is based on summary statistics from all physicians in Germany published every year by the German Medical Association. The statistical unit of IMS uses these statistics to determine the panel design according to the following categories: specialist group, German federal state, community size category, and age of physician.

This panel design forms the basis for the acquisition of the practices processed in the Disease Analyzer. The acquisition of and support for the practices is performed by cooperating software companies using a standardized interface that enables the practices to collect the required data and send them to IMS in an anonymized form. To account for natural fluctuations in the practices and an annual check of the summary statistics by the German Medical Association, the panel design is adjusted each year. Whenever a practice ends its collaboration with IMS, it is replaced by a new one. Altogether, eleven specialist fields are taken into account in the random sampling plan. For this purpose, the field of internal medicine has been subdivided into five subgroups. Furthermore, the field of neurology also includes pediatric and adolescent psychiatrists.

The sampling plan is subdivided into eight regions, which are summaries of the 16 German federal states. This stratification results in 176 cells derived from the summary statistics with regard to specialist fields and proportional to the summary statistics with regard to the German federal states. Within each specialist field, at least 30 doctors must be sampled. Within each region, a minimum of seven physicians must be sampled within each specialist field to allow for estimates at the specialist field level for each region (Ogdie et al., 2012).

The main strength of studies based on the Disease Analyzer database is the large number of patients available for analysis. Another strength is the use of real-world data in primary care practices where diagnoses are continuously documented, allowing for an unbiased exposure assessment without recall bias.

The Disease Analyzer database has been the basis of a large number of peer-reviewed scientific publications in the fields of epidemiology, health economics, pharmacovigilance, compliance/persistence, pharmaceutical guidelines, prescribing behavior, and drug application. This book

presents several epidemiological and health-economic studies based on the Disease Analyzer database published between 2010 and 2016.

References

Andersohn & Walker 2016:
Andersohn F,
Walker J Characteristics and external validity of the German Health Risk Institute (HRI)
Database. Pharmacoepidemiol Drug Saf. 2016 Jan;25(1):106-9

Hoffmann 2009:
Hoffmann F.
Review on use of German health insurance medication claims data for epidemiological research
Pharmacoepidemiol Drug Saf 2009; 18(5):349-356.

Ogdie et al. 2012:
Ogdie A, Langan S, Parkinson J, Dattani H, Kostev K, Gelfand JM.
Medical Record Databases
In: Strom BL, Kimmel S, Hennessy S, eds. Pharmacoepidemiology. 5th ed. Philadelphia, PA; University of Pennsylvania; 2012: 224-43

Pigeot & Ahrens 2008:
Pigeot I, Ahrens W.
Establishment of a pharmacoepidemiological database in Germany: methodological potential, scientific value and practical limitations
Pharmacoepidemiol Drug Saf 2008; 17(3): 215-223.

Chapter 1. Diabetes

Predictors for the initiation of basal supported oral therapy in type 2 diabetic patients

The study by Kostev et al. assessed the predictors for the initiation of basal supported oral therapy (BOT) in type 2 diabetic patients under real-life conditions. The study included 194,967 patients with type 2 diabetes mellitus on oral antidiabetic drug (OAD) therapy. A total of 24,964 patients were switched to BOT during the observational period. The probability of switching to insulin therapy was associated with three main predictors. These were (1) poor metabolic control, (2) middle age, and (3) number and type of OAD before insulinization. The variation of the HbA1c threshold to HbA1c ≥ 7.5 led to comparable outcomes with significant HR. The highest probability of initiating basal supported oral therapy under real life conditions was found for patients with poor metabolic control, middle age, and pre-treatment with specific OADs such as SU, GLI or AGI before initiation of insulin therapy. Previous studies were fairly comparable to these findings [Kostev et al. 2012a].

Duration of first prescribed long-acting insulin therapy in type 2 diabetes

Kostev investigated the duration of first insulin use in type 2 diabetes. A total of 13,503 diabetes patients were identified who were prescribed insulin for the first time between 2000 and 2010 after oral antidiabetic therapy in primary care practices: 7,428 commenced treatment with glargine, 1,174 with detemir, and 4,901 with NPH. The chance of a treatment change was significantly higher for female patients, older people, patients with private health insurance coverage, and patients

with higher HbA1c values. The data confirmed the results of other studies [Kostev 2012].

Changes in type 2 diabetes mellitus patients in German primary care practices prior to (2006) and after (2010, 2014) the launch of new drugs

The study of Jacob et al. analyzed the changes in a German type 2 diabetes population prior to (2006) and after (2010, 2014) the launch of new drugs. Patients with T2DM in 2006, 2010, and 2014 were recruited for the study. Demographic data included age, gender, and health insurance type (private/statutory). Drug prescriptions, mean costs per patient, HbA1c levels, macrovascular complications, and time before first insulin prescription were analyzed. The study found that prescriptions for new T2DM drugs increased between 2006 and 2014. The new drugs analyzed in this study had positive effects on HbA1c levels, macrovascular complications, and mean time before first insulin treatment. In total, 64,098, 77,219, and 85,004 T2DM patients were included for 2006, 2010, and 2014, respectively. The mean age, proportion of men, and proportion of patients with private health insurance coverage differed significantly for each of the 3 years. There was a 1.25-fold increase in the total costs per patient, linked with an increase in the costs associated with the use of new drugs and a decrease in the costs associated with the use of old drugs. HbA1c levels were slightly better regulated in 2014 than in 2006 and 2010. The percentage of patients with macrovascular complications decreased significantly over time, dropping from 27.4% in 2006 to 24.6% in 2014. The mean duration before first insulin treatment increased from 1,225 days in 2006 to 1,406 days in 2014. The results were in line with the literature [Jacob et al. 2015].

Influence of macro- and microvascular comorbidities on time to insulin initiation in type 2 diabetes patients in Germany, France, and the UK

Kostev et al. investigated if micro- and macrovascular comorbidities have an influence on the time to insulin initiation in type 2 diabetes patients. From 1995 to 2009, 44,440 patients in Germany, 10,148 patients in France, and 25,499 patients in the UK with newly diagnosed diabetes (index date) and treated in general practices were analyzed. The association of newly diagnosed micro- and macrovascular complications (ICD-10) on the time to insulin initiation adjusted for age, sex, antidiabetic therapy, and comorbidities (hypertension, lipid disorders) was examined. In primary care practices (Germany, France, UK) the diagnosis of a microvascular complication or coronary heart disease was associated with a higher likelihood of initiating insulin therapy in type 2 diabetes. Patients on oral hypoglycemic agents were more likely to start insulin therapy, except for DPP-4 inhibitor users, who were less likely than patients on biguanides to progress to insulin. Insulin treatment was started in 9,747 (22%) patients in Germany within 10 years after the index date (France: n=702, 7%; UK: n=3,936, 14%). In all three countries, the occurrence of microvascular complications (neuropathy, nephropathy) was significantly associated with a higher likelihood of receiving insulin. Among macrovascular complications, only coronary heart disease was related to insulin initiation in all three countries. In primary care practices in Germany, France, and the UK, type 2 diabetes patients who developed microvascular complications or coronary heart disease were more likely to receive insulin. The study showed that the use of DPP-4 inhibitors may delay the use of insulin in primary care patients. The findings were similar to previous studies [Kostev et al. 2013a].

Changes in time to insulin initiation in type 2 diabetes patients in Germany and the UK

Another study by Kostev et al. analyzed whether the time to insulin therapy in type 2 diabetic patients in primary care practices in Germany and the UK has increased. Patients who started their insulin treatment between 2005 and 2010, including 6,368 patients in Germany and 1,998 patients in the UK, were analyzed with regard to the time elapsed from their first diabetes diagnosis in the practices (index date) to the first insulin prescription they received. The time to start of insulin therapy in type 2 diabetes patients significantly increased from 2005 to 2010 in primary care practices in both Germany and the UK. The median time to insulin therapy in the practices increased significantly, from 943 days in 2005 to 1,549 days in 2010. In the UK, the time to onset of insulin treatment increased significantly, from 1,700 days in 2005 to 2,061 days in 2010. The last HbA1c values prior to insulin initiation were high and slightly increased during the study period (Germany: 8.2% in 2005 and 8.4% in 2010; UK: 9.5% in 2005 and 9.8% in 2010). This was the first primary care study that showed an increase in the duration to insulin therapy initiation in European patients with type 2 diabetes [Kostev et al. 2013b].

Different injection frequencies of basal insulins in type 2 diabetes patients

The study by Rathmann et al. compared injection frequencies of basal insulins in type 2 diabetes in primary care practices, both for basal supported oral therapy (BOT) and basal-bolus treatment [intensified conventional therapy (ICT)] regimens. Data from 4,211 glargine (BOT/ICT, 2,247/1,964), 1,290 detemir (490/800), and 3,876 NPH (1,331/2,425) insulin users were retrospectively analyzed (May 2009-April 2012). Glargine was associated with significantly lower injection frequencies than other basal insulins. Overall, a frequency of >1 daily

injections was observed in 7.5% of glargine users, which was lower than for detemir and NPH insulin users. The adjusted odds of having >1 injection were lower for glargine users than for detemir and NPH-insulin users. Similar results were found for BOT and ICT and after propensity score matching. The outcomes were in line with other studies [Rathmann et al. 2013a].

Predictors of insulin initiation in metformin and sulfonylurea users in primary care practices: The role of kidney function

The study by Kostev et al. investigated the predictors of insulin initiation in new users of metformin or sulfonylureas in primary care practices and, in particular, the association between insulin initiation and decreased renal function. Data from 9,103 new metformin and 1,120 new sulfonylurea users with normal baseline glomerular filtration rate (eGFR) >90 ml/min /1.73 m2 were analyzed (01/2003-06/2012). Insulin treatment was initiated in 394 (4.3%) metformin and in 162 (14.5%) sulfonylurea users within 6 years. Kaplan-Meier curves (propensity score matched patients) showed that the metformin group was at a lower risk of insulin initiation compared to sulfonylurea users throughout the study period. A substantial eGFR decline was significantly associated with a higher likelihood of initiation of insulin therapy in metformin but not in sulfonylurea users. New users of sulfonylurea monotherapy in primary care practices were about three times more likely to start insulin therapy than new users of metformin. Kidney function decline was associated with earlier insulin initiation in metformin but not in sulfonylurea users. As a novel finding, this study indicated that a substantial decline in eGFR was a significant predictor of insulin initiation in metformin but not in sulfonylurea users in general practices [Kostev et al. 2014b].

Early discontinuation and related treatment costs after initiation of basal insulin in type 2 diabetes patients

Anderten et al. compared early discontinuation and related treatment costs in type 2 diabetes patients treated in primary care practices after initiation of insulin glargine or human basal insulin (NPH). A total of 2,765 glargine and 1,554 NPH patients from general practices were analyzed. Early discontinuation was defined as switching to a different basal insulin or another insulin treatment regimen within 90 days after first basal insulin prescription (index date, ID). Treatment costs were assessed 365 days prior to and post ID in both groups. Cost differences were adjusted for age, sex, diabetes duration, antidiabetic co-medication, diabetologist care, disease management program participation, costs before ID, and Charlson Comorbidity Index. The study showed that adherence to BOT with insulin glargine resulted in significantly lower total annual treatment and diabetes-related prescription costs than adherence to BOT with NPH insulin. Within 3 months after ID, 13% of glargine patients switched to other insulin treatment regimens (NPH: 18%). After propensity score matching, adjusted cost differences in 146 discontinued versus 1,342 continued glargine patients were calculated (NPH: 146 vs 1,342). Diabetes-related prescription costs were lower among persistent glargine patients compared to persistent NPH patients (EUR-49). The mean cost difference for diabetes-related prescriptions was lower among those who persisted on glargine compared to those who switched to other treatment regimens (EUR-74). Previous descriptive health economic studies were in line with this data [Anderten et al. 2015].

Predictors of early discontinuation of basal insulin therapy in type 2 diabetes patients

The study by Kostev et al. identified patient-related characteristics and other impact factors predicting early discontinuation of basal insulin therapy in type 2 diabetes patients treated in primary care. A total of

4,837 patients who started basal insulin therapy (glargine: *n* = 3,175; NPH: *n* = 1,662) in 1,072 general and internal medicine practices throughout Germany were retrospectively analyzed (01/2008-03/2014). Early discontinuation was defined as switching back to oral antidiabetic drug (OAD) therapy within 90 days after first basal insulin prescription (index date, ID). Patient records were assessed 365 days prior to and post ID. Logistic regression models were used to adjust for age, sex, diabetes duration, diabetologist care, disease management program participation, HbA1c, and comorbidity. Less than 7% of type 2 diabetes patients switched back to oral antidiabetic drugs within 90 days after initiation of basal insulin therapy. The findings also characterized primary care patients with type 2 diabetes who had a higher likelihood for early discontinuation of basal supported oral therapy (e.g., depression, frequent or severe hypoglycemia). Within 3 months after ID, 202 (6.8%) glargine patients switched back to OAD (NPH: 130 [8.5%]). In multivariate logistic regression models, predictors of early basal insulin discontinuation were at least one documented hypoglycemia event before ID, diagnosed depression, and referrals to specialists within 90 days after ID. Diabetologist care and glargine treatment were related to a lower chance of early insulin discontinuation [Kostev et al. 2015c].

Treatment persistence after initiating basal insulin in type 2 diabetes patients

The study by Pscherer et al. compared persistence and its predictors in type 2 diabetes patients in primary care, initiating either basal supported oral therapy (BOT) or intensified conventional therapy (ICT) with glargine, detemir, or NPH insulin. In the BOT cohort, 1,398 glargine, 292 detemir, and 874 NPH users from 918 practices were retrospectively analyzed (2008-2012). The ICT group incorporated 866 new users of glargine, 512 of detemir, and 1,794 of NPH. Persistence was defined as the proportion of patients remaining on the initial basal insulin (glargine,

detemir, or NPH insulin) over a period of two years. Persistence was adjusted for age, sex, diabetes duration, antidiabetic co-therapy, comorbidities, specialist care, and private health insurance. The study showed that treatment persistence among type 2 diabetes patients initiating basal insulin was influenced by type of insulin, antidiabetic co-medication, and some disease-specific patient characteristics. In BOT, two-year persistence was 65%, 53%, and 59% in glargine, detemir, and NPH users, respectively. In ICT, persistence was higher without differences between the groups: 84%, 85%, 86% in glargine, detemir, and NPH users, respectively. With BOT, detemir, and NPH users were more likely to discontinue basal insulin compared with glargine. Heart failure was another predictor of non-persistence, whereas higher age, metformin, and sulfonylurea co-medication were associated with lower discontinuation rates. The findings were in line with previous observational studies. A novel finding in this study was that diagnosed heart failure was independently associated with a 40% increased risk of discontinuing basal insulin therapy in BOT [Pscherer et al. 2015]

Diabetic retinopathy at diagnosis of type 2 diabetes in the UK

The study by Kostev et al. estimated the prevalence of diabetic retinopathy and its associated risk factors in newly diagnosed type 2 diabetes patients treated in general practices in the UK. A total of 12,524 patients with newly diagnosed (between 2005 and 2009) type 2 diabetes were identified and the presence of retinopathy was defined based on the ICD code (E11.3) or on the original diagnosis text. The time period between first diabetes diagnosis and first retinopathy diagnosis was calculated. The prevalence of diagnosed retinopathy was 19.0%. The median time to first retinopathy diagnosis was 309 days. Diabetic retinopathy was diagnosed in about one out of five patients with type 2 diabetes during the first year following their diabetes diagnosis in UK general practices. Age, male sex, hyperglycemia, and hypertension were

identified as risk factors of early retinopathy in type 2 diabetes patients. The prevalence was lower than reported in the past but higher than that reported in population-based screenings [Kostev et al. 2012b].

Amputation rate and risk factors in type 2 patients with diabetic foot syndrome

The study of Pscherer et al. assessed the risk of amputation and the influencing factors for amputation for patients with type 2 diabetes and diabetic foot syndrome. It included 3,892 type 2 diabetes patients with a first-time diagnosis of diabetic foot syndrome between 01/2000 and 12/2004 and at least a five-year follow-up documentation in the practices. The cumulative incidence of diabetes-associated lower limb amputations was 18.2%. Amputations were independently associated with older age, male gender, higher HbA1c value, and longer diabetes duration, as well as with several other diabetes complications. This was the first study describing the risk of amputation on the basis of an existing foot lesion for patients with type 2 diabetes treated within the German healthcare system [Pscherer et al. 2012].

Predictors of hypoglycemia in insulin-treated type 2 diabetes patients

The study by Kostev et al. investigated the frequency and predictors (diabetes care and treatment, comorbidities) of documented hypoglycemia in primary care patients with insulin-treated type 2 diabetes. Data from 32,545 patients were analyzed (09/2011-08/2012). Logistic regression (≥1 documented hypoglycemia) was used to adjust for confounders (age, sex, practice characteristics, diabetes treatment regimen). Both individual patient characteristics (e.g., comorbidities) and regional factors (practice location) had a substantial impact on hypoglycemia in primary care patients receiving insulin therapy. The

prevalence of patients (12 months) with at least one reported hypoglycemia was 2.2%. The adjusted odds of having hypoglycemia were increased for patients with renal failure, autonomic neuropathy, or adrenocortical insufficiency. Patients with mental disorders including dementia, depression, anxiety, and affective disorders also had higher odds of developing hypoglycemia. Location of the practice in an urban area was associated with a lower odds ratio. The outcome was in line with previous studies and added new findings to the current literature [Kostev et al. 2013c].

Macro- and microvascular outcomes in patients with type 2 diabetes treated with rapid-acting insulin analogs or human insulin

Another study by Rathmann et al. investigated the risk of macro- and microvascular complications in patients with type 2 diabetes receiving rapid-acting insulin analogs (IA) or human insulin (HI). A total of 2,764 patients on IA (insulin lispro, glulisine, aspart) and 4,193 patients on HI treated in general practices were included. After long-term (≥ 3 years) continuous treatment with IA or HI under real-life conditions, there was no difference in the risk of macro- or microvascular complications, thereby contradicting previous short-term analyses. No significant differences were detected between IA and HI regarding the incidence of vascular complications or regarding the time-to-onset of such complications, after adjusting for sex, age, comorbidities, and time on IA/HI, or by propensity-score-based matching. However, in an additional short-term analysis of a larger sample (no continuous insulin treatment required) with a greater number of comorbidities, time-to-onset of macrovascular complications was significantly longer for IA than for HI. This was the first study to include all available IA formulations and a required continuous IA or HI prescription for a longitudinal period of ≥3 years [Rathmann et al. 2014].

Use of antidiabetic agents in the treatment of gestational diabetes mellitus

The study by Heilmaier et al. evaluated the use of different antidiabetic agents during pregnancy to control gestational diabetes mellitus (GDM), as it is known to have adverse effects on the mother and child. Data from 6,516 women diagnosed with GDM treated in diabetology practices were collected from January 2008 to December 2012. Patients with known type 1 or 2 diabetes mellitus were excluded. Within the given timeframe, medication-based treatment for GDM significantly rose to reach 30.8% of all women with GDM. Both the administration of insulin and metformin increased considerably within the five-year period, with metformin being increasingly used without supplemental insulin and at lower dosages. Within the insulin treatment arm, insulin analogs became increasingly important. The proportion of sulfonylurea remained stable (0.2%). The study was the first that confirmed in a large cohort that GDM was increasingly treated with antidiabetic agents and that metformin was increasingly seen as an effective and safe agent for this purpose [Heilmaier et al. 2014].

Effects of selected antidiabetic agents on weight loss

The study by Kostev et al. compared sulfonylurea (SU), a dipeptidyl peptidase-4 inhibitor (DPP-4), and a glucagon-like-peptide-1 agonist (GLP-1) with metformin regarding body weight in type 2 diabetes patients. Data from 2,641 patients who initiated therapy with either metformin, SU, DPP-4 inhibitors or GLP-1 agonists with baseline BMI >30 were retrospectively analyzed (11/2008-10/2012). A comparison was performed between each patient's weight after 1 year of therapy and the last value prior to therapy. Differences between SU, DPP-4, GLP-1 versus metformin were estimated using a regression model adjusted for age, gender, health insurance status, defined co-diagnoses, and body weight at baseline. The study detected that metformin significantly

outperforms both SU and DPP-4 in terms of weight reduction, while weight loss with regard to GLP-1 was comparable to metformin. In absolute values, metformin patients lost an average of 2.6 kg, subjects treated with SU gained 0.3 kg. Body weight in the DPP-4 group decreased by 1.8 kg and GLP-1 patients lost 3.3 kg in body weight after one year of treatment. After adjustment for other variables, comparisons with metformin revealed the following results: SU +3.4 kg, DPP-4 +1.0 kg, and GLP-1 −0.4 kg. The study was the first to directly compare the effects of metformin, as the gold standard. with SU and two new oral antidiabetics, namely DPP-4 and GLP-1 [Kostev et al. 2014c].

Glycemic control following initiation of basal insulin therapy in patients with type 2 diabetes

Kostev et al. described the predictors of glycemic control (strict criterion: HbA1c ≤6.5%) during the first year after initiation of basal insulin therapy in primary care patients. A total of 4,062 type 2 diabetes patients (January 2008 to December 2011) in general and internal medicine practices started basal insulin, of whom 295 (7.2%) achieved an HbA1c ≤6.5% during the one-year follow-up. Factors positively associated with HbA1c ≤6.5% in the logistic regression were male sex, insulin glargine, short-acting insulin, and prior treatment with metformin, dipeptidyl peptidase-4 inhibitors, and diuretics. Lipid-lowering drugs were associated with lower odds of reaching the glycemic target. The study showed that achievement of the glycemic target among patients with type 2 diabetes initiating basal insulin was associated with the type of basal insulin, additional short-acting insulins, previous antidiabetic medication, and other co-medication [Kostev et al. 2015a].

Risk of hypoglycemia in type 2 diabetes patients under different insulin regimens

The study by Kostev et al. compared the rates and predictors of documented hypoglycemia in type 2 diabetes patients treated with either basal insulin supported oral therapy (BOT), conventional therapy (CT), or supplementary insulin therapy (SIT) in primary care settings. Data from 10,842 anonymous patients from primary care practices receiving BOT, 2,407 subjects receiving CT, and 7,480 patients receiving SIT were retrospectively analyzed (01/2005-07/2013). Stepwise logistic regression (≥1 documented hypoglycemia) was used to evaluate risk factors of hypoglycemia. The odds of having a documented hypoglycemia were higher in type 2 diabetes patients who initiated conventional therapy with premixed insulin or were started on short-acting insulin than in those who began a basal insulin supported oral therapy. The unadjusted rates per 100 patient-years of documented hypoglycemia were 1.01 (BOT), 1.68 (CT), and 1.61 (SIT), respectively. The odds of having ≥1 hypoglycemia were increased for CT and SIT. Previous hypoglycemia, duration of insulin treatment (days), history of transient ischemic attack (TIA)/stroke, and former salicylate prescriptions also increased the odds of hypoglycemia. Older age was associated with a slightly lower odds ratio. The results were in line with previous randomized controlled trials [Kostev et al. 2015b].

Diabetes treatment in people with type 2 diabetes and schizophrenia

The study by Rathmann et al. compared outcomes (HbA1c, BMI) and antidiabetic treatments in type 2 diabetes patients with and without schizophrenia under real-life conditions in primary care practices. A total of 1,321 type 2 diabetes patients with schizophrenia and 1,321 matched controls (age, sex, diabetes duration, diabetologist care, practice) without schizophrenia treated in 1,072 general practices were retrospectively

analyzed (01/2009-12/2013). Antidiabetic treatment, HbA1c, and BMI were compared using paired *t*-tests, McNemar's tests, and conditional logistic regression adjusting for macro- and microvascular comorbidities (ICD-10). There was no evidence that type 2 diabetes patients with schizophrenia had worse diabetes control than those without a severe mental illness in general practices. Novel cost-intensive antidiabetic agents (DPP-4 or SGLT2 inhibitors, GLP-1 receptor agonists) were less often prescribed in some cases. However, multivariate logistic regression showed that schizophrenia was not associated with prescription use of novel antidiabetic agents (reference: other antidiabetic agents) after adjusting for private health insurance coverage and comorbidities. The results were in line with other studies [Rathmann et al. 2015a].

Fracture risk in patients with newly diagnosed type 2 diabetes

Rathmann et al. investigated whether fracture risk was increased in newly diagnosed type 2 diabetes patients. In addition, fracture risk of various sites (hip, spine, upper extremities) was analyzed. The study included 299,104 primary care patients from practices who received a first type 2 diabetes diagnosis during the index period (01/2000-12/2013). Furthermore, 299,104 non-diabetic controls were included after individual matching (1:1) to diabetes cases based on age, sex, type of health insurance (private or statutory), and index date (visit at date of first diabetes diagnosis). Cumulative incidence of fractures was estimated for 10 years after the index date using the product limit method. Newly diagnosed type 2 diabetes in primary care practices was associated with an increased risk of fractures overall as well as with hip, spine, and upper extremity fractures. Type 2 diabetes patients had a 36% higher risk of experiencing a fracture during an average of 2.9 years of follow-up after diabetes diagnosis compared to the non-diabetic controls. The highest relative risks were found for hip and upper

arm/shoulder fractures (hazard ratios about 1.6). The findings were in line with other studies [Rathmann et al. 2015b].

Fracture risk in patients with type 2 diabetes under different antidiabetic treatment regimens

The study by Pscherer et al. investigated the fracture risk related to various types of insulin therapy in primary care practices. Data from 105,960 type 2 diabetes patients treated in general and internal medicine practices were retrospectively analyzed (01/2000-12/2013). The fracture risks of the following therapies were compared using multivariate logistic regression models adjusting for age, sex, diabetes care, comorbidity, and glycemic control (HbA1c): 1) incident insulin therapy versus oral antidiabetic drugs; 2) basal supported oral therapy versus supplementary insulin therapy versus conventional insulin therapy; and 3) insulin glargine versus insulin detemir versus NPH insulin. The study indicated that initiation of insulin therapy in patients with type 2 diabetes was associated with an increased risk of fractures overall. There was a lower chance of incident fractures in the oral antidiabetic drug group compared to incident insulin users, although this was not significant. Increased odds of fractures were found for conventional insulin therapy and supplementary insulin therapy compared to basal supported oral therapy, though these were also not significant. Overall, no significant differences in fracture risk were found for basal insulins (glargine, detemir, NPH insulin). After a treatment duration ≥2 years, insulin glargine users had lower odds of having ≥1 fracture compared to NPH users. Previous findings were in line with this study [Pscherer et al. 2016].

Clinical and patient-related variables associated with initiation of GLP-1 receptor agonist therapy in type 2 diabetes patients

The study by Qiao et al. investigated real-world clinical and patient-related variables associated with initiating GLP-1 receptor agonist (GLP-1 RA) treatment relative to the initiation of other glucose-lowering therapies in type 2 diabetes (T2D) patients treated in primary care practices. Data from 938 T2D patients who started therapy with a GLP-1 RA in primary care practices were retrospectively analyzed (01/2011-03/2014). A total of 5,197 T2D patients who initiated other non-GLP-1 RA antidiabetic therapies were selected as controls. patients. The choice of GLP-1 RA therapy instead of a different glucose-lowering drug class was associated with obesity, private health insurance coverage, younger age, male sex, diabetologist care, and geographic location of the practice. Among co-medications, angiotensin II antagonists (increased) and non-steroidal antirheumatic agents (decreased) were associated with GLP-1 RA prescriptions. The findings were consistent with German guidelines and in line with previous reports [Qiao et al. 2016].

Changes in glycated hemoglobin levels after initiating second-line therapy in type 2 diabetes patients

The study by Rathmann et al. compared the absolute reduction in glycated hemoglobin (HbA1c) levels at 6 months after initiating second-line glucose-lowering therapy in patients with type 2 diabetes treated with metformin monotherapy in general practices. A total of 7,009 patients were identified (January 2004 to December 2014). The initiated second-line therapies included: dipeptidyl peptidase-4 (DPP-4) inhibitors (38.7%), sulfonylureas (36.3%), insulin (13.3%), glucagon-like peptide-1 receptor agonists (GLP-1 RAs: 2.5%), thiazolidinediones (5%), and other agents (glinides, aldose-reductase inhibitors; 4.1%). In patients with type 2 diabetes on metformin monotherapy requiring a second glucose-lowering agent, the addition of incretins, sulfonylureas, thiazolidinediones

or other non-insulin glucose-lowering drugs led to a similar absolute 6-month HbA1c reduction of −0.7 to −0.9%. The mean absolute HbA1c change from baseline was −0.9% (DPP-4 inhibitors: −0.9%; sulfonylureas: −0.9%; insulin: −1.1%; GLP-1 RAs: −0.7%; thiazolidinediones: −0.9%, and other: −0.7%1). Overall, 58% of patients reached the HbA1c target of <7% (DPP-4 inhibitors: 61.7%; sulfonylureas: 56.7%; insulin: 45.6%; GLP-1 RAs: 62.2%; thiazolidinediones: 69.7%; and other: 57.5%). Compared with sulfonlyureas, DPP-4 inhibitors, GLP-1 RAs and thiazolidinediones were associated with increased odds of reaching HbA1c <7%, whereas insulin was associated with lower odds. In conclusion, patients with type 2 diabetes achieved very similar reductions in HbA1c after 6 months of second-line therapy, regardless of the type of therapy. The findings were in line with other studies [Rathmann et al. 2016].

Impact of disease management programs on HbA1c values in type 2 diabetes patients

The study by Kostev et al. analyzed the impact of disease management programs on HbA1c values in type 2 diabetes mellitus (T2DM) patients. This study included 9,017 patients followed in disease management programs (DMPs) who started an antihyperglycemic treatment upon inclusion in a DMP. Standard care (SC) patients were included after individual matching (1:1) to DMP cases based on age, gender, physician (diabetologist versus non-diabetologist care), HbA1c values at baseline, and index year. The main outcome was the share of patients with HbA1c <7.5% or <6.5% after at least 6 months and less than 12 months of therapy in the DMP and SC groups. DMPs had a positive impact on the reduction of HbA1c levels in T2DM patients. Interestingly, the effect of DMPs was stronger in people treated in diabetologist practices compared to those treated in general practices. The mean HbA1c level at baseline was equal to 8.7%. In diabetologist practices, 64.7% of DMP

patients and 55.1% of SC patients had HbA1c levels <7.5%, while 23.4% of DMP patients and 16.9% of SC patients had HbA1c levels <6.5%. By comparison, in general practices, 72.4% of DMP patients and 65.7% of SC patients had HbA1c levels <7.5%, while 29.0% of DMP patients and 25.4% of SC patients had HbA1c levels <6.5%. DMPs increased the likelihood of HbA1c levels lower than 7.5% or 6.5% after 6 months of therapy in both diabetologist and general care practices. The outcomes were in line with other studies [Kostev et al. 2016].

Psoriasis risk in patients with type 2 diabetes

Jacob et al. analyzed psoriasis risk in type 2 diabetes mellitus (T2DM) patients treated in primary care practices. A total of 72,148 T2DM patients (≥40 years) who received their initial diabetes diagnosis between 2004 and 2013 were included. To these, 72,148 non-diabetic controls were matched (1:1) based on age, gender, type of health insurance (private or statutory), number of medical visits, and index date. The primary outcome was the diagnosis of psoriasis. Skin infections, dermatitis/eczema, hyperlipidemia, and medications associated with psoriasis (beta blockers, angiotensin-converting enzyme (ACE) inhibitors, lithium, antimalarials, non-steroidal anti-inflammatory drugs, and benzodiazepines) were included as potential confounders. T2DM was positively associated with an increase in the risk of developing psoriasis in the ten years following the diabetes diagnosis. Hyperlipidemia, dermatitis/eczema, and skin infections were more frequent in T2DM patients than in controls. Beta blockers, ACE inhibitors, and non-steroidal anti-inflammatory drugs were also more commonly used in people with T2DM than in controls. A total of 3.4% of T2DM patients and 2.8% of matched controls developed psoriasis within ten years of follow-up. T2DM patients were at a higher risk of developing psoriasis than controls. The study was the first to show that T2DM increased the odds of being diagnosed with psoriasis [Jacob et al. 2016].

Changes in HbA1c, body weight, and systolic blood pressure in type 2 diabetes patients initiating dapagliflozin therapy

The study of Scheerer et al. examined changes in glycated hemoglobin (HbA1c), body weight (BW), and systolic blood pressure (SBP) in type 2 diabetes (T2D) primary care patients initiating dapagliflozin treatment. A total of 1,169 T2D patients who started dapagliflozin in general or diabetologist practices (December 2012-October 2014) were analyzed (3- and 6-month follow-up). Multivariate linear regression analyses were used to identify the clinical characteristics and comorbidities associated with changes in HbA1c, BW, and SBP. T2D patients treated with dapagliflozin exhibited statistically significant reductions in HbA1c (−0.8%), BW (−2.5 kg), and SBP (−2.3 mmHg) after 6 months of treatment. In addition, HbA1c reductions were greater in patients with poor glycemic control. At the 3-month stage, dapagliflozin significantly reduced HbA1c compared to the baseline. Changes were maintained after 6 months. Patients with high baseline HbA1c values (>9%) showed greater reductions in HbA1c than the overall sample (3 months −1.8%, 6 months −1.8%). BW and SBP also showed statistically significant reductions with dapagliflozin over 3 and 6 months (−2.2 kg, −2.2 mmHg, and −2.5 kg −2.3 mmHg, respectively). After 3 months, 53% of patients achieved a reduction in both HbA1c and BW; the same holds true for 45% of patients at the 6-month mark. Similar results were observed both in general and diabetologist practices. In multivariate analyses, baseline HbA1c and diabetologist care were independent predictors of HbA1c change (6 months). The results were comparable to previous clinical trials. This was the first real-world study evaluation of the shortterm changes in HbA1c, BW, and SBP in T2D patients initiating dapagliflozin treatment in primary care settings [Scheerer et al. 2016].

Prevalence and risk factors of neuropathy in newly diagnosed type 2 diabetes in Germany and the UK

Kostev et al. estimated the prevalence and risk factors of diabetic neuropathy in newly diagnosed type 2 diabetes patients treated in general practices. Patients with newly diagnosed (<1 year) type 2 diabetes (2008-2012) were identified, including 45,633 patients in Germany and 14,205 patients in the UK. Neuropathy was identified by ICD code (E11.4) or the original diagnosis. Prevalence of diagnosed neuropathy at the time of type 2 diabetes diagnosis was low in primary care practices (Germany: 5.7%, UK: 2.4%). In Germany, factors independently associated with neuropathy in the stepwise logistic regression were age (>70 years), retinopathy, peripheral artery disease, insulin treatment, and oral antidiabetic drugs. In the UK, male sex, nephropathy, peripheral artery disease, antihypertensives, insulin, and oral antidiabetic drugs were identified as corresponding factors. The results were in line with previous studies [Kostev et al. 2014a].

Treatment persistence, hypoglycemia and clinical outcomes in type 2 diabetes patients with dipeptidyl peptidase-4 inhibitors and sulfonylureas

The study by Rathmann et al. investigated therapy persistence, frequency of hypoglycemia and macrovascular outcomes among type 2 diabetes patients with dipeptidyl peptidase-4 inhibitors (DPP-4) and sulfonylureas (SU). Data from 19,184 DPP-4 and 31,110 SU users with new prescriptions (index date), without additional antidiabetics except metformin, in general practices in Germany were analyzed. Therapy discontinuation (prescription gap >90 days), hypoglycemia, and macrovascular outcomes (two-year follow-up) were compared adjusting for age, sex, diabetes duration, metformin, previous hypoglycemia, health insurance, hypertension, hyperlipidemia, antihypertensives, lipid-lowering and antithrombotic drugs, microvascular complications, and

Charlson co-morbidity score. Two years after the index date, prescription of DPP-4 inhibitors was associated with a lower risk of therapy discontinuation, a fivefold lower frequency of patients with documented hypoglycemias and a lower short-term risk of macrovascular events compared to SU in type 2 diabetes patients in primary care settings, taking into account a number of potential confounders (co-morbidity, co-medication). Hypoglycemias (≥1) were documented in 0.18% patients with DPP-4 and in 1.00% with SU. Hypoglycemias were significantly associated with incident macrovascular complications. Risk of macrovascular events was 26% lower in DPP-4 than in SU users [Rathmann et al. 2013b].

Lower incidence of recorded cardiovascular outcomes in patients with type 2 diabetes using insulin aspart vs. those on human insulin

The study by Rathmann et al. collected and compared the incidence of recorded macro- and microvascular events in patients with type 2 diabetes treated with insulin aspart or regular human insulin in general practices. 3,154 aspart and 3,154 regular insulin users (January 2000 to July 2011) were analyzed after matching for age, sex, health insurance, and diabetes treatment period in the general practice. Hazard ratios for macro- or microvascular outcomes (follow-up: 3.5 years) were further adjusted for diabetologist care, practice region, hypertension, hyperlipidemia, co-medication (basal insulin, oral antidiabetics, antihypertensives, lipid-lowering agents, and antithrombotic drugs), previous treatment with rapid-acting insulins, hypoglycemia and the Charlson co-morbidity score. Prescription of the rapid-acting insulin analog aspart was associated with a decreased recorded risk (15% lower) of macrovascular events compared with regular human insulin in type 2 diabetes patients, taking into account a number of potential confounders (e.g., co-morbidity and co-medication). For insulin aspart there was also a decreased risk of incident stroke, myocardial infarction,

and peripheral vascular disease. For microvascular complications (retinopathy, neuropathy and nephropathy), no significant differences were observed. The results were in line with other publications [Rathmann et al. 2013c].

References

Kostev K 2012:
Kostev K
Duration of first prescribed long acting insulin therapy in type 2 diabetes
Diabetes Res Clin Pract. 2012 Jul;97(1):e3

Kostev et al. 2012a:
Kostev K, Dippel FW
Predictors for the initiation of a basal supported oral therapy (BOT) in type 2 diabetic patients under real-life conditions in Germany
Prim Care Diabetes. 2012 Dec;6(4):329-35

Kostev et al. 2012b:
Kostev K, Rathmann W
Diabetic retinopathy at diagnosis of type 2 diabetes in the UK: a database analysis
Diabetologia. 2013 Jan;56(1):109-11

Kostev et al. 2013a:
Kostev K, Rathmann W
Influence of macro- and microvascular comorbidity on time to insulin initiation in type 2 diabetes patients: A retrospective database analysis in Germany, France, and UK Prim Care Diabetes. 2013 Jul;7(2):167-71

Kostev et al. 2013b:
Kostev K, Rathmann W
Changes in time to insulin initiation in type 2 diabetes patients: A retrospective database analysis in Germany and UK (2005-2010)
Prim Care Diabetes. 2013 Oct;7(3):229-33

Kostev et al. 2013c:
Kostev K, Dippel FW, Rathmann W
Predictors of hypoglycaemia in insulin-treated type2 diabetes patients in primary care: A retrospective database analysis
Prim Care Diabetes. 2014 Jul;8(2):127-31

Kostev et al. 2014a:
Kostev K, Jockwig A, Hallwachs A, Rathmann W
Prevalence and risk factors of neuropathy in newly diagnosed type 2 diabetes in primary care practices: A retrospective database analysis in Germany and UK
Prim Care Diabetes. 2014 Oct;8(3):250-5

Kostev et al. 2014b:
Kostev K, Dipperl FW, Rathmann W
Predictors of Insulin Initiation in Metformin and Sulfonylurea Users in Primary Care Practices: The Role of Kidney Function
J Diabetes Sci Technol. 2014 Sep;8(5):1023-8

Kostev et al. 2014c:
Kostev K, Rex J, Rockel T, Heilmaier C
Effects of selected antidiabetics on weight loss – A retrospective database analysis
Prim Care Diabetes. 2015;9:74-77

Kostev et al. 2015a:
Kostev K, Dippel FW, Rathmann W
Glycemic control after initiating basal insulin therapy in patients with type 2 diabetes: a primary care database analysis
Diabetes Metab Syndr Obes. 2015 Jan 14;8:45-8

Kostev et al. 2015b:
Kostev K, Dippel FW, Rathmann W
Risk of hypoglycaemia in type 2 diabetes patients under different insulin regimens: a primary care database analysis
Ger Med Sci. 2015 Jan 12;13:Doc01

Kostev et al. 2015c:
Kostev K, Dippel FW, Rathmann W
Predictors of early discontinuation of basal insulin therapy in type 2 diabetes in primary care
Prim Care Diabetes. 2016 Apr;10(2):142-7

Kostev et al. 2016:
Kostev K, Rockel T, Jacob J
Impact of Disease Management Programs on HbA1c Values in Type 2 Diabetes Patients in Germany
J Diabetes Sci Technol. 2016 May 30. pii: 1932296816651633. [Epub ahead of print]

Pscherer et al. 2012:
Pscherer S, Dippel FW, Lauterbach S, Kostev K
Amputation rate and risk factors in type 2 patients with diabetic foot syndrome under real-life conditions in Germany
Prim Care Diabetes. 2012 Oct;6(3):241-6

Pscherer et al. 2015:
Pscherer S, Chou E, Dippel FW, Rathmann W, Kostev K
Treatment persistence after initiating basal insulin in type 2 diabetes patients: A primary care database analysis
Prim Care Diabetes. 2015 Oct;9(5):377-84

Pscherer et al. 2016:
Pscherer S, Kostev K, Dippel FW, Rathmann W
Fracture risk in patients with type 2 diabetes under different antidiabetic treatment regimens: a retrospective database analysis in primary care
Diabetes Metab Syndr Obes. 2016 Feb 19;9:17-23

Rathmann et al. 2013a:
Rathmann W, Dippel FW, Kostev K
Different Injection Frequencies of Basal Insulins in Type 2 Diabetes Patients under Real-Life Conditions: A Retrospective Database Analysis
J Diabetes Sci Technol. 2013 September, 7(5): 1354-1358

Rathmann et al. 2013b:
Rathmann W, Kostev K, Gruenberger JB, Dworak M, Bader G, Giani G
Treatment persistence, hypoglycaemia and clinical outcomes in type 2 diabetes patients with dipeptidyl peptidase-4 inhibitors and sulphonylureas: a primary care database analysis
Diabetes Obes Metab. 2013 Jan;15(1):55-61

Rathmann et al. 2013c:
Rathmann W, Kostev K
Lower incidence of recorded cardiovascular outcomes in patients with type 2 diabetes using insulin aspart vs. those on human regular insulin: observational evidence from general practises
Diabetes Obes Metab. 2013 Apr;15(4):358-63.

Rathmann et al. 2014:
Rathmann W, Schloot NC, Kostev K, Reaney M, Zagar AJ, Haupt A
Macro- and Microvascular Outcomes in Patients with Type 2 Diabetes Treated with Rapid-Acting Insulin Analogues or Human Regular Insulin: a Retrospective Database Analysis
Exp Clin Endocrinol Diabetes. 2014 Feb;122(2):92-9

Rathmann et al. 2015a:
Rathmann W, Pscherer S, Konrad M, Kostev K
Diabetes treatment in people with type 2 diabetes and schizophrenia: Retrospective primary care database analyses
Prim Care Diabetes. 2016 Feb;10(1):36-40

Rathmann et al. 2015b:
Rathmann W, Kostev K
Fracture risk in patients with newly diagnosed type 2 diabetes: a retrospective database analysis in primary care
J Diabetes Complications. 2015 Aug;29(6):766-70

Rathmann et al. 2016:
Rathmann W, Bongaerts B, Kostev K
Change in glycated haemoglobin levels after initiating second-line therapy in type 2 diabetes: a primary care database study
Diabetes Obes Metab. 2016 Aug;18(8):840-3

Heilmaier et al. 2014:
Heilmaier C, Thielscher C, Ziller M, Altmann V, Kostev K
Use of antidiabetic agents in the treatment of gestational diabetes mellitus in Germany, 2008-2012
J Obstet Gynaecol Res. 2014 Jun;40(6):1592-7

Anderten et al. 2015:
Anderten H, Dippel FW, Kostev K
Early Discontinuation and Related Treatment Costs After Initiation of Basal Insulin in Type 2 Diabetes Patients: A German Primary Care Database Analysis
J Diabetes Sci Technol. 2015 May;9(3):644-50

Jacob et al. 2015:
Jacob L, Waehlert L, Kostev K
Changes in Type 2 Diabetes Mellitus Patients in German Primary Care Prior to (2006) and After (2010, 2014) Launch of New Drugs
J Diabetes Sci Technol. 2016 Feb 10;10(2):414-20

Jacob et al. 2016:
Jacob L, Kostev K
Psoriasis risk in patients with type 2 diabetes in German primary care practices
Prim Care Diabetes. 2016 Jul 23. pii: S1751-9918(16)30054-7

Qiao et al. 2016:
Qiao Q, Grandy S, Hiller J, Kostev K
Clinical and Patient-Related Variables Associated with Initiating GLP-1 Receptor Agonist Therapy in Type 2 Diabetes Patients in Primary Care in Germany
PLoS One. 2016 Mar 28;11(3):e0152281

Scheerer et al. 2016:
Scheerer M, Rist R, Proske O, Meng A, Kostev K
Changes in HbA1c, body weight, and systolic blood pressure in type 2 diabetes patients initiating dapagliflozin therapy: a primary care database study
Diabetes Metab Syndr Obes. 2016 Oct 31;9:337-345

Chapter 2. Cancer

Cancer and intraoperative complications

The retrospective study demonstrated that cancer – in particular breast cancer, gastro-intestinal cancer, cancer of female genital organs, and cancer of the hematopoietic and lymphoid tissues – increased the risk of intraoperative and postoperative complications (IPCs). The data of 5,817 IPC patients and 5,817 controls from general practitioners were analyzed in this study. At the time of publication, there were very few studies on the effect of cancer on IPCs. Therefore, the findings of this study were new and indicated that cancer may play an important role in the development of postoperative complications. The primary hypothesis for explaining this important outcome suggests that patients with cancer are weaker than other patients and are thus at a higher risk for IPCs (i.e. vomiting, malabsorption, or hemorrhage). Among the seven types of cancer that were included, gastro-intestinal cancer had the strongest association with surgical complications [Jacob et al. 2016a].

Cancer and diabetes therapy

Many observational studies linked metformin use in type 2 diabetes to a lower risk of cancer, and in meta-analyses, cancer risk was shown to be much lower in metformin users than in non-users. However, the results were very controversial. Several studies investigating cancer risk in diabetes patients as a function of antihyperglycemic therapy were performed.

Kowall et al. compared cancer incidence in users of sulfonylurea, insulin, and other diabetes medications to cancer incidence in metformin users. They included 22,556 patients from 1,143 general practices who had received a diagnosis of type 2 diabetes in the period from January 2000

to December 2012 and who used a diabetes drug after diagnosis of diabetes. None of the analyses described in this publication showed that the risk of cancer (in all sites) was lower in users of metformin than in users of other diabetes medications [Kowall et al. 2015a].

In their next study, Kowall et al. assessed whether metformin users differed from sulfonylurea and insulin users in terms of their risk of developing colorectal, breast, prostate, and lung cancer. This study used data from Germany and the UK, and included 19,692 and 60,571 patients treated in primary care practices in Germany and Great Britain, respectively. The study found no evidence of a cancer-protective effect of metformin in patients with diabetes, since different statistical methods were used and compared [Kowall et al. 2015b].

A study performed by Kostev investigated the risk of breast cancer in women with type 2 diabetes. A total of 9,222 female diabetes patients treated with insulin treatment in primary care practices were analyzed. The study compared the time elapsed from the start of insulin therapy to the first primary care diagnosis of breast cancer in patients treated with insulin glargine, insulin detemir, and insulin NPH, adjusting for age, sex, private insurance status, urban location of a practice, region, and HbA1c level. The use of insulin glargine was not associated with a higher risk of breast cancer compared with insulin NPH [Kostev 2012].

The study by Jacob et al. analyzed the impact of glucose-lowering drugs on metastases in women living in Germany who have been diagnosed with breast cancer and type 2 diabetes mellitus (T2DM). It included 4,953 women treated in general practices and demonstrated that the use of metformin and incretins significantly decreased the risk of metastases. The presented study followed patients diagnosed with T2DM and breast cancer (BC) for five years and was thus able to demonstrate that metformin was associated with a 30% reduction in the risk of developing metastases. A potential protective effect of metformin against the development of primary tumors in T2DM patients has been discussed for

several years and was in line with this outcome. Another important result was that the prescription of incretins protected against BC metastases. However, in past years there has been a major debate on the safety of the use of incretin-based treatments, particularly with regard to cancer [Jacob et al. 2016b].

Cancer and depression

The study by Jacob et al. analyzed the prevalence of depression and anxiety, as well as their risk factors in women with breast cancer in general practices (GP) and gynecological practices (GYP) in Germany. In total, 24,537 women from GP and 20,018 women from GYP were analyzed between 2009 and 2013. The women were included only if they had not suffered from depression or an anxiety disorder within the 12 months prior to the index date. Within 5 years of follow-up, 36.9% of GP patients and 35.1% of GYP patients had been diagnosed with depression or anxiety. Jacob et al. showed that depression and anxiety occur frequently in women diagnosed with BC and demonstrated that the number of patients with depression and/ or anxiety increased after BC diagnosis. This confirmed the findings of other studies. Furthermore, Jacob et al. showed that an age over 50 years, statutory health insurance, patient history of depressive/anxiety episodes, and the presence of metastases were linked, to a significant extent, with a higher risk of depression and/or anxiety. Patients with metastases or with previous episodes of depression/anxiety had a higher risk of depression/anxiety. Finally, women with private health insurance coverage had a lower risk of depression and anxiety. A number of authors have studied the prevalence of mood disorders in women with early- or late-stage BC and their conclusions were in line with these results [Jacob et al. 2016c].

An additional study by Jacob et al. focused on the treatment of depression in patients with and without cancer diagnosis and analyzed

the use of antidepressants. A total of 604 depressed cancer patients and 604 depressed controls were included. All of them were treated in neuropsychiatric practices between 2004 and 2013. Five different types of cancer were included. The results demonstrated that patients in Germany who have been diagnosed with both cancer and depression were less frequently treated for the psychiatric condition than controls who only suffered from depression. As a matter of fact, tricyclic antidepressant prescriptions were more common in people without cancer, although there was no difference in prescriptions of selective serotonin reuptake inhibitors (SSRIs) and prescriptions of serotonin and norepinephrine reuptake inhibitors (SNRIs), while benzodiazepines were prescribed more frequently in patients with cancer. This study has been the first to date to compare the treatment of depression in cancer patients and in non-cancer patients in Germany. Up to now, no study has focused on the suboptimal management of depression in cancer patients in Germany [Jacob et al. 2016d].

Cancer and compliance/persistence

The importance of compliance and persistence is often underestimated in breast cancer treatment. However, taking the prescribed medication for a sufficient period of time is crucial to the success of any therapy. The following studies investigated compliance and persistence in patients with BC, taking several other factors into account.

The study by Hadji et al. analyzed persistence with tamoxifen and aromatase inhibitors in postmenopausal women with hormone-receptor-positive BC. A total of 12,412 women on tamoxifen, 2,796 on anastrozole, 647 on exemestane, and 1,657 on letrozole met the inclusion criteria. Patients withfirst-time tamoxifen or aromatase inhibitor prescriptions from October 2001 to December 2010 from general and gynecological practices were included. The study indicated that, by the end of the third year of treatment, 48% of women with BC on tamoxifen

as well as 45-56% women with BC on aromatase inhibitors remained in treatment without treatment gaps exceeding 90 days. The results were in line with other long-term study results [Hadji et al. 2013a].

In this analysis Hadji et al. investigated the persistence of four oral and intravenous bisphosphonates in women with metastatic breast cancer. Furthermore, they identified determinants of non-persistence among gynaecologists and general practitioners in Germany. A total of 1,045 patients with a diagnosis of bone metastases following breast cancer and a first-time prescription of bisphosphonate therapy were identified and included in the analysis. The majority of the patients received intravenous bisphosphonates (763 injectable bisphosphonates vs. 280 oral bisphosphonates). The study indicated that, by the end of the first year of treatment, only 64.7% of women with BC and bone metastases on intravenous bisphosphonates and 54.4% on oral bisphosphonates remained in treatment without treatment gaps exceeding 90 days. The insurance status of the patient, urban residency, and the specialty of the physician had no impact on persistence with oral or intravenous bisphosphonates. However, because of the observational study design, only associations related to reasons for treatment discontinuation were detected. In line with these results, other studies generally demonstrated that the persistence rates for oral bisphosphonates were significantly lower compared with those for intravenous bisphosphonates. The study in question found that women under the age of 50 years had a significantly higher risk of treatment discontinuation compared with women over 70 years. This finding was in agreement with other recent reports [Hadji et al. 2013b].

The aim of the study by Kostev et al. was to investigate, quantify, and critically discuss the effect that treating physicians have on the compliance of their breast cancer patients. A total of 6,926 patients with a confirmed breast cancer diagnosis who started therapy (tamoxifen or aromatase inhibitors) between January 2001 and December 2011 were selected from the database and analyzed with regard to their

compliance. These patients were treated by either gynecologists or primary care physicians. Practices were grouped into two categories with regard to the compliance of all treated patients. A breast cancer patient who was treated in a practice with a trend toward poor compliance had a nearly 60% higher risk for treatment discontinuation than would be the case in a practice with good compliance. Previous studies found that physicians had a significant impact on patient compliance and their results were in line with these data. Thus far, no database-based studies published in German-speaking countries have empirically examining the influence of the physician on the compliance of patients [Kostev et al. 2014].

Gender differences in persistency to bisphosphonates in patients with metastatic breast or prostate cancer

In this study, Hadji et al. investigated for the first time gender-specific differences in persistence with bisphosphonate prescriptions from January 2001 to December 2011. The patients were diagnosed with metastatic bone disease (MBD) following breast cancer (BC) or prostate cancer (PC) diagnosis. A total of 1,007 patients were included in this analysis. These patients were treated in 98 gynecological, 121 urological, and 248 general practices. The results indicated that, by the end of the first year of treatment, 35.3% of women with BC and MBD and 26.6% of men with PC and MBD discontinued their bisphosphonate treatment. In recent years, only a few studies have focused on persistence with bisphosphonates in cancer patients. They generally investigated the differences in persistency rates for oral vs. iv bisphosphonates. Because of the observational study design, only associations related to reasons for treatment discontinuation were detected by Hadji. The study in question did not find any influence of age on persistency. This finding was different from previous observational

studies, which pointed to younger age as a factor associated with lower compliance in women with BC and osteoporosis [Hadji et al. 2014].

Age-related differences in women with breast cancer

Jacob et al. investigated age-related persistence with bisphosphonates (BIS) in women with breast cancer and bone metastases. Therapy discontinuation was defined as a period of at least 90 days without treatment. A dataset of 1,541 patients from general and gynecological practices initially treated with BIS between 1994 and 2013 was included. The study demonstrated that women aged ≥70 discontinued their BIS treatment less frequently (34.8%) than women aged <70 years (44.3%) during the one-year follow-up period. In addition, the study showed that residing in western Germany and having private health insurance coverage increased the risk of therapy discontinuation, whereas more advanced age, gynecological care, chemotherapy, endocrine treatment, pain medications, and the number of drugs taken per day decreased this risk. These findings were in line with previous reports and demonstrated that advanced age positively impacts BIS treatment persistence in women with BC and bone metastases [Jacob et al. 2016e].

In another study Jacob et al. investigated age-related differences in persistence in women with breast cancer treated with tamoxifen (TAM) or aromatase inhibitors (AI). A total of 29,245 patients from general and gynecological practices diagnosed with metastatic or non-metastatic breast cancer and initially treated with TAM or AI between 2004 and 2013 were included. The study showed that the persistence rate was low after 5 years of hormonal therapy (between 11% and 18%). Within 5 years after treatment initiation, 88.8% of women <70 of age and 82% of women ≥70 years of age had terminated treatment. The results of this study also demonstrated that women aged ≥70 were less likely to discontinue their endocrine treatment than younger women. Furthermore, when adjusting for potential confounders, the study found

that women <70 were at a higher risk of discontinuing their treatment than older women. In addition, gynecological care, DMPs, and high Charlson comorbidity scores increased treatment persistence. Initial treatment (TAM vs. AI) had no significant effect on the risk of therapy discontinuation. These findings were in line with other analyses and demonstrated that advanced age positively impacts BIS treatment persistence in women with BC and bone metastases. Previous studies have also reported age as a major factor influencing therapy discontinuation [Jacob et al. 2016f].

Breast cancer and possibility of pregnancy

The study was an examination of the change in frequency of pregnancies after breast cancer treatment and the time from the first breast cancer diagnosis to pregnancy over one decade, i.e. the period from 2010-2012 compared to the period from 2000-2002. Data from 102 gynecological practices were available and included women aged 20-45 with breast cancer. A total of 179 pregnant women were included in this study from 2000-2002 and 2010-2012. There was a significant increase in pregnancies within the first 2 years after the breast cancer diagnosis. Additionally, the duration from cancer diagnosis to pregnancy was reduced significantly.

Disease management programs and persistence in women with breast cancer

The study by Jacob et al. analyzed the impact of disease management programs (DMPs) on adherence in women with breast cancer (BC). Data on 4,915 BC patients [1,874 DMP and 3,041 standard care (SC)] who started hormone therapy between 2008 and 2013 in 234 gynecological practices were included. The primary outcome measure was the rate of discontinuation of hormone therapy within 3 years of the start of

treatment. Discontinuation of therapy was defined as a period of at least 90 days without treatment. The study showed a significant difference between DMPs and SC in terms of age and region, but not initial therapy. Depression was also more common in patients in DMPs than in those in SC. Within 3 years of therapy initiation, 32.7% of DMP patients and 39.6% of SC patients had discontinued their treatment. Women with BC who were enrolled in a DMP had a lower risk of discontinuing therapy. This risk was also slightly higher in western Germany. Participation in DMPs has a positive impact on the adherence of BC patients. These results confirmed the findings of previous studies, which had shown that more than half of BC patients discontinue their hormone therapy prematurely [Jacob et al. 2015].

Aromatase inhibitor therapy and fracture risk

Schmidt et al. analyzed the impact of compliance with aromatase inhibitor (AI) treatments on fracture risk in women with breast cancer. This study included 8,732 women with BC treated with AI, 8,732 treated with tamoxifen (TAM), and 8,732 age-matched women without BC. The main outcome measure was the impact of compliance with AI treatment on fracture risk. Overall, 17.6%, 8.7%, and 8.8% of AI, TAM, and non-cancer patients, respectively, were diagnosed with fracture within 5 years after the index date. The proportion of women with fracture receiving AI increased with treatment compliance, rising from 8.6% when treatment lasted less than a year to 18.0% when it lasted between 4 and 5 years. By contrast, the proportion of fractures in women with BC receiving TAM for the same time periods decreased. The risk of fracture was higher in women with BC using AI than in the non-cancer group. Finally, current smoking status, BMI, dementia, and prescription of corticosteroids had a significant impact on fracture risk. The study results demonstrated for the first time that the use of AIs in women with BC is associated with a

compliance-related increase in the risk of fracture in a real-world setting [Schmidt et al. 2016].

References

Hadji et al. 2013a:
Hadji P, Ziller V, Kyvernitakis J, Bauer M, Haas G, Schmidt N,Kostev K
Persistence in Patients with breast cancer treated with tamoxifen or aromatase inhibitors: A Retrospective Database Analysis
Breast Cancer Res Treat. 2013 Feb;138(1):185-91

Hadji et al. 2013b:
Hadji P, Ziller V, Kyvernitakis J, Schmidt N, Kostev K .
Persistence with bisphosphonates in patients with metastatic breast cancer: A retrospective database analysis
J Cancer Res Clin Oncol. 2013 Jul;139(7):1149-55

Hadji et al. 2014:
Hadji P, Kyvernitakis J, Albert U, Jockwig A, Jockwig B, Kostev K
Gender differences in persistency to bisphosphonates in patients with metastatic breast and prostate cancer
Int J Clin Pharmacol Ther. 2014 May;52(5):352-9

Kalousidou et al. 2015:
Kalousidou N, Kyvernitakis I, Waehlert L, Engelhard J, Kostev K, Ziller V..
Pregnancy after breast cancer in Germany – results of a retrospective database analysis
Z Geburtshilfe Neonatol. 2015 Aug;219(4):176-80

Kostev 2012:
Kostev K.
Risk of breast cancer in patients on insulin glargine and insulin detemir in comparison with those on human insulin
Diabetologia. 2012 May;55(5):1554-5

Kostev et al. 2014:
Kostev K, Waehlert L, Jockwig A, Jockwig B, Hadji P .
Physicians influence on breast cancer patient compliance
Ger Med Sci. 2014 Jan 20;12:Doc03. doi: 10.3205/000188. eCollection 2014

Kowall et al. 2015a:
Kowall B, Rathmann W, Kostev K
Are sulfonylurea and insulin therapies associated with a large risk of cancer than metformin therapy? A retrospective database analysis
Diabetes Care. 2015 Jan;38(1):59-65

Kowall et al. 2015b:
Kowall B, Stang A,Rathmann W, Kostev K
No reduced risk of overall, colorectal, lung, breast and prostate cancer with metformin therapy in diabetic patients: Database analyses from Germany and the United Kingdom
Pharmacoepidemiol Drug Saf. 2015 Aug;24(8):865-74

Jacob et al. 2015:
Jacob L, Waehlert L, Albert US, Hadji P, Kostev K
Impact of disease management program s on women with breast cancer in Germany
Breast Cancer Res Treat. 2015 Sep;153(2):391-5

Jacob et al. 2016a:
Jacob L, Kostev K
Cancer is associated with intraoperative and postprocedural complications and disorders
J Cancer Res Clin Oncol. 2016 Apr;142(4):777-81

Jacob et al. 2016b:
Jacob L, Kostev K, Rathmann W, Kalder M
Impact of Metformin on Metastases in Patients with Breast Cancer and Type 2 Diabetes
J Diabetes Complications. 2016 Apr 11. pii: S1056-8727(16)30102-7

Jacob et al. 2016c:
Jacob L, Bleicher L, Kostev K, Kalder M
Prevalence of depression, anxiety and their risk factors in German women with breast cancer in general and gynecological practices
J Cancer Res Clin Oncol. 2016 Feb;142(2):447-52

Jacob et al. 2016d:
Jacob L, Kostev K, Kalder M
Treatment of depression in cancer and non-cancer patients in German neuropsychiatric practices
Psychooncology. 2016 Jan 20. doi: 10.1002/pon.4066. [Epub ahead of print]

Jacob et al. 2016e:
Jacob L, Hadji P, Kostev K
Age-related differences in persistence with bisphosphonates in women with metastatic breast cancer
J Bone Oncol. 2016 Mar 2;5(2):63-6

Jacob et al. 2016f:
Jacob L, Hadji P, Kostev K
Age-related differences in persistence in women with breast cancer treated with tamoxifen or aromatase inhibitors in Germany
J Geriatr Oncol. 2016 Apr 16. pii: S1879-4068(16)30019-4

Schmidt et al. 2016:
Schmidt N, Jacob L, Kostev K, Kyvernitakis I, Hadji P
The impact of treatment compliance on fracture risk in women in the United Kingdom with breast cancer treated with aromatase inhibitors
Breast Cancer Res Treat. 2016 Jan;155(1):151-7

Chapter 3. Cardiovascular diseases

Occupational therapy after myocardial or cerebrovascular infarction

The study by Drosselmeyer et al. assessed how many patients received occupational therapy after brain or cardiac infarction, how long it took until first therapy after the ischemic attack occurred, and which factors influenced whether a patient did or did not receive occupational therapy. The study population included 7,440 patients who were examined by a cardiologist following a stroke or myocardial infarction (MI). In addition to baseline characteristics, the presence of certain cardiovascular risk factors or comorbidities was recorded. This study showed that only 1,779 (24%) patients were referred to occupational therapy by a cardiologist within three years after their first diagnosis. Of these, 88.5% had been diagnosed with MI and 11.5% with stroke. In the group without referral (n = 5,661), 60.7% had experienced an MI and 39.3% a stroke. No significant gender-related differences were observed. Younger age, an MI diagnosis, and the presence of hypertension positively influenced referral rate, time, and the chance of being offered occupational therapy, while risk factors, such as obesity delayed therapy. The Charlson Comorbidity Index was higher in the group referred to occupational therapy. These findings were in line with previous studies [Drosselmeyer et al. 2014].

Risk of non-fatal myocardial infarction in patients with coronary heart disease: disease management programs versus standard care

Jacob et al. compared the risk of myocardial infarction in coronary heart disease (CHD) patients who were enrolled in disease management programs (DMPs) with that of patients receiving standard care (SC). A total of 147,411 primary care patients and 27,939 patients treated in cardiology practices with an initial diagnosis of CHD (2005-2013) were

included. This constituted the first time that the difference between CHD patients in DMPs versus those in SC was compared, showing that CHD patients treated in cardiology practices had a lower risk of myocardial infarction if they were enrolled in a DMP than if they only receveived SC. However, the findings indicated that there was no difference between DMP and SC patients treated in general practitioner practices with regard to the risk of myocardial infarction. Additionally, this work demonstrated that patients treated in general practitioner practices received on average more medications than patients treated in cardiology practices [Jacob et al. 2015].

Persistence with antihypertensive treatments

The study by Hasford et al. evaluated persistence with antihypertensive treatment. In total, 13,763 hypertensive patients newly diagnosed between September 2000 and May 2001 were identified at general practitioner practices and internist practices, and observed for three years after their first antihypertensive prescription. The median duration of persistence with any antihypertensive treatment was no longer than 110 days. One of every eight patients received just one prescription in three years and neither sex nor insurance status or comorbidity had a relevant impact. This study confirmed that persistence in prescribing antihypertensive medicines declines within a short time [Hasford et al. 2007].

Real-life treatment patterns, compliance, persistence, and medication costs in patients with hypertension

A study by Breitscheidel et al. described current treatment patterns used by general practitioners in Germany for patients with arterial hypertension. A particular focus was put on compliance, persistence, and medication costs of fixed-dose and unfixed combinations of angiotensin

receptor blockers (ARBs), amlodipine (AML), and hydrochlorothiazide (HCT). Out of 406,888 patients who received a diagnosis of essential hypertension between September 2009 and August 2010, 88,716 received prescriptions including ARBs, monotherapy (18.6%), or unfixed combinations with other anti-hypertensives (19.3%). Compliance with fixed-dose combinations of ARB with HCT, either dual or in conjunction with one other anti-hypertensive drug, was significantly better compared to unfixed combinations. Fixed-dose combinations of ARB with HCT, ARB with AML, dual only, or prescribed with another anti-hypertensive medication resulted in a substantial increase of persistence, especially for patients on fixed-dose dual combinations. Fixed-dose combinations were cheaper on average than unfixed combinations. Fixed-dose combinations were cheaper on average than unfixed combinations. The results were in line with findings from prior studies assessing compliance and persistence in hypertensive patients, suggesting that treatment with ARBs is associated with significantly higher compliance and persistence rates than other anti-hypertensive drugs [Breitscheidel et al. 2012]

References

Drosselmeyer et al. 2014:
Drosselmeyer J, Jockwig A, Kostev K, Heilmaier C (2014)
Occupational Therapy After Myocardial or Cerebrovascular Infarction: Which Factors Influence Referrals?
The Open Journal of Occupational Therapy
http://scholarworks.wmich.edu/ojot/vol2/iss3/3
DOI: 10.15453/2168-6408.1090/10.15453/2168-6408.1090

Jacob et al. 2015:.
Jacob J, Kostev K
Risk of non-fatal myocardial infarction in German patients with coronary heart disease: disease management programs versus standard care
Perfusion 05/2015; 28: 160-165

Hasford et al. 2007:
Hasford J, Schröder-Bernahrdi D, Rottenkolber M, Kostev K, Dietlein G
Persistence with antihypertensive treatments: results of a 3-year follow-up cohort study
Eur J Clin Pharmacol. 2007 Nov;63(11):1055-61

Breitscheidel et al. 2012:
Breitscheidel L, Ehlken B, Kostev K, Oberdiek M.S A, Sandberg A, Schmieder RE
Real-life treatment patterns, compliance, persistence, and medication costs in patients with hypertension in Germany
J Med Econ. 2012;15(1):155-65

Chapter 4. Osteoporosis

Proton pump inhibitor therapy and osteoporosis risk

In this work Jacob et al. investigated the association between the use of proton pump inhibitors (PPIs) and osteoporosis in postmenopausal women. This study included 3,092 women with osteoporosis and 3,092 women without osteoporosis. Cases and controls were matched on the basis of age, health insurance, index year, and physician. Osteoporosis development was found to be associated with disorders of the esophagus and gastritis/duodenitis. Interestingly, the use of PPIs also led to an increase in the risk of developing osteoporosis. Finally, the odds of being diagnosed with osteoporosis increased with the duration of PPI therapy, from 1.58 with 1 year of therapy or less to 1.72 with at least 5 years of therapy. The association between the prescription of PPIs and osteoporosis has been the subject of controversial literature, and the causal relation between gastrointestinal diseases and osteoporosis has been known for years [Jacob et al. 2016a].

Non-Compliance and the associated risk of fractures

The study of Hadji et al. investigated persistence and compliance with oral bisphosphonate regimens, and their association with fracture incidence in women with osteoporosis. Data from 4,147 women were evaluated, with a median oral bisphosphonate treatment duration of 145.5 days. Persistence rates after 1 and 2 years were 27.9% and 12.9%, respectively, and 66.3% of women were compliant. After 24 months of therapy, compliant women had fewer fractures than non-compliant women. Treatment compliance was the only factor that significantly decreased fracture risk. The conclusion of the study was that compliance and persistence with oral bisphosphonate regimens in women with osteoporosis were inadequate. Better compliance and

persistence can prevent fractures in these women. The presented analysis was the first study in Germany to link clinical outcomes for all available oral bisphosphonates with compliance and persistence. The results confirmed prior findings that a high degree of compliance and persistence was associated with a significantly decreased risk of osteoporotic fracture [Hadji et al. 2012].

Persistence with teriparatide therapy

The analysis by Kyvernitakis et al. investigated persistence with teriparatide treatment in patients with osteoporosis according to gender and health care provider. A total of 829 patients with osteoporosis treated by general practitioners or orthopedic surgeons who received first-time teriparatide prescriptions from January 2005 to December 2012 were included. After 18 months of follow-up, 39.5% of the female and 34% of the male patients had discontinued their treatment (gap > 90 days), while 39.4% of female and 47.8% of male patients were still persistent with their treatment. The finding was a highly significant decreased risk of treatment discontinuation in patients with fractures prior to treatment initiation, compared to those without such fractures. Female patients presented higher discontinuation rates of teriparatide compared to males. Patients treated in the practices of orthopedic surgeons were more persistent than patients treated in GP practices. The results were consistent with those from similar studies conducted in other countries and, for the first time, considered the gender-specific persistence in patients receiving teriparatide [Kyvernitakis et al. 2014].

Fractures and treatment compliance

Jacob et al. analyzed treatment persistence in patients with osteoporosis after fracture diagnosis in primary care practices. This study included postmenopausal women with osteoporosis aged between 40 and 90

years and treated in general or orthopedic practices with treatment start between 2004 and 2013. A total of 13,975 patients were included in the group that presented fractures before therapy initiation and 18,138 in the group without such fractures. The analysis found that within 12 months after treatment initiation, treatment discontinuation was less common in subjects with an extended delay between osteoporosis diagnosis and treatment initiation (13-36 and > 36 months: 40.7%) than in subjects with a shorter delay (≤12 months: 44.3%). Fractures only increased persistence when pain medications were not accounted for, suggesting that pain improves osteoporosis treatment continuation. Discontinuation of treatment was defined as a period of at least 90 days without therapy. This work underlined the fact that age, denosumab/injectable bisphosphonate prescriptions, orthopedic care, and a delay of up to 36 months between osteoporosis diagnosis and treatment initiation had a positive impact on persistence. By contrast, depression increased discontinuation rates. Finally, the intake of both analgesics and opioids was associated with improved persistence. Thus, persistence with osteoporosis treatment was favored by pain, but not by experiencing fractures. These results suggest that fracture-related pain may have an impact on treatment persistence. Although no studies have yet investigated this intriguing relationship, pain may represent the missing link between fractures and increased persistence [Jacob et al. 2016b].

Gender- and age-related treatment compliance in osteoporosis patients

This study by Hadji et al. retrospectively analyzed treatment compliance in osteoporotic patients treated with osteoporosis medications. A total of 10,265 patients treated in general or orthopedic practices were included in the analysis who had been diagnosed with osteoporosis with or without fractures and had started anti-osteoporotic therapy (bisphosphonates, denosumab, or strontium ranelate) between 2011 and

2014. Noncompliance was observed in 55.2% of the patients. Patients in the age group ≤ 60 years were at a higher risk of being noncompliant when compared to those in the age group of 61-70 years. Men and patients who received oral drugs were also more likely to be noncompliant than women and patients who received injectable or intravenous drugs. Finally, therapies that were given every three or six months were associated with a decrease in the risk of noncompliance when compared to weekly therapy, whereas daily and monthly treatments were associated with an increased risk. Compliance was insufficient in osteoporotic patients treated with bisphosphonates, denosumab, and strontium ranelate. This outcome was in line with previous studies [Hadji et al. 2016].

Prevalence and type of antidepressant therapy used by general practitioners in Germany to treat female patients with osteoporosis

Drosselmeyer et al. estimated the prevalence and type of antidepressant medication prescribed by primary care physicians in Germany to patients with depression and osteoporosis. The study population included 3,488 female osteoporosis patients aged between 40 and 90 years, recruited from 1,179 general practitioner practices who were initially diagnosed with depression during the index period (January 2004 to December 2013). Also included in this study were 3,488 non-osteoporotic controls who were matched (1:1) to osteoporosis cases on the basis of age, health insurance coverage, severity of depression, and physician carrying out the diagnosis. Osteoporosis patients were treated initially with antidepressants more often than non-osteoporosis patients, especially within the groups of patients with moderate or severe depression. TCA was the most frequently used antidepressant therapy class upon initial diagnosis in both patient groups. Osteoporosis patients received referrals to hospitals or psychiatrists more often than patients without osteoporosis. Several studies have demonstrated that

depression is associated with an increase in fracture incidence and is believed to lead to worsening of the disease [Drosselmeyer et al. 2016].

Impact of depot medroxyprogesterone acetate on fracture risk

The study of Kyvernitakis et al. examined the association between use of depot medroxyprogesterone acetate (DMPA) or combined oral contraceptives and the risk of incident fracture. A total of 4,189 women between 20 and 44 years of age with a first-time fracture diagnosis were identified, matched with 4,189 random controls, and the relation with DMPA exposure was investigated. The study showed that DMPA exposure was associated with increased fracture risk and that fracture risk increased with longer DMPA exposure. The highest fracture risk was identified in young patients less than 30 years of age with longer DMPA exposure (≥ 10 prescriptions), as well as in patients in their late reproductive years with past use of DMPA. The results were in line with other previous studies [Kyvernitakis et al. 2016].

References

Drosselmeyer et al. 2016:
Drosselmeyer J, Rapp MA, Kostev K
Prevalence and type of antidepressant therapy used by German general practitioners to treat female patients with osteoporosis
Int J Clin Pharmacol Ther. 2016 Oct;54(10):743-9

Hadji et al. 2012:
Hadji P, Claus V, Steinle T, Intorcia M, Kostev K, Ziller V
GRAND: the German retrospective cohort analysis on compliance and persistence and the associated risk of fractures in osteoporotic women treated with oral bisphosphonates
Osteoporos Int. 2012 Jan;23(1):223-31.

Hadji et al. 2016:
Hadji P, Jacob L, Kostev K
Gender- and age-related treatment compliance in patients with osteoporosis in Germany
Patient Prefer Adherence. 2016 Nov 23;10:2379-2385

Jacob et al. 2016a :
Jacob L, Hadji P, Kostev K
The use of proton pump inhibitors is positively associated with osteoporosis in postmenopausal women in Germany
Climacteric. 2016 Oct;19(5):478-81

Jacob et al. 2016b :
Jacob L, Dreher M, Kostev K, Hadji P
Increased treatment persistence and its determinants in women with osteoporosis with prior fracture compared to those without fracture
Osteoporos Int. 2016 Mar;27(3):963-9

Kyvernitakis et al. 2014:
Kyvernitakis I, Kostev K, Kurth A, Albert US, Hadji P
Differences in persistency with teriparatide in patients with osteoporosis according to gender and health care provider
Osteoporos Int. 2014 Dec;25(12):2721-8

Kyvernitakis et al. 2016:
Kyvernitakis I, Kostev K, Nassour T, Thomasius F, Hadji P
The impact of depot medroxyprogesterone acetate on fracture risk: a case-control study from the UK
Osteoporos Int. 2016 Jul 26. [Epub ahead of print]

Chapter 5. Dementia

Prescription patterns and drug costs in patients with dementia

The study by Jacob et al. analyzed prescription patterns and drug costs in patients with dementia who lived in home-care settings and nursing homes. The analysis included 41,064 patients treated by general practitioners (GPs) and 20,649 patients treated by psychiatric practitioners (PPs). All patients had been diagnosed with dementia in 2014. Antidementives were more frequently prescribed to patients in home-care settings, whereas antidepressants, antipsychotics, and benzodiazepines were more commonly administered to nursing-home patients in both the GP and the PP groups. Individuals residing in nursing homes had a lower likelihood of receiving antidementives but exhibited a higher likelihood of being prescribed antidepressants, antipsychotics, and benzodiazepines. The total cost of therapy was higher in nursing homes than in home-care settings (GPs: difference of €27.20; PPs: difference of €107.90). The cost of antidementives was significantly lower in GP patients residing in nursing homes than in GP patients living at home. There was no significant difference in the cost of antidementives between the PP groups. By contrast, for both practice types, the costs of the three other families of drugs were lower in individuals cared for at home than in individuals residing in nursing homes. Prescription patterns and drug costs in dementia patients significantly differed between home settings and nursing homes [Jacob et al. 2016].

Antihypertensive treatment and risk of dementia

Wagner et al. investigated the association between antihypertensive prescriptions and incident dementia. The analysis was based on 575 general and internal medicine practices (10/2003 - 09/2008).

Antihypertensive medication use in the three years prior to initial dementia diagnoses in 1,297 patients was compared to antihypertensive medication use in 1,297 controls without dementia after matching for age, sex, and date of diagnosis. A significantly lower risk of dementia was observed in primary care patients who were continuously treated with beta blockers over a period of three years after adjusting for demographic covariates, health care use, and cardiovascular and neurological comorbidities. In the fully adjusted model, ACE inhibitors also tended to be inversely associated with incident dementia, but failed to achieve statistical significance. Calcium channel blockers were positively related to cognitive impairment only in the crude analysis. The other drug groups were not significantly related to dementia [Wagner et al. 2012].

Hip fracture risk in patients with dementia

The study by Bohlken et al. analyzed the risk of hip fracture in German primary care patients with dementia. The study included patients aged 65-90 from primary care practices who were first diagnosed with dementia between 2010 and 2013. Controls were matched (1:1) to cases for age, sex, and type of health insurance. A total of 53,156 dementia patients and 53,156 controls were included. A total of 5.3% of patients and 0.7% of controls displayed hip fractures after three years. Hip fractures occurred more frequently in dementia subjects living in nursing homes than in those living at home (9.2% versus 4.3%). Dementia, residence in nursing homes, and osteoporosis were risk factors for fracture development. Dementia increased hip fracture risk in German primary care practices. These findings were in line with other literature on the subject [Bohlken et al. 2015a].

Continuous treatment with antidementia drugs

In a long-term study, Bohlken et al. investigated continuous treatment in dementia patients. Data from 12,910 outpatients with dementia treated by general practitioners and specialist physicians between January 2003 and December 2013 were included. Higher age and female sex were risk factors for treatment discontinuation. After one year of follow-up, nearly 60% of patients continued drug treatment. Donepezil and memantine patients were less likely to discontinue treatment as compared to rivastigmine users. Patients were less likely to discontinue treatment if they were treated by specialist physicians as compared to general practitioners. Younger male patients and patients who had private health insurance had a lower discontinuation risk. Regarding comorbidity, patients were more likely to be continuously treated with the index substance if heart failure or hypertension had been diagnosed at baseline. In line with other studies, this report showed that donepezil and memantine were associated with a lower risk of discontinuation than rivastigmine and galantamine [Bohlken et al. 2015b].

Progression of mild cognitive impairment to dementia

The following study by Bohlken et al. estimated the rate of progression of mild cognitive impairment to dementia and identified the potential risk factors in specialist practices from 2005 to 2015. The study included 4,633 patients aged 40 years and over from 203 neuropsychiatric practices who were initially diagnosed with mild cognitive impairment between 2005 and 2013. More than one-third of the individuals treated in neuropsychiatric practices developed dementia in the five years following their mild cognitive impairment diagnoses. The percentage of subjects with dementia increased with age, was higher in women than in men and also higher for patients with public health insurance coverage. [Bohlken et al. 2016].

Risk factors for dementia diagnosis

Booker et al. also estimated dementia risk factors in primary care patients. Their case-control study included primary care patients (70-90 years) who received their initial diagnosis of (all-cause) dementia during the index period (01/2010-12/2014) and controls without dementia matched (1:1) to cases on the basis of age, sex, type of health insurance, and physician. A total of 11,956 cases and 11,956 controls were analyzed. Diabetes, lipid metabolism, stroke incl. TIA, Parkinson's disease, intracranial injury, coronary heart disease, mild cognitive impairment, as well as mental and behavioral disorders due to alcohol use were associated with an increased risk of dementia. The use of statins, proton-pump inhibitors, and antihypertensive drugs was associated with a decreased risk of developing dementia. Risk factors for dementia found in this study were consistent with the literature [Booker et al. 2016a].

Persistence with antidepressant drugs in patients with dementia

The following study conducted by Booker et al. determined what proportion of patients with dementia received antidepressants, over what period the treatment was administered, and what factors increased the risk of discontinuation. It included 12,281 patients with dementia treated by general practitioners and neurologists/psychiatrists with an initial prescription of an antidepressant drug between January 2004 and December 2013. By the end of the sixth month of treatment, only 47% of dementia patients treated with antidepressants remained in treatment without medication gaps exceeding 90 days. Patients using selective serotonin reuptake inhibitors or serotonin and norepinephrine reuptake inhibitors exhibited a significantly decreased risk of treatment discontinuation as compared to patients who received tricyclic antidepressants. By contrast, older patients and patients treated by neurologists/psychiatrists exhibited a significantly increased risk of

treatment discontinuation. Comorbidity of diabetes or history of stroke were associated with a decreased risk of treatment discontinuation. According to the author, this was the first primary care observational study on persistence with antidepressant therapy in dementia patients to be conducted worldwide [Booker et al. 2016b].

Persistence with antipsychotics in dementia patients

Booker et al. analyzed the duration of treatment with antipsychotics in dementia patients. A total of 12,979 patients with dementia aged 60 years and over treated by psychiatrists were included. The percentage of dementia patients treated with antipsychotics was very high. Persistence with antipsychotics increased with age, from 54.8% for patients aged between 60 and 69 years to 65.4% for patients aged between 90 and 99 years after 24 months of follow-up. The study further showed that older subjects, women, patients living in nursing homes, and subjects treated with atypical antipsychotics exhibited a higher risk for long-term use of antipsychotics. By contrast, depression and Parkinson's disease decreased persistence. The findings corroborated the results of previous studies [Booker et al. 2016c].

References

Bohlken et al. 2015a:
Bohlken J, Jacob L, Schaum P, Rapp MA, Kostev K
Hip fracture risk in patients with dementia in German primary care practices
Dementia (London). 2015 Dec 23. pii: 1471301215621854. [Epub ahead of print]

Bohlken et al. 2015b:
Bohlken J, Weber S, Rapp MA, Kostev K
Continuous treatment with antidementia drugs in Germany 2003-2013: a retrospective database analysis
Int Psychogeriatr. 2015 Apr 22:1-8

Bohlken et al. 2016:
Bohlken J, Jacob L, Kostev K
Progression von leichter kognitiver Störung zur Demenz in deutschen Hausarztpraxen Eine retrospektive, Datenbank gestützte Auswertung / Progression of mild cognitive impairment to dementia in German primary care practices- a retrospective database analysis
Fortschr Neurol Psychiatr. 2016 Nov 15. [Epub ahead of print]

Booker et al. 2016a:
Booker A, Jacob L, Rapp MA, Bohlken J, Kostev K
Risk factors for dementia diagnosis in German primary care practices
Int Psychogeriatr. 2016 Jan 8:1-7.

Booker et al. 2016b:
Booker A, Rapp MA, Bohlken J, Kostev K
Persistence with antidepressant drugs in patients with dementia: a retrospective database analysis
Int J Clin Pharmacol Ther. 2016 May;54(5):323-9

Booker et al. 2016c:
Booker A, Jacob L, Bohlken J, Rapp MA, Kostev K
Persistence with antipsychotics in dementia patients in Germany
Int J Clin Pharmacol Ther. 2016 Nov;54(11):835-840.

Jacob et al. 2016:
Jacob L, Bohlken J, Kostev K
Prescription patterns and drug costs in German patients with dementia in nursing homes and home-care settings
Int J Clin Pharmacol Ther. 2016 Nov 23. [Epub ahead of print]

Wagner et al. 2012:
Wagner G, Icks A, Abholz HH, Schröder-Bernhardi D, Rathmann W, Kostev K
Antihypertensive treatment and risk of dementia: a retrospective database study
Int J Clin Pharmacol Ther. 2012 Mar;50(3):195-201.

Chapter 6. Depression

Risk of developing depression when suffering from neurological diseases

Thielscher et al. investigated the comorbidity of Alzheimer's/dementia, epilepsy, multiple sclerosis, and Parkinson's with depression. A total of 42,914 patients who had been newly diagnosed with the four comorbid diseases were included. The study analyzed how many of these patients developed depression within five years. Overall, 8.3% of all the patients who met the inclusion criteria were diagnosed with depression in the five-year period after the index date. This was in line with earlier findings on incidence and the first time that the longitudinal risk of developing depression in patients with neurological diseases has been estimated for a sample of approximately 40,000 patients [Thielscher et al. 2013].

Risk of psychiatric and neurological diseases in patients with workplace mobbing experience

Kostev et al. analyzed the incidence of certain neurological and psychiatric diseases as a consequence of mobbing as compared with a control group and examined the possible influence of diseases that occurred within one year prior to the first documented incidence of mobbing. A total of 2,625 patients who had experienced mobbing were matched based on age, gender, and health insurance status with a control group (2,625) of patients who had not reported workplace mobbing and who were being treated by the same physicians between 2003 and 2012. Those who would later become the victims of bullying were more prone to suffer from diseases in general, even before any mobbing occurred. This underlines the importance of support for (chronically) ill patients in order to protect them against bullying. Some of

these results have been described in earlier literature [Kostev et al. 2014a].

Prevalence of depression in type 2 diabetes patients

The study by Jacob et al. focused on depression in type 2 diabetes patients with or without diabetes complications treated in general practices. A total of 90,412 people initially diagnosed with type 2 diabetes (2004-2013) were included. Ten years after their type 2 diabetes diagnosis, 30.3% of patients showed symptoms of depression. Depression was more common in women and in individuals without private health insurance coverage. Prevalence also increased with the number of diabetes complications. Retinopathy, neuropathy, nephropathy, coronary heart disease, and stroke were associated with a higher risk of developing depression. High levels of HbA1c had the strongest effect on the risk of developing depression in type 2 diabetes patients. The results have been confirmed by previous studies [Jacob et al. 2016a].

Gender-based differences in the antidepressant treatment of patients with depression

The following study by Jacob et al. compared treatment initiation in men and women treated in German neuropsychiatric practices after a diagnosis of depression. A total of 35,495 men and 54,467 women aged between 18 and 80 and first diagnosed with depression by psychiatrists between 2010 and 2013 were included. Three subgroups of different disease severity (mild, moderate, and severe depression) were investigated. After three years of follow-up, 77.3% of men and 78.5% of women diagnosed with mild depression, 89.2% of men and 90.7% of women with moderate depression, and 88.6% of men and 89.5% of women with severe depression had been treated. Gender did not have

an impact on therapy initiation in depressed patients. The outcome was in line with the existing literature [Jacob et al. 2016b].

Influence of adverse effects on the dropout rate in selective serotonin reuptake inhibitor treatment

The study by Kostev et al. assessed the most common adverse drug reactions of SSRIs, as well as their impact on dropout rate in a large study population. The study investigated a total of 50,824 patients from general practices initially treated for major depressive disorder with SSRIs between January 2009 and December 2012. The adverse effects mentioned most frequently were: “discomfort” of the digestive system (10%), sleep disorders (8.6%), and heart rhythm disorders (4%); however, these were of tolerable severity as they did not significantly influence the dropout rate. By contrast, somnolence and younger age (≤50 years), in particular, increased the risk of premature treatment discontinuation, while patients suffering from cardiovascular risk factors or osteoporosis tended to adhere to the therapy [Kostev et al. 2014b].

Treatment of depression in patients with cardiovascular diseases

The study by Konrad et al. estimated the prevalence and the type of antidepressant medication prescribed by German psychiatrists to patients with depression and cardiovascular diseases (CVD). The population included 2,288 cardiovascular patients between 40 and 90 years of age from 175 psychiatric practices and 2,288 non-cardiovascular controls matched (1:1) on the basis of age, gender, health insurance coverage, and depression severity. The observation period was between 2004 and 2013. No association was found between cardiovascular disease and the initiation of depression treatment. Furthermore, cardiovascular patients received SSRIs/SNRIs more frequently. Mild, moderate, or severe depression was present in 18.7%,

60.7%, and 20.6% of patients, respectively. Most patients received treatment within a year, many of them immediately after a depression diagnosis. Patients with moderate and severe depression were more likely to receive treatment than patients with mild depression. There was no difference between CVD and non-CVD patients in the proportion of patients treated. Nonetheless, CVD patients received selective serotonin reuptake inhibitors/serotonin-noradrenaline reuptake inhibitors significantly more frequently. Conversely, patients without CVD were more often treated with TCA. The results were in line with the recommendations of current guidelines [Konrad et al. 2016a].

Depression risk in female patients with osteoporosis

Drosselmeyer et al. analyzed the incidence of depression in female patients with osteoporosis and evaluated the risk factors for depression diagnosis within this patient population. The study population included 70,966 patients between 40 and 80 years of age from primary care practices. The observation period was between 2004 and 2013. A total of 35,483 female osteoporosis patients were compared with 35,483 patients without osteoporosis regarding the incidence of depression. The risk of depression was significantly increased for patients with osteoporosis as compared with patients without osteoporosis in primary care practices. After the five-year follow-up, depression diagnoses were present in 33.0% of the osteoporosis group and in 22.7% of the control group. Dementia, cancer, heart failure, coronary heart disease, and diabetes were associated with a higher risk of developing depression. Private health insurance coverage was associated with a lower risk of depression. There was no significant effect of fractures on depression risk. The results confirmed previous studies [Drosselmeyer et al. 2016a].

Depression risk in patients with heart failure treated in primary care practices

The study by Konrad et al. estimated the prevalence of, and risk factors for, depression in heart failure (HF) patients. The study population included 132,994 patients between 40 and 90 years of age from primary care practices. The observation period was between 2004 and 2013. A total of 66,497 HF patients and 66,497 controls were selected and matched (1:1) to HF patients on the basis of age, sex, health insurance, depression diagnosis in the past, and follow-up duration after the index date. HF was significantly associated with increased depression risk. A total of 10.5% of HF patients and 6.3% of matched controls had developed depression after one year of follow-up. Depression had been documented in 28.9% of the HF group and 18.2% of the control group after the five-year follow up. Cancer, dementia, osteoporosis, stroke, and osteoarthritis were associated with a higher risk of developing depression. Male gender and private health insurance coverage were associated with a lower risk of depression. The results were consistent with previous research [Konrad et al. 2016b].

Depression risk in patients with late-onset rheumatoid arthritis

The study by Konrad et al. determined the prevalence of depression and its risk factors in patients with late onset rheumatoid arthritis (RA) treated in general primary care practices. A total of 7,301 patients initially diagnosed with RA between 2009 and 2013 were included and matched (1:1) to 7,301 controls. Late-onset RA was associated with an increased risk of developing depression. Depression diagnoses were present in 22.0% of the RA group and 14.3% of the control group after a five-year follow-up period. In the multivariate regression model, RA was a strong risk factor for the development of depression. There was significant interaction of RA and diagnosed inflammatory polyarthropathies. Furthermore, dementia, cancer, osteoporosis, hypertension, and

diabetes were associated with a higher risk of developing depression. Previous studies were in line with these results [Drosselmeyer et al. 2016b].

Depression risk in patients with coronary heart disease

A subsequent study by Konrad et al. determined the prevalence of depression and its risk factors among patients with coronary heart disease (CHD) treated in primary care practices. Individuals initially diagnosed with CHD (2009-2013) were identified, and 59,992 patients were included and matched (1:1) to 59,992 controls. The primary outcome measure was an initial diagnosis of depression within five years after the index date among patients with or without CHD. CHD was associated with an increased risk of developing depression. Moreover, prior depressive episodes and co-diagnoses such as dementia, stroke, cancer, osteoporosis, heart failure, osteoarthritis, hypertension, cardiac arrhythmias, and diabetes were also risk factors for this psychiatric disorder. Individuals aged 60 years or younger and individuals aged over 70 years were more likely to develop depression compared with patients aged 61-70 years. Finally, men were at a lower risk of being diagnosed with depression than women. The outcomes were in line with previous data [Konrad et al. 2016c].

Impact of comorbidities on the cost of depression drug therapy in general practices

Jacob et al. analyzed the impact of comorbidities on the cost of antidepressant drug therapy in patients with depression treated in German general practices (GPs). The study included 31,741 patients diagnosed with depression and treated with antidepressant drugs in 2015. Demographic data included age, gender, type of health insurance coverage, and comorbidities. The annual antidepressant treatment cost

per patient was calculated based on pharmacy sale prices. This retrospective study estimated the annual cost of antidepressant treatments per patient at about €100. This cost was similar in men and in women, but was higher in individuals with private health insurance coverage than in individuals with public health insurance coverage. Moreover, the cost of antidepressant drugs increased with age and with the number of comorbidities. Interestingly, disorders of adult personality and behavior, epilepsy, and diabetes had the strongest impact on this cost. Finally, the number of antidepressant drugs taken increased with the number of comorbidities. The study was in line with other literature [Jacob et al. 2016c].

References

Drosselmeyer et al. 2016a:
Drosselmeyer J, Rapp MA, Hadji P, Kostev K
Depression risk in female patients with osteoporosis in primary care practices in Germany
Osteoporos Int. 2016 Sep;27(9):2739-44

Drosselmeyer et al. 2016b:
Drosselmeyer J, Jacob L, Rathmann W, Rapp M, Kostev K
Depression risk in patients with late-onset rheumatoid arthritis in Germany
Qual Life Res. 2016 Aug 8. [Epub ahead of print]

Jacob et al. 2016a:
Jacob L., Kostev K
Prevalence of depression in type 2 diabetes patients in German primary care practices
J Diabetes Complications. 2016 Apr;30(3):432-7

Jacob et al. 2016b:
Jacob L, Kostev K
Gender-based differences in the antidepressant treatment of patients with depression in German psychiatric practices
Ger Med Sci. 2016 Feb 15;14:Doc02. doi: 10.3205/000229

Jacob et al. 2016c:
Jacob L, Kostev K
Impact of comorbidities on the cost of depression drug therapy in general practices in Germany
J Psychiatr Res. 2016 Aug 26;83:130-136. doi: 10.1016/j.jpsychires.2016.08.017. [Epub ahead of print]

Konrad et al. 2016a:
Konrad M, Jacob L, Rapp MA, Kostev K
Treatment of depression in patients with cardiovascular diseases by German psychiatrists
Int J Clin Pharmacol Ther. 2016 Aug;54(8):557-63

Konrad et al. 2016b:
Konrad M, Bohlken J, Rapp MA, Kostev K
Depression risk in patients with heart failure in primary care practices in Germany
Int Psychogeriatr. 2016 Jun 16:1-6

Konrad et al. 2016c:
Konrad M, Jacob L, Rapp MA, Kostev K.
Depression risk in patients with coronary heart disease in Germany
World J Cardiol. 2016 Sep 26;8(9):547-552.

Kostev et al. 2014a:
Kostev K, Rex J, Eith T, Heilmaier C
Which adverse effects influence the dropout rate in selective serotonin reuptake inhibitor (SSRI) treatment? Results for 50,824 patients
Ger Med Sci. 2014 Oct 16;12:Doc15. doi: 10.3205/000200. eCollection 2014

Kostev et al. 2014b:
Kostev K, Rex J, Waehlert L, Hog D, Heilmaier C
Risk of psychiatric and neurological diseases in patients with workplace mobbing experience in Germany: a retrospective database analysis
Ger Med Sci. 2014 May 27;12:Doc10. doi: 10.3205/000195. eCollection 2014

Thielscher et al. 2013:
Thielscher C, Thielscher S, Kostev K
The risk of developing depression when suffering from neurological diseases
Ger Med Sci. 2013;11:Doc02. Epub 2013 Jan 14.

Chapter 7. Neurologic diseases

Sociodemographic disparities in the administration of antiepileptic drugs to adults with epilepsy

Hamer et al. investigated the use of antiepileptic drugs (AEDs) in the treatment of epilepsy. A total of 43,712 adult patients with an epilepsy diagnosis (ICD-10 code: G40.X) seen between 2010 and 2012 by neurologists were retrospectively analyzed according to sociodemographic characteristics, comorbidities, and AED treatment. men were less likely than women to receive lamotrigine and were usually treated with carbamazepine. Patients with statutory health insurance coverage were treated more frequently with valproate and exhibited a higher rate of obesity than patients covered by private health insurance, while PHI was associated with more frequent administration of levetiracetam. Carbamazepine and primidone were administered more frequently in rural versus urban areas. Lamotrigine was used more frequently in western than in eastern Germany. Residence in an urban community increased the likelihood of being treated with levetiracetam. In spite of common guidelines, AED treatment differed significantly among adults with epilepsy in Germany. Besides gender, the type of health insurance and place of residence strongly influenced AED administration [Hamer et al. 2014].

Association of time-to-levodopa with initial anti-Parkinsonian medication

The study by Reese et al. determined the initial distribution of medication in patients with de novo Parkinson's disease (PD), estimated the share of patients who had not received a recommended initial therapy according to current German guidelines, and compared the time-to-

levodopa. A representative sample of 108,885 de novo patients diagnosed with PD was included. 71.8% of patients received levodopa as a first line treatment. Initial treatment with anticholinergics was correlated with a significantly longer levodopa-free period when compared to treatment with the dopamine agonist amantadine or to monoamine oxidase B inhibitor monotherapy. 29.0% of patients not starting with levodopa switched to levodopa within 5 years. After 5 years, more than 80% of PD patients using anticholinergics as their initial treatment remained levodopa-free [Reese et al. 2015].

Persistence with opioid treatment in patients suffering from chronic non-malignant or cancer pain

The study by Kostev et al. assessed factors influencing opioid persistence in a large patient cohort of 32,158 patients receiving opioid treatment for either chronic non-malignant or cancer pain. Data from 32,158 patients with a first-time prescription of an opioid in the period from January 2009 until December 2013 treated in orthopedic, neurological, and general practitioner practices were retrospectively analyzed. After 1 year of follow-up, 69% of patients treated with opioids had stopped medication intake (refill gap of 90 days). There was a significantly increased risk of treatment discontinuation for younger patients compared with patients aged >70. Cancer pain was associated with a significantly lower risk of therapy discontinuation, whereas persistence was considerably less probable for diagnoses such as various kinds of back pain, osteoarthritis, and spondyloarthritis. Chronic comorbidities such as diabetes, hypertension, heart insufficiency, and dementia were associated with a decreased risk of treatment discontinuation [Kostev et al. 2015].

Non-adherence to antiepileptic drugs

Gollwitzer et al. assessed the effect of patient and drug characteristics on medication adherence in people with epilepsy (PWE) in a large cohort representative of the German population. From 2010 to 2013, 31,317 adult PWE were retrospectively analyzed regarding demographic characteristics, comorbidities, and treatment with antiepileptic drugs (AED). Adherence was measured using the medication possession ratio (MPR). Individuals with an MPR of 80% were classified as non-adherent. A third of PWE treated with AED in Germany showed poor adherence, which was related to demographic characteristics and drug properties. Administration of new, well-tolerated drugs in simple dosage regimens improved AED compliance. The mean MPR was 81.1%, with 64.7% of patients showing good adherence. Patient-related factors associated with good adherence to AED treatment were residence in western Germany and learning disability. Adherence was higher in patients treated with new AEDs than in patients treated with old ones and with branded rather than generic ones. Among the most common AEDs, levetiracetam achieved the best adherence and valproate the lowest. Two or more daily dosages reduced adherence. The findings were in agreement with previous studies [Gollwitzer et al. 2016].

References

Hamer et al. 2014:
Hamer HH, Kostev K
Sociodemographic Disparities in Administration of Antiepileptic Drugs to Adults with Epilepsy in Germany: A Retrospective, Database Study of Drug Prescriptions
CNS Drugs. 2014 Aug;28(8):753-9

Reese et al. 2015:
Reese JP, Hamer H, Oertel WH, Strzelczyk A, Mueller UO, Heilmaier C, Kostev K
Association of time-to-levodopa with initial Parkinsonian medication: a retrospective cohort study
Int J Clin Pharmacol Ther. 2015 Feb;53(2):107-114.

Kostev et al. 2015:
Kostev K, Wartenberg F, Richter H, Reinwald M, Heilmaier C
Persistence with opioid treatment in Germany in patients suffering from chronic non-malignant or cancer pain
Curr Med Res Opin. 2015 Mar 25:1-28

Gollwitzer et al. 2016:
Gollwitzer S, Kostev K, Hagge M, Lang J, Graf W, Hamer HH
Nonadherence to antiepileptic drugs in Germany
Neurology. 2016 Aug 2;87(5):466-72

Chapter 8. Obstetrics and Gynecology

Prevalence of female subfertility in German gynecological practices

The study of Ziller et al. calculated the number of women with a subfertility diagnosis in gynecological practices between 2006 and 2010. A total of 1,975,253 women with a confirmed diagnosis of female infertility (ICD-10: N97) and/or with documentation of procreative management (ICD 10: Z31) were identified and included. They were grouped under the term ‘subfertility’. Estimates for patients with subfertility among women living in Germany (aged 18-45) were 2.44% in 2006, 2.52% in 2007, 2.56% in 2008, 2.68% in 2009, and 2.69% in 2010. The difference was significant. In total, between 2006 and 2010 an estimated 8.91% of all German women had been diagnosed as subfertile. When calculated for 5 years, the results show that almost 1 out of 10 women aged 18 to 45 was counseled, investigated, or treated by her gynecologist for subfertility. The findings were congruent with international data [Ziller et al. 2013].

Risk of venous thrombosis in users of hormonal contraceptives in gynecological practices

Ziller et al. evaluated different progestogens in combination with ethinylestradiol in terms of their impact on the risk of venous thrombosis. Data from 68,168 contraceptive users treated in gynecological practices were analyzed. The adjusted odds ratios for risk of thrombosis were estimated in users of different oral contraceptive (OC) formulations relative to users of levonorgestrel-containing preparations. In total, 38 (0.06%) of the 68,168 contraceptive users had a recorded diagnosis of thrombosis within 365 days after the initial prescription. The study showed low incidence rates of thrombosis in OC users. The adjusted risk was 1.95 for desogestrel, 2.97 for dienogest, 1.57 for drospirenone, 2.54

for chlormadinone, and 3.24 for norgestimate compared to levonorgestrel. None of these findings reached statistical significance. The maximum absolute increase versus levonorgestrel was 6 cases per 10,000 women (n.s.). The results were in line with several other studies [Ziller et al. 2014].

Time to pregnancy in subfertile women treated in gynecological practices in Germany

Another study by Ziller et al. assessed the time from the first subfertility diagnosis to pregnancy (TTP), corroborating several factors influencing TTP for patients in gynecological practices, comprising a representative sample of such patients, and drawing a realistic picture of the current situation in Germany. Data from 61,815 women treated in gynecological practices with a first diagnosis of female infertility or an unfulfilled desire for children from 1 January 2001 to 31 December 2012 were analyzed. A total of 22,744 patients (36.8%) became pregnant during the first year of observation. The highest cumulative pregnancy rate was seen in women between 18 and 30 years of age (74.8%). The older the women were, the lower the cumulative pregnancy rate dropped. Age, endometriosis, diabetes mellitus, ovarian dysfunction, PCOS, and previous infection of the genitourinary tract impaired the chances of pregnancy. By contrast, several factors were proven to increase pregnancy rates, namely previous use of hormonal contraceptives, private insurance, previous delivery, previous pregnancy, and progesterone therapy (at any time). The study confirmed a number of established facts [Ziller et al. 2015].

Trends and patterns of hormonal contraceptive prescribing for adolescents

The study of Rashed et al. investigated trends and patterns of hormonal contraceptive prescribing to adolescents aged 12-18 years in UK primary

care. All females aged 12-18 years with ≥1 prescription for a contraceptive drug between 1 January 2002 and 31 December 2011 were included. The annual prevalence of contraceptive drug prescriptions was calculated, and indications for prescribing, as well as types of contraceptive drugs prescribed, were examined. Use of hormonal contraceptives among adolescents increased between 2002 and 2011, and combined oral contraceptive (COC) use was dominant. In 2002, 13.7% of female adolescents received prescriptions for hormonal contraceptives, compared to 19.0% in 2011. The majority of female adolescents [2002: 76.2%; 2011: 65.7%] received a contraceptive drug for 'contraceptive management'. The COC progestogen+estrogen was the most commonly prescribed. Although use of progestogen-only contraceptives was lower than that of COCs, the number of patients who received desogestrel pills and etonogestrel implants increased during the study period; levonorgestrel pill use declined. Only one injectable progestogen, long-acting depot medroxyprogesterone acetate, was prescribed. The study was the first population-based study to investigate prescribing patterns of hormonal contraceptives to female adolescents in the UK in the general practice setting [Rashed et al. 2015].

Discontinuation rates of menopausal hormone therapy among postmenopausal women

The study of Kyvernitakis et al. investigated the persistence rates of combined MHT in the last decade, reflecting changes in the post-Women's Health Initiative (WHI) era. A total of 17,020 patients who received combined MHT from 2004 to 2013 were analyzed. The results indicated that patients beginning their treatments in the years 2010-2013 were more treatment-persistent than patients beginning with menopausal hormone therapy (MHT) in the early years following the publication of the Women's Health Initiative study (2004-2009). After 12 months of follow-up, 44.6% and 33.5% of patients receiving 1 mg and 2 mg of oral

combined MHT, respectively, were still continuing treatment. The persistence rate of patients receiving <50 µg of transdermal MHT was 39.1% after 1 year of treatment and presented no differences compared to patients receiving ≥50 µg of transdermal MHT, who had a persistence rate of 38.2%. MHT initiation during the years 2007-2009 was associated with higher discontinuation rates than MHT initiation during the years 2010-2013. The study was the first to assess the year-dependent changes in discontinuation rates in post-WHI times [Kyvernitakis et al. 2015a].

Persistency with estrogen replacement therapy among hysterectomized women after the Women's Health Initiative study

Another study by Kyvernitakis et al. investigated the persistence rates with estrogen replacement therapy (ERT) in hysterectomized women over the past decade, which reflected changes in the post-Women's Health Initiative (WHI) era. A total of 8,045 patients who received ERT from 2004 to 2013 were included. The results indicated low persistency rates in women on ERT irrespective of the dose and the route of administration. However, a decrease in discontinuation rates was found when comparing women in the early vs. late post-WHI era. After 12 months of follow-up, only 24.6% of patients receiving 1 mg and 24.5% of patients receiving 2 mg of oral ERT were still continuing treatment. The persistency rate of patients receiving 550 mg of transdermal ERT was 28.6% compared to 33.5% for patients receiving 450 mg within the 12 months of follow-up. ERT that was initiated between 2007 and 2009 was associated with a higher discontinuation rate than ERT that was initiated between 2010 and 2013. The study was the first to assess the year-by-year changes of discontinuation rates of ERT in post-WHI times [Kyvernitakis et al. 2015b].

Risk of stillbirth in pregnant women with obesity in the United Kingdom

Jacob et al. analyzed the risk of stillbirth in pregnant women with and without an increased BMI in the United Kingdom. A total of 44,060 pregnant women with or without an increased BMI who gave birth to a single child were examined in general practices. Pregnant women who were obese or even moderately overweight exhibited an increased risk of stillbirth in UK primary care practices over a period of 20 years. Increased BMI was associated with an increase in stillbirths in the group of pregnant women with a BMI higher than or equal to 50 kg/m^2. The outcome was in accordance with previous studies [Jacob et al. 2016a].

Impact of cesarean section on mode of delivery, pregnancy-induced and pregnancy-associated disorders, and complications in a subsequent pregnancy

The study of Jacob et al. investigated the impact of cesarean section (CS) on the mode of delivery, pregnancy-induced and pregnancy-associated disorders, as well as complications in a subsequent pregnancy in gynecological practices. A total of 1,801 women with CS and 1,801 matched women with vaginal delivery (VD) were included. The impact of previous CS on the mode of delivery and pregnancy-associated disorders, as well as complications prior to or during birth in a subsequent pregnancy were analyzed. Women with CS were less likely to have a single spontaneous delivery and more likely to undergo CS in a subsequent pregnancy compared to women with VD. CS was also associated with a higher risk of certain outcomes such as gestational hypertension, polyhydramnios, hemorrhage in early pregnancy, maternal care for known or suspected disproportion, and long labor in a subsequent pregnancy. By contrast, previous CS was associated with a lower risk of medical abortion, prolonged pregnancy, preterm labor, abnormal forces of labor, and perineal laceration during delivery in the

next pregnancy compared to VD. Medical abortions and single spontaneous deliveries were significantly less frequent in women with a history of CS compared to VD, whereas CS after CS was the significantly more common mode of delivery. Gestational hypertension without significant proteinuria, gestational hypertension with significant proteinuria, and polyhydramnios were more frequent in women with CS than in women with VD. Hemorrhage and maternal care for known or suspected disproportion were more common in the CS group than in the VD group. Prolonged pregnancy, preterm labor, abnormalities arising from forces of labor, and perineal laceration during delivery were significantly less frequent in women with CS than in women with VD, whereas long labor was more common. The findings were in line with other studies [Jacob et al. 2016b].

Cesarean section and its impact on fertility and time to a subsequent pregnancy

Jacob et al. analyzed the impact of cesarean section (CS) on fertility and time to pregnancy in gynecological practices. Women who had undergone a vaginal delivery (VD) or CS between 2000 and 2013 were identified by 227 gynecologists. They were included if they were aged between 16 and 40 years and had not been previously diagnosed with female sterility. The two main outcomes were the first-time diagnosis of female sterility and the time between the first delivery and the next pregnancy within 10 years. CS was associated with an increased risk of sterility and a decreased number of subsequent pregnancies. A total of 6,483 patients were included in the CS group and 6,483 in the VD group. Within 10 years of the index date, 19.5% of women who delivered by CS and 18.3% of women who delivered vaginally were diagnosed with sterility. CS and polycystic ovary syndrome significantly increased the risk of sterility. Within 10 years of the index date, 57.9% of women who underwent a CS and 64.0% of women who delivered vaginally were

pregnant for the second time. CS, polycystic ovary syndrome, and the deterioration of the menstrual cycle significantly decreased the chance of becoming pregnant a second time. The outcomes were in agreement with previous literature [Jacob et al. 2016c].

References

Ziller et al. 2013:
Ziller V, Hadji P, Thielscher C, Ziller M, Kostev K
Prevalence of female subfertility in German gynecological practices
Gynecol Endocrinol. 2013 Aug;29(8):767-70

Ziller et al. 2014:
Ziller M, Haas G, Ziller V, Rex J, Kostev K
Risk of venous thrombosis in users of hormonal contraceptives in German gynaecological practices: a patient database analysis
Arch Gynecol Obstet. 2014 Feb;289(2):413-9

Ziller et al. 2015:
Ziller V, Heilmaier C, Kostev K
Time to pregnancy in subfertile women in German gynecological practices: analysis of a representative cohort of more than 60,000 patients
Arch Gynecol Obstet. 2015 Mar;291(3):657-62

Rashed et al. 2015:
Rashed AN, Hsia Y, Wilton L, Ziller M, Kostev K, Tomlin S
Trends and patterns of hormonal contraceptive prescribing for adolescents in primary care in the U.K.
J Fam Plann Reprod Health Care. 2015 Jul;41(3):216-22

Kyvernitakis et al. 2015a:
Kyvernitakis I, Kostev K, Hars O, Albert US, Hadji P
Discontinuation rates of menopausal hormone therapy among postmenopausal women in the post-WHI study era
Climacteric. 2015 Apr 7:1-22

Kyvernitakis et al. 2015b:
Kyvernitakis I, Kostev K, Hars O, Albert US, Kalder M, Hadji P
Persistency with estrogen replacement therapy among hysterectomized women after the Women's Health Initiative study
Climacteric. 2015 Dec;18(6):826-34

Jacob et al. 2016a:
Jacob L, Kostev K, Kalder M
Risk of stillbirth in pregnant women with obesity in the United Kingdom
Obes Res Clin Pract. 2016 Sep - Oct;10(5):574-579

Jacob et al. 2016b:
Jacob L, Taskan S, Macharey G, Sechet I, Ziller V, Kostev K
Impact of caesarean section on mode of delivery, pregnancy-induced and pregnancy-associated disorders, and complications in the subsequent pregnancy in Germany
Ger Med Sci. 2016 Jun 14;14:Doc06. doi: 10.3205/000233. eCollection 2016

Jacob et al. 2016c:
Jacob L, Weber K, Sechet I, Macharey G, Kostev K, Ziller V
Caesarean section and its impact on fertility and time to a subsequent pregnancy in Germany: a database analysis in gynecological practices
Arch Gynecol Obstet. 2016 Aug 3. [Epub ahead of print]

Chapter 9. Children's Health

Referral for occupational therapy after diagnosis of a developmental disorder

The study of Konrad et al. assessed how many patients received occupational therapy after diagnosis of a developmental disorder (DD) in child psychiatrist practices and which factors influenced the prescription of occupational therapy. The study population included 11,112 children aged between 3 and 17 from 13 child psychiatrist practices. The observation period was five years in total. The results showed that 3,545 (32%) were referred for occupational therapy by a child psychiatrist within three years of first diagnosis of DD. *Of these, 72.4% had been diagnosed with acquired aphasia with epilepsy, 35.2% with a specific DD of motor function, and 31.6% with a specific DDs of speech and language. 52.9% were diagnosed with more than one DD. General practitioners (30.8%) and child and adolescent physicians (23%) were the main prescribers of occupational therapy.* Younger age, female gender, statutory health insurance, specific DD of motor function, or reaction to severe stress and adjustment disorders positively influenced the referral rate and time of occupational therapy. The outcomes were confirmed by previous studies [Konrad et al. 2015].

Pain medication for children and adolescents in primary care

Trebst et al. investigated the pain prevalence and pain treatment in children and adolescents treated by general practitioners and pediatricians in primary care settings. The study investigated 146,204 patients diagnosed with pain in 2010 (68% by pediatricians, 32% by general practitioners). Almost a third of all patients experienced at least one of the investigated pain diagnoses. The share of pain medication

was the highest in children aged <2, followed by 2-11 and then 12-18 years old. Back pain was the most frequent diagnosis in adolescents aged 12-18. Paracetamol and Ibuprofen were prescribed most frequently. The findings were in line with other studies [Trebst et al. 2013].

The prescribing of contraceptives to adolescents

The study of Ziller et al. examined the prescribing trend of contraceptives in adolescent girls aged 12-18 years and compared prescribing patterns of the most frequently used contraceptives among this population. In total, 21,026 teenage girls in 2007 and 18,969 in 2011 received contraceptive prescriptions. The number of contraceptive prescriptions rose significantly between 2007 and 2011. Additionally, the prescribing behavior of doctors changed. The percentage of teen girls who received prescriptions of levonorgestrel and chlormadinone pills was significantly higher in 2011 compared to 2007. However, the proportion of contraceptive pills containing drospirenone or desogestrel significantly decreased in 2011 compared to 2007. This study provided an update on the patterns of contraceptive use among adolescent women [Ziller et al. 2013].

Off-label drug prescriptions among outpatient children and adolescents

The study of Sonntag et al. analyzed the number of off-label drug prescriptions among children and adolescents receiving outpatient treatment. The aim was to outline age-, gender-, region-, and insurance-specific differences and to determine risk factors for an off-label prescription. In total 189,285 children and adolescents with analgesics, 147,089 with antibiotic, and 15,405 with antidepressant prescriptions were identified. The percentages of patients with off-label prescriptions

were 0.9% for analgesics, 2.5% for antibiotics and 8.5% for antidepressants. The number of off-label prescriptions issued by general practitioners was significantly higher than the number of such prescriptions issued by pediatricians and child psychiatrists. The number of off-label prescriptions in rural areas was higher than in cities. More off-label prescriptions were issued in the eastern states than in the western states of Germany. The study showed that outpatient treatment of children and adolescents is widespread, with drugs corresponding to age and dosage. Off-label prescriptions not conforming to indication were not included in the study. However, several studies confirmed that off-label treatment for children and adolescents was less frequent in out-patient settings than in hospital settings [Sonntag et al. 2013].

Prevalence of medically treated children with ADHD and type 1 diabetes

The aim of the study of Kapellen et al. was to analyze the prevalence of attention deficit hyperactivity disorder (ADHD) in children and adolescents with type 1 diabetes mellitus (T1DM) using two representative databases. In 2014, 677,587 children and adolescents aged 0-18 years were treated by pediatricians and documented in the Disease Analyzer database. Of these patients, 16,833 received the ICD-10 diagnosis of ADHD (2.5%) and 3,668 patients were treated for T1DM (0.1%). Of these 3,668 patients, a total of 153 children were also diagnosed with ADHD (4.2%). In the LRx database, the overall prevalence of children who received both drugs for the treatment of ADHD and insulin in 2014 amounted to 2.9%. The diagnosis of ADHD was 2.4-3.3 times more frequent in boys than in girls. The highest prevalence was seen in the age group of 12-15 years (3.5%) and the lowest in the age group of 6-11 years (2.5%). The findings corresponded roughly to the outcomes of other studies and were comparable with

previous outcomes regarding the prevalence of ADHD [Kapellen et al. 2016].

References

Konrad et al. 2015:
Konrad M, Drosselmeyer J, Kostev K:
Referral for occupational therapy after diagnosis of developmental disorder by German child psychiatrists
Early Child Development and Care; Volume 186, 2016 (186); 6: 959-970

Trebst et al. 2013:
Trebst D, Sonntag D, Kiess W, Bertsche T, Kistev K
Verschreibung von Schmerzmedikamenten für Kinder und Jugendliche in hausärztlichen und pädiaterischen Praxen in Deutschland / Pain medication for children and adolescents in primary care
Dtsch Med Wochenschr. 2013 Jun;138(24):1322-4

Ziller et al. 2013:
Ziller M, Rashed A.N., Ziller V, Kostev K
The Prescribing of Contraceptives for Adolescents in German Gynecologic Practices in 2007 and 2011: A Retrospective Database Analysis
J Pediatr Adolesc Gynecol. 2013 Oct;26(5):261-4

Sonntag et al. 2013:
Sonntag D, Trebst D, Kiess W, Kapellen T, Bertsche T, Kostev K
Verwendung von off-label Medikamenten bei ambulant betreuten Kindern und Jugendlichen in Deutschland / Off-label drug prescriptions among outpatient children and adolescents in Germany – a database analysis
Dtsch Med Wochenschr. 2013 Oct;138(44):2239-45

Kapellen et al. 2016:
Kapellen TM, Reimann R, Kiess W, Kostev K
Prevalence of medically treated children with ADHD and type 1 diabetes in Germany – Analysis of two representative databases
J Pediatr Endocrinol Metab. 2016 Oct 18. pii: /j/jpem.ahead-of-print/jpem-2016-0171/jpem-2016-0171.xml. doi: 10.1515/jpem-2016-0171

Chapter 10. Allergy

Topical therapy of hand eczema

Soost et al. investigated the prescription profile of topical treatments of chronic hand eczema (CHE) in dermatologists' private practices. Data sets from 13,191 patients with hand eczema were analyzed. Corticosteroid treatment (72.6%) was most commonly prescribed by private practice physicians. Betamethasone was the most frequently prescribed, but other substances such as mometasone furoate, prednicarbate, clobetasol, and methylprednisolone aceponate were often prescribed as well [Soost et al. 2012].

Persistence with inhaled corticosteroid therapy

The study by Voshaar et al. investigated inhaled corticosteroid (ICS) therapy with two different inhalers (Novolizer® and Turbuhaler®) by comparing persistence, concomitant use of additional asthma medication, and occurrence of exacerbations in real life. Treatment persistence in asthma patients using 200 µg budesonide either via Novopulmon®/Budecort® (Novolizer group = NOV) or Pulmicort® (Turbuhaler group = TUR) was compared. Eligible patients received their first prescription of ICS medication (index day) between June 2001 and September 2007. In total 2,444 patients were included (1,780 NOV, 664 TUR) who were treated by general practitioners, specialists in internal medicine, ear, nose, and throat physicians, pulmonologists, and pediatrics. One year after treatment initiation, 89% of NOV patients remained on their ICS – and had better therapy persistence – compared to 85% of TUR patients. NOV patients changed to another ICS later and significantly less often. There was a trend towards fewer prescriptions of systemic corticosteroids in NOV patients [Voshaar et al. 2012].

Economic prescribing of corticosteroid nasal sprays

Becker et al. investigated to which extent the reference-price group and defined daily dose (DDD) system were suitable for tapping economic reserves, based on prescribed corticosteroid nasal sprays containing the active substances budesonide (BNS) or mometasone (MNS). Data from 16,163 MNS and 4,218 BNS patients treated in GP, plus 11,103 MNS and 2,521 BNS patients treated in ENT practices, were analyzed. The volumes of MNS actually prescribed were significantly lower than those of BNS in the compared patient populations. Based on the actual consumption of the substances, there was no treatment-cost advantage for BNS in comparison to MNS from the statutory health insurer's point of view [Becker et al. 2013].

Prevalence and treatment profiles of patients with grass pollen and house dust mite allergy

The study by Worm et al. examined the data provided by various medical practices specialized in allergic diseases regarding patients with rhinoconjunctivitis, including patients' demographic data and the treatment(s) prescribed by different medical specialists. The data were collected from a total of 1,472 private practices (111 dermatology, 1,043 general practices, 164 pediatric practices, 128 ENT practices, and 26 pulmonology practices in 2010). The results from 49,910 patients with a grass pollen allergy and 5,751 patients with a house dust mite allergy showed that people with house dust mite allergies were primarily seen by specialists, while people with grass pollen allergies were usually seen by general practitioners and internists. Treatment was primarily symptomatic, usually consisting of antihistamines. Allergen-specific immunotherapy, the only known causal treatment for IgE-mediated allergies at present, was rarely performed. The data confirmed observations found in the existing literature [Worm et al. 2013].

Impact of comorbidities on the treatment of atopic dermatitis

The study by Werner-Busse et al. analyzed the treatment data pertaining to atopic dermatitis patients with regard to the presence of other atopic comorbidities, and investigated whether the presence of atopic codiagnoses had an impact on the treatment of atopic dermatitis (AD) patients. The analysis included 39,642 patients treated by dermatologists, 17,124 treated by pediatricians, and 15,774 treated by general practitioners in 2010, who had a documented diagnosis of atopic dermatitis. Among AD patients, the percentage of patients diagnosed with atopic diseases was significantly higher than among patients without AD. AD outpatients with concomitant atopic comorbidities received topical as well as systemic corticosteroid prescriptions more frequently [Werner-Busse et al. 2014].

Lactose intolerance and comorbidities

The study by Schiffner et. al explored whether lactose-intolerant (LI) patients exhibit more frequent comorbidities than non-LI patients. The study was conducted on a case-control basis and 6,758 data records (3,379 LI vs. 3,379 non-LI patients) from 2012 were analyzed. There were significant correlations between LI and the incidence of osteoporosis, changes in mental status, and the presence of additional food intolerances. A comparison between LI and non-LI patients revealed that 34.5% vs. 17.7%, respectively, suffered from abdominal pain; 30.6% vs. 17.2% from gastrointestinal infections; and 20.9% vs. 16.0% from depression. Adjusted odds ratios were the highest in the LI group for fructose intolerance, irritable bowel syndrome, and bloating. The study confirmed that LI should not be regarded as an isolated illness but considered a possible trigger for further diseases, which was in line with many previous studies. The work showed significant correlations between LI and the incidence of osteoporosis, as well as the presence of additional food intolerances. The results demonstrated that depression

and LI often occurred together. To date, this issue has not yet been adequately addressed in the scientific literature [Schiffner et al. 2016].

References

Soost et al. 2012:
Soost S, Abdollahnia M, Kostev K, Worm M
Topical therapy of hand eczema – analysis of the prescription profile from dermatologists in private practice
J Dtsch Dermatol Ges. 2012 Mar;10(3):180-4.

Voshaar et al. 2012:
Voshaar T, Kostev K, Rex J, Schröder-Bernhardi D, Maus J, Munzel U
A retrospective database analysis on persistence with inhaled corticosteroid therapy: comparison of two dry powder inhalers during asthma treatment in Germany
Int J Clin Pharmacol Ther. 2012 Apr;50(4):257-64.

Becker et al. 2013:
Becker B, Kruppert S, Kostev K
Economic prescribing of corticosteroid nasal sprays in Germany. Comparison of mometasone and budesonide nasal sprays on the basis of the DDD, the PDD and reference prices
Int J Clin Pharmacol Ther. 2013 Jan;51(1):12-8.

Worm et al. 2013:
Worm M, Lee H, Kostev K
Prevalence and treatment profile of patients with grass pollen and house dust mite allergy
J Dtsch Dermatol Ges. 2013 Jul;11(7):653-61

Werner-Busse et al. 2014:
Werner-Busse A, Kostev K, Heine G, Worm M
Impact of comorbidities on the treatment of atopic dermatitis in clinical practice
Int J Clin Pharmacol Ther. 2014 Sep;52(9):726-31

Schiffner et al. 2016:
Schiffner R, Kostev K, Gothe H
Do patients with lactose intolerance exhibit more frequent comorbidities than patients without lactose intolerance? An analysis of routine data from German medical practices
Ann Gastroenterol. 2016 Apr-Jun;29(2):174-179.

Chapter 11. Limitations

Retrospective primary care database analyses are generally limited by the validity and completeness of the data on which they are based. When performing epidemiological studies based on the Disease Analyzer data the following limitations should be mentioned:

1) Each patient is observed retrospectively in only one practice and as treated by only one specialty physician. A follow up treatment or a parallel treatment by another physician or specialty might not be recorded.

2) Lifestyle variables (smoking, alcohol consumption, physical activity, and diet) are not documented. These variables are very important by cancer or diabetes related studies

3) No information on the severity of disease is available. For example, there is no information about the severity of heart failure. The most commonly used classification system for heart failure, the New York Heart Association (NYHA) Functional Classification, is not available in the Disease Analyzer data.

4) In diabetes related studies, detailed dosage information on insulin cannot be obtained.

5) Only severe or frequent hypoglycemia episodes are documented by the primary physicians. No documentation of mild or moderate hypoglycemia. Information from hospitalization or emergency visits due to hypoglycemia is not documented in the database.

6) Therapy costs are calculated as the sum of the pharmacy sale prices, which can differ significantly from the actual

reimbursed prices due to contracts between statutory health insurance funds and manufacturers, resulting in lower costs.

7) Due to laws on privacy protection, data on the geographic location of practices is not available.

8) No valid information on the TNM Classification of Malignant Tumours (TNM) is available. This information is of high relevance for investigation the cancer area. Moreover, no information on chemo- and radio therapy is available; only long-time therapy like hormone medications can be analyzed.

9) In compliance studies, the exact data on patient compliance is lacking. Compliance can only be estimated by using information about prescribed daily dosage, number of prescribed refills, and day of the next prescription.

10) No information about mortality is available. When patients get lost to follow-up in the database, no reason is known. The reasons can be death, change of the physician or relocation.

11) No information on the diagnosis assessment procedure is documented. When defined diagnoses are documented, it is no information about tests or methods of diagnosing.

12) In the studies about depression or other psychiatric diseases, medical treatment but no psychotherapy can be analyzed.

13) The reason for treatment discontinuation is not documented.

14) Therapy information is based on prescriptions that were dispensed, and there is no information whether drugs had actually been taken or not.

15) No information about the duration of chronical diseases like diabetes.

16) No investigation of the association between gynecological therapy and orthopedic diseases like osteoporosis is possible, as fractures and osteoporosis are often documented by orthopedists while contraceptive therapy is prescribed by gynecologists.

17) No valid information on biological markers associated with some chronical diseases is available.

18) Data on hospital-based patients are missing. Data from family planning clinics or hospital are is also not captured.

19) Precise pregnancy duration is not documented.

20) Number of disabled patients and severity of disability are not captured.