Leibniz Institute for Prevention Research and Epidemiology – BIPS

Study Report (Version 1.2)

Observational Study on the Incidence of Thromboembolic Events in Patients with Renal Anemia Treated with Erythropoietin-Zeta as Compared with Erythropoietin-Alpha and other Erythropoiesis-Stimulating Agents

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Abbreviations

ATC	Anatomical-therapeutic-chemical code
BIPS	Leibnitz Institute for Prevention Research and Epidemiology – BIPS GmbH
CCI	Charlson Comorbidity Index
CIs	Confidence intervals
CKD	Renal anemia (chronic kidney disease)
CPR	Central pharmaceutical reference database
DDD	Defined Daily Dose
ESA	Erythropoiesis-stimulating agents
GePaRD	German Pharmacoepidemiological Research Database
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practice
GPS	Good Practice of Secondary Data Analysis
OPS	Operation and procedure code
OR	Odds ratio
OTC	Over the counter
PASCO	Post-Authorisation Safety Chort Observation
PZN	Central pharmaceutical number
SHI	Statutory health insurance
SOPs	Standard operating procedures
SPC	Summaries of Product Characteristics
VTE	Venous thromboembolism

1 Introduction

1.1 Background

Erythropoietin is an essential growth factor required for production of red blood cells. The stimulus for erythropoietin production is believed to be the oxygen content of blood delivered to the renal interstitial cells. When the peritubular renal cells are functioning correctly, individuals with low haemoglobin concentrations will produce increased quantities of erythropoietin, resulting in increased red blood cell production.[1-3] Chronic renal failure is characterised by a progressive loss of kidney function resulting from inherited disorders or conditions such as diabetes mellitus or hypertension. In patients with chronic renal failure, the production of erythropoietin is impaired leading to the deficiency being the primary cause of anemia. Partial correction of anemia in renal failure with erythropoiesis-stimulating agents (ESA) has been reported to reduce exercise-induced cardiac ischemia[4, 5] and to ameliorate left ventricular hypertrophy[4, 6].

On the other hand, randomized clinical trials have reported an increased risk of thromboembolic events with ESA if target hematocrit or haemoglobin values were too high. The Normal Hematocrit Study in patients with kidney and heart disease identified a 1- to 5-fold increased risk of myocardial infarctions and vascular access thrombosis when ESAs were administered with a target hematocrit of 42 percent as compared with a target hematocrit of 30 percent.[7] Similarly, the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR Study) of 1,432 patients with chronic kidney disease identified increased risks of mortality and congestive heart failure among patients targeted to achieve a hemoglobin level of 13.5 g per deciliter as compared with patients targeted to achieve a level of 11.3 g per decilitre.[8] Contrary to these studies, the Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) trial found no benefit regarding the occurrence of cardiovascular outcomes and of adverse events such as stroke or thrombosis in a correction of anemia to a haemoglobin of 10.5 to 11.5 g per decilitre compared to an early complete correction to a hemoglobin of 13 to 15 g per decilitre. Event rates were similar and risk estimations did not show significant results.[9]

Bennett et al. analysed the risk of venous thromboembolism (VTE) and mortality in cancer-associated anemia treated with recombinant erythropoietin and darbepoetin as compared with placebo in phase III clinical trials. In the combined analysis the authors reported increased risks of 1.57 (95% confidence interval (CI): 1.31-1.87) for VTE and a hazard ratio of 1.10 for all-cause mortality (95% CI: 1.01-1.20).[10] The Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) found an almost 2-fold increased risk of ischemic stroke in patients treated with ESA (darbepoetin alpha) with a target haemoglobin of 13.0 g

per decilitre compared to placebo. Also, there were significantly more events of venous thromboembolism (VTE) in the ESA-group.[11]

Given the available evidence it seems likely that ESA can increase the risk of thromboembolic events, most probably due to their pharmacologic effect on the haematocrit and the haemoglobin. Whether different ESA vary concerning their thromboembolic risk is still uncertain. A review based on clinical safety data for different ESA from dossiers of the European Medicines Agency (EMA) and journal publications concerning approval studies found similar safety profiles among all agents reviewed (epoetin alfa, theta, and zeta) including thromboembolic risk.[12] However, all studies reviewed "were of limited size and illustrated relatively homogenous samples from carefully selected centres". Following the findings by Abraham et al., a recent cohort study comparing the safety profiles of epoetin alfa and darbepoetin alfa did not find a difference in the risk for myocardial infarction and stroke as adverse outcomes.[13] Palmer et al. concluded in a meta-analysis, that (comparative) evidence on the safety of different ESA is insufficient[14], which in combination with the findings presented emphasizes the need for a risk quantification conducted in larger populations with greater heterogeneity regarding patient characteristics and treatment strategies.

1.2 Objectives

1.2.1 Primary Objective

To compare the incidence of thromboembolic events (composite endpoint) in patients with renal anemia treated with epoetin zeta and patients with renal anaemia treated with epoetin alpha based on data from the German Pharmacoepidemiological Research Database (GePaRD).

1.2.2 Secondary Objective

To compare the incidence of thromboembolic events (composite endpoint) in patients with renal anaemia treated with epoetin zeta and patients with renal anemia treated with all other epoetins available during the study period (epoetin alfa, epoetin beta, epoetin delta, epoetin theta, darbepoetin alfa, methoxy polyethylene glycol [MPG]-epoetin beta) based on data from the German Pharmacoepidemiological Research Database (GePaRD). If numbers allow, the the endpoints acute myocardial infarction, deep vein thrombosis and/or pulmonary embolism and cerebrovascular event will be analyzed separately as secondary outcomes.

To compare the results of this database study with the results of the PASCO Study (Post-Authorisation Safety Cohort Observation of Silapo®/Retacrit® (epoetin zeta) Administered Intravenously for the Treatment of Renal Anemia) by linking the PASCO participants to epoetin zeta users in this database study. For this purpose, the definition of exposure, outcomes, and covariables, as well as study design, was aligned as much as possible with the PASCO study.

2 Data Source

2.1 Database Description

Source of data for this study was the German Pharmacoepidemiological Research Database (GePaRD) that has been built by the Leibniz Institute for Prevention Research and Epidemiology – BIPS GmbH (BIPS). GePaRD consists of claims data from four German statutory health insurance providers (SHI) covering over 17 million people throughout Germany. The population contained in this database represents approximately 20% of the German population of 82 million inhabitants and includes all SHI members, who have been enrolled in one of the four SHIs since 2004.

The database contains core data, hospitalization data, outpatient prescription data, and outpatient care data/diagnoses. Drugs that are purchased over the counter (OTC) are not contained in the database. With a few exceptions the same applies to medication administered in hospital. For data protection reasons information is pseudonymized and coarsened (e.g. instead of a person's birthday only the respective birth year is included).

Membership in an SHI is compulsory in Germany for employees below an annual income threshold (approximately 47,000€ in 2004 and approximately 49,000€ in 2009). Subjects with higher incomes can choose private health insurance providers instead of an SHI and are somewhat underrepresented in SHIs. However, around 75% of these higher-income patients remain voluntary members of SHIs, most often because SHIs provide free health insurance for unemployed family members (children and spouse) whereas in private health insurance plans all family members have to be paid for. About 70 million people (85% of the German population) are SHI members, including about five million voluntary members, children and patients who are retired or unemployed.

On the other hand, there may also be some overrepresentation of patients with middle to higher socio-economic status in the database, since three of the four SHIs contributing to the database are so called 'Ersatzkassen' which are more likely to insure patients of middle to higher socio-economic status. However, the database also includes patients from one AOK

(AOK Bremen-Bremerhaven), an SHI which has traditionally insured patients of lower socio-economic status.

An advantage of data from German SHIs is the stability of their membership which makes long term follow-up studies feasible. In a pilot database of more than 3.5 million people from three SHIs, membership was stable in about 75% of all subjects over four years.[15] However, patients leaving a specific SHI and entering one of the other three participating SHIs could at the time of the study not be identified as the same individual (synonym error).

The database covers all geographical regions of Germany. Two large SHIs contributing to the database together insure more than 15 million subjects all over Germany; the smaller SHIs include people from Bremen and Lower Saxony. In previous studies, the data has been shown to be adequately representative with respect to age, sex, and drug dispensations.[16, 17]

The structure of the German Pharmacoepidemiological Research Database (GePaRD) and the central pharmaceutical reference database (CPR) are displayed in Table 1. Information from the CPR such as the anatomical-therapeutic-chemical (ATC) code or the Defined Daily Dose (DDD) is linked to the SHI database via the PZN (central pharmaceutical number).

Table 1: German Pharmacoepidemiological Research Database (GePaRD): Structure and Content of Data Files from Statutory Health Insurance Providers (SHI) and Central Pharmaceutical Reference Database (CPR)

SHI				**CPR**
Core data (socio-demographic)	Hospital data	Outpatient data[$]	Prescription data[$$]	Pharmaceutical information
Pseudonymized subject ID No. Birth year Sex SHI code Region of residence Nationality (German/other) Dates of insurance coverage (entry and exit) Occupational code Reasons for exit (e.g. death) Insurance status (self/relative-spouse/child)	Pseudonymized subject ID No. Pseudonymized hospital ID No. Day of admission/ discharge Admission diagnosis* Reason for admission Discharge diagnoses* Secondary and ancillary diagnoses* OPS-code (Diagnostic and surgical/medical procedures) Reasons for discharge	Pseudonymized subject ID No. Pseudonymized physician ID No. Physician specialty Diagnoses* (quarterly**) Types and dates of treatment / diagnostic procedures (EBM code) [$] Provided to SHIs by Regional Associations of Statutory Health Insurance Physicians	Pseudonymized subject ID No. Central pharmaceutical No. (PZN) Pseudonymized pharmacy ID No. Date of prescription Date of dispensation Pseudonymized physician ID No. Physician specialty Quantity prescribed	Central pharmaceutical No. (PZN) Generic name Brand Manufacturer Packaging size Strength Defined daily dose (DDD) Pharmaceutical formulation ATC GM code***

Family ID No. Participation in Disease Management Program (DMP)	(incl. deathl) Day of delivery Weight of infants less than 1 year old * All diagnoses: ICD-10-GM, at least 4 digits	*All diagnoses: ICD-10-GM, at least 4 digits ** Diagnoses refer to a period of three months, as physicians' services are settled quarterly	[$$] Provided to SHIs by pharmacies' electronic data processing centers	*** Anatomical Therapeutic Chemical Classification System

2.2 Legal Restrictions and Ethical Issues

Access to the data is only possible in the context of approved projects. E.g. preliminary investigations regarding the number of prescriptions of a specific drug or the number of patients diagnosed with a specific disease are not allowed.

Approval of a project is based on the endorsement of the project by the SHIs and their responsible authority (that is the German Federal Insurance Authority for nationwide operating SHIs). To gain approval, a proposal is written and sent to each SHI. If they endorse the project, they ask approval from their responsible authority, which will be granted according to §75 SGB X if the public health interest in the project outweighs the data privacy concerns.

Access to data is only allowed for BIPS employees. It is not possible to give access or analysis data sets to a third party.

3 Study Design

A retrospective cohort study was conducted to compare the crude incidence rate (with 95% CIs) of thromboembolic events (composite endpoint) in patients with renal anaemia treated with epoetin zeta vs. epoetin alfa / all other epoetins (including epoetin alpha).

Due to the time varying exposure, the relatively low number of events and the relatively high number of confounders, an adjusted analysis of the cohort was not feasible. Thus, a nested case-control study was performed to calculate crude and adjusted odds ratios (ORs) with 95% CIs.

Additionally, participants of the PASCO study were linked to epoetin zeta users in GePaRD to compare the results of this database study with the results of the PASCO study.

3.1 Study Period

The study period started on 01.01.2008, as both epoetin zeta biosimilars were approved in the end of 2007, and ended on 31.12.2011 (end of data availability) in order to have four full years of observation time. The time between 01.01.2007 and 31.12.2007 was used for confounder assessment for patients entering the cohort in 2008.

3.2 Source and Study Population

The source population of this study was the GePaRD as described in chapter 2. As no specific ICD-10-GM code for renal anaemia exists, the study population was composed of all patients with chronic kidney disease (CKD) included in the GePaRD exposed for the first time to epoetin zeta, epoetin alfa or other epoetins available on the market during the study period.

3.2.1 Cohort Definition

An inception cohort of CKD patients with a first prescription of epoetins was created.

3.2.1.1 Inclusion Criteria

All insurants included in the GePaRD fulfilling all of the following inclusion criteria were eligible for cohort membership:

- At least 12 months of continuous insurance time before the first outpatient epoetin prescription (see Appendix I: ATC codes of Epoetins),
- no outpatient epoetin prescription within the 12 months before cohort entry, and
- at least one outpatient or inpatient diagnosis of CKD or a corresponding treatment code (e.g. dialysis treatment) prior to cohort entry (see Appendix II: Codes used for identification of CKD)

3.2.1.2 Cohort Entry

All patients fulfilling the inclusion criterial entered the cohort on the date of the first epoetin prescription.

3.2.1.3 Cohort Exit

Cohort exit was defined as the first of the following events:

- End of study period, i.e. December 31, 2011 or longest available follow-up in the database
- Outcome of interest
- Interruption of insurance of more than three days (standard definition in GePaRD)
- End of insurance or death of any cause
- Dispensation of different epoetins on the same day, as it is very unlikely that a patient starts his epoetin treatment with two different epoetins. We assume that most of these cases are errors and as it is not possible to assess which was the “true” epoetin these cases have to be excluded.

Re-entry after cohort exit is not possible. Switching during the study period from one epoetin to another is not an exclusion or exit criterion.

3.3 Exposure Definition

3.3.1 Estimation of Supply

Only outpatient epoetin prescriptions were considered as data on epoetin treatment during hospitalisation is not available. Moreover, the prescribed duration of drug treatment had to be estimated since GePaRD does not contain the respective information. The estimation was conducted based on recommendations included in the respective Summaries of Product Characteristics (SPC), in national or international guidelines, as well as based on the opinions of expert in the field of renal anaemia treatment. Following assumptions were made:

- As all epoetins are available in several different dosages, each prescribed epoetin syringe corresponded to one epoetin administration.
- The prescription date of the first epoetin corresponded to the beginning of epoetin treatment. Though the dispensation date was also available, it was not preferred, as patients often get treated with epoetins stored at the physician’s practice first and then get a prescription. This means that dispensation may take place several days after treatment.
- If the recommended treatment pattern between the correction phase and the maintenance phase differed, it was assumed that both phases are of the same duration and a ‘mean algorithm’ of both phases was created. If more than one treatment pattern was recommended for the same phase and epoetin, the ‘mean’ of

the most and the least intensive treatment pattern was considered. In sensitivity analyses we also used the maximum and minimum.

Thus the average [maximum and minimum] supply with x being the prescribed number of epoetin syringes on the respective prescription was calculated as follows:

- Patients on epoetin alfa undergoing dialysis: duration of use = x/3 weeks [x/3 and x/3]
- Patients on epoetin alfa not undergoing dialysis: duration of use = x/3 weeks [x/3 and x/3]
- Patients on epoetin beta undergoing dialysis: duration of use = x/3 weeks [x/3 and x/3]
- Patients on epoetin beta not undergoing dialysis: duration of use = x/3.375 weeks [x/0.5 and x/7]
- Patients on epoetin delta undergoing dialysis: duration of use = x/2.75 weeks [x/2 and x/3]
- Patients on epoetin delta not undergoing dialysis: duration of use = x/3.125 weeks [x/2 and x/3.75]
- Patients on epoetin theta undergoing dialysis: duration of use = x/3 weeks [x/3 and x/3]
- Patients on epoetin theta not undergoing dialysis: duration of use = x/2.5 weeks [x/1 and x/3]
- Patients on epoetin zeta undergoing dialysis: duration of use = x/3 weeks [x/3 and x/3]
- Patients on epoetin zeta not undergoing dialysis: duration of use = x/2.375 weeks [x/0.5 and x/3]
- Patients on darbepoetin undergoing dialysis: duration of use = x/0.8125 weeks [x/0.25 and x/1]
- Patients on darbepoetin not undergoing dialysis: duration of use = x/0.625 weeks [x/0.25 and x/1]
- Patients on methoxy polyethylene glycol-epoetin beta undergoing dialysis: duration of use = x/0.3125 weeks [x/0.25 and x/0.5]
- Patients on methoxy polyethylene glycol-epoetin beta not undergoing dialysis: duration of use = x/0.3125 weeks [x/0.25 and x/0.5]

3.3.2 Exposure Status

Exposure status was defined as a time dependent variable:

- **Current use**: all time between the prescription date and the end of supply. Overlapping supplies of the same epoetin were added. As concomitant use is not expected it was assumed that the current epoetin was stopped when patients became exposed to a different epoetin ("switch").
- **Recent use**: 14 days after the end of exposure with no start of new exposure, to assess whether outcomes occur lagged.
- **Past use**: all other time intervals.

Thus for each patient person time was divided into current, recent and past use.

3.4 Outcome Definition

The main study endpoint is the composite endpoint of the three thromboembolic events:

- Acute myocardial infarction (ICD-10-GM code: I21)
- Deep vein thrombosis (ICD-10-GM-code: I80) and/or pulmonary embolism (ICD-10-GM-code: I26)
- Cerebrovascular event (ICD-10-GM-codes: G45, G46, H340, I60, I61, I62, I63, I64) i.e. cerebrovascular accident, cerebral infarction, transient ischaemic attack or cerebral haemorrhage.

These events were analysed separately as secondary outcomes.

For myocardial infarction or cerebrovascular event only main hospital discharge diagnoses were considered and the event date was set to the admission date.

For deep vein thrombosis and/or pulmonary embolism additionally to hospital diagnoses, also outpatient diagnoses coded as "certain" in combination with a dispensation of an antithrombotic agent in the same or the following quarter or main hospital discharge diagnoses. For these cases the event date was set to the prescription date of the first antithrombotic agent.

Events were assigned to the respective exposure periods.

3.5 Confounder and Effect Modifier Definition

Demographic information (age and sex) was assessed at cohort entry.

Co-morbidity was assessed in the 12 months preceding cohort entry from the in- and outpatient setting and included all types of diagnoses, except outpatient codes with diagnosis certainties indicating “diagnosis ruled out”, “status post” or “suspected diagnosis”. Co-medication, i.e. use of anti-diabetic, antithrombotic or thrombogenic drugs was also assessed in the 12 months preceding cohort entry.

An adaptation of the Charlson Comorbidity Index (CCI) was used[18], taking both inpatient and outpatient diagnoses into account. “Moderate to severe renal disease” is also part of the CCI with a CCI weight of 2. However, as CKD was one of the inclusion criteria meaning that all cohort participants were “renal-disease-positive”, the respective ICD-10-GM codes was not applied and all patients had a minimum CCI value of two.

As medication intake can vary over time, antithrombotic or thrombogenic drugs were also assessed in the last 30 days before the event date.

3.5.1 Risk factors for acute myocardial infarction

To adjust for potentially confounding effects the following acute myocardial infarction risk factors, as recently published[19], were assessed: coronary artery disease excl. history of myocardial infarction, history of myocardial infarction, obesity, arterial hypertension, dyslipidaemia, diabetes mellitus, peripheral artery disease, ischaemic stroke. Kidney disease is a further acute myocardial infarction risk factor. However, as CKD was one of the inclusion criteria meaning that all cohort participants were “renal-disease-positive”, kidney disease was not considered as a possible confounder in this analysis. Dispensations of antithrombotic agents which might be used for thrombosis prevention in patients with known risk factors were also assessed.

3.5.2 Risk factors for cerebrovascular events

To adjust for potentially confounding effects the following cerebrovascular event risk factors, as recently published[20], were assessed: obesity, dyslipidaemia, arterial hypertension, history of myocardial infarction, diabetes mellitus, cardiomyopathy, history of cerebrovascular event, valvular heart disease, sickle cell disease, atrial fibrillation, patent foramen ovale/atrial septal aneurysm, cardiac tumours, aortic atherosclerosis. Dispensations of antithrombotic agents which might be used for thrombosis prevention in patients with known risk factors were also assessed and considered as protective factor.

3.5.3 Risk factors for deep vein thrombosis/pulmonary embolism

To adjust for potentially confounding effects the following deep vein thrombosis/pulmonary embolism risk factors, as recently published[21-23], were assessed: history of deep vein thrombosis or pulmonary embolism, coronary artery disease, arterial hypertension, dyslipidaemia, diabetes mellitus, obesity, angina pectoris, incl. unstable angina, cancer.

4 Data Analysis and Statistical Methods

4.1 Cohort Analyses

Patients' demographic data (age, sex), comorbidities as well as medication use (thrombogenic drugs and antithrombotic drugs in the last 12 months before cohort entry) were described and compared between the different treatment groups based on the epoetin used at cohort entry (index epoetin).

Additionally, we compared the pattern of use between the groups by assessing the year of cohort entry, length of follow-up, numbers of switchers and number of epoetin episodes.

Finally, crude incidence rates for the composite endpoint, as well as for acute myocardial infarction, cerebrovascular events and deep vein thrombosis/pulmonary embolism separately, were calculated by dividing the number of events by the respective person time.

4.2 Nested case-control analysis

For each case, up to 10 controls were matched by age, sex, and SHI.

A conditional logistic regression was performed to estimate confounder-adjusted ORs and respective 95% CIs for current use of different epoetins compared to the respective reference (epoetin alpha / all other epoetins).

Important risk factors for the respective endpoints and potential confounders for the association with the exposure were a-priori included in the model. Other potential confounders were tested in a backward elimination process.

4.3 Sensitivity Analyses

In the first sensitivity analysis, all switchers were excluded as switching itself might be a risk factor for the outcome and the exposure status of the switchers has a higher potential of misclassification.

In the second sensitivity analysis the maximum and minimum of the recommended treatment pattern (see 3.3.1) was used to assess the impact of potential misspecification of exposure.

4.4 Linkage

The population for the linkage study was composed of all CKD patients included in the GePaRD exposed to epoetin zeta during the study period (BIPS cohort) and of all PASCO participants (PASCO cohort).

Epoetin zeta patients from the two cohorts were linked via probabilistic linkage using the following variables: year of birth, sex, SHI, and date of the first epoetin zeta prescription (± 30 days).

5 Results

5.1 Demographic and clinical characteristics of the study cohort

During the study period 16,986 patients with CKD receiving treatment with epoetin could be identified. Of these 1,049 (6%) started with epoetin zeta, 4,114 with epoetin alpha (24%) and 12,872 (70%) with one of the other epoetins than epoetin zeta or alpha. Almost 50% of these 70% were taking darbepoetin.

Patients starting with epoetin zeta had a median age of 73 years which is similar to the median age of 72 years of the patients starting with any of the other epoetins and 73 years of patients starting with epoetin alpha (see Table 2). The sex distribution was also comparable between these three groups. About 61% of the patients the epoetin zeta group were male, compared to 59% in the all other epoetins (incl. alpha) group and 61% in the epoetin alpha group.

Table 2: Demographic characteristics of the patients included into the study cohort by index epoetin

		Epoetin zeta	Epoetin alpha	Other epoetins
Variable		**N = 1,049**	**N = 4,114**	**N = 15,937**
Sex	Female	412 (39.3%)	1,613 (39.2%)	6,592 (41.4%)
	Male	637 (60.7%)	2,501 (60.8%)	9,345 (58.6%)
Age at entry	Median	73	73	72

No considerable differences regarding CKD statdium and comorbidities were observed between the three groups (see Table 3). The prevalence of risk factors for acute myocardial infarction was slightly lower (e.g. for coronary artery disease, diabetes mellitus) for patients staring with epoetin zeta compared to patients starting with epoetin alpha, but patients starting with epoetin zeta had slightly more often a previous myocardial infarction. Risk factors for cerebrovascular events were slightly less prevalent in patients starting with epoetin zeta and these patients also had slightly less often a previous cerebrovascular event. Regarding deep vein thrombosis/pulmonary embolism, the prevalence of risk factors and the frequency of previous events were comparable between both groups. However, all observed differences were small. This is also reflected in the CCI which has in all three groups a median of 6.

Use of antidiabetic medication was comparable between the three groups but antithrombotic drugs were more often used in the epoetin alpha group whereas thrombogenic drugs were more often used in the epoetin zeta group.

Table 3: Comorbidities of the patients included into the study cohort by index epoetin

Variable		Epoetin zeta N =1,049	Epoetin alpha N =4,114	Other epoetins (incl. alpha) N = 15,937
CKD statium	I	4 (0.4%)	21 (0.5%)	81 (0.5%)
	II	23 (2.2%)	114 (2.8%)	519 (3.3%)
	III	131 (12.5%)	394 (9.6%)	2,212 (13.9%)
	IV	89 (8.5%)	240 (5.8%)	1,807 (11.3%)
	V	709 (67.6%)	3,032 (73.7%)	9,847 (61.8%)
	Missing	93 (8.9%)	313 (7.6%)	1,471 (9.2%)
Prior history of	Atrial fibrillation	44 (4.2%)	156 (3.8%)	536 (3.4%)
	Arterial hypertension	949 (90.5%)	3,676 (89.4%)	14,267 (89.5%)
	Angina pectoris	103 (9.8%)	366 (8.9%)	1,422 (8.9%)
	Aortic atherosclerosis	54 (5.1%)	180 (4.4%)	676 (4.2%)
	Cardiac tumours	1 (0.1%)	1 (0.0%)	2 (0.0%)
	Cardiomyopathy	73 (7.0%)	287 (7.0%)	1,026 (6.4%)
	Cancer	347 (33.1%)	1,266 (30.8%)	4,487 (28.2%)
	Cancer with chemotherapy	136 (13.0%)	437 (10.6%)	1,388 (8.7%)
	Cerebrovascular event	251 (23.9%)	1,108 (26.9%)	4,015 (25.2%)
	Congestive heart failure	502 (47.9%)	2,093 (50.9%)	7,242 (45.4%)
	Coronary artery disease	471 (44.9%)	1,916 (46.6%)	6,933 (43.5%)

Variable		Epoetin zeta N =1,049	Epoetin alpha N =4,114	Other epoetins (incl. alpha) N = 15,937
	Deep vein thrombosis	54 (5.1%)	195 (4.7%)	661 (4.1%)
	Diabetes Mellitus	496 (47.3%)	2,033 (49.4%)	7,620 (47.8%)
	Dialysis	709 (67.6%)	3,032 (73.7%)	9,847 (61.8%)
	Dyslipidaemia	588 (56.1%)	2,318 (56.3%)	9,169 (57.5%)
	Ischaemic stroke	86 (8.2%)	359 (8.7%)	1,209 (7.6%)
	Myocardial infarction	190 (18.1%)	699 (17.0%)	2,309 (14.5%)
	Obesity	250 (23.8%)	973 (23.7%)	3,543 (22.2%)
	Peripheral vascular disease	385 (36.7%)	1,671 (40.6%)	5,878 (36.9%)
	Pulmonary embolism	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Sickle cell disease	0 (0.0%)	1 (0.0%)	5 (0.0%)
	Valvular heart disease	263 (25.1%)	1,047 (25.4%)	4,039 (25.3%)
CCI value	Min	0	0	0
	Lower quartile	4	4	4
	Median	6	6	6
	Upper quartile	8	8	8
	Max	18	22	22
Previous use of	Antidiabetic medication	338 (32.2%)	1,393 (33.9))	5,257 (22.2%)
	Antithrombotic drugs	515 (49.1%))	2,158 (52.5%))	7,817 (49.0%)
	Thrombogenic drugs	332 (31.6%)	1,117 (27.2%)	4,579 (28.7%)

The number of patients entering the cohort with epoetin zeta – which was approved at the beginning of the study period – increased from 7% (2008) to 42% (2011), whereas the number of patients entering the cohort was relatively constant for the other two groups (see

Table 4). Thus, the median follow-up in the epoetin zeta group is with 276 days shorter than for epoetin alpha with 387 days and all other epoetins with 456 days.

Table 4: Number of patients entering the study cohort by year and index epoetin and duration of follow up by index epoetin

Variable		Epoetin zeta N = 1,049	Epoetin alpha N = 4,114	Other epoetins (incl. alpha) N = 15,937
Year of entry	2008	73 (7.0%)	1,088 (26.4%)	4,193 (26.3%)
	2009	198 (18.9%)	1,214 (29.5%)	4,601 (28.9%)
	2010	341 (32.5%)	918 (22.3%)	3,712 (23.3%)
	2011	437 (41.7%)	894 (21.7%)	3,431 (21.5%)
Follow-up	Min	1	1	1
	Lower quartile	120	156	183
	Median	276	387	456
	Upper quartile	533	793	853
	Max	1,366	1,427	1,429

Patients had a median number of 3 courses of current use, with some patients having up to 61 courses (see Table 5). During the study period 4,550 switches between groups were observed. Most of these switches were from other epoetins to other epoetins (72%), 19% from other epoetins to epoetin zeta and 9% from epoetin zeta to other epoetins.

Table 5: Switching behaviour and number of courses of current use per patient in the study cohort

Variable		
Number of courses of current use per patient	Min	1
	Lower quartile	1
	Median	3
	Upper quartile	7
	Max	61
Switching	To epoetin zeta	848
	From epoetin zeta	427
	Other switches	3,281

In a sensitivity analysis, all patients who switched at least once were excluded, i.e. 179 patients (17%) who started with epoetin zeta, 847 patients (21%) who started with epoetin alpha and 3,843 patients (24%) who started with any other epoetin than zeta. The

demographic characteristics, CKD stadium and the comorbidity of the resulting cohort are very similar to those of the full cohort (see Table 6 and Table 7).

Table 6: Demographic characteristics of the patients included into the study cohort by index epoetin without switchers

Variable		Epoetin zeta N = 870	Epoetin alpha N = 3,267	Other epoetins (incl. alpha) N = 12,094
Sex	Female	344 (39.5%)	1,278 (39.1%)	5,048 (41.7%)
	Male	526 (60.5%)	1,989 (60.9%)	7,046 (58.3%)
Age at entry	Median	73	73	73

Table 7: Comorbidities of the patients included into the study cohort by index epoetin without switchers

Variable		Epoetin zeta N = 870	Epoetin alpha N = 3,267	Other epoetins (incl. alpha) N = 12,094
CKD stadium	I	4 (0.5%)	17 (0.5%)	64 (0.5%)
	II	20 (2.3%)	90 (2.8%)	418 (3.5%)
	III	120 (13.8%)	329 (10.1%)	1,802 (14.9%)
	IV	79 (9.1%)	185 (5.7%)	1,394 (11.5%)
	V	558 (64.1%)	2,385 (73.0%)	7,191 (59.5%)
	Missing	89 (10.2%)	261 (8.0%)	1,225 (10.1%)
Prior history of	Atrial fibrillation	40 (4.6%)	129 (3.9%)	433 (3.6%)
	Arterial hypertension	782 (89.9%)	2,913 (89.2%)	10,793 (89.2%)
	Angina pectoris	89 (10.2%)	289 (8.8%)	1,073 (8.9%)
	Aortic atherosclerosis	42 (4.8%)	143 (4.4%)	541 (4.5%)
	Cardiac tumours	1 (0.1%)	1 (0.0%)	2 (0.0%)
	Cardiomyopathy	63 (7.2%)	232 (7.1%)	794 (6.6%)
	Cancer	298 (34.3%)	1,045 (32.0%)	3,591 (29.7%)
	Cancer with chemotherapy	127 (14.6%)	379 (11.6%)	1,200 (9.9%)
	Cerebrovascular event	206 (23.7%)	889 (27.2%)	3,089 (25.5%)
	Congestive heart failure	420 (48.3%)	1,691 (51.8%)	5,589 (46.2%)
	Coronary artery disease	394 (45.3%)	1,561 (47.8%)	5,344 (44.2%)
	Deep vein thrombosis	50 (5.7%)	170 (5.2%)	583 (4.8%)
	Diabetes Mellitus*	401 (46.1%)	1,617 (49.5%)	5,744 (47.5%)

Variable		Epoetin zeta N = 870	Epoetin alpha N = 3,267	Other epoetins (incl. alpha) N = 12,094
	Dialysis	558 (64.1%)	2,385 (73.0%)	7,191 (59.5%)
	Dyslipidaemia	486 (55.9%)	1,843 (56.4%)	6,932 (57.3%)
	Ischaemic stroke	64 (7.4%)	283 (8.7%)	926 (7.7%)
	Myocardial infarction	160 (18.4%)	583 (17.8%)	1,790 (14.8%)
	Obesity	201 (23.1%)	759 (23.2%)	2,637 (21.8%)
	Peripheral vascular disease	318 (36.6%)	1,356 (41.5%)	4,543 (37.6%)
	Pulmonary embolism	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Sickle cell disease	0 (0.0%)	1 (0.0%)	2 (0.0%)
	Valvular heart disease	218 (25.1%)	860 (26.3%)	3,147 (26.0%)
CCI value	Min	0	0	0
	Lower quartile	4	4	4
	Median	6	6	6
	Upper quartile	8	9	8
	Max	18	21	21
Previous use of	Antidiabetic medication	267 (30.7%)	1,096 (33.5%)	3,906 (32.3%)
	Antithrombotic drugs	432 (49.7%)	1,760 (53.9%)	6,096 (50.4%)
	Thrombogenic drugs	278 (32.0%)	890 (27.2%)	3,594 (29.7%)

5.2 Cohort study

Of all patients included in the study, 1,940 (11%) developed the composite endpoint. Most of these patients had a deep vein thrombosis/pulmonary embolism (n=759), followed by a cerebrovascular event (n=634) and an acute myocardial infarction (n=547).

Table 8: Crude incidence rates of the composite endpoint in current users of ESA

Variable	Events	Person-time (per 1,000 person-years)	Incidence Rate (per 1,000 person-years)	95% CI
Current users				
Epoetin zeta	63	0.76	83.07	(63.83, 106.28)
Epoetin alpha	288	2.89	99.81	(88.61, 112.03)
All other epoetins (incl.alpha)	990	10.73	92.30	(86.64, 98.23)

Table 8 displays the crude incidence rates of the composite endpoint for current users of epoetins. Crude incidence rates of the composite endpoint of patients currently receiving epoetin zeta are slightly lower compared to those of patients receiving epoetin zeta and patients receiving all other epoetins (incl. alpha). However, confidence intervals of all treatment groups are overlapping.

The crude incidence rates for the secondary outcomes are displayed in Table 9. Current users of epoetin zeta had a higher crude incidence rate of pulmonary embolism, but lower incidence rates of myocardial infarction, deep vein thrombosis and cerebrovascular events than current users of epoetin zeta or all other epoetins (incl. alpha). Again, the confidence intervals are overlapping.

Table 9: Crude incidence rates of study endpoints in current users of ESA

Variable	Events	Person-time (per 1,000 person-years)	Incidence Rate (per 1,000 person-years)	95% CI
Myocardial infarction				
Epoetin zeta	18	0.76	23.73	(14.07, 37.51)
Epoetin alpha	75	2.89	25.99	(20.44, 32.58)
Other epoetins (incl. alpha)	259	10.73	24.15	(21.30, 27.27)
Deep vein thrombosis				
Epoetin zeta	13	0.76	17.14	(9.13, 29.31)
Epoetin alpha	76	2.89	26.34	(20.75, 32.97)
Other epoetins (incl. alpha)	299	10.73	27.88	(24.81, 31.22)
Pulmonary embolism				
Epoetin zeta	10	0.76	13.19	(6.32, 24.25)
Epoetin alpha	31	2.89	10.74	(7.30, 15.25)
Other epoetins (incl. alpha)	117	10.73	10.91	(9.02, 13.07)
Cerebrovascular event				
Epoetin zeta	23	0.76	30.33	(19.22, 45.50)
Epoetin alpha	111	2.89	38.47	(31.65, 46.32)
Other epoetins (incl. alpha)	335	10.73	31.23	(27.98, 34.76)

5.3 Case-control analysis

Nearly all cases (1,939 of 1,940) could be matched to at least one control by birth year, sex, and SHI.

The results of the multivariate analyses for the composite endpoint are displayed in Table 10. In the primary analysis, current use of epoetin zeta was not associated with an increased risk of the composite endpoint compared to current use of epoetin alpha or all other epoetins (incl. alpha). Exclusion of switchers or varying the assumed treatment pattern (as described in 4.3) did not change these results substantially.

Table 10: Adjusted odds ratios of the composite endpoint*

Variable	Adjusted Odds Ratio (95% CI)			
	Primary analysis	**Excluding Switchers**	**Minimum treatment pattern**	**Maximum treatment pattern**
Epoetin zeta vs. epoetin alpha (ref.)	0.90 (0.67, 1.21)	0.69 (0.47, 1.01)	0.93 (0.69, 1.26)	0.98 (0.75, 1.29)
Epoetin zeta vs. other epoetins (ref.)	0.80 (0.58, 1.09)	0.83 (0.58, 1.18)	0.83 (0.61, 1.14)	0.90 (0.68, 1.20)

* adjusted for recent and past use of epoetins, risk factors, co-morbidity and co-medication.

Table 11 displays the results the multivariate analyses for the secondary endpoints. Current use of epoetin zeta was not associated with an increased risk of myocardial infarction, cerebrovascular event or deep vein thrombosis / pulmonary embolism compared to current use of epoetin alpha or all other epoetins (incl. alpha).

Table 11: Adjusted odds ratios of the secondary endpoints*

Variable	**Adjusted Odds Ratio (95% CI)**
Myocardial infarction	
Epoetin zeta vs. epoetin alpha (ref.)	1.11 (0.64, 1.93)
Epoetin zeta vs. other epoetins (ref.)	0.81 (0.45, 1.45)
Cerebrovascular event	
Epoetin zeta vs. epoetin alpha (ref.)	0.82 (0.51, 1.34)
Epoetin zeta vs. other epoetins (ref.)	0.91 (0.53, 1.56)

Deep vein thrombosis / Pulmonary embolism	
Epoetin zeta vs. epoetin alpha (ref.)	0.73 (0.42, 1.28)
Epoetin zeta vs. other epoetins (ref)	0.64 (0.36, 1.11)

* adjusted for recent and past use of epoetins, risk factors, co-morbidity and co-medication.

5.4 Linkage of PASCO and GePaRD

In this part of the study, epoetin zeta users from the cohort described in chapter 3.2.1 were linked to patients from the PASCO study using probabilistic linkage methods. As the DAK did not give approval to use their data for the linkage, only patients who used epoetin zeta and were insured with one the other two SHI (n = 1,225) were used.

The PASCO data included 1,652 patients. However,

- n = 10 did not have a valid birth year (linkage variable),
- n = 16 were not treated with epoetin zeta,
- n = 68 had no valid SHI,
- n = 1,425 were not insured with an SHI that gave approval for the linkage with the BIPS cohort, and
- n = 56 did not give details on the specific AOK,

so that only n = 77 patients remained for linkage with the BIPS cohort. Of these eligible patients, 54 (70%) could be linked. 1

Baseline characteristics of available GePaRD patients (i.e. cohort members who started with epoetin zeta) and PASCO patients (i.e. patients in the safety data set) are displayed in Table 13..

Table 12: Baseline characteristics of the available GePaRD and PASCO patients before

		GePaRD Epoetin zeta	**PASCO**
Variable		**N = 1,049**	**N = 1,634**
Sex	Female	412 (39.3%)	943 (57.7%)
	Male	637 (60.7%)	691 (42.3%)
Age at entry	Mean (standard deviation)	70.4 (12.85)	69.0 (13.4)

Baseline characteristics of the patients before and after the linkage are displayed in Table 13. Due to the low number of matched patients no further analyses were performed.

Table 13: Baseline characteristics of the patients before and after the linkage

		Before Linkage		After Linkage	
		BIPS	PASCO	BIPS	PASCO
Variable		N = 1,225	N = 77	N = 54	N = 54
Sex	Male	825 (67.3%)	54 (70.1%)	37 (68.5%)	37 (68.5%)
	Female	400 (32.7%)	23 (29.9%)	17 (31.5%)	17 (31.5%)
Age at entry	Median	70	70	71	71

6 Quality Assurance and Data Privacy

The study was conducted according to the Guidelines for Good Pharmacoepidemiology Practice (GPP), Good Practice of Secondary Data Analysis (GPS), Good Epidemiological Practice (GEP) as well as the ENCePP Guide on Methodological Standards in Pharmacoepidemiology.

All procedures from the initial inquiry to the final report for projects based on data from the project-based German Pharmacoepidemiological Research Database (GePaRD) are governed by standard operating procedures (SOPs).

All documents were reviewed by a second epidemiologist/statistician and - for junior staff - by a senior epidemiologist/statistician.

SHI data were checked by numerous plausibility checks before they were entered into GePaRD. All programs were programmed according to agreed coding standards and were validated by double programming or source code review with second programmer involvement.

7 Discussion

Our study quantified the thromboembolic risk associated with current use of epoetin zeta compared to epoetin alpha and all other epoetins (incl. alpha). It did not show an increased thromboembolic risk for current use of epoetin zeta regarding the composite endpoint or any of the separate secondary endpoints. Several sensitivity analyses (excluding switchers, variation of the assumed exposure pattern) corroborated the results of the main analysis.

This is in line with the resultsof a review by Abraham et a.[12] which found similar safety profiles among epoetin alfa, theta, and zeta, including thromboembolic risk and a recent cohort study which did not find a difference in the risk for myocardial infarction and stroke as between epoetin alfa and darbepoetin alfa.[13]

The cumulative incidence of thromboembolic events in our study was with as 11% higher than in PASCO where an overall percentage for thromboembolic events of 6.4% was observed. The same was seen for the separate endpoints acute myocardial infarction, deep vein thrombosis and/or pulmonary embolism and cerebrovascular event[24]. Possible explanations for this discrepancy include the longer observational period (a maximum of 4 years compared to a maximum of 1 year) and the higher prevalence of most comorbidities associated with an increased thromboembolic risk in our study compared to PASCO.

Comparison of our event rates with the Normal Hematocrit study[7], the CHOIR study[8] and the CREATE trial[9] is hampered by the fact we have no information on the target haematocrit or haemoglobin values. It is also not possible to assess whether patients with a higher target haematocrit or haemoglobin values where at higher risk or whether the epoetin groups differed regarding the targeted haematocrit or haemoglobin values.

The strengths of this study are the size and the representativeness of the GePaRD data with a complete coverage of all age groups and the lack of non-response due to the nature of administrative data.[25] The study was not restricted to treatment episodes of a selected population and provides real-life data for a 4-year study period.

Our study has several limitations, mostly due to the use of secondary data. Lifestyle information (smoking, alcohol, body mass index, physical activity), socio-economic status, as well as use of over-the counter medication were not - or only very limited - available. However, assessment of co-morbidity and co-medication might capture this information indirectly.

Another potential limitation is the lack of information with respect to epoetin use in hospital, as inpatient therapy is - with few exceptions - not coded in GePaRD. We don't assume that this had much impact on our results as epoetins in CKD patients are mostly prescribed in the out-patient setting. Exposure assessment had to be conducted based on several assumptions from the information contained in the respective SPC, as treatment duration and prescribed dose are not included in the GePaRD database. However, sensitivity analyses in which the definition of exposure was varied showed that the results are robust to potential misspecification of exposure. Moreover, determination of drug therapy based on pharmacy dispensing data is considered the gold standard as recall bias can be ruled out and information is precise in time and dispensed dose.[26]

Some misclassification of the outcome is possible, but hospital discharge diagnoses are usually very reliable and have shown good positive predictive values in claims databases.

Confounding by indication is a common problem in observational studies, but is probably of minor importance in this study which is based on the relatively homogenous group of patients with CKD and epoetins are rarely used off-label.

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Appendix I: ATC codes of Epoetins

ATC	Description
B03XA01	Erythropoietin
B03XA02	Darbepoetin alfa
B03XA03	Methoxy-Polyethylenglycol-Epoetin beta
B03XA05	Epoetin delta

Appendix II: Codes used for identification of CKD

List of ICD10-GM codes to identify CKD

ICD 10-GM	DESCRIPTION
N180	Terminal kidney disease
N181	Chronische Nierenkrankheit, Stadium 1
N182	Chronische Nierenkrankheit, Stadium 2
N183	Chronische Nierenkrankheit, Stadium 3
N184	Chronische Nierenkrankheit, Stadium 4
N185	Chronische Nierenkrankheit, Stadium 5
N188	Sonstige chronische Nierenkrankheit
N1880	Einseitige chronische Nierenfunktionsstörung
N1881	Chronische Niereninsuffizienz, Stadium I
N1882	Chronische Niereninsuffizienz, Stadium II
N1883	Chronische Niereninsuffizienz, Stadium III
N1884	Chronische Niereninsuffizienz, Stadium IV
N1889	Sonstige chronische Nierenkrankheit, Stadium nicht näher bezeichnet
N189	Chronische Nierenkrankheit, nicht näher bezeichnet
N19	Nicht näher bezeichnete Niereninsuffizienz
Z490	Preparatory care for dialysis
Z491	Extracorporeal dialysis
Z492	Other dialysis
Z992	Dependence on renal dialysis

List of treatment codes to identify CKD

EBM	DESCRIPTION
04564	Additional charge paediatric nephrology, hemodialysis
13600	Additional charge continuous care of patients with chronic renal failure
13602	Additional charge continuous care of patients depending on renal dialysis
13610	Additional charge medical attendance hemodialysis, peritonealdialysis and special procedures
13611	Additional charge medical attendance peritoneal dialysis
13612	Additional charge training dialysis
40813	Additional charge intermittent peritoneal dialysis
40801	Hemodialysis (insurants 18-58 years of age, holiday or commuter dialysis)
40803	Hemodialysis (insurants >= 59 years of age, holiday or commuter dialysis)
40805	Hemodialysis (insurants >= 18 years of age with manifest diabetes mellitus, holiday or commuter dialysis)
40806	Hemodialysis (insurants 18-58 years of age, residence dialysis)
40807	Hemodialysis (insurants >= 59 years of age, residence dialysis)
40808	Hemodialysis (insurants >= 18 years of age with manifest diabetes mellitus, residence dialysis)
40821	Children’s dialysis, holiday, job-related stay
40822	Children’s dialysis, residence dialysis

List of procedures codes to identify the cohort

OPS	DESCRIPTION
8853	Hemofiltration
8854	Hemodialysis
8855	Hemodiafiltration
8856	Hemoperfusion
8857	Peritoneal dialysis

Appendix III: Codes used for Calculation of the Charlson Comorbidity Index

Diseases and ICD-10-GM codes used for the Charlson Comorbidity Index

Disease	ICD-10-GM codes	Weight
Myocardial infarction	I21.x, I22.x, I25.2	1
Congestive heart failure	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5-I42.9, I43.x, I50.x, P29.0	1
Peripheral vascular disease	I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9	1
Cerebrovascular disease	G45.x, G46.x, H34.0, I60.x-I69.x	1
Dementia	F00.x-F03.x, F051, G30.x, G31.1	1
Chronic pulmonary disease	I27.8, I27.9, J40.x-J47.x, J60.x-J67.x, J68.4, J70.1, J70.3	1
Rheumatic disease	M05.x, M06.x ,M31.5, M32.x-M34.x, M35.1, M35.3, M36.0	1
Peptic ulcer disease	K25.x-K28.x	1
Mild liver disease	B18.x, K70.0, K70.1-K70.3, K70.9, K71.3-K71.5, K71.7, K73.x, K74.x, K76.0 ,K76.2-K76.4, K76.8, K76.9, Z94.4	1
Diabetes mellitus without chronic complication	E10.0, E10.1, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9	1
Diabetes mellitus with chronic complication	E10.2, E10.3, E10.4, E10.5, E10.7, E11.2, E11.3, E11.4, E11.5, E11.7, E12.2, E12.3, E12.4, E12.5, E12.7, E13.2, E13.3, E13.4, E13.5, E13.7, E14.2, E14.3, E14.4, E14.5, E14.7	2
Hemiplegia or paraplegia	G04.1, G11.4, G80.1,G80.2, G81x, G82x, G83.0-G83.4, G83.9	2
Renal disease	I12.0, I13.1, N03.2, N03.3, N03.4, N03.5, N03.6, N03.7, N05.2, N05.3, N05.4, N05.5, N05.6, N05.7, N18, N19, N25.0, Z49, Z94.0, Z99.2	2
Any malignancy, including lymphoma and leukaemia, except malignant neoplasm of skin	Per definition of inclusion criteria valid for each patient in cohort	2
Moderate or severe liver disease	I85.0, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5-K76.7	3
Metastatic solid tumour	C77.x-C80	6
AIDS/HIV	B20-B22, B24	6

Appendix IV: List of Outcome Codes

ICD-10 GM	Description	Outcome
I210	Acute transmural myocardial infarction of anterior wall	acute myocardial infarction
I211	Acute transmural myocardial infarction of inferior wall	acute myocardial infarction
I212	Acute transmural myocardial infarction of other sites	acute myocardial infarction
I213	Acute transmural myocardial infarction of unspecified site	acute myocardial infarction
I214	Acute subendocardial myocardial infarction	acute myocardial infarction
I219	Acute myocardial infarction, unspecified	acute myocardial infarction
G450	Arteria-vertebralis-Syndrom mit Basilaris-Symptomatik	cerebrovascular event
G4501		cerebrovascular event
G4502		cerebrovascular event
G4503		cerebrovascular event
G4509		cerebrovascular event
G451	Arteria-carotis-interna-Syndrom (halbseitig)	cerebrovascular event
G4511		cerebrovascular event
G4512		cerebrovascular event
G4513		cerebrovascular event
G4519		cerebrovascular event
G452	Multiple und bilaterale Syndrome der extrazerebralen hirnversorgenden Arterien	cerebrovascular event
G4521		cerebrovascular event
G4522		cerebrovascular event
G4523		cerebrovascular event
G4529		cerebrovascular event
G453	Amaurosis fugax	cerebrovascular event
G4531		cerebrovascular event
G4532		cerebrovascular event
G4533		cerebrovascular event

G4539		cerebrovascular event
G454	Transiente globale Amnesie [amnestische Episode]	cerebrovascular event
G4541		cerebrovascular event
G4542		cerebrovascular event
G4543		cerebrovascular event
G4549		cerebrovascular event
G458	Sonstige zerebrale transitorische Ischämie und verwandte Syndrome	cerebrovascular event
G4581		cerebrovascular event
G4582		cerebrovascular event
G4583		cerebrovascular event
G4589		cerebrovascular event
G459	Zerebrale transitorische Ischämie, nicht näher bezeichnet	cerebrovascular event
G4591		cerebrovascular event
G4592		cerebrovascular event
G4593		cerebrovascular event
G4599		cerebrovascular event
G460	Arteria-cerebri-media-Syndrom (I66.0+)	cerebrovascular event
G461	Arteria-cerebri-anterior-Syndrom (I66.1+)	cerebrovascular event
G462	Arteria-cerebri-posterior-Syndrom (I66.2+)	cerebrovascular event
G463	Hirnstammsyndrom (I60-I67+)	cerebrovascular event
G464	Kleinhirnsyndrom (I60-I67+)	cerebrovascular event
G465	Rein motorisches lakunäres Syndrom (I60-I67+)	cerebrovascular event
G466	Rein sensorisches lakunäres Syndrom (I60-I67+)	cerebrovascular event
G467	Sonstige lakunäre Syndrome (I60-I67+)	cerebrovascular event
G468	Sonstige Syndrome der Hirngefäße bei zerebrovaskulären Krankheiten	cerebrovascular event
H340	Transitorischer arterieller retinaler Gefäßverschluss	cerebrovascular event
I600	Subarachnoidalblutung, vom Karotissiphon oder der Karotisbifurkation ausgehend	cerebrovascular event

I601	Subarachnoidalblutung, von der A. cerebri media ausgehend	cerebrovascular event
I602	Subarachnoidalblutung, von der A. communicans anterior ausgehend	cerebrovascular event
I603	Subarachnoidalblutung, von der A. communicans posterior ausgehend	cerebrovascular event
I604	Subarachnoidalblutung, von der A. basilaris ausgehend	cerebrovascular event
I605	Subarachnoidalblutung, von der A. vertebralis ausgehend	cerebrovascular event
I606	Subarachnoidalblutung, von sonstigen intrakraniellen Arterien ausgehend	cerebrovascular event
I607	Subarachnoidalblutung, von nicht näher bezeichneter intrakranieller Arterie ausgehend	cerebrovascular event
I608	Sonstige Subarachnoidalblutung	cerebrovascular event
I609	Subarachnoidalblutung, nicht näher bezeichnet	cerebrovascular event
I610	Intrazerebrale Blutung in die Großhirnhemisphäre, subkortikal	cerebrovascular event
I611	Intrazerebrale Blutung in die Großhirnhemisphäre, kortikal	cerebrovascular event
I612	Intrazerebrale Blutung in die Großhirnhemisphäre, nicht näher bezeichnet	cerebrovascular event
I613	Intrazerebrale Blutung in den Hirnstamm	cerebrovascular event
I614	Intrazerebrale Blutung in das Kleinhirn	cerebrovascular event
I615	Intrazerebrale intraventrikuläre Blutung	cerebrovascular event
I616	Intrazerebrale Blutung an mehreren Lokalisationen	cerebrovascular event
I618	Sonstige intrazerebrale Blutung	cerebrovascular event
I619	Intrazerebrale Blutung, nicht näher bezeichnet	cerebrovascular event
I620	Subdurale Blutung (nichttraumatisch)	cerebrovascular event
I6200	Subdurale Blutung (nichttraumatisch), Akut	cerebrovascular event
I6201	Subdurale Blutung (nichttraumatisch), Subakut	cerebrovascular event
I6202	Subdurale Blutung (nichttraumatisch), Chronisch	cerebrovascular event
I6209	Subdurale Blutung (nichttraumatisch), Nicht näher	cerebrovascular event

	bezeichnet	
I621	Nichttraumatische extradurale Blutung	cerebrovascular event
I629	Intrakranielle Blutung (nichttraumatisch), nicht näher bezeichnet	cerebrovascular event
I630	Hirninfarkt durch Thrombose präzerebraler Arterien	cerebrovascular event
I631	Hirninfarkt durch Embolie präzerebraler Arterien	cerebrovascular event
I632	Hirninfarkt durch nicht näher bezeichneten Verschluss oder Stenose präzerebraler Arterien	cerebrovascular event
I633	Hirninfarkt durch Thrombose zerebraler Arterien	cerebrovascular event
I634	Hirninfarkt durch Embolie zerebraler Arterien	cerebrovascular event
I635	Hirninfarkt durch nicht näher bezeichneten Verschluss oder Stenose zerebraler Arterien	cerebrovascular event
I636	Hirninfarkt durch Thrombose der Hirnvenen, nichteitrig	cerebrovascular event
I638	Sonstiger Hirninfarkt	cerebrovascular event
I639	Hirninfarkt, nicht näher bezeichnet	cerebrovascular event
I64	Schlaganfall, nicht als Blutung oder Infarkt bezeichnet	cerebrovascular event
I801	Phlebitis and thrombophlebitis of femoral vein	Deep vein thrombosis
I802	Phlebitis and thrombophlebitis of other deep vessels of lower extremities	Deep vein thrombosis
I803	Phlebitis and thrombophlebitis of lower extremities, unspecified	Deep vein thrombosis
I809	Phlebitis and thrombophlebitis of unspecified site	Deep vein thrombosis
I26	Pulmonary embolism	Pulmonary embolism
I260	Lungenembolie mit Angabe eines akuten Cor pulmonale	Pulmonary embolism
I269	Lungenembolie ohne Angabe eines akuten Cor pulmonale	Pulmonary embolism