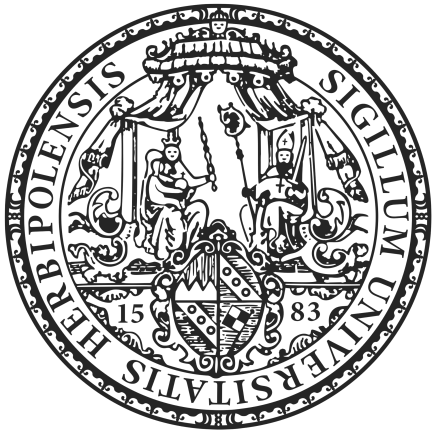


# Time trends and determinants of stroke mortality in Germany

# Zeitliche Trends und Einflussfaktoren auf die Schlaganfall-Sterblichkeit in Deutschland

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# 1 Summary

In several countries, a decline in mortality, case-fatality and recurrence rates of stroke was observed. However, studies investigating sex-specific and subtype-specific (pathological and etiological) time trends in stroke mortality, case-fatality and recurrence rates are scarce, especially in Germany. The decline in ischemic stroke mortality and case-fatality might be associated with the high quality of acute care of ischemic stroke, but the exact determinants of early outcome remains unknown for Germany.

Therefore, as first step of this thesis, we investigated the time trends of subtype- and sex-specific age-standardized stroke mortality rates in Germany from 1998 to 2015, by applying joinpoint regression on official causes of death statistics, provided by the Federal Statistical Office. Furthermore, a regional comparison of the time trends in stroke mortality between East and West was conducted. In the second step, time trends in case-fatality and stroke recurrence rates were analyzed using data from a population-based stroke register in Germany between 1996 and 2015. The analysis was stratified by sex and etiological subtype of ischemic stroke. In the third step, quality of stroke care and the association between adherence to measures of quality of acute ischemic stroke care and in-hospital mortality was estimated based on data from nine regional hospital-based stroke registers in Germany from the years 2015 and 2016.

We showed that in Germany, age-standardized stroke mortality declined by over 50% from 1998 to 2015 both, in women and men. Stratified by the pathological subtypes of stroke, the decrease in mortality was larger in ischemic stroke compared to hemorrhagic stroke. Different patterns in the time trends of stroke were observed for stroke subtypes, regions in Germany (former Eastern part of Germany (EG), former Western part of Germany (WG)) and sex, but in all strata a decline was found. By applying joinpoint regression, the number of changes in time trend differed between the regions and up to three changes in the trend in ischemic stroke mortality were detected. Trends in hemorrhagic stroke were in parallel between the regions with up to one change (in women) in joinpoint regression. Comparing the regions, stroke mortality was higher in EG compared to WG throughout the whole observed time period, however the differences between the regions started to diminish from 2007 onwards.

Further it was found that, based on the population-based Erlangen Stroke Project (ESPro), case-fatality and recurrence rates in ischemic stroke patients are still high in Germany. 46% died and 20% got a recurrent stroke within the first five years after stroke. Case-fatality rates declined statistically significant from 1996 to 2015 across all ischemic stroke patients and all etiological subtypes of ischemic stroke. Based on Cox regression no statistically significant decrease in stroke recurrence was observed.

Based on the pooled data of nine regional hospital-based stroke registers from the years 2015 and 2016 covering about 80% of all hospitalized stroke patients in Germany, a high quality of care of acute ischemic stroke patients, measured via 11 evidence-based quality indicators (QI) of process of care, was observed. Across all registers, most QI reached the predefined target values for good quality of stroke care. 9 out of 11 QI showed a significant association with 7-day in-hospital mortality. An inverse linear association between overall adherence to QI and 7-day in-hospital mortality was observed.

In conclusion, stroke mortality and case-fatality showed a favorable development over time in Germany, which might partly be due to improvements in acute treatment. This is supported by the association between overall adherence to quality of care and in-hospital mortality. However, there might be room for improvements in long-term secondary prevention, as no clear reduction in recurrence rates was observed.

# 2 Zusammenfassung

Ein Rückgang der Mortalität-, Letalität- und Rezidivraten nach einem Schlaganfall konnte in einigen Ländern in den letzten Jahren beobachtet werden. Es gibt, insbesondere für Deutschland, jedoch nur wenige Daten, die diese zeitlichen Trends stratifiziert nach Geschlecht und Schlaganfallsubtyp (pathologischer und ätiologischer Subtyp) ausgewertet haben. Der Rückgang der Mortalität und Letalität nach ischämischem Schlaganfall könnte mit der beobachteten hohen Qualität der Versorgung des akuten ischämischen Schlaganfalls zusammenhängen, jedoch sind für Deutschland die genauen Determinanten der frühen Sterblichkeit nach Schlaganfall noch unbekannt.

Aus diesem Grunde wurden in der vorliegenden Dissertation, im ersten Schritt zeitliche Trends von 1998 bis 2015 der altersstandardisierten und nach Subtyp und Geschlecht stratifizierten Mortalitätsraten untersucht. Dazu wurden die vom Statistischen Bundesamtes bereitgestellten Daten zur Todesursachenstatistik mittels Joinpoint Regression ausgewertet. Zusätzlich wurde ein regionaler Vergleich der zeitlichen Trends in der Schlaganfallmortalität zwischen der östlichen und westlichen Region von Deutschland durchgeführt. Im zweiten Schritt, wurde basierend auf einem deutschem bevölkerungsbasierten Schlaganfallregister mittels Cox Regression die zeitlichen Trends der Letalitätsraten und Rezidivraten des ischämischen Schlaganfalls zwischen 1996 und 2015 geschätzt. Die Analyse wurde stratifiziert nach Geschlecht und ätiologischem Subtyp des ischämischen Schlaganfalls. Im dritten Schritt wurde, basierend auf Daten von neun regionalen krankenhausbasierten Schlaganfallregistern der Jahre 2015 und 2016, die Qualität der Behandlung des akuten ischämischen gemessen und ein möglicher Zusammenhang zwischen dem Grad der Erfüllung von evidenzbasierten Qualitätsindikatoren und der Krankenhaussterblichkeit untersucht.

Wir konnten zeigen, dass von 1998 bis 2015 die altersstandardisierten Schlaganfall Mortalitätsraten über 50%, sowohl bei Männern als auch bei Frauen, abgenommen haben. Stratifiziert nach pathologischem Schlaganfallsubtyp zeigte sich ein stärkerer Rückgang in den Mortalitätsraten nach ischämischem Schlaganfall als in der Mortalitätsrate nach hämorrhagischem Schlaganfall. In allen Strata sind die Mortalitätsraten gesunken, jedoch unterschieden sich die zeitlichen Verläufe zwischen den Strata

(Geschlecht, Region). Die mittels Joinpoint Regression geschätzten Anzahlen an Änderungen im zeitlichen Trend der ischämischen Schlaganfall Mortalitätsraten variierten zwischen 0 und maximal 3 Änderungen, zwischen den Regionen und Geschlechtern. Die zeitlichen Trends der Mortalitätsraten nach hämorrhagischem Schlaganfall der beiden Regionen verliefen hingegen parallel zueinander und es zeigte sich nur bei Frauen eine Änderung in der Mortalitätsrate nach der Joinpoint Regression. Die Schlaganfall Mortalitätsraten im östlichen Teil von Deutschland waren über die gesamte Zeit hinweg höher als im westlichen Teil von Deutschland, jedoch glichen sich die Raten ab 2007 immer mehr einander an und es zeigte sich nur noch ein geringer Unterschied in 2015.

Die altersadjustierten Letalitätsraten und Rezidivraten nach ischämischem Schlaganfall waren in Deutschland, basierend auf Daten des bevölkerungsbasierten Erlanger Schlaganfall Registers, relativ hoch. Innerhalb der ersten fünf Jahre nach einem ischämischen Schlaganfall sterben 46% und 20% aller Patienten bekommen einen erneuten Schlaganfall. Von 1996 bis 2015 haben die Letalitätsraten nach Schlaganfall signifikant abgenommen, dies zeigte sich in allen Subtypen des ischämischen Schlaganfalls. Die Rezidivraten zeigten keinen signifikanten Rückgang.

Basierend auf gepoolten Daten aus den Jahren 2015/2016 von neun krankenhausbasierten Schlaganfall Registern in Deutschland, die ca. 80% aller hospitalisierten Schlaganfälle in Deutschland abdecken, ist die, mittels 11 evidenzbasierter Prozessindikatoren gemessene Qualität der Behandlung des ischämischen Schlaganfalls, hoch. In allen Registern lagen die meisten Qualitätsindikatoren über dem vorabdefinierten Referenzwert für eine gute Qualität an Schlaganfallversorgung. Ein Zusammenhang zwischen 7-Tage Krankenhaussterblichkeit und Erfüllung von einzelnen Qualitätsindikatoren, konnte bei 9 von 11 Qualitätsindikatoren gezeigt werden. Zusätzlich zeigte sich ein inverser Zusammenhang zwischen der Gesamteinhaltung von Qualitätsindikatoren und 7-Tage Krankenhaussterblichkeit.

Schlaganfall Mortalitätsrate und Letalitätsraten zeigten eine positive Entwicklung in allen Subtypen des Schlaganfalls über die letzten 20 Jahre. Dies könnte mit Verbesserungen in der Behandlung des akuten ischämischen Schlaganfalls im Krankenhaus zusammenhängen, da ein Zusammenhang zwischen der Erfüllung von Qualitätsindikatoren und der Krankenhaussterblichkeit besteht. Jedoch besteht

möglicherweise noch Verbesserungspotenzial in der langfristigen Sekundärprävention, da in den Rezidivraten kein klarer Rückgang erkennbar war.

# 3 Introduction

## 3.1 Disease condition stroke

According to the World Health Organization (WHO) stroke is defined as "rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin"[1]. Globally, around 1,079 out of 100,000 people suffered a stroke in 2016 of whom 51.3% were female, based on the data from Global Burden of Disease Study (GBD) [2]. Over a million incident stroke cases were observed in the European Union in 2017[3]. In 2016, globally 5.5 million people died due to stroke and stroke is accountable for 116.4 million disability-adjusted life-years lost[2]. In the European Union there were 460 000 deaths and more than 7 million disability-adjusted life years lost due to stroke in 2017[2, 3]. Stroke is also a leading cause of adult disability in the world[2, 4]. Stroke can cause neurological deficits such as aphasia, dysarthria and motor disorders and patients after stoke have a high risk of recurrent vascular events and death[5-9]. As a disease of older age, stroke affects both men and women. For example, in Germany the prevalence of stroke was 3.3% in men and 2.5% in women between the ages of 40 to 79 years, based on representative survey data, collected between 2008-2011[10]. The median age of stroke patients in Germany was 75 years and 55% were female[11, 12]. The mean age of the first stroke is in women about five years higher than in men[13, 14]. Because of this and the higher life-expectancy of women, in absolute numbers more women than men suffer from a stroke, whereas men have an up to two times higher age-adjusted stroke incidence rates compared to women[13, 15].

Stroke can be classified into two major pathological subtypes, ischemic and hemorrhagic stroke, the latter comprising primary intracerebral hemorrhage and subarachnoid hemorrhage. About 80% of all strokes are of ischemic origin, followed by 12% of primary intracerebral hemorrhage and 3% subarachnoid hemorrhage and 5% stroke of unspecific origin[11].

There are different underlying etiological causes of acute ischemic stroke, which can be classified according to mechanism based classification systems such as the "Trial of ORG 10172 in Acute Stroke

Treatment" (TOAST) classification[16]. As prognosis of ischemic stroke and its management in terms of acute treatment and long-term prevention varies between the etiological subtypes, determination of subtypes is important[8, 16-18]. According to the TOAST classification the five major etiological subtypes are: large-artery atherosclerosis, cardioembolism, small-vessel occlusion, stroke of other determined etiology, and stroke of undetermined etiology. Among ischemic stroke patients, the distribution of subtypes in Germany was as follows: 10% large-artery atherosclerosis, 25% cardioembolism, 26% small-vessel occlusion, 2% other determined etiology and 38% undetermined etiology[11].

Recurrent events are likely to be more severe and increase the risk of mortality, disability and dementia and patients with recurrent stroke have a higher risk of a prolonged in-hospital stay compared to patients after first stroke[19-21]. Therefore, they play a major role in the burden of stroke[20, 21]. Within the first year after an index stroke, between 5% to 21% suffer from a recurrent event[22, 23]. The highest risk of stroke recurrence is observed within the first 90 days after the index event[4, 24, 25]. Risk of a recurrent stroke is especially high in patients with subarachnoid hemorrhage in the early phase[25]. In the long-term, up to five years, patients with ischemic stroke and primary intracerebral hemorrhage have a higher risk to get recurrent stroke compared to patients with subarachnoid hemorrhage[25]. Dependent on the etiological subtype of ischemic stroke, the recurrence rates differ. According to the TOAST classification the early risk of stroke recurrence (within 90 days) is highest in large-artery atherosclerosis and lowest in small-artery occlusion[26]. In the long-term, risk of recurrent stroke is highest among patients with cardioembolic stroke[8, 27] Previous analyses of the ESPro showed differences in stroke recurrence and case-fatality rate between the subtypes of ischemic stroke according to TOAST classification. Etiology according to TOAST criteria influenced the case-fatality, but had no effect on stroke recurrence during the first two years after stroke[8].

## 3.2 Risk factors and prevention of stroke

Risk factors for stroke can be divided into modifiable and non-modifiable. Ischemic and hemorrhagic stroke patients share several non-modifiable risk factors such as age, sex, race/ethnicity[12]. Genetic predisposition is also a risk factor for both subtypes[12]. There are small differences in modifiable risk factors between ischemic and hemorrhagic stroke. Most common modifiable risk factors for ischemic stroke are, according to the case-control study INTERSTROKE study, covering 32 countries, hypertension, current smoking, waist-to-hip ratio (obesity), unhealthy diet, physical inactivity, hyperlipidemia, diabetes mellitus, alcohol consumption, cardiac causes, and apolipoprotein B to A1 ratio[12, 28]. Further risk factors for ischemic stroke comprise atrial fibrillation and psychosocial stress with atrial fibrillation as major risk factors for cardioembolic stroke[12, 28]. The most frequent modifiable risk factors for hemorrhagic stroke are hypertension, current smoking, waist-to-hip ration, alcohol consumption, and diet[12, 28].

To lower the burden of stroke for the society it is necessary to substantially decrease incidence, recurrence and case-fatality rates by adequate prevention of stroke on the population level and on the individual level. Prevention can be divided into primary (preventing the first stroke), secondary prevention (preventing a recurrent stroke), and tertiary prevention (minimizing disability)[29, 30]. Primordial prevention strategies are aiming to modify the risk factors on the population level, e.g. by implementing public health measures to quit smoking, to promote a healthy diet, or to increase physical activity[12]; in addition, promoting a healthy diet is also important, as shown by a Cochrane review[31].

To identify patients with a high risk of fatal or non-fatal stroke on the individual level, risk scores such as the Framingham Stroke Risk Profile or the Systematic Coronary Risk Evaluation (SCORE) score can be applied to estimate stroke risks based on the individual risk factor distribution[32-34]. These scores can be used to communicate stroke risks for individual patients and to support the physicians in guiding prevention measures such as prescribing medicine for high risk individuals[32-35]. For example, according to current clinical guidelines, high blood pressure reduction, lifestyle modifications and/or antihypertensive therapy can be recommended depending on the treatment target and age[36].

## 3.3 Acute Treatment

Stroke is a medical emergency and each stroke should be treated as soon as possible in hospital due to the time critical application of specific therapies, such as intravenous thrombolysis or thrombectomy[37-40]. The longer it takes from onset to treatment, the more brain cells die, as there is a linear relationship between time after stroke and the loss of brain cells. For example, in patients with large vessel ischemic stroke around 120 million neurons are lost per hour[41]. This relationship and the need of an urgent reaction after stroke is compromised in the concept "time is brain"[41].

The aim of acute stroke management is, therefore, to prevent death and to reduce disability as soon as possible. The evidence for adequate treatment and management strategies in stroke patients have been summarized and recommended in national and international clinical guidelines[29, 42, 43]. According to the German clinical guidelines for acute therapy of ischemic stroke, acute treatment can be divided into five categories: general treatment /basic therapy; specific therapy; early secondary prevention; screening, diagnostic and treatment of complications and early rehabilitation[29].

In the following some examples for the five acute treatment categories will be given. An examples for effective general treatment of ischemic stroke is the treatment on a Stroke Unit. It is recommended for all stroke patients, as it reduces the 5-year odds of death by 25% according to an updated Cochrane review of 2013[44]. Intravenous thrombolysis with alteplase or mechanical thrombectomy are example of specific therapies. In ischemic stroke patients depending on different factors such as stroke severity or time from onset to treatment, intravenous thrombolysis with alteplase or mechanical thrombectomy given within the appropriate time window have shown to improve good outcome[29, 38-40, 45, 46]. An example for early secondary prevention is the treatment with antiplatelet within 48hours after stroke onset which reduces the risk of death or dependency[29, 47]. An example for a diagnostic procedure is the conduction of brain imaging. To diagnose the pathological subtype of stroke and to start the appropriate treatment, brain imaging via computed tomography (CT) or magnetic resonance imaging (MRI) should be done as

soon as possible, as time is brain. The UK guideline from 2017 recommend brain imaging within one hour after admission to the hospital[45]. An example for a screening procedure is the screening of dysphagia, which can reduce the risk of pneumonia after stroke by identification and adequate management of patients with swallowing disorders[48]. Another example for screening is the screening for atrial fibrillation via ECG monitoring. Identification of patients with atrial fibrillation is important, as atrial fibrillation is a substantial risk factor for first and recurrent stroke that are potentially preventable, e.g. by oral anticoagulation[29]. An example for early rehabilitation is mobilization, it should be started as soon as possible to mobilize the patients[49].

The clinical guidelines for the management and treatment of acute stroke are being constantly adapted and improved. For example, it was first shown that intravenous thrombolysis with tissue Plasminogen Activator (tPA) is beneficial only in patients presenting within 3 hours after the onset of a stroke[39]. Later this time window was extended to 4.5hours[40]. Furthermore, it was recently shown that administration of tPA is safe and beneficial also in patients older than 80 years old as well as in patients with a wake-up stroke if therapy is guided by imaging [50, 51]

## 3.4 Management of acute stroke and stroke mortality

Effect of treatments on mortality and disability are mostly investigated in randomized clinical trials under strict conditions, including pre-specified inclusion and exclusion criteria. To measure the effectiveness of treatment and management options of acute stroke care on the population level, the standard of care in routine data needs to be monitored. In Germany quality of care of stroke patients is monitored by regional stroke registers, which collaborate in the German Stroke Registers Study Group (Arbeitsgemeinschaft Deutschsprachiger Schlaganfall Register (ADSR))[52, 53]. Data from the ADSR are pooled and analyzed regularly to measure the quality of stroke care in Germany[53-55]. Based on these audit data standardized and evidence-based quality indicators (QI) are calculated to measure the performance of health care providers in routine clinical care[56, 57]. These evidence-based QI were

developed by a multidisciplinary expert board, based on a structured process including e.g. a systematic review, independent external review of experts and a pilot study[53]. Each QI should reflect a meaningful outcome (such as case-fatality or poor outcome) to the patients and society or be associated with a meaningful outcome to be valid[58]. QI can be categorized into the health care dimensions: process of care, structure and outcome[59]. Example for quality indicators are the treatment on a Stroke Unit or antiplatelet therapy for ischemic stroke patients[60]. Several national initiatives exist in and outside of Europe to develop quality indicators for stroke care[53, 56, 61-65]. However, the definition and the reporting of the results for these performance measures varies between countries. In Europe, the European Implementation Score (EIS) Collaboration observed a substantial variability in QI being used on a national level[62]. However, all national audits provided a benchmarking, a comparison of one hospital against all hospitals, although the frequency of reporting differes[62]. Generally, it has been shown that the implementation of QI and giving feedbacks within audits improves the performance of health care providers[66, 67]. For example, an increase in quality of stroke care, measured via adherence to QI was observed from 2004 to 2009 in five national stroke audits collaborating within the European Implementation Score (EIS), that might be partly associated with the implementation of specific performance measures[68].

The association between adherence to distinct QI and mortality was investigated in several studies and systematic reviews, but the results are equivocal[60, 69]. For example, the Australian Stroke Clinical Registry found an improvement in survival after 180 days in patients receiving treatments defined via processes of care (such as Stroke Unit, antihypertensive as secondary prevention, discharge)[70]. Furthermore, a recent meta-analysis on published key performance indicators revealed that most of the common QI (such as swallowing/nutritional assessment, Stroke Unit admission, antiplatelet use for ischemic stroke, brain imaging and anticoagulant use for ischemic stroke with atrial fibrillation, lipid management, deep vein thrombosis prophylaxis and early physiotherapy/mobilization) was associated with a significantly reduced case-fatality rate[60]. However, within this review, few QI showed no significant effect on case-fatality or poor outcome after stroke[60].

As all stroke patients should receive more than one treatment and management option depending on their individual needs, it is important to know how the adherence to the combination of these standards of care, reflecting the overall performance of the health care providers, is associated with mortality. Most previous reports investigated the association of a distinct QI on mortality and not the combination of a defined set of QI as proxy of the overall performance of a respective health care facility. In a systematic review, seven studies were identified which reported an association between the number of processes achieved and mortality[60]. Adherence to a combination of performance indicators was associated with a reduction in risk of death[60]. Such data are currently lacking for Germany.

## 3.5 Time trends in stroke incidence, recurrence and case-fatality

Over the last 25 years acute treatment and prevention of first and recurrent stroke has improved, e.g. Stroke Units, intravenous thrombolysis or thrombectomy were introduced as acute treatment and management options and uptake of oral anticoagulants increased as secondary prevention option[71, 72]. All these changes in acute treatment and prevention might have influenced the incidence, case-fatality and recurrence rates, as trends in these disease frequency measures are determined by different factors such as primary prevention, secondary prevention as well as acute treatment and management of stroke patients.

To study time trends in stroke incidence, recurrence and case-fatality prospective population-based stroke registers with a long follow-up are the gold standard[73, 74]. To ensure comparable high quality of data, population-based stroke registers should follow standardized criteria in design, data collection, definition of cases and presentation of the data, such as the criteria defined by Sudlow and Warlaw[73]. For example, the criteria comprise a complete and community-based case ascertainment, including hospitalized and non-hospitalized cases by using overlapping sources of information for detecting all suspected stroke cases in the community. The number of population-based registers which fulfill all those criteria is limited. Therefore, data on time trends in stroke incidence, case-fatality and recurrence

rates are scarce. Example for European stroke registers which fulfill all those criteria are the Dijon Stroke Registry, South London Stroke Register and ESPro[11, 75-77]. ESPro was started in 1994 and is still ongoing[7, 8, 11]. Thus, it is the longest running population-based stroke register in Germany.

The GBD combines registers and other sources to study time trends in incidence and mortality and disability-adjusted life years. In this study, a decline for the global age-standardized incidence of 8% was observed from 1990 to 2016[2]. Only in the middle quintile group of the socio-demographic index, no decline in incidence rates could be documented[2]. Additionally, substantial differences in time trends in incidence, recurrence and case-fatality between countries were detected[2, 3].

There are also differences in time trends in stroke incidence between men and women. Based on data from the population-based ESPro ischemic stroke incidence rates in Germany decreased in men, whereas in women no statistically significant time trend was found[11]. Moreover, differences in incidence, prevalence and recurrence rate between etiological subtypes of ischemic stroke were observed according to the underlying mechanism of the index stroke, classified e.g. by the TOAST classification[8, 17, 18]. For example in Germany, age-adjusted incidence rates of stroke due to large-artery atherosclerosis decreased statistically from 1995 to 2010 in men, whereas incidence rates in stroke due to small-artery occlusion increased in women[11]. Furthermore, no statistically significant changes in the other etiological subtypes of ischemic stroke according to TOAST criteria were observed in Germany[11].

Results from the few studies reporting time trends in stroke recurrence were controversial. The South London Stroke Register reported a decrease in recurrence rates of first ever in a live time stroke from 1995 to 2005, but no further changes from 2005 to 2018 onwards[27]. A systematic review, comprising hospital-based or community-based stroke registers published before 2010, found decreasing 5-year recurrence rates[22]. However, the Australian Perth Community Stroke Study observed no statistically significant decrease in 5-year recurrence rates[78]. For Germany, so far data on time trends in stroke recurrence, especially by pathological and etiological subtype, are lacking.

Another factor driving the burden of stroke for the society are case-fatality rates. Case-fatality rate, which is the proportion of patients dying among all the patients who suffered a stroke, decreased in the

last years in many countries[79]. In a Danish population-based cohort study the 30-day, 1-year and 5-year case-fatality rates in ischemic stroke decreased by approximately 45% from 1994-2011, adjusted for age, sex and comorbidity by Charlson Comorbidity index[80].

In Germany also reductions in case-fatality rates and in-hospital mortality rates were observed[81-84]. For example, based on claims data including the two time periods 2006-2008 to 2014-2016 and including more than 40,000 incident stroke cases, a significant reduction in risk of death after stroke over time was found[81]. This was present in all income groups (low or high income group) and in men and women[81]. Furthermore in-hospital mortality after ischemic stroke decreased from 6.6% in 2000 to 4.6% in 2008 in the Stroke Register of Northwestern Germany[82]. In addition based on the German diagnostic related groups statistics, also a decline in in-hospital mortality from 2005 to 2010 was found[83]. From 2006 to 2014 30-day case-fatality after stroke decreased based on annual hospital panel data[84]. However, data on long-term time trends of case-fatality in Germany are missing.

## 3.6 Time trends in stroke mortality

Not only case-fatality, but also stroke mortality rates declined, even though stroke remains one of the leading causes of death worldwide, especially in the developed countries[85, 86 87, 88]. Time trends in stroke mortality rates differ between countries. For example, age-adjusted total stroke mortality rates in the USA declined from 2000-2015, based on descriptive analysis[89]. However, recent studies indicate that the decline might be flattening. According to routine statistics the decline in cardiovascular-disease mortality (including stroke) slowed down starting in the midst 2010s in 23 high-income countries in at least one sex[90]. Furthermore, starting in 2015, an increase in cardiovascular disease mortality rates was observed in patients between 35-74 years old in North America in men and women and in Canada in women[90].

Even though in most developed countries a decline in stroke mortality was observed, time trends in stroke mortality varies between European countries, especially between Eastern and Western European

countries. In most of the Western European countries cerebrovascular disease mortality steadily declined between 1980 and 2011[91, 92]. Compared to Western European countries, Eastern European countries had higher rates and experienced a slower decrease in stroke mortality[92, 93]. For example in Romania only age-adjusted stroke mortality declined from 1994 to 2017, but ischemic stroke mortality increased from 1994 to 2005 with an annual percentage change of 6.39% and decreased from 2005 onwards with an annual percentage change of -2.83%[94].

There are also substantial regional differences in stroke mortality within countries. An analysis of the all-cause mortality from 1960 to 1997 in Germany, comparing the Eastern part and Western part of Germany, showed that there were higher mortality rates in Eastern part of Germany compared to the Western part[95, 96]. The German reunification in 1990 changed the political, social and health care systems in Eastern Germany and might have also influence stroke mortality rates. Prior to the reunification of Germany, a huge gap in all-cause mortality rates was observed[95]. After the reunification all-cause mortality rates converged, but there were still differences between the Eastern and Western part of Germany, especially due to circulatory disease[96, 97].

Regional specific time trends in stroke mortality were analyzed up to the year 2013 in Germany[98]. They revealed a decrease in stroke mortality in the former Eastern and former Western part of Germany and showed increasing total stroke mortality rates around 1990 and afterwards decreasing rates in both regions. Further differences in trends between the age-groups were observed. The analysis of age-specific rates revealed that the decrease was highest in the age group 65-74 with an average-annual percentage change of -5.4% in women and -4.8% in men[98]. However, direct comparisons of the trends in stroke mortality between Eastern and Western part of Germany for the different subtypes of stroke (ischemic and hemorrhagic stroke) are lacking[98], although time trends between ischemic and hemorrhagic stroke mortality may differ. For example, between 1990 and 2013 a significant decrease was only observed in ischemic stroke mortality, but not in hemorrhagic stroke mortality[99]. However, in China based on age-period-cohort model, a reduction in ischemic stroke and hemorrhagic stroke mortality was observed from 1993 to 2017[100]. These results underline the need of a subtype-specific analysis of time trends in stroke mortality.

The comparison of time trends in incidence, case-fatality, recurrence and stroke mortality for the same time periods is important, as changes in mortality can be affected by changes in incidence, case-fatality and recurrence rates. If mortality declines, this can be on the one hand due to a decrease in incidence, leading to a reduction in the absolute number of stroke victims in the population. However, it might also be due to a decrease in recurrence rates, because a second stroke is associated with an increased risk of dying[21]. In addition, also lower case-fatality rates after the event might be associated with a decreased mortality in the population due to a lower absolute number of stroke deaths.

Changes in incidence, recurrence and case-fatality also lead to changes in the prevalence of stroke in the population. For example, if case-fatality rate decreases, but the incidence rates remains stable the overall prevalence of stroke increases[101]. In 2017 in the European Union more than 9 million prevalent strokes occurred[3]. A projection to the year 2047 estimated that the number of prevalent cases will increase by 27%, whereas the incidence will only increase by 3%[76], due to an aging of the source population and a decrease in mortality[3].

However, up to now it is unclear to what extent changes in stroke incidence, recurrences rate and case-fatality rates contribute to time trends in stroke mortality. Therefore, investigating country and subtypes specific trends in incidence, case-fatality and recurrence for different populations is crucial to assess the effects of stroke treatment strategies and prevention programs over time in the population [102]. It further might help to guide local health care providers in identifying areas for improving future strategies for treatment or prevention of stroke [102].

# 4 Aims and objectives

Within this thesis, we want to investigate time trends in stroke mortality, case-fatality and recurrent rates in different settings and stroke populations and we want to identify determinants driving early mortality.

The thesis is subdivided in three work packages (WP) with aims and objectives detailed below:

Aim of the first work package (WP1) “Time trends in stroke mortality” is to analyze possible time trends in age-adjusted stroke mortality rates on a national level in Germany between 1998 and 2015 stratified by pathological stroke subtype (ischemic stroke, hemorrhagic stroke, other types of stroke) using aggregated data from the Federal Statistical Office. In addition, we want to compare the different time trends in mortality between the former Eastern part of Germany (EG) and the former Western part of Germany (WG) stratified by subtype. We hypothesize that age-adjusted stroke mortality decreased between 1998 and 2015 in Germany with differences between the two regions, with EG having higher rates than WG.

The objective of the second work package (WP2) “Time trends in case-fatality and stroke recurrence rates” is to estimate case-fatality rates and recurrence rates in ischemic stroke and to investigate long-term time trends in case-fatality and recurrence rates between 1996 and 2015 using the population-based stroke register ESPro. In addition, we want to compare long-term time trends in case-fatality and recurrence rates by ischemic stroke etiology according to the mechanism-based TOAST classification. We hypothesize that case-fatality and recurrence rates in ischemic stroke patients decreased between 1996 and 2015 with substantial differences between underlying stroke etiology.

The third work package (WP3) “Association of quality indicators and early in-hospital mortality” focus on factors determining early mortality in the acute stroke setting in the years 2015 /2016 in Germany based on routine data of the German Stroke Register Study group. The objective of this work package is to investigate the association between 7-day in-hospital mortality and adherence to a set of evidence-based indicators of quality of care in ischemic stroke patients. We hypothesize that a higher adherence to quality indicators of process of care is associated with a lower 7-day in-hospital mortality.

# 5 Methods

## 5.1 Data Sources

### 5.1.1 Causes of death statistics Germany (WP1)

#### 5.1.1.1 Study population

Number of inhabitants and number of deaths due to stroke specific causes in Germany in the years 1998 to 2015 were collected from the Federal Statistical Office. The dataset was based on the official causes of death statistics in Germany and was provided in an aggregated way by the Federal Statistical Office.

#### 5.1.1.2 Data collection and definition

Cause specific causes of death were defined as International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10): I60-I69 (total stroke), I60 (subarachnoid hemorrhage), I61 (intracerebral hemorrhage), I63 (ischemic stroke) and I64 (stroke not defined as hemorrhage or infarct). As ischemic stroke is the major cause of stroke, we defined the causes of death I63 and I64 as ischemic stroke and combined the causes of death I60 and I61 as hemorrhagic stroke similar to previous studies[103-105]. Aggregated data were provided stratified by age in categories (<55, 55-64, 65-74, 75-84, 85>=), sex and region. Region was defined as EG and WG, where according to recommendations from previous studies we allocated East Berlin to WG[106].

#### 5.1.1.3 Ethics and Data protection

Data on causes of death and number of inhabitants was routinely collected on an aggregated basis, therefore, the data used was completely anonymous and no ethics board approval or individual informed consent of the patients was needed[105]. This was confirmed by the Ethic Committee of the Medical Faculty of the University of Würzburg (20180523 01). The data set is publicly available at the Information System of the Federal Health Monitoring (http://www.gbe-bund.de)[105].

### 5.1.2 Erlangen Stroke Project (WP2)

#### 5.1.2.1 Study population

ESPro is a prospective population-based stroke register which continuously collects data since 1994[7]. ESPro covers all hospitalized and non-hospitalized stroke cases in the city of Erlangen in Bavaria, with a population size of 105,164 inhabitants in 2010[107]. Aim of the register is to monitor stroke incidence and outcome over time. All hospitalized and non-hospitalized stroke patients with registered residence in Erlangen are identified on a regular basis and included without restrictions in age or stroke severity. Most stroke cases are admitted to the Department of Neurology of the University Hospital Erlangen. To identify all hospitalized and non-hospitalized stroke patients, several overlapping sources of information are checked regularly, including: hospital admissions, discharge records, nursing homes, general practices and death certificates. Completeness of case ascertainment is warranted by using standardized criteria[7, 73]. To identify non-hospitalized patients, also general practitioners are contacted regularly and asked whether they treated a suspected stroke patient. All patients are followed-up after 3 and 12 months, and thereafter annually until death[7, 8]. (see Results Section 6.2.2)

#### 5.1.2.2 Data collection and definition

Stroke was defined according to the WHO criteria as "rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 h or leading to death with no apparent cause other than that of vascular origin"[1]. Images from brain CT or MRI scans were used to determine the classification of pathological subtypes of stroke[7]. Patients with first ever ischemic stroke in the years 1996 to 2015 were included in our analysis[107].

We defined etiological subtype of the first ever ischemic stroke according to TOAST classification[16]. For the analysis the five major categories of TOAST were used: large-artery atherosclerosis including large-artery thrombosis and artery-to-artery embolism, cardioembolism , small-artery occlusion, stroke of other determined cause and stroke of undetermined cause comprising stroke of undefined and concurrent etiology[107]. We defined recurrent stroke according to the WHO definition as new

neurological deficit at least 24 hours after the incident stroke excluding oedema, mass effect, brain shift syndrome or hemorrhagic transformation and procedure related strokes[107, 108].

#### 5.1.2.3 Ethics and data protection

All patients or their legal representatives gave written informed consent to participate[107]. The study was approved by the Ethics Committee of the Medical Faculty of FAU Erlangen-Nürnberg (Reference number: 249_15 Bc)[107]. Data were pseudonymized and the analyzing center had no information about the identity of the patient. For the referred analysis for the years 1994 to 2015 only information on ID, age, sex, TOAST, data of first stroke and recurrent stroke was transferred to the Institute of Clinical Epidemiology and Biometry, University of Würzburg.

### 5.1.3 German Stroke Register Study Group (WP3)

#### 5.1.3.1 Study population

The German Stroke Register Study Group (ADSR) is a voluntary network of regional hospital-based stroke registers in Germany for quality assurance, collaborating under this name since 1999[53, 55]. The aim of ADSR is to ensure a standardized data collection of stroke care and to monitor in-hospital quality of stroke care in Germany. The network consists of the following regional audits: Bavarian Permanent Working Party for Quality Assurance (BAQ), Office for Quality Assurance in Health Care Baden-Württemberg (QiG BW GmbH), Berlin Stroke Register (BSR), Externe Qualitätssicherung Hamburg, Institute of Quality Assurance Hesse (GQH), Quality Assurance in Stroke management in North Rhine-Westphalia, Quality Assurance Project “Stroke Register Northwest Germany”, Quality Assurance Stroke Rhineland-Palatinate, Quality Association for Acute Stroke Treatment Schleswig-Holstein). Participation in a register is mandatory in five federal states (Hamburg, Baden-Wuerttemberg, Bavaria, Hessen, Rhinland-Palatine) and for all certified Stroke Units, defined according to the criteria of the German Stroke Society and the German Stroke Foundation[109, 110].

All stroke patients aged ≥18 years, treated in one of the participating hospitals, were included in the register[109]. Data of the registers were pooled regularly. For the following analysis, data from 2015 and 2016 were pooled for all registers excluding ESPro (as patients from ESPro were also included in the dataset from Bavaria). In 2016 the network of nine regional stroke registers covers about 80% of all hospitalized stroke patients in Germany[109, 111].

#### 5.1.3.2 Data collection

Patient data was collected prospectively in each hospital during hospital stay in a standardized way[109]. Each hospital sent data, mostly electronically, to the coordinating center of the regional stroke register[109]. To pool the register data, each register sent anonymous datasets to the data pooling center at the Institute of Clinical Epidemiology and Biometry, University of Würzburg. Pooled data was anonymous on the patient level. The identity of the respective hospital was only known to the coordinating center of the respective register. Data were collected only on case level. Although a core set of variables was agreed in the ADSR, still differences in coding and number of variables collected existed between the registers, as the final decision of data collection and coding of variables was made by each register. To homogenize the coding of variables in the different regions, the datasets from the different regions were checked for consistency. Further, a core set of variables with the maximum possible amount of information, based on the variables collected in 2015 and 2016, was defined. Afterwards data was checked for plausibility.

#### 5.1.3.3 Data definitions

Stroke was defined according to the WHO criteria[1]. MRI or CT scans were used to confirm the diagnosis of stroke subtypes[109]. Only patients with a diagnosis of ischemic stroke with ICD-10 of I63 were included in the analysis[109]. Data on demography (age, sex, living condition pre stroke), comorbidities, stroke severity, acute treatment, secondary prevention, screening and rehabilitation and early functional status (Barthel Index) during the hospitalization were collected (for the exact definition please see Results Section 4.3.2)[112]. Death within 7-days during hospitalization was defined as 7-day in-hospital mortality[109].

#### 5.1.3.4 Indicators of quality of care

A multidisciplinary board of the ADSR network develops and updates the definition and application of the QI based on published evidence and defined methodological criteria[53]. The board also defined the reference and target values based on national recommendations and expert consensus[54, 55]. The QI and their target values were updated on a regular basis. In 2015/2016 20 QI were collected covering the three dimensions of health care quality: structure, process and outcome[109]. To model the association between process of care and in-hospital mortality, we selected the eleven process of care QI at admission or during hospital stay for our analysis[109]. We divided them into three categories: early rehabilitation; imaging and screening; acute therapy and treatment[109]. As we analyzed the association between QI and outcome, outcome indicators and indicators of processes at hospital discharge were excluded[109]. To measure the adherence to quality of acute stroke care, the QI of process care were combined in the variable proportion of QI fulfilled[109]. Each quality indicator was defined, through pre-specified inclusion and exclusion criteria, as denominator and as nominator, reflecting the fulfilment of a QI. The numerator was part of the eligibility criterion, meaning only patients who were eligible for the QI can fulfil the QI[109] . If a patient fulfilled a QI, but was not eligible for the QI, then that person was excluded for the specific QI. Not every patient was eligible for all QI, due to the eligibility criteria. Proportion of QI fulfilled was defined as number of QI fulfilled divided through the number of QI the individual patient was eligible for[109]. It was calculated on the individual patient level[109] (for an example and more information please see Results 6.3.2).

#### 5.1.3.5 Ethics and data protection

The ethics committee of the Charité-Universitätsmedizin Berlin (EA4/043/10) approved the pooling of the ADSR data[109]. The ADSR data pooling is registered by the University of Würzburg (20170703 02)[109]. Collection of informed consent of the patients was not necessary, as the data set was anonymous[109]. For the data pooling center, the data set was also anonymized on the hospital level, as they had no information on the hospital identities[109].

## 5.2 Statistical Methods

The description of the statistical methods are based on the respective parts of the included manuscripts and are further elaborated here[105, 107, 109].

### 5.2.1 WP 1 "Time trends in stroke mortality"

Crude mortality rate per year was calculated by dividing the number of stroke deaths through the number of inhabitants[105]. To account for migration and changes in age distribution over time and to allow a comparison between different population, rates were age-standardized using the WHO European standard population from 1976 as reference[105, 113]. For the age-standardization age was categorized in five groups (<55, 55-64, 65-74, 75-84, >=85). The rates were stratified by sex, region and pathological subtype[105].

To investigate temporal trends and joinpoints (significant changes in the trend) in age-standardized stroke mortality rates joinpoint regression was performed by applying Joinpoint® software Version 4.5.01[105]. The software was developed by the National Cancer Institute to estimate time trends in mortality rates[105]. Joinpoint regression calculates different joined linear regression curves with different slopes[105]. At the point of a significant change in the slopes, a joinpoint and a new slope was estimated[105]. Slopes reflect the annual percentage change in the rates. No pre-specification of time periods was necessary[114]. Grid search method was applied to estimate the joinpoint regression models[105]. The following parameters were set a priori for the Grid search method: maximum number of joinpoints = 3, minimum number of years between two joinpoints = 2, minimum number of years from a joinpoint to the either end of the data = 2, number of points to place between adjacent observed x values (years) in the grid search = 0. The first model had zero joinpoints, further joinpoints up to the maximum of three joinpoints were added[105]. To compare two joinpoint regression models with different number of joinpoints, the ratio of the sum of squared errors of these two models was calculated and tested for statistical significance with the Permutation test. For the Permutation test Monte Carlo samples of the

permuted data set with 4499 permutations were generated. The p-values was corrected for multiple testing using the Bonferroni correction. The overall significance level was defined as 0.05.

To measure the trend, annual percentage change and averaged annual percentage change with 95%-confidence intervals (CI) were reported, based on the best model of the join point regression. To test the data for a monotonic trend the Mann-Kendall test was conducted[105]. The estimated trends of the two regions (EG, WG) were tested for parallelism using the comparability test.

Ratios of age-standardized mortality rates between WG and EG with the corresponding log-normal 95%-Confidence Interval (CI) were estimated with SAS Software version 9.4 (SAS Institute Inc., Cary, NC, USA)[105] (for more information please see Results Section 6.1.2).

### 5.2.2 WP 2 "Time trends in case-fatality and stroke recurrence rates"

The European standard population from 1976 was used to age-standardize the incidence rates for the year 2015[113]. First recurrent stroke after the index ischemic stroke was defined as recurrent stroke, regardless of the pathological subtype[107]. Case-fatality rates and stroke recurrence rates at 3 months, 1 year and 5 years were calculated as 1 - Kaplan-Meier estimates. Kaplan-Meier plots were stratified by etiological subtype according to TOAST classification and year of event in 5-year groups (1996-2000, 2001-2005, 2006-2010, 2011-2015)[107]. Sex-specific time trends in case-fatality and stroke recurrence rates were investigated by Cox proportional hazard regression models with year of event as independent variable[107]. The continuous variable year of event was used as a proxy for temporal trends. Adjusted Cox regression models for age, sex and year of event and stratified Cox regression models by etiological subtypes according to the TOAST classification and sex were calculated[107]. All models were tested for interaction between age and sex. As the interaction was significant in the Cox models for the hazard of stroke recurrence an interaction term was added to the model. As death can be interpreted as competing event of recurrent stroke[115], a sensitivity analysis with competing risk with death from any cause as competing event and recurrent stroke as event of interest, was conducted[107]. Under competing risk the

cumulative incidence function of recurrent stroke was calculated using the Aalen-Johansen estimator[116]. Fine and Gray's subdistribution hazard regression was performed to analyze time trends in cumulative risk of recurrent stroke under competing risks[107, 117]. The Fine and Gray model was adjusted for age, sex and stratified for etiological subtype according to TOAST classification[117]. Crude probabilities of death or recurrent stroke at 1 year based on Kaplan-Meier estimates were plotted for two years combined.

A level of significance of 5% was defined for all the analysis, no adjustment for multiple comparison was done as this was explorative analysis. Stroke of other determined causes were excluded for the stratified analysis according to TOAST criteria, as the sample size was too small[107]. Three patients were excluded in the sex-stratified analysis due to missing information on sex. All analysis were conducted using the software RStudio Team (2018). RStudio: Integrated Development for R. RStudio, Inc., Boston, MA www.rstudio.com (for more information please see Results Section 6.2.2).

### 5.2.3 WP 3 "Association of quality indicators and early in-hospital mortality"

Descriptive statistics were calculated for the demographical and clinical characteristics of all patients and presented as frequencies (proportion), mean (standard deviation) or median (interquartile range) according to the distribution of the variables[109]. Proportion of QI fulfilled was subdivided in seven groups (<50%, 50-59%, 60-69%, 70-79%, 80-89%, 90-99%, 100%)[109].

The effect of fulfilment of distinct QI and proportion of QI fulfilled on 7-day in-hospital mortality was estimated with univariable and multivariable generalized linear mixed models (GLMM) using a logit link function and assuming a binary distribution of the outcome[109]. To account for a possible within-hospital correlation of patients treated at the same hospital, a random intercept for the variable hospital using a G-side variance was included[109]. All multivariable analysis were adjusted for age, sex, NIHSS, and living will of a patient[109]. A sensitivity analysis for type of reporting of the registers (mandatory, voluntary) on a descriptive level was conducted[109]. Multiple sensitivity analyses on the association of the proportion of QI fulfilled and 7-day in-hospital mortality were performed. First, patients with living

will were excluded[109]. In a second sensitivity analysis, further adjustments were made for the provision of a Stroke Unit services (defined as treating more than ten patients on a Stroke Unit per year) or the size of the hospital (defined through the number of stroke patients treated per year)[109, 118]. A GLMM including proportion of QI fulfilled as a dichotomous variable (100% vs <100%) was estimated[109]. Moreover, the multivariable model was stratified for the provision of a Stroke Unit[109]. To investigate whether the effect of distinct QI on the outcome differed between NIHSS groups (reflecting stroke severity), multivariable GLMM were stratified for NIHSS groups for some of the distinct groups (results not shown)[109]. Due to missing information on thrombectomy or Stroke unit admission, data from the register Hesse of the year 2015 and from the register Hamburg of the years 2015 and 2016 were excluded for descriptive and multivariable analysis of the association of 7-day in-hospital mortality and QI[109]. Patients with missing information in the outcome or independent variables were excluded from the models[109]. Two-tailed test with a significance level of 5% were used for all the analysis[109]. Statistical analyses were performed with SAS Version 9.4 software. Copyright © [2002-2012] SAS Institute Inc. SAS and all other SAS Institute Inc., Cary, NC, USA (for more information please see Results Section 6.3.2).

# 6 Results

## 6.1 Manuscript 1: "Time trends in stroke mortality in Germany"

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### 6.1.1 Summary

Data from Federal Statistical office were used to analysis time trends in stroke mortality. Age-standardized total stroke mortality declined in Germany from 1998 to 2015 from 78 per 100,000 to 34 per 100,000 in men and from 62 to 28 per 100,000 in women. Ischemic stroke mortality declined by 66% in men and 63% in women and hemorrhagic stroke mortality declined by 40% in men and 31% in women.

Stratified joinpoint analysis was applied to estimate changes in the time trends. Analysis was stratified by region (EG, WG), sex and pathological subtype of stroke based on ICD-10 codes. Age-standarized stroke mortality was higher in EG than in WG in all subtypes and in both sexes, but the differences between EG and WG diminished. In 1998 the ratio of WG to EG of age-standardized total stroke mortality rates was 0.65 in men and 0.64 in women, whereas in 2015 the ratio was 0.86 in men and 0.92 in women.

Average annual percentage changes from 1998 to 2015 was in men -4-4% in WG, -6.4% in EG and in women -4.1% in WG and 6.1% in EG. The number of joinpoints, reflecting the changes in the trend differed between the regions and sexes. The trend of ischemic stroke mortality in men changed twice, with two joinpoints (2007, 2012) in WG and was linear in EG with zero joinpoints. For the trend of ischemic stroke mortality in women zero joinpoints were detected in WG and three jointpoins (2003, 2007, 2010) in EG. Average annual percentage change from 1998 to 2015 ranged from -6.9% in men in EG to -5.0% in women in WG.

Time trends of hemorrhagic stroke mortality were in parallel between the regions with zero joinpoints in men and an average annual percentage change of -3.2% in men and one joinpoint in 2004 and an average annual percentage change of -2.3% from 1998 to 2015 in women.

## 6.1.2 Manuscript (as accepted)

# Decline in regional trends in mortality of stroke subtypes in Germany from 1998-2015

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**Key words:** stroke, ischemic; stroke, hemorrhagic; mortality rate; trends

**Subject Terms:** Epidemiology, Mortality/Survival, Ischemic Stroke, Intracranial Hemorrhage, Cerebrovascular Disease/Stroke

**Abstract**

***Background and Purpose****:* Data on recent time trends in stroke mortality by subtypes and regions are lacking for Germany. We investigated sex- and age-standardized trends in stroke mortality in Germany for different stroke subtypes from 1998-2015 and assessed potential regional variations between the former Eastern (EG) and former Western part (WG) of Germany.

***Methods:*** Mortality and population data from the German Federal Statistical Office were used to calculate sex- and age-standardized mortality rates for hemorrhagic stroke , ischemic stroke and total strokes from 1998-2015 for all age-groups. Joinpoint® regression was used to examine trends and its changes. Estimations were stratified for EG and WG.

***Results:*** From 1998-2015 age-standardized total stroke mortality decreased by over 50% in men (from 78.0 to 34.1 per 100,000) and women (from 62.1 women to 28.4 women per 100,000). The decrease was more pronounced for ischemic stroke mortality (rate-change: men=-66%, women=-63%) than for hemorrhagic stroke mortality (men=-40%, women=-31%). Total and ischemic stroke mortality declined more in EG than in WG. From 1998-2015 there were no differences in the decline between the regions in hemorrhagic stroke mortality. Total stroke mortality was higher in EG compared to WG throughout the study period. Differences in subtype- and sex-specific mortality between the regions decreased from 1998 to 2015.

***Conclusion****:* Between 1998 and 2015 stroke mortality declined substantially in Germany with differing time trends in stroke subtypes between sexes and regions. Differences in stroke mortality rates between East and West Germany are negligible 24 years after the German reunification.

## Introduction

Stroke is one of the main causes of death worldwide[1, 2]. Recent studies show a decline in total stroke mortality worldwide, especially in the developed countries[3, 4]. Between 1990 and 2013 there was a significant decrease in ischemic stroke mortality worldwide, whereas the decrease in hemorrhagic stroke mortality was not statistically significant over the same time period[5]. Most western European countries experienced a steady decline in mortality from cerebrovascular diseases over recent decades[6, 7]. However, stroke mortality rates as well as time trends differ significantly between European countries, with higher rates and slower declines observed in Eastern Europe[7, 8].

In Germany, all-cause mortality was higher in Eastern compared to Western Germany for people older than 40 years old between 1960 and 1997[9, 10], a period that included the societal changes around German reunification in the 90s. After reunification the mortality gap showed a complex trend with a sustained reduction in the latest years[11]. The latest analysis of time trends in stroke mortality from Germany was performed up to the year 2013 and showed a recent flattening of the decline in mortality rates in some population subgroups, but it did not include a detailed description of stroke subtype-specific regional trends through the German reunification period and beyond[11, 12]. Currently, data on stroke subtype-specific trends for the old and new federal states in Germany are lacking.

This study aims to investigate recent changes in the trends of age-standardized stroke mortality rates in Germany until 2015, to analyze differences in time trends in stroke mortality between the former Eastern (EG) and former Western part of Germany (WG) during 1998-2015 and to compare subtype specific trends in stroke mortality between EG and WG.

## Methods

Aggregated data, including number of inhabitants of Germany, from 1998 to 2015 were collected from the Federal Statistical Office for the following stroke specific causes of death: ICD10: I60-I69 (total stroke), I60 (subarachnoid hemorrhage), I61 (intracerebral hemorrhage), I63 (ischemic stroke) and I64

(stroke not defined as hemorrhage or infarct). For the main subtype specific analyses, ischemic stroke was defined similar to previous studies as ICD10 codes I63 or I64 and hemorrhagic stroke as I60 or I61[13, 14]. All data were stratified for age, sex and region according to the status before the German reunification in 1990 (EG, WG). Crude mortality rate was calculated as the number of stroke deaths in one year divided through the number of inhabitants in the same year. The World Health Organization (WHO) European standard population of the year 1976 was used to calculate age-standardized mortality rates for each region[15]. Data collection was completely anonymous, only aggregated data from routine mortality statistics were used. Thus, no specific ethics board approval was needed according to local regulations confirmed by the Ethic Committee of the Medical Faculty of the University of Würzburg. All data are publicly available at the Information System of the Federal Health Monitoring and can be accessed at https://gbe-bund.de .

We used joinpoint® software Version 4.5.01 to estimate trends of mortality rates to detect joinpoints, where significant changes in trends occurred. Joinpoint® was developed by the National Cancer Institute to estimate time trends in mortality rates. Joinpoint regression analysis estimates different regression curves with different slopes. Every time a significant change in the slope is observed, a joinpoint is estimated. The advantage of joinpoint is that this methodology is able to identify periods of similar annual percentage change with no need of pre-specifications of time periods[16]. The analyses started with zero joinpoints, and tested whether models with one or up to a maximum of three joinpoints were significantly different and joinpoints must be added to the model. A minimum of two years had to be between two joinpoints as well as before and after the last joinpoint. The Grid search method was used to search for the best model. Annual percentage change with corresponding 95%-confidence-intervals (CI) and average annual percentage changes were also estimated with joinpoint® software as the main measures of trend. The Mann-Kendall Test was used to test the data for a monotonic trend. Ratios of age-standardized mortality rates between WG and EG with corresponding log-normal 95%-CI were generated with SAS Software version 9.4 (SAS Institute Inc., Cary, NC, USA).

## Results

Age-standardized stroke mortality rates in Germany decreased by over 50% from 1998 to 2015 in total and ischemic stroke with a flattening trend since 2007 (Figure 1 & Figure 2). Total stroke mortality decreased in men from 78.0 to 34.1 per 100,000 and in women from 62.1 to 28.4 per 100,000. The largest decline in mortality rates was observed in ischemic stroke with a decrease of 66% for men and 63% for women. For hemorrhagic stroke, mortality decreased by 40% in men and 31% in women.

*Total stroke mortality*

Table 1 shows the results of the joinpoint regression stratified by stroke subtype, region and sex (table 1). Decline in total stroke mortality in EG was higher than in WG with average annual percentage change of -4.4 in men in WG and -6.4 in men in EG. Similar relations of the declines between the regions could be observed for women with an average annual percentage change of -4.1 in WG and -6.1 in EG. Total stroke mortality was higher in men than in women throughout the study period with minor differences between the regions in 2015.

*Ischemic stroke mortality*

In 1998 ischemic stroke mortality rates in EG were higher than in WG, the difference between the two rates diminished in 2015 (Table 2). The decrease in ischemic stroke mortality was higher in WG than in EG. Women had higher average decline in terms of the average annual percentage change in ischemic stroke mortality than men.

*Hemorrhagic stroke mortality*

Regional hemorrhagic stroke mortality trends were in parallel with a steady decline in men and an accelerating decline in 2004-2015 in women.

Joinpoint regression stratified by sex, stroke-subtype and region revealed the highest decline from 2003-2007 for women in ischemic stroke mortality in EG (average annual percentage change -10.4) and for men in total stroke mortality in EG (average annual percentage change -10.4). The smallest decrease

was found in hemorrhagic stroke mortality in women from 1998-2004 with an annual percentage change of -1.2.

The substantial differences between the regions in 1998 diminished from 2007 onwards. Most of the time stroke mortality rates were higher in EG than in WG (Table 2). The 95%-CI mortality rate ratio of WG vs. EG of total and ischemic stroke in men and women never exceeds one. Hemorrhagic stroke mortality ratio of WG vs. EG was only significant in 2015 for men.

Stratified analysis of subarachnoidal and intracerebral hemorrhagic stroke mortality rates revealed decreasing parallel trends in subarachnoidal hemorrhages in women and changes in the direction of the slope of the trends in EG and a steady decline in WG in men. Intracerebral hemorrhagic stroke mortality slowly decreased without changes in time trends in both sexes (please see http://stroke.ahajournals.org).

**Discussion**

In Germany, total stroke, ischemic stroke, and hemorrhagic stroke mortality decreased substantially from 1998 to 2015 with notable differences in time trends between stroke subtypes and regions. The declines in total and ischemic stroke were steep with up to three changes in the decline, whereas the decrease in hemorrhagic stroke was more flat with only change in the trend in WG. Total, ischemic and hemorrhagic stroke mortality rates in men were always higher than in women.

For total stroke and ischemic stroke mortality, the observed time trends differed between the two regions with a steeper decline in mortality rates in EG than in WG for men as well as for women. There was no significant difference between the regions in hemorrhagic stroke trends for men and women. In 2015, the remaining differences in total stroke, ischemic stroke and hemorrhagic stroke mortality rates between the two regions were negligible with smaller differences observed for women than for men.

Joinpoint analysis comparing recent trends in stroke mortality were also available from other developed countries. For example, studies from Northern Ireland and the Republic of Ireland described similar time

point of changes in the decline of total stroke mortality compared to our analysis[17]. Total stroke mortality in US slowly decreased from 1969-2013 and revealed significant changes in the declining trend in 2000, 2009 in male and 2001, 2007 in female in the period after 1998[18]. In Austria a steady decline in ischemic stroke and changes in the direction of the trend of ICH mortality were observed between 1980-2008[19].

Changes in vascular disease mortality, such as stroke, can in general be caused by changes in incidence - due to changes in population risk factors e.g. by improvement in primary prevention - or by changes in case fatality rates - e.g. due to changes in acute treatment or improvement in secondary prevention[20-23].

The main risk factors for ischemic and hemorrhagic stroke in the population is hypertension followed by hyperlipidemia and smoking[24]. All of these risk factors showed favorable development within the German population in the recent years, e.g. systolic blood pressure decreased and antihypertensive treatment among people with documented hypertension increased between 1997-2011 for men and women[25-27]. This might have led to a decrease in stroke incidence and therefore, a subsequent decrease in stroke mortality. However, data on time trends in stroke incidence in Germany are scarce. Data on time trends in stroke incidence in Germany are available from the population-based Stroke Register in Erlangen. Within this register total stroke and ischemic stroke incidence statistically significantly decreased from 1995 to 2010 in men but not in women[28]. A study in Norway analyzing the causes for a decrease in ischemic stroke incidence from 1995-2012, showed that 17% of the decrease is accountable to changes in smoking prevalence[23]. Additionally smoking bans lead to an immediate reduction in ischemic stroke incidence[29]. In Germany smoke-free legislation started in 2007, the year we observed a significant change in ischemic stroke and total stroke mortality.

Reasons for the decline can also be due to improvements in the health care systems, e.g. the implementation of stroke units[30]. In Germany, the first stroke unit was introduced in 1994/1995 with a constant increase in the number of stroke units over time reaching a nearly complete coverage in Germany with a total number of 255 in 2012[31]. In addition, the process of certification of stroke units started in 1998 with a change in the certification process in 2002[32], when a significant change in the

decrease in total and ischemic stroke mortality in women in EG was estimated. Also routine data for reimbursement purpose provided by the nationwide German Diagnosis Related Groups statistics showed that in-hospital total stroke mortality was lower in patients admitted to stroke units and additionally overall in-hospital stroke mortality decreased from 2005 to 2010[33]. Intravenous administration of tissue plasminogen activator (tPA) as therapeutic option for patients with acute ischemic stroke was approved in Germany in 2000 and in Europe in 2002[34, 35], the year the slope of the trend of total stroke mortality in men in EG and women in both regions changed. Results from the Northwest German stroke audit showed an association between improvements in patient management, such as antiplatelet therapy during the first 24hrs and physiotherapy, and a decline in in-hospital mortality after ischemic stroke from 2000-2011[36]. Additionally, the usage of appropriate secondary prevention increased in Germany over time. For example, the uptake of statins after stroke increased from 17.1% in 1997-1999 to 50.1% in 2008-2011 according to a trend analysis with data from two national health interview and examination surveys for adults in Germany (GNHIES98 and DEGS1)[37] .The uptake of oral anticoagulants as most effective secondary preventive medication after ischemic stroke or transient ischemic attack increased from 9.8% in 2006 to 24% in the year 2015 within a German federal-state-wide hospital-based stroke registry of more than 20,000 patients per year[37, 38].Thus, the introduction and wider availability of new treatment and preventive options for the population could explain some of the decreasing time trend in stroke mortality. However, due to the constant improvement of these therapies over time it is difficult to link a specific inflection point in the observed time trends.

There were substantial differences observed in time trends in stroke mortality between WG and EG. Comparing the two regions, trends in hemorrhagic stroke mortality were parallel with a small difference in the death rates. In ischemic stroke mortality, however, there were substantial divergences between the two regions. In 1998, ischemic stroke mortality rate in EG was 1.2 times as high as in WG, but more than fifteen years later this difference was marginal. The exact reasons for the observed regional differences in ischemic stroke and total stroke mortality between the two regions are unclear. One of the possible reasons is that every region or federal state has its own coding procedures for coding causes of death which might contribute to small differences in documented mortality rates for the different causes

of death[39]. Additionally, before 1990 the German Democratic Republic used a different approach in collecting the cause-of death data than the Federal Republic of Germany[11, 40]. These differences in coding causes of death might still have an impact in the next decades after the reunification in the EG but might diminish over time. However, diminishing regional differences were observed first from 2007 onwards, sugessting that coding artifacts might not play a prominent role to our findings. But, differences in the prevalence of cardiovascular risk factors and of major cardiovascular disease are observed between the regions, with a higher proportion of cardiovascular risk factors and disease in EG compared to WG[41, 42]. These differences might be caused by differences in life style factors , such as less healthy dietary patterns and a higher proportion of current smokers in EG versus WG in 1998[43, 44]. Additionally with the known inverse association of socioeconomic status and stroke risk, the higher mean household net equivalence income in WG and the lower unemployment rate in WG might also contribute to the differences in stroke mortality rates[45-47]. No population based stroke register in the EG with continuous registration over time exists, therefore direct comparisons of time trends in stroke incidence between the EG and WG are not possible. Case fatality rates especially in the older population in EG might be affected through improvements in medical infrastructure in EG. For example, in 1990 only five hospitals in EG were specialized in cardiac treatments, e.g. catheterization, whereas in 1997 there were already more than 30 specialized hospitals in EG offering these therapies[48].

Our paper has strengths and limitations. Methodologically, not every joinpoint needs to reflect a true change in the time trend, as for the joinpoint definition the best model fit (regarding the number of joinpoints) is chosen based on the smallest p-value. Due to the use of routine observational data on an aggregated level any conclusions based on our ecological study remain on a hypothesis generating level only. Also due to the small sample size of subarachnoid hemorrhage deaths, trends in subarachnoid hemorrhage and intracerebral hemorrhage mortality rates were analyzed combined as hemorrhagic stroke in the main study. The strengths of our analysis are the use of joinpoint regression over a long time period. This allows the identification of time points of changes that are not set a priori and, thus, limiting a potential bias by assuming constant trends in average annual percentage change in the pre-specified time periods.

## Conclusions

Stroke mortality declined in Germany between 1998 and 2015 with different time trends in stroke mortality between the subtypes between WG and OG. However, the differences in mortality rates between the two regions diminished over the years and are negligible 25 years after the German reunification.


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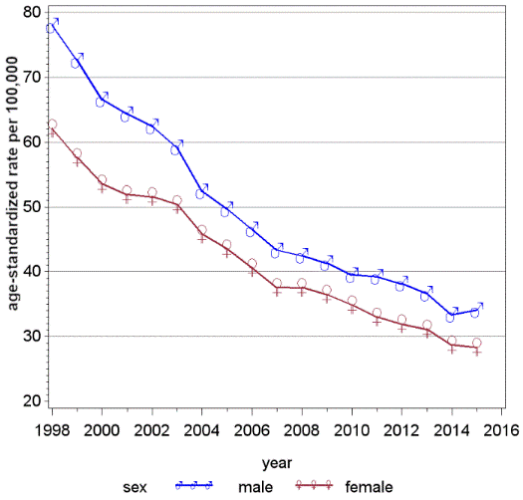


**Figure 1**. Age-standardized total stroke mortality rate (ICD10 I60-I69) in Germany stratified by sex

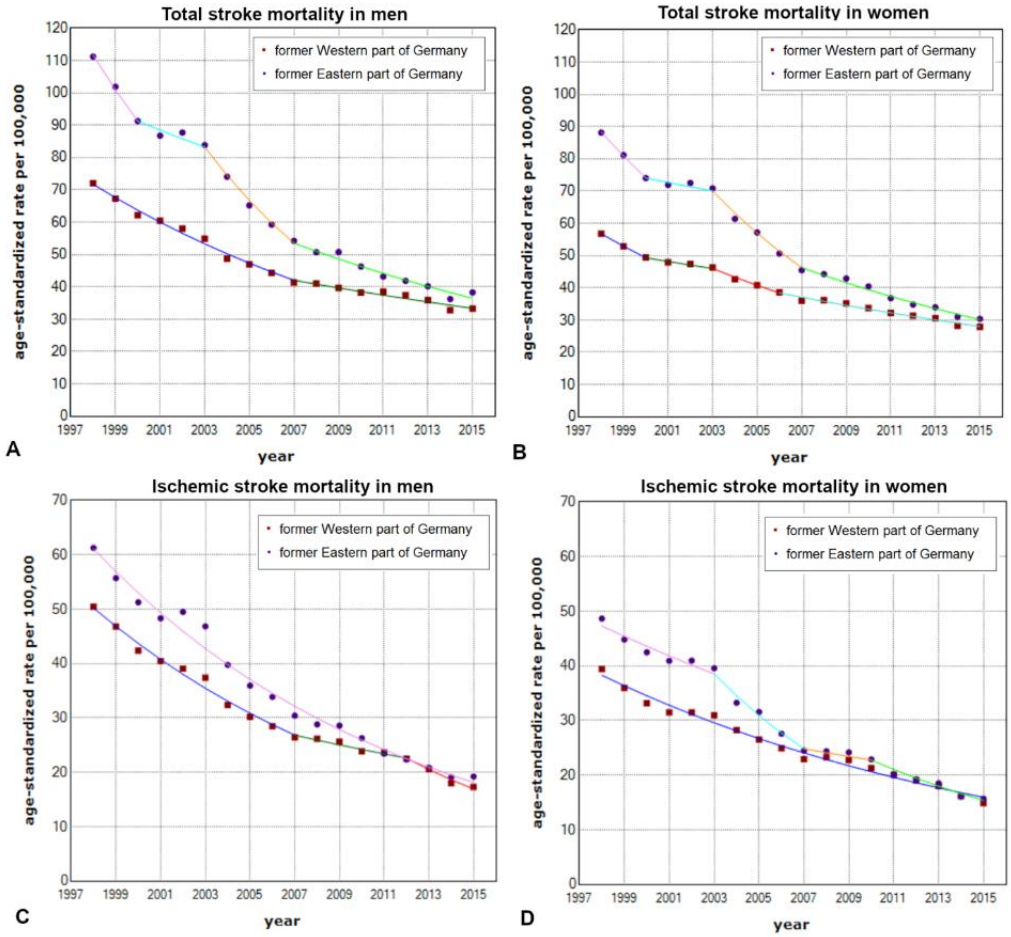


**Figure 2**. Age-standardized mortality rates stratified by sex, region (WG, EG) and stroke subtypes. **Total stroke mortality rates (ICD10 I60-I69)**: **A**: men, **B**: women; **Ischemic stroke mortality rates (ICD10 I63, I64)**: **C**: men, **D**: women

**Table 1.** Time trends in stroke mortality rates given as annual percentage change and average annual percentage change - stratified by stroke subtype, sex and region.

| | | First time period | | Second time period | | Third time period | | Fourth time period | | Average annual percentage change | p-value for trend# |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Years | Average annual percentage change (95%-CI) | Years | Average annual percentage change (95%-CI) | Years | Average annual percentage change (95%-CI) | Years | Average annual percentage change (95%-CI) | 1998-2015 | |
| Total stroke mortality (I60-I69) | | | | | | | | | | | |
| Men* | WG | 1998-2007 | -5.8 (-6.3; -5.2) | 2007-2015 | -2.8 (-3.6; -2.1) | | | | | -4.4 (-4.8; -4.0) | <0.001 |
| | EG | 1998-2000 | -9.6 (-16.9; -1.6) | 2000-2003 | -3.0 (-11.7; 6.5) | 2003-2007 | -10.4 (-15.0; -5.7) | 2007-2015 | -4.7 (-5.8; -3.5) | -6.4 (-8.2; -4.5) | <0.001 |
| Women* | WG | 1998-2000 | -6.8 (-11.5; -1.9) | 2000-2003 | -2.3 (-7.5; 3.2) | 2003-2006 | -5.8 (-11.1; -0.2) | 2006-2015 | -3.4 (-4.0; -2.9) | -4.1 (-5.3; -2.8) | <0.001 |
| | EG | 1998-2000 | -8.4 (-12.6; -4.1) | 2000-2003 | -1.8 (-6.6;3.2) | 2003-2007 | -9.9 (-12.4; -7.3) | 2007-2015 | -5.2 (-5.9; -4.5) | -6.1 (-7.1; -5.1) | <0.001 |
| Ischemic stroke mortality (I63, I64) | | | | | | | | | | | |
| Men | WG | 1998-2007 | -6.7 (-7.4; -6.0) | 2007-2012 | -3.4 (-6.2; -0.5) | 2012-2015 | -9.2 (-13.6; -4.5) | | | -6.2 (-7.3; -5.1) | <0.001 |
| | EG | 1998-2015 | -6.9 (-7.3; -6.5) | | | | | | | -6.9 (-7.3; -6.5) | <0.001 |
| Women | WG | 1998-2015 | -5.0 (-5.3; -4.7) | | | | | | | -5.0 (-5.3; -4.7) | <0.001 |
| | EG | 1998-2003 | -4.0 (-5.9; -2.2) | 2003-2007 | -10.4 (-14.8; -5.8) | 2007-2010 | -2.9 (-12.8; 8.2) | 2010-2015 | -7.6 (-10.1; -5.0) | -6.4 (-8.3; -4.5) | <0.001 |
| Hemorrhagic stroke mortality (I60, I61) | | | | | | | | | | | |
| Men | WG | 1998-2015 | -3.2 (-3.3; -3.0) | | | | | | | -3.2 (-3.3; -3.0) | <0.001 |
| | EG | 1998-2015 | -3.2 (-3.3; -3.0) | | | | | | | -3.2 (-3.3; -3.0) | <0.001 |
| Women | WG | 1998-2004 | -1.2 (-2.0; -0.5) | 2004-2015 | -2.8 (-3.1; -2.5) | | | | | -2.3 (-2.6; -2.0) | <0.001 |
| | EG | 1998-2004 | -1.2 (-2.0; -05) | 2004-2015 | -2.8 (-3.1; -2.5) | | | | | -2.3 (-2.6; -2.0) | <0.001 |

* Average annual percentage change difference between regions is significantly different from zero; # Mann-Kendall Test for monotonic trend

**Table 2.** Ratio of Western part of Germany to Eastern part of Germany of the age-standardized mortality rates in the years 1998, 2007 and 2015 – stratified by stroke subtype and sex.

| | Western part of Germany / Eastern part of Germany (95%-CI) | | |
|---|---|---|---|
| | 1998 | 2007 | 2015 |
| Total stroke mortality (I60-I69) | | | |
| Men | 0.65 (0.63 – 0.66) | 0.76 (0.74 – 0.79) | 0.86 (0.84 – 0.90) |
| Women | 0.64 (0.63 – 0.66) | 0.79 (0.77 – 0.81) | 0.92 (0.89 – 0.95) |
| Ischemic stroke mortality (I63, I64) | | | |
| Men | 0.82 (0.80 – 0.85) | 0.87 (0.83 – 0.91) | 0.90 (0.86 – 0.95) |
| Women | 0.81 (0.79 – 0.83) | 0.94 (0.91 – 0.97) | 0.94 (0.91 – 0.99) |
| Hemorrhagic stroke mortality (I60, I61) | | | |
| Men | 0.93 (0.86 – 1.00) | 0.94 (0.87 – 1.02) | 0.86 (0.79 – 0.93) |
| Women | 0.97 (0.90 – 1.04) | 1.01 (0.94 – 1.10) | 1.04 (0.95 – 1.13) |

## 6.2 Manuscript 2: "Time trends in stroke recurrence and case-fatality rates – The Erlangen Stroke Project"

Rücker V, Heuschmann PU, O'Flaherty M, Weingärtner M, Hess M, Sedlak C, et al. Twenty-year time trends in long-term case-fatality and recurrence rates after ischemic stroke stratified by etiology. *Stroke*. 2020;51:2778-2785[107] https://doi.org/10.1161/STROKEAHA.120.029972, 

### 6.2.1 Summary

We used data from the population-based stroke register in Erlangen to estimate time trends in case-fatality and recurrence rates after first in a lifetime ischemic stroke. 3346 patients with a first ever in a lifetime ischemic stroke between January 1996 and December 2015 were included. Mean age of patients was 74 years and 47% of all patients were men. According to TOAST classification etiological subtypes of ischemic stroke were distributed as follows: 8% large-artery atherosclerosis, 23% cardioemoblism, 28% small-artery occlusion, 2% OC and 39% undefined.

3-month case-fatality rate was 9% in men and 6% in women, 1-year case-fatality rate was 17% in men and 14% in women, 5-year case-fatality rates was 41% in men and 49% in women. Case-fatality rates varied by etiological subtype. 5-year case-fatality rates were highest in cardioembolic stroke (59% in all, 52% in men, 64% in women) and lowest in small-artery occlusion (26% in all, 24% in men, 28% in women). Year of event was significantly associated with the hazard of death after stroke. A statistically significant decline in case-fatality after stroke (HR for year of event 0.98 (95%-CI: 0.97-0.99)), after cardioembolic strokes (HR 0.98 (95%-CI: 0.96-0.99)), small-artery occlusion (HR 0.97 (95%-CI: 0.95-1.00)) and undefined (HR 0.98 (95%-CI: 0.97-1.00)) was detected. In men case-fatality decreased significantly in all subtypes as well as in the subtypes cardioembolic strokes and undefined. In women case-fatality decreased significantly in all subtypes as well as after small-artery occlusion.

3-month recurrence rates of 3.2% in men, 3.0% in women, 1-year recurrence rates of 7.5% in men and women, 5-year recurrence rates of 20.1% in men and women were observed. Highest 5-year recurrence rates were reported for undefined (22% in all, 21% in men, 22% in women) and cardioembolic stroke (21.1% in all, 19.6% in men and 22.3% in women) and lowest for small-artery occlusion (17% in all, 18 in women, 16% in men). No significant time trends in stroke recurrence rates were observed.

### 6.2.2 Manuscript (as accepted)

## 20-year time trends in long-term case-fatality and recurrence rates after ischemic stroke stratified by aetiology

*Cover title: The population-based Erlangen Stroke Project*

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The study was presented in part as an oral presentation at the European Stroke Organisation Conference, Milano, 22-24 May 2019

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**Keywords***:* ischemic stroke, survival analysis, recurrent event, case-fatality

**Subject Terms**: Epidemiology, Mortality/ Survival

**Abstract**

**Background and Purpose**-Data on long-term survival and recurrence after stroke are lacking. We investigated time trends in ischemic stroke case-fatality and recurrence rates over 20-years stratified by aetiological subtype according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification within a population-based stroke register in Germany.

**Methods**-Data was collected within the Erlangen Stroke Project, a prospective, population-based stroke register covering a source population of 105,164 inhabitants (2010). Case fatality and recurrence rates for 3months, 1year and 5years were estimated with Kaplan-Meier estimates. Sex-specific time trends for case-fatality and recurrence rates were estimated with Cox regression. We adjusted for age, sex and year of event and stratified for aetiological subtypes. A sensitivity analysis with competing risk analysis for time trends in recurrence were performed.

**Results**-Between 1996 and 2015, 3,346 patients with first ischemic stroke were included; age-standardized incidence per 100,000 was 75.8 in women and 131.6 in men (2015). Overall, 5-year survival probabilities were 50.4% (95%-CI: 47.9-53.1) in women and 59.2% (95%-CI: 56.4-62.0) in men; 5-year survival was highest in patients with first stroke due to small-artery occlusion (women: 71.8% (95%-CI: 67.1-76.9); men: 75.9% (95%-CI: 71.3-80.9)) and lowest in cardioembolic stroke (women: 35.7% (95%-CI: 31.0-41.1); men: 47.8% (95%-CI: 42.2-54.3)). 5-year recurrence rates were 20.1% (95%-CI: 17.5-22.6) in women and 20.1% (95%-CI 17.5-22.7) in men ; 5-year recurrence rate was lowest in women in stroke due to small artery occlusion 16.0% (95%-CI: 11.7-20.1) and in men in large-artery atherosclerosis 16.6% (95%-CI: (8.7-23.9); highest risk of recurrence was observed in undefined strokes (women: 22.3% (95%-CI: 17.8-26.6); men: 21.4% (95%-CI: 16.7-25.9)). Cox regression revealed improvements in case-fatality rates over time with differences in stroke aetiologies. No time trends in recurrence rates were observed.

**Conclusion**-Long-term survival and recurrence varied substantially by first stroke aetiology. Survival probabilities improved over the last two decades, no major trends in stroke recurrence rates were observed.

**Non-standard Abbreviations and Acronyms**

| | |
|---|---|
| **CE** | cardioembolism |
| **CI** | Confidence Interval |
| **CFR** | case-fatality rates |
| **HR** | Hazard Ratio |
| **LAA** | large-artery atherosclerosis |
| **OC** | stroke of other determined cause |
| **SAO** | small-artery occlusion |
| **TOAST** | Trial of Org 10172 in Acute Stroke Treatment |
| **UND** | stroke of undetermined cause |

## Introduction

Based on routine mortality statistics ischemic stroke mortality decreased between 1998 and 2015 about 50% in Germany[1]. It is unclear, to what extent this decline is attributable to changes in stroke incidence or to changes in case fatality and recurrence rates. Previous analysis from the Erlanger Stroke Project showed that ischemic stroke incidence in Germany decreased between 1995 to 2010 in men but not in women with substantial differences in aetiological subtypes of ischemic stroke according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification[2]. However, the burden of stroke in the population is not only influenced by incidence but also by case-fatality rates (CFR) as decreasing CFR accompanied by constant incidence rates leads to increasing prevalence[3]. Another important factor that drives the burden of stroke in the population are recurrence rates, because a second stroke is associated with a longer in-hospital stay, higher mortality and a higher degree of disability[4, 5].

Epidemiological data on the long-term time trends in CFR and recurrence rates in ischemic stroke patients are scarce. Recent publications from the population-based South London Stroke Register showed improved survival rates in all pathological subtypes of stroke[6, 7]. A systematic review showed that the 5-year stroke recurrence rates decreased over time across the 13 hospital- or community-based stroke registers included[8]. However, in the population of Perth in Australia no significant time trends in 5-year stroke recurrence rates were found[9]. CFR and recurrence rates differ substantially between aetiological subtypes of ischemic stroke based on TOAST criteria[10-12]. To the best of our knowledge, long-term data on patterns of CFR and recurrence rate from a population-based register stratified by ischemic stroke aetiology are lacking.

Therefore, by updating a prior analysis from the Erlangen Stroke Project from 1994-1996, we investigated long-term time trends in CFR and stroke recurrence rates by ischemic stroke aetiology over a 20-year time period based on data from the population-based Erlangen Stroke Project[11].

## Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

*Erlanger Stroke Register*

The Erlanger Stroke Project is an ongoing prospective population-based stroke register in Germany, covering a source population of 105,164 inhabitants (2010). Within this source population incidence and outcome of stroke is continuously monitored since 1994. The methodology of the study has been described in detail elsewhere[13]. All hospitalized and non-hospitalized stroke patients with registered residence in Erlangen were identified by regular checks of hospital admission, discharge records, nursing homes and general practices using standardized criteria to ensure completeness of case ascertainment[13]. Every patient is followed-up 3 months, 12 months and annually until death. Patients are contacted for follow-up by study nurses and research assistants. In case the patient could not be contacted for follow-up, the Population Register of the City of Erlangen is checked for a possible change of address or death. If the patient died during the follow-up period, the death certificates is reviewed, and the cause of death is ascertained from all available medical records.

Stroke was determined according to the WHO criteria[14]. Classification of pathological subtypes of stroke was determined based on brain CT or MRI scan, with 95% imaging rate[13]. For the present analysis, patients with first-ever ischemic stroke from 1996 to 2015 were included.

Aetiological subtype of ischemic stroke was defined according to Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification[15]. We used the five major categories of TOAST: large-artery atherosclerosis (LAA) including large-artery thrombosis and artery-to-artery embolism, cardioembolism (CE), small-artery occlusion (SAO), stroke of other determined cause (OC) and stroke of undetermined cause (UND) comprising stroke of undefined and concurrent aetiology. Interrater reliability of the classification of TOAST for the present analysis was good (kappa=0.65 [95%-CI 0.35-0.96] between 1995 and 1998 and 0.63 [95%-CI 0.43-0.83] between 1999 and 2010) as previously

published[2, 11]. Recurrent stroke was defined as new neurological deficit at least 24 hours after the incident stroke according to the WHO definition excluding oedema, mass effect, brain shift syndrome or hemorrhagic transformation and procedure-related strokes[16].

*Statistical Analysis*

Incidence rates were age-standardized according to the European standard population[17]. Recurrent stroke was defined as first recurrent stroke after the index event (ischemic stroke) regardless of the pathological subtype (ischemic, hemorrhagic stroke or other) of recurrent stroke. Crude 3 months, 1 year and 5 years CFR and recurrence rates at were estimated with Kaplan-Meier and stratified by sex and according to TOAST classification. Age-adjusted CFR and recurrence rates were estimated using Cox regression. Sex-specific time trends for CFR and recurrence rates were estimated Cox proportional hazard regression models. The Cox regression models were adjusted for age, sex and year of event and stratified by aetiological subtypes according to the TOAST classification. Due to the small sample size, stroke of other determined cause was excluded in survival analysis. Competing risk analysis were performed as sensitivity analysis for time trends in recurrence rates[18] with death from any cause being used as a competing event and recurrent stroke as an event of interest. Competing risk calculates the probability of getting a recurrent stroke under the condition that no recurrent event occurred before or that the person might have died. We used Aalen Johansen estimator to estimate the cumulative incidence as a function of recurrent stroke[19]. The subdistribution hazard regression from Fine and Gray was used to investigate time trends in the cumulative risk of recurrent stroke under competing risks adjusted for age, sex and stratified for aetiological subtype according to TOAST classification[20].

*Ethics*

Written informed consent to participate was given by patients or their legal representatives. The study was approved by the Ethics Committee of the Medical Faculty of FAU Erlangen-Nürnberg (Reference number: 249_15 Bc).

## Results

Overall, 3,346 ischemic stroke patients were registered in the Erlanger Stroke Project between January 1996 to December 2015. Mean age was 74±13 years, 53.2% were women. Distribution of subtypes was as follows: LAA 8.4 %; CE 23.0%; SAO 28.0 %; OC 2.1%; and UND 38.5%. Mean age in years was 71±12 in LAA, 77±11 in CE, 71±12 in SAO, 58±17 in OC and 75±13 in UND; 41.5% of LAA, 56.7% of CE, 50.1% of SAO, 55.5% of SAO, 55.9% of OC and 55.5% of UND were women. The average annual age-standardized incidence rate of total ischemic stroke from 1996-2015 was 109.7 per 100,000 overall, 75.8 in women and 131.6 in men; average annual age-standardized incidence rate per stroke subtypes per 100,000 was as follows: 11.2 in LAA; 22.7 in CE; 32.2 in SAO; 4.4 in OC; and 39.5 in UND.

*Case-fatality rates*

Overall, 3 month, 1-year and 5-year survival probabilities by sex and TOAST subtype are shown in Table 1 and Figure 1; 5-year survival probability was highest in patients with stroke due to SAO (73.8%, 95%-CI: 70.4-77.3) and lowest in CE stroke (40.9%, 95%-CI: 37.2–45.0): Table 2 shows time trends determined by Hazard Ratios (HR) for the year of event of the adjusted Cox proportional hazard regression for death for the entire observation period as well as censored after 3 months, 1 year and 5 years. The same linear trends were observed in Kaplan-Meier survival estimates stratified for the year of event in 5-year groups with 1996-2000 having the lowest and 2011-2015 having the highest survival rates (for details, please see https://www.ahajournals.org/journal/str, Figure I). Overall, Cox regression showed a trend for declining stroke mortality during the entire time period (HR for year of event 0.98, 95%-CI: 0.97–0.99, p-value: <0.001). Stratified Cox regression revealed a significant decrease in stroke mortality over time in men as well as in women. Further significant decreases over time in stroke mortality were observed in CE in total as well as for men. In SAO we observed statistically significant declining stroke mortality rates in all for all and in women. In UND stroke mortality decreased significantly over time in total and in men.

*Stroke Recurrence*

Pathological subtypes of second strokes were as follows: 84.5% ischemic stroke; 5.7% intracerebral haemorrhage; 0.2% subarachnoid haemorrhage; and 9.6% stroke pathology not specified or missing. Overall, 3 month, 1-year and 5-year recurrence rates by sex and TOAST subtype were shown in Table 3 and Figure 2. Undefined strokes had the highest (21.9%, CI:18.7-25.0) and SAO in women (16.0%, 95%-CI:11.7-20.1) and LAA in men (16.6%, 95%-CI:8.7-23.9) the lowest rate of stroke recurrence after 5 years. There were no significant trends for decline in stroke recurrence estimated with Cox Regression (Table 4). In the sensitivity analysis taking death as competing risk into account the UND had the highest risk of recurrent stroke followed by SAO (for details please see https://www.ahajournals.org/journal/str Table I). After considering death as competing risks, there were significant trends for a decline in stroke recurrence in all the patients. Stratified competing risk analysis showed significant decreases in risk of recurrent stroke in women and in women with UND (for details please see https://www.ahajournals.org/journal/str Table II). There was no linear trend in recurrence rates stratified for 5-year groups of year of event (for details please see https://www.ahajournals.org/journal/str Figure II).

**Discussion**

In our population-based sample, nearly every second patient died 5 years after the first event. There were substantial variations in survival rates across aetiological subtypes observed with highest rates for CE and lowest for SAO, respectively. CFR decreased over the 20 years of observation, showing similar trends across stroke aetiological subtypes except for LAA. About every fifth patient suffered from a recurrent stroke within 5 years after the first event with the highest recurrence rates observed in CE and UND. Cox Regression revealed no significant decrease in long-term recurrence rates over time. Competing risks analysis showed similar patterns with additional decreasing patterns in stroke recurrence overall and in women.

Our 3-month CFR of 13% are lower than the mean weighted CFR of 21.8% reported from the European Registers of Stroke (EROS) collaboration of six population-based stroke registers in Europe in 2004-2006, but similar to the lowest rate across the participating registers observed in Dijon[21]. On the other hand, the 1-year (63.7%) and 5-year survival rates (42.8%.) for ischemic and haemorrhagic stroke in the South London Stroke Register were lower compared to our study[22]. This might be caused by the fact that haemorrhagic strokes were included in the South London Stroke Register which had lower survival rates than ischemic strokes. Only few studies investigated time trends in long-term CFR, most of them showing decreasing CFR. For example, in a Danish population-based cohort found a decrease in 30-day and 5-year mortality rates after IS between 1994-2011[23]. In addition, in the Netherlands in a linkage study of national registries, age-and sex-specific 30-day and 1-year (excluding the first 30 days) CFR decreased between 1997 and 2005 in most age-groups[24]. Controversially, 90-days CFR increased in the Swedish Stroke Registry between 1995 to 2010, which the authors referred to the higher proportion of more severe strokes[25].

To the best of our knowledge, our study is the first to investigate long-term time trends in CFR stratified by aetiological stroke subtypes according to standardized mechanism-based classification scheme such as the TOAST classification. The patterns of the stratified 5-year CFR by TOAST are in line with previously published data from our group reporting survival up to 2 years[11]. In the Nanjing Stroke Registry, highest one-year survival rates were reported for patients with SAO (92.7%), followed by UND (89.4%), CE (88.1%) and LAA (84.2%)[26]. Most CFRs in our study were lower compared to this data, and we found the lowest 1-year survival rates in CE (67.9%). Furthermore, the Dijon Stroke Registry analyzed 28-days CFR stratified by aetiology (defined as macroartheromics, microatheroma and cardioembolic). They reported significantly improvements CFR in stroke due to microatheroma from 1985 to 2004, similar to our findings[27].

The decrease in CFR might be caused by improvements in stroke management and treatment. For example, after the introduction of stroke units in 1994/1995 the number of stroke units, one of the most effective options in stroke management[28], increased in Germany up to 255 in 2012[29]. Also, an increased uptake in acute therapies, such as thrombolytic therapy and improved overall care, might have led to the observed reduction in CFR in Germany. For example, based on German administrative hospital data proportion of stroke patients being admitted to a stroke unit increased between 2005 and 2010 from 15% to 52%[30]. The decrease in CFR might also be attributed to changes over time in patient characteristics affecting outcome such as stroke severity, comorbidities or frequency of early complications. For example, in the Austrian Stroke Unit Registry the stroke severity significantly decreased by 1 Point in the National Institutes of Health Stroke Scale between 4 and 3 in men and between 5 to 4 in women[31].

The recurrence rates observed in our study are in line with the pooled estimates of a recent meta-analysis based on population-based studies[8]. There are only a few studies reporting recurrence rates stratified by stroke aetiology. We found that patients with LAA have a high risk to get a second stroke within the first year, whereas after five years the risk in the LAA subgroup was relatively small in comparison to the other stroke subtypes. This higher risk might be because the CFR after 5 years in patients with LAA is high and, therefore, a substantial proportion of the patients died before they can get a second stroke. The rates in SAO are relatively low over the whole observation period. A previous systematic review found lower recurrence rates up to 1 month in lacunar vs. non-lacunar infarctions, however, these differences were not statistically significant in time period up to 12 months[32]. The risk of a recurrent stroke in CE and UND remains high after the first year after the event. The high risk in CE might be attributable to patients with atrial fibrillation having a higher risk of recurrence[33]. The high risk of recurrent stroke in the UND group might be caused by a substantial proportion of patients with undetected AF in this group as recent studies revealed that intensified monitoring for AF in this group yield to a proportion of 16.1% patients with potential cardioembolic stroke[34].

We found no clear time trends in overall stroke recurrence rates as well after stratification for sex or stroke subtype in our main analysis using Cox regression, whereas we found a few significant time trends in stroke recurrence rates after taking competing risks into account. Our main analysis is in line with a systematic review from 2018 comprising 34 RCT, hospital-based and community-based studies published before December 11, 2016, which also found no statistically significant time trends in stroke recurrence rates after ischemic stroke or transient ischemic attack[35]. The authors concluded that this might partly be due to heterogeneity in stroke aetiology as no stratification for stroke subtype was performed[35]. However, after stratification for ischemic stroke aetiology in our study, we did not find any clear time trend in recurrence rate in our main analysis despite substantial heterogeneity in stroke recurrence rates by aetiological subgroups. We only found a decrease in stroke recurrence rates over time in patients in the UND group, when we considered competing risks. One possible reason might be, that, although new medication for stroke prevention are available such as non-vitamin K oral anticoagulants, the control of cardiovascular risk factors (e.g. hypertension, atrial fibrillation) after a stroke is still not optimal in Germany[36]. Besides, adherence to secondary preventive measures might decrease during follow-up, leading to a decrease in the effect of secondary prevention. An alternative explanation could be that our study was underpowered to detect a small decrease in stroke recurrence rates due to the small sample size, especially in the later years. Another reason might be that people die before they can get a second stroke. Therefore, we included as a sensitivity analysis an analysis accounting for competing risks, where we observed a significant decrease in stroke recurrence in total and in women.

Our study has several strength and limitations. One of the strengths is the population-based design and the long-follow up over 20 years with constant standardized data collection over the entire time period. In addition, our data is able to report data on the TOAST classification of the first event over the whole time period which allows stratifying time trends in CFR and recurrence rates by aetiological subtypes of the first event. Our study also has several limitations. First, we have a high rate of undefined causes according to TOAST classification. However, the proportion of patient with undefined stroke is within the range of other population-based registers[37, 38]. Second, no information on the aetiological subtype of

recurrent stroke was available, which might influence time trends in stroke recurrence. Third no adjustment for stroke severity was possible, as stroke severity is not collected in the register by a standardized scale such as the NIHSS. Fourth, the source population of our registry is relatively small, which might limit the statistical power of the study. However, the Erlanger Stroke Project is the largest and longest running population-based stroke registry in Germany and only a limited number of other registers worldwide comprise such a long observation period.

## Conclusions

Decreasing CFR over the last 20 years were observed across all stroke subtypes that might be associated by improved acute treatment options. However, there is still room for improvement secondary prevention measures in ischemic stroke survivors, as we did not observe a clear reduction in stroke recurrence rates.

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**Supplemental Materials**

Table I-III

Figure I-IV

**Table 1.** Survival probabilities for death after ischemic stroke stratified according to TOAST classification and sex

| TOAST categories | Number at risk | Survival probability in % (95%-CI) | | |
|---|---|---|---|---|
| | | 3 months | 1 year | 5 years |
| All | 3346 | 87.0 (85.9-88.2) | 79.0 (77.7-80.5) | 54.4 (52.5-56.4) |
| Men | 1563 | 90.7 (89.3-92.2) | 82.8 (80.9-84.7) | 59.2 (56.4-62.0) |
| Women | 1780 | 83.8 (82.1-85.5) | 75.9 (73.9-77.9) | 50.4 (47.9-53.1) |
| LAA | 272 | 82.4 (78.0-87.1) | 73.7 (68.6-79.3) | 49.4 (43.3-56.5) |
| Men | 159 | 84.4 (78.8-90.3) | 75.5 (68.9-82.7) | 53.8 (45.7-63.3) |
| Women | 113 | 79.6 (72.5-87.4) | 71.3 (63.4-80.2) | 43.7 (34.9-54.8) |
| CE | 742 | 80.0 (77.2–83.0) | 67.9 (64.6-71.4) | 40.9 (37.2–45.0) |
| Men | 321 | 86.1 (82.4–90.0) | 74.0 (69.3–79.0) | 47.8 (42.2-54.3) |
| Women | 421 | 75.5 (71.5-79.7) | 63.4 (58.9-68.2) | 35.7 (31.0-41.1) |
| SAO | 904 | 97.7 (96.8-98.7) | 93.5 (91.9-95.2) | 73.8 (70.4-77.3) |
| Men | 451 | 98.4 (97.3-99.6) | 94.0 (91.8-96.3) | 75.9 (71.3-80.9) |
| Women | 453 | 97.1 (95.5-98.7) | 93.0 (90.6-95.4) | 71.8 (67.1-76.9) |
| UND | 1245 | 86.2 (84.3-88.1) | 77.7 (75.4-80.1) | 50.3 (47.2-53.7) |
| Men | 554 | 90.8 (88.4-93.3) | 81.8 (78.6-85.1) | 54.3 (49.7-59.4) |
| Women | 691 | 82.5 (79.7-85.4) | 74.5 (71.2-77.8) | 47.2 (43.1-51.7) |

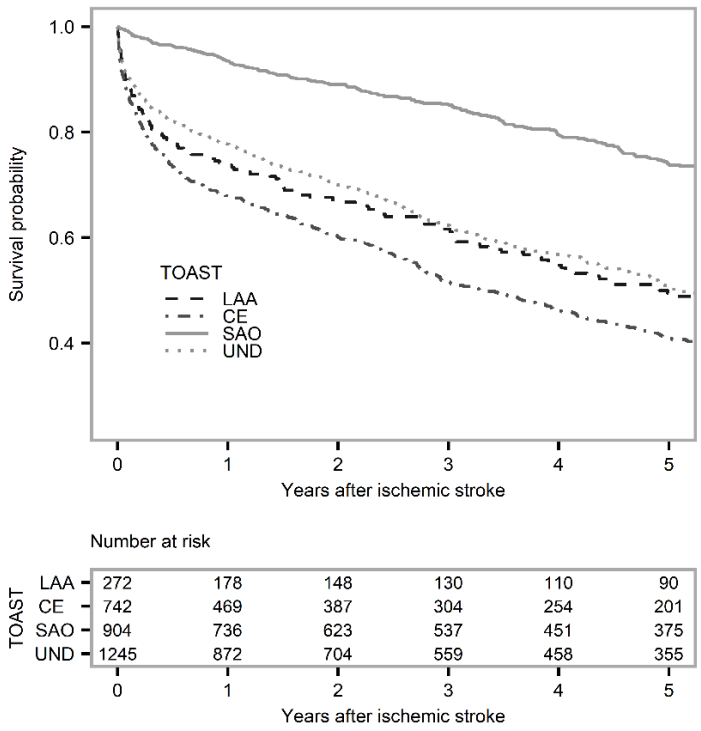


**Figure 1**. Survival probabilities (Kaplan-Meier estimates) after incident ischemic stroke between 1996–2015 stratified by aetiological subtype.

**Table 2.** Hazard ratio for year of event for risk of death adjusted for age by Cox regression and stratified according to TOAST classification and sex.

| TOAST categories | Hazard Ratio (95%-CI) for year of event | | | | | |
|---|---|---|---|---|---|---|
| | All* | p-value | Men | p-value | Women | p-value |
| All | 0.98 (0.97–0.99) | <0.001 | 0.97 (0.96–0.99) | <0.001 | 0.98 (0.97–0.99) | <0.001 |
| LAA | 1.00 (0.97–1.03) | 0.816 | 1.00 (0.96–1.05) | 0.914 | 0.99 (0.94–1.04) | 0.579 |
| CE | 0.98 (0.96–0.99) | 0.010 | 0.97 (0.94–1.00) | 0.020 | 0.98 (0.96–1.00) | 0.106 |
| SAO | 0.97 (0.95–1.00) | 0.022 | 0.98 (0.95–1.02) | 0.367 | 0.96 (0.93–0.99) | 0.015 |
| UND | 0.98 (0.97–1.00) | 0.018 | 0.97 (0.94–0.99) | 0.006 | 0.99 (0.97–1.01) | 0.402 |

*Adjusted for age and sex . p-values are for each HR of the continuous variable year of event.

**Table 3**. Cumulative risk of recurrent stroke (1 - Kaplan Meier estimator) stratified according to TOAST classification and sex

| TOAST categories | Number at risk | Stroke recurrence rates % (95%-CI) | | |
|---|---|---|---|---|
| | | 3 months | 1 year | 5 years |
| All | 3346 | 3.1 (2.5-3.7) | 7.5 (6.5-8.4) | 20.1 (18.3-21.9) |
| Men | 1563 | 3.2 (2.3-4.1) | 7.5 (6.1-8.9) | 20.1 (17.5-22.7) |
| Women | 1780 | 3.0 (2.1-3.8) | 7.5 (6.1-8.8) | 20.1 (17.5-22.6) |
| LAA | 272 | 6.2 (3.1-9.2) | 7.7 (4.2–11.0) | 17.7 (11.4-23.6) |
| Men | 159 | 7.7 (3.2-12) | 8.6 (3.8-13.1) | 16.6 (8.7-23.9) |
| Women | 113 | 4.0 (0.1-7.8) | 6.4 (1.3-11.2) | 19.3 (8.6-28.8) |
| CE | 742 | 3.1 (1.8-4.5) | 8.0 (5.7-10.2) | 21.1 (16.9-25.1) |
| Men | 321 | 2.4 (0.6-4.2) | 6.5 (3.5-9.5) | 19.6 (13.7-25.1) |
| Women | 421 | 3.7 (1.7-5.6) | 9.2 (5.9-12.4) | 22.3 (16.2–28.0) |
| SAO | 904 | 1.8 (0.9-2.7) | 5.6 (4.0-7.2) | 17.2 (14.1-20.2) |
| Men | 451 | 2.1 (0.7-3.4) | 6.1 (3.7-8.4) | 18.4 (13.8-22.8) |
| Women | 453 | 1.6 (0.4-2.8) | 5.2 (3.0-7.3) | 16.0 (11.7-20.1) |
| UND | 1245 | 3.3 (2.3-4.3) | 8.2 (6.5-9.9) | 21.9 (18.7–25.0) |
| Men | 554 | 3.5 (1.9-5.1) | 8.2 (5.7-10.7) | 21.4 (16.7-25.9) |
| Women | 691 | 3.1 (1.7-4.5) | 8.3 (5.9-10.6) | 22.3 (17.8-26.6) |

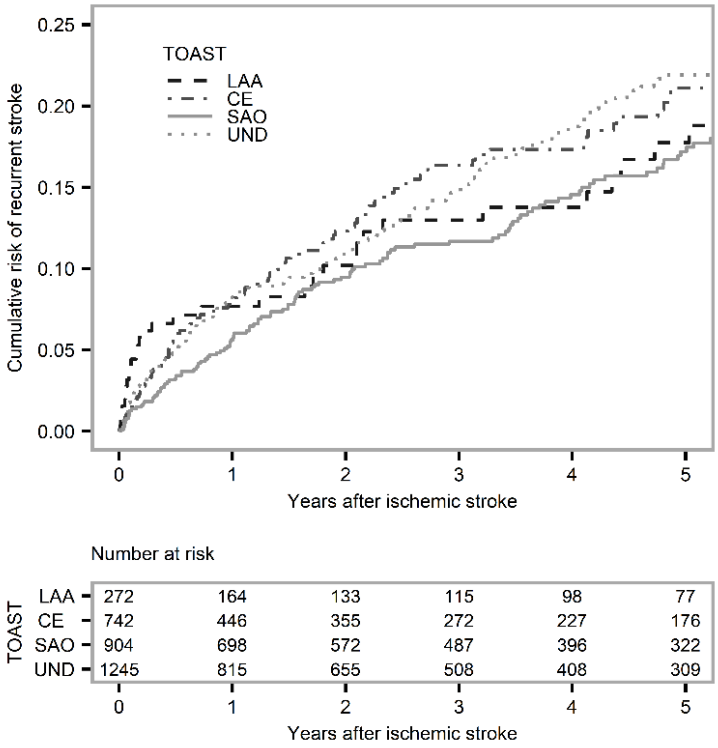


**Figure 2**. Cumulative risk of recurrent stroke (1-Kaplan-Meier estimates) after incident ischemic stroke between 1996–2015 stratified by aetiological subtype.

**Table 4**. Hazard Ratios for year of event for risk of stroke recurrence adjusted for age by Cox regression and stratified according to TOAST classification and sex

| TOAST categories | Hazard Ratio (95%-Confidence Interval) for year of event[#] | | | | | |
|---|---|---|---|---|---|---|
| | All* | p-value | Men | p-value | Women | p-value |
| All | 0.99 (0.97–1.00) | 0.160 | 1.00 (0.97–1.02) | 0.837 | 0.98 (0.96–1.00) | 0.073 |
| LAA | 1.00 (0.93–1.06) | 0.890 | 1.00 (0.92–1.08) | 0.934 | 0.99 (0.88-1.10) | 0.803 |
| CE | 0.98 (0.94–1.02) | 0.239 | 0.96 (0.91-1.02) | 0.217 | 0.99 (0.94–1.04) | 0.566 |
| SAO | 1.00 (0.97-1.03) | 0.856 | 1.02 (0.97-1.06) | 0.608 | 0.98 (0.94–1.03) | 0.406 |
| UND | 0.99 (0.96–1.01) | 0.339 | 1.00 (0.96-1.04) | 0.972 | 0.98 (0.94–1.01) | 0.191 |

*Adjusted for age and sex, and interaction between age and sex, # year of event was included as continuous factor, +Adjusted for age and sex

## 6.3 Manuscript 3: "Adherence to quality indicators and mortality after stroke - the German Stroke Registers Study Group"

Haas K, Rücker V, Hermanek P, Misselwitz B, Berger K, Seidel G, et al. Association between adherence to quality indicators and 7-day in-hospital mortality after acute ischemic stroke. *Stroke*. 2020;51:3664-3672[109]. https://doi.org/10.1161/STROKEAHA.120.029968, copyright © 2020. Reprinted by permission of Wolters Kluwer to include the final peer-reviewed manuscript.

### 6.3.1 Summary

388,012 patients with ischemic stroke from 736 hospitals within the nine regional stroke registers of the ADSR were documented between January 2015 and December 2016. Patients were in median 76 years and 52% male. 1.3% of the patients had a high stroke severity with an NIHSS above 25+, 3.4% died within the first 7-days and 16.5% had a living will. Differences between patients from hospitals with mandatory and voluntary documentation in patient characteristics were very small. Eleven evidence-based indicators of process of stroke care (Physiotherapy /occupational therapy within first two days, speech therapy within first two days, mobilization within the first two days, vascular imaging within 48 hours, brain imaging within 30 minutes, dysphagia screening, screening for atrial fibrillation, antiplatelets within 48 hours, intravenous thrombolysis in eligible patients within 4 hours from onset, door-to-needle time within one hour, treatment on a stroke unit) were combined as proportion of QI fulfilled to measure performance of hospitals in acute routine stroke care. A high quality of care was observed as most QI reached the predefined target value. A significant association between distinct QI and 7-day in-hospital mortality was observed in 9 out of the 11 QI (adjusted for hospitals as random effects and for sex, NIHSS and living will as fixed effects). No significant association was found in brain imaging within 30 minutes and door-to-needle time within one hour. In generalized linear mixed models, adjusted for hospital as random effects, a significant association between proportion of QI fulfilled, age, NIHSS, sex and living will was found. The association between proportion of QI fulfilled and 7-day in-hospital mortality was linear.

## 6.3.2 Manuscript (as accepted)

# Association between adherence to quality indicators and 7-day in-hospital mortality after acute ischemic stroke

*Cover title*: quality of care and early mortality

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**Keywords**: stroke, quality indicators, in-hospital mortality, ischemic stroke

**Subject terms**: Quality and Outcome, Mortality/Survival, Health Services

**Abstract**

**Background and Purpose**-Quality indicators (QI) are an accepted tool to measure performance of hospitals in routine care. We investigated the association between quality of acute stroke care defined by overall adherence to evidence-based QI and early outcome in German acute care hospitals.

**Methods**-Patients with ischemic stroke admitted to one of the hospitals cooperating within the German Stroke Register Study Group (ADSR) were analyzed. The ADSR is a voluntary network of 9 regional stroke registers monitoring quality of acute stroke care across 736 hospitals in Germany. Quality of stroke care was defined by adherence to 11 evidence-based indicators of early processes of stroke care. The correlation between overall adherence to QI with outcome was investigated by assessing the association between 7-day in-hospital mortality with the proportion of QI fulfilled from the total number of QI the individual patient was eligible for. Generalized linear mixed model analysis was performed adjusted for the variables age, sex, NIHSS and living will and as random effect for the variable hospital.

**Results**-Between 2015 and 2016, 388,012 patients with ischemic stroke were reported (median age 76 years, 52.4% male). Adherence to distinct QI ranged between 41.0% (thrombolysis in eligible patients) and 95.2% (early physiotherapy). 7-day in-hospital mortality was 3.4%. The overall proportion of QI fulfilled was median 90% (IQR 75%-100%). In multivariable analysis, a linear association between overall adherence to QI and 7-day in-hospital-mortality was observed (OR adherence <50% vs 100% 12.7, 95%-CI 11.8-13.7; p<0.001).

**Conclusion**-Higher quality of care measured by adherence to a set of evidence-based process QI for the early phase of stroke treatment was associated with lower in-hospital mortality.

**Non-standard Abbreviations and Acronyms**

| | |
|---|---|
| **ADSR** | German Stroke Register Study Group (*Arbeitsgemeinschaft Deutschsprachiger Schlaganfall Register)* |
| **IS** | Ischemic stroke |
| **NIHSS** | National Institutes of Health Stroke Scale (score) |
| **QI** | Quality indicator |

## Introduction

The evidence for effective strategies in stroke treatment, management and prevention is substantial, and has been translated in several international and national clinical guidelines[1-4]. For measuring performance of individual hospitals in delivering appropriate stroke care, quality indicators (QI) are a widely used tool[5-8]. QI are understood as evidence-based standards of care for all appropriate patients and must be either a meaningful outcome to patients and society or be closely linked to such an outcome[9]. There are a number of initiatives in Europe and the US to define QI that were developed in a standardized evidence-based way and implemented on a national level[5, 10, 11]. There is evidence that implementation of QI within the settings of audit activities leads to improvement in quality of care[12].

However, uncertainty exists whether quality improvement strategies are translated into better patient outcome[13]. There are inconsistent data regarding the association between adherence to QI and patient outcome, ranging from positive to no significant relationships between increased adherence to process measures and patient outcome[14, 15].

Therefore, we investigated the association between quality of acute stroke care defined by overall adherence to evidence-based indicators of processes of stroke care and early outcome defined as 7-day in-hospital mortality within a pooled analysis of large hospital-based stroke registers in Germany.

## Subjects and methods

The data that support the findings of this study are available from the corresponding author upon reasonable request. Data were collected within the *German Stroke Registers Study Group* (*Arbeitsgemeinschaft Deutschsprachiger Schlaganfall Register* - ADSR). The ADSR is a network of 9 regional hospital-based stroke registers, monitoring quality of stroke care in Germany[16]. The participation in the stroke registers in the ADSR is mandatory in some regions (Bavaria, Baden-Württemberg, Hamburg, Hesse, Rhineland-Palatinate) as well as for hospitals with a certified stroke unit defined according to the criteria of the German Stroke Society and the German Stroke Foundation[17] and voluntary in other regions (Berlin, North-Rhine, Northwest Germany, Schleswig-Holstein). The data from different stroke registers collaborating within the ADSR are pooled regularly. The current analysis includes data from 388,012 patients with ischemic stroke (IS) admitted to 736 hospitals participating in the ADSR between January 2015 and December 2016.

### *Data collection and variable definition*

Data collection in the treating hospitals was standardized and each hospital sent the documented forms mainly electronically to the coordinating center of the regional stroke register. Only a small proportion of patients in one register were still documented on paper-based CRFs. In the coordinating center all data were checked for plausibility and completeness and a regular external evaluation of quality of stroke care was performed. Data were collected prospectively by the treating hospital physician; information

was documented continuously from admission (first presentation to the hospital) to discharge. The following definitions were used: age (categorized into 18-64y; 65-74y; 75-84y; 85y+); living conditions pre stroke (independent/dependent at home; institutional care, e.g. residential/nursing home), time from stroke onset to admission (admission within 4 hours; admission after 4 hours; unknown onset), diabetes mellitus (reported pathological elevated fasting blood glucose level (Premeal (fasting) plasma glucose ≥126 mg/dL (≥7,0 mmol/L) patient's self-report of diabetes, or use of antidiabetic drugs); hypertension (reported elevated systolic and/or diastolic blood pressure (Increased blood pressure values (>140 mm Hg systolic and / or >90 mm Hg diastolic) with repeated measurements or patient's self-report of treated hypertension); previous stroke (vascular neurological deficit with symptoms >24h, prior to current event); atrial fibrillation (documented by ECG); neurological deficits of stroke: motor deficits (paresis), speech disturbances (aphasia, dysarthria), disturbances of level of consciousness (somnolence to coma), Barthel Index and modified Rankin Scale (mRS) at admission[18], discharge destination (dead, home, institutional care, e.g. nursing/residential home, rehabilitation unit, other hospital/ward). In-hospital mortality was defined as death within the first 7 days of hospitalization. Stroke was defined according to the WHO criteria[19]. The diagnosis of stroke subtype was confirmed by CT or MRI scan. Only patients with age≥18 years and with a diagnosis of IS (ICD-10: I63) were included in the current analyses, patients with other stroke diagnosis or with TIA were excluded.

*Indicators of quality of care*

For investigating quality of acute stroke care, a set of evidence-based QI was developed and its definition and use is updated regularly by a multidisciplinary quality indicator board of the ADSR following defined methodological criteria and published evidence. The method has been published previously[8]. Target values of QI were defined based on national recommendations and expert consensus by the working group[16, 20]. During the study period 2015 and 2016, a set of 20 evidence-based QI were collected comprising the different health care dimensions structure, process and outcome from the perspective of hospitals providing acute stroke care. For our analyses we selected 11 indicators related to process of

care at admission or during hospital stay, assigned to three categories: early rehabilitation; imaging and screening; acute therapy and treatment. QI related to processes at hospital discharge as well as outcome indicators were excluded as our analyses focused on outcome at discharge. (detailed QI definitions please see https://www.ahajournals.org/journal/str, Table I).

The proportion of QI fulfilled was defined as a proxy for the overall quality of acute stroke care. The proportion of QI fulfilled was calculated on patient level as the number of QI fulfilled divided through the number of QI the individual patient was eligible for; for example, if a patient is eligible for 9 QI and fulfilled 4 of those, the proportion of QI fulfilled would be 4/9=45%. The maximum number QI one patient was eligible for ranged from 1 to 11.

*Statistical analyses*

Descriptive analysis for demographic and clinical characteristics were calculated. We categorized the proportion of QI fulfilled in seven a priori defined groups (<50%, 50-59%, 60-69%, 70-79%, 80-89%, 90-99%, 100%) to distinguish the level of QI fulfillment as accurate as possible. No further subclassification for patients fulfilling less than 50% was performed due to the small numbers in this subgroup. Univariable and multivariable generalized linear mixed models with logistic link function were calculated to estimate the influence of distinct QI and the proportions of QI fulfilled on the risk of 7-day in-hospital mortality. We adjusted all models for age, sex, NIHSS on admission and living will. To adjust for the correlation within hospitals we included hospital as random effect. We also adjusted for the number of patients treated per year in the respective hospital (<250, 251-499, 500-749, 750-999, >=1000) and for the provision of any stroke unit services (defined as documenting 10 or more patients treated on a stroke unit documented in the respective hospital per year)[21]. In descriptive and multivariable analysis of association of 7-day in-hospital mortality and QI one register (Hesse) was excluded in the year 2015 and one register (Hamburg) for the whole time period as they did not collect comparable information on thrombectomy or stroke unit admission, respectively. In addition, 2.7% patients were excluded from multivariable analyses because of missing values in one of the variables;

the number of missing values ranged from 0% in age to 4.3% in intravenous thrombolysis. Several sensitivity analyses were conducted. First descriptively comparing registers with mandatory and voluntary documentation, second excluding those patients with a living will, because they might receive palliative care affecting treatment modalities. Third a multivariable analysis stratified by provision of stroke unit services, fourth including QI fulfillment as a dichotomous variable (100% vs <100%). All tests were two-tailed and statistical significance was determined at an alpha level of 0.05. Statistical analyses were performed with SAS Version 9.4 software. Copyright © [2002-2012] SAS Institute Inc. SAS and all other SAS Institute Inc., Cary, NC, USA.

*Ethics*

The data pooling of the study was approved by the ethics committee of the Charité-Universitätsmedizin Berlin (EA4/043/10) and is registered by the University of Würzburg (20170703 02). The identity of an individual patient was completely anonymous; thus, no specific informed consent was obtained from patients. The investigators who performed the data analyses were blinded to hospital identities. These identities were known only to the coordinating centre of the respective regional stroke registers.

**Results**

A total of 388,012 patients with IS were documented within the ADSR collaboration between January 2015 and December 2016. 736 hospitals cooperated within the ADSR; of those, 55.6% (n=411) provided stroke unit services. Table 1 shows the demographic and clinical characteristics of these patients. Median age of stroke patients was 76 years (IQR 66-83) and 52.4% were male. Overall 7-day in-hospital mortality was 3.4% and the median duration of hospital stay was 8 days (IQR 5–12). The sensitivity analysis comparing registers with mandatory and voluntary documentation showed no major differences

in demographic and clinical characteristics as well as in early outcome (Table 1). For the following analysis, 35,669 patients were excluded due to missing variables or differences in documentation across the registers.

*Adherence to quality indicators and association with 7-day in-hospital mortality*

Overall, the adherence for the selected quality indicators was high, meeting most of the pre-defined target values. (for the definition of the target values please see https://www.ahajournals.org/journal/str, Table II).

More than half of the patients fulfilled all QI they were eligible for (please see https://www.ahajournals.org/journal/str, Table II). Table 2 presents the association between adherence to distinct QI and 7-day in-hospital mortality. Adhering to distinct QI was in general associated with a lower risk of dying within the first 7 days, except for door-to-needle time and early brain imaging which showed no statistically significant association. There was an inverse association of 7-day in-hospital mortality and the proportion of QI fulfilled (Figure 1). For patients fulfilling less than 50% of the set of QI, the mortality rate was 19% and declined to 1.8% if all QI were fulfilled. Based on a logistic regression model considering identical factors, 15% of the variance of the full model was explained by QI fulfilled and 46% by patients factors such as NIHSS and age. In univariate analyses, decreasing proportion of QI fulfilled as well as increasing age, stroke severity, female sex and the presence of a living will were significantly associated with a higher 7-day in-hospital mortality (Table 3). In multivariable analyses, the association between mortality and proportion of QI fulfilled remained stable, solely the effect of female sex was no longer statistically significant (Table 3). In a sensitivity analysis excluding patients with living will no substantial alteration in the effect size for different proportion of QI fulfilled was observed (data not shown). Additionally, after adjustment for the size of the hospital or provision of stroke unit services the associations between QI fulfilled and mortality did not alter (please see https://www.ahajournals.org/journal/str,Table III). The association between QI fulfilled and

mortality was also present, when QI fulfillment was included as a dichotomous variable (100% vs <100%) (please see https://www.ahajournals.org/journal/str,Table V).

**Discussion**

We examined the association between adherence to distinct QI as well as overall quality of stroke care with 7-day in-hospital mortality in a large network of hospital-based stroke registers in Germany. Overall, adherence to predefined evidence-based QI was high in the network. Most distinct QI of the early phase of treatment showed a beneficial effect on in-hospital mortality. The analyses showed an inverse association between overall quality of care defined by the proportion of QI fulfilled the patients was eligible for and in-hospital stroke mortality. Patients receiving a more complete set of process QI had a reduced risk of death within in the first seven days after stroke.

Overall patients with ischemic stroke receive high-quality care, as the most of the predefined target values of QI were achieved. Acute hospital care for stroke patients in Germany has been rated excellent[16] and, in comparison to the former study further improvement has been made for few defined QI (treatment on a stroke unit, dysphagia screening, speech therapy), while adherence the others QI remained at the previous high level (physiotherapy/occupational therapy, early mobilization, antiplatelet therapy). Due to revisions of the QI, further distinct QI could not be mutually compared.

According to a recent systematic review, previous studies showed inconsistent results regarding the association between distinct evidenced-based QI and mortality[15]. Heterogeneity of the studies in design and adjustment of case mix and length of follow up might be one explanation for the different results[14, 15]. Additionally, measuring an association between a distinct QI and outcome has also several methodological challenges that might also contribute to the heterogeneity of previous study results. For

example, many of the defined QI are mutually dependent, as the fulfillment of QI on admission might affect the results of QI of later phases such as early dysphagia-screening and occurrence of stroke-related pneumonia[22]. Furthermore, patients may receive during their treatment phase several components of different process QI at the same time, such as early rehabilitation strategies.

In our study, we found a positive relationship between increased adherence to distinct QI and early mortality in 9 QI, while 2 QI showed no statistically significant relationships. The effect of early rehabilitation on early outcome in our study are in line with the results of a recent meta-analysis[15]. For imaging and screening, the importance of early vascular imaging for guiding appropriate management of patients symptomatic carotid stenosis was confirmed in previous implementation studies from routine care[23, 24]. The impact of dysphagia screening on early outcome shown in our analysis are in line with recent studies and meta-analysis, showing reduced risk of mortality if swallow assessment was done[15, 25, 26], probably due to a reduced risk of aspiration pneumonia[27]. Screening for atrial fibrillation was found to be associated with a reduced mortality in our study which was confirmed in studies in routine care, showing that early anticoagulant use for IS with atrial fibrillation being associated with reduced early and late case fatality[15]. For QI of acute therapy and treatment, the effect of early antiplatelet therapy on outcome is in line with the results of a recent meta-analysis[15]. The association of early intravenous thrombolysis with good outcome is time dependent[28] and was replicated in a number of studies from clinical routine[29], such as our data. Analog to our findings a strong association between treatment on a stroke unit and mortality have been shown in several clinical trials[30] and was confirmed in a meta-analysis of studies in routine care[15]. The only QI that showed no statistically significant association with early outcome in our data were early brain imaging and door-to-needle time. This might be caused by confounding as patients prioritized for an early brain imaging might be more severely affected and, thus, also have a greater risk of complications or death[31]. Additionally early brain imaging is unlikely to show any effect to outcome if its results are not leading to an appropriate action. Door-to-needle time is strongly associated with a timely thrombolysis but also with the selection of eligible patients (for thrombolysis). It might be that patient benefit from thrombolysis - as they are within the timeframe of thrombolysis – even if there are out of the door-to-needle timeframe. The effect of a distinct QI on in-

hospital mortality needs to be interpreted with caution. Confounding by indication might have increased the magnitude of the positive effects we observed for QI such as early rehabilitation, vascular imaging ≤48 hours, antiplatelet ≤48 hours or screening for atrial fibrillation, as at the time point for deciding to apply the processes underlying these QI is more distant to the time of stroke onset and, thus, based on a clearer perception of the potential prognosis of the patient.

Most previous studies assessing a combination of selected QI, showed a decrease in early stroke mortality with better performance, even if the number and distinct QI combined substantially differed[15]. An analysis of national Danish health study (DNIP) showed for example an inverse dose response relationship between number of QI met with 30 day and 90-day mortality[32]. A maximum of six QI (early admission to a stroke unit, early initiation of antiplatelet or oral anticoagulant therapy, early examination with CT/MRI scan, and early assessment by a physiotherapist, an occupational therapist, of nutritional risk), selected by a national panel of experts, could be met. Additionally, analysis of the Stroke Improvement National Audit Programme in England found a reduction in the odds of 30-day mortality if minimum five of six selected process QI (stroke unit admission, seen by a stroke consultant, swallow/nutrition assessment, antiplatelets therapy, early nurse/rehabilitation assessment and early physiotherapy/mobilization, early CT/MRI brain imaging) were fulfilled[25]. Another study from Australia showed inconsistent results on in-hospital mortality when combining a complex set of indicators of process of care, reflecting early stroke care and management at discharge (CT scan<24h, swallowing assessment<24h, allied health assessment<24h, neurological observations<24h, physiotherapist<24h, occupational therapist<24h, speech pathologist<24h, documentation of premorbid function and discharge needs; enteric feeding if nil by mouth<48h, measures to avoid aspiration, incontinence addressed, deep vein thrombosis prophylaxis, fever management, use of antiplatelet agents at discharge)[33]. Although not the same treatment processes were combined in the previous studies, there was a substantial overlap in the chosen set of QI, ranging from 2 to 15 QI[13, 24-26, 32-35]. The QI mostly combined were stroke unit admission, swallow/nutrition assessment, antiplatelets and anticoagulants for IS, early nurse/rehabilitation assessment and early physiotherapy/mobilization, CT/MRI brain imaging.

The observed association between higher adherence to QI and early outcome might be mediated by other unmeasured processes of care[25]. Additionally, (pre)-selection of the items included in combination of QI and inappropriate weighting might not reflect the true quality of care[36] and might overemphasize specific components of acute stroke care. However, acute stroke care requires that the entire diagnostic, decision-making, and treatment pathway has to be undertaken as effective as possible. Thus, in contrast to these previous studies, we investigate the performance of individual acute care hospitals using a comprehensive approach combing all predefined evidence-based measures of process of early stroke care and considering eligibility of an individual patient for these processes. We observed a linear trend between in-hospital mortality and overall quality of care defined as proportion of QI fulfilled the patient was eligible for. This association was consistent when adjusting for potential confounders on the patient level, such as age, sex, stroke severity, living will as well as for confounders on the hospital level (number patients treated per year, stroke unit service provision). The positive outcome effects of introducing quality improvement programs[37], clinical pathways[38] or integrating a multidisciplinary team in stroke care[34] underline that a bundle of action taken and not one task alone might result in a better outcome of stroke patients.

Our study has several strengths including the large sample size, the nationwide population-based sampling frame and the clustered analysis. Thus, it provides representative data for stroke care in Germany. There are also limitations of our study. Due to the anonymous character of the data collection we cannot completely excluded that some of the patients were documented twice, e.g. if they were transferred from one hospital to another. Further, we could only adjust our multivariable models for variables documented in a comparable way throughout the hospitals. Thus, we cannot exclude that other important baseline characteristics that are not documented within the ADSR, such as ethnicity, might have influenced the observed associations. Precautions were taken to minimize the impact of possible confounding by adjustment for potential confounders, including the living will. Furthermore, the overall adherence rate to QI was calculated with regard to eligibility for QI by defining dedicated inclusion and exclusion criteria. We cannot exclude that the observed associations were caused by residual

confounding or confounding by indication. However, a series of additionally sensitivity analyses showed a persistent association between QI and mortality across patients grouped by stroke severity. Furthermore, the definition of the QI vascular imaging does not distinguish between intracranial and extracranial imaging, therefore it is not a measure for a certain vascular territory. The examined vascular territory is determined by the clinical and imaging presentation of ischemic stroke. But as 90% of all patients receive intracranial and extracranial imaging, the percentage of patients receiving only one imaging is very small (0.48% of patients get only intracranial vascular imaging). Due to data protection regulations in Germany, there is no routine data linkage with mortality registers or health insurance data for providing information on long-term outcome. Thus, our analyses are restricted to in-hospital outcome only.

## Conclusions

The performance of health care providers measured by overall adherence to evidence-based QI of acute stroke care showed a substantial impact on in-hospital mortality in clinical routine. This finding underlines the importance of monitoring quality of care by evidence-based quality indicators to improve outcome of IS in the populations.

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**Disclosures**

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KH, VR, PH, BM, KB, GS, AJ, SR, CB, CM report no competing interests. HCK reports receiving honoraria for auditing stroke units on behalf of the German Stroke Society.

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**Supplemental Materials**

Table I -V

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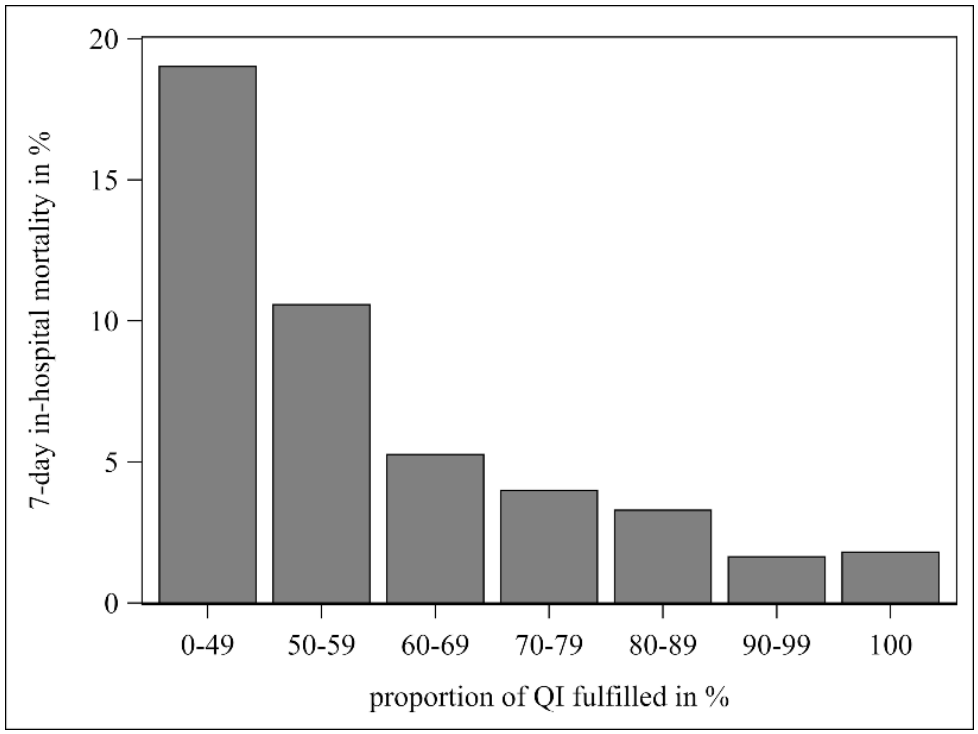


**Figure 1**. Association between 7-day in-hospital mortality and proportion of QI fulfilled

**Table 1**. Patient demographic and clinical characteristics stratified by registers with voluntary or mandatory documentation*

| | Overall | Mandatory documentation | Voluntary documentation |
|---|---|---|---|
| Number of patients, n (%) | 388,012 (100) | 180,344 (46.5) | 207,668 (53.5) |
| Age, yr | | | |
| Median (IQR) | 76 (66-83) | 77 (67-84) | 76 (65-83) |
| Age group, yr, n (%) | | | |
| 18-64 | 88,804 (22.9) | 38,177 (21.2) | 50,627 (24.4) |
| 65-74 | 81,417 (21.0) | 37,349 (20.7) | 44,068 (21.2) |
| 75-84 | 137,846 (35.5) | 65,042 (36.1) | 72,804 (35.1) |
| ≥ 85 | 79,945 (20.6) | 39,776 (22.1) | 40,169 (19.3) |
| Male, n (%) | 203,186 (52.4) | 94,552 (52.4) | 108,634 (52.4) |
| NIHSS on admission categories, n (%) | | | |
| 0-3 | 183,267 (48.1) | 85,128 (49.0) | 98,139 (47.3) |
| 4-15 | 159,946 (42.0) | 71,954 (41.4) | 87,992 (42.4) |
| 16-25 | 33,038 (8.7) | 14,567 (8.4) | 18,471 (8.9) |
| 25+ | 4,967 (1.3) | 2,168 (1.2) | 2,799 (1.3) |
| Time from onset to admission, n (%) | | | |
| ≤ 4 hrs | 149,899 (38.7) | 68,689 (38.1) | 81,210 (39.1) |
| >4 hrs | 197,038 (50.8) | 94,628 (52.5) | 102,410 (49.4) |
| unknown | 40,878 (10.5) | 17,027 (9.4) | 23,851 (11.5) |
| Comorbidities, n (%) | | | |
| Atrial fibrillation | 110,643 (28.6) | 50,391 (27.9) | 60,252 (29.2) |
| Hypertension | 323,403 (83.7) | 147,370 (82.3) | 176,033 (84.9) |
| Diabetes | 108,766 (28.1) | 48,382 (26.8) | 60384 (29.1) |
| mRS 3-5 at admission, n (%) | 224,118 (57.8) | 104,841 (58.1) | 119277 (57.5) |
| Barthel Index at admission | | | |
| Median (IQR) | 75 (25-100) | 75 (25-100) | 75 (25-100) |
| Barthel Index >60, n (%) | 230,636 (60.0) | 104764 (59.3) | 125,872 (60.7) |
| Living will, n (%) | 59,322 (16.5) | 24,715 (16.1) | 34,607 (16.8) |
| Length of stay, d, Median (IQR) | 8 (5-12) | 7 (5-11) | 8 (5-12) |
| 7d in-hospital mortality, n (%) | 13,160 (3.4) | 6,290 (3.5) | 6,870 (3.3) |

* Patients with missing values for the respective variable were excluded; NIHSS – National Institutes of Health Stroke Scale (score); mRS - modified Rankin Scale ;

**Table 2**. Association between adherence to quality indicators and 7-day in-hospital mortality

| Quality Indicator | Quality Indicator fulfilled | | | | | |
|---|---|---|---|---|---|---|
| | Alive >7 days | | Dead ≤ 7 days | | OR (95%-CI) for 7-day in-hospital mortality* | |
| | Eligible for QI | % QI fullfilled | Eligible for QI | % QI fullfilled | Univariable | Multivariable |
| *Early Rehabilitation* | | | | | | |
| Physiotherapy/occupational therapy ≤2 days | 159835 | 96.4 | 8567 | 77.6 | 0.11 (0.10-0.12) | 0.14 (0.13-0.15) |
| Speech therapy≤ 2 days | 188898 | 93.5 | 8553 | 72.8 | 0.16 (0.15-0.17) | 0.18 (0.17-0.19) |
| Mobilization ≤2 days | 179626 | 93.6 | 5982 | 69.4 | 0.11 (0.11-0.12) | 0.17 (0.16-0.18) |
| *Imaging and screening* | | | | | | |
| Vascular imaging ≤ 48 hours | 340527 | 92.2 | 11816 | 73.9 | 0.21 (0.20-0.22) | 0.29 (0.27-0.31) |
| Brain imaging within ≤30 min | 81448 | 69.5 | 1513 | 78.2 | 1.64 (1.44-1.86) | 1.02 (0.89-1.17) |
| Dysphagia Screening | 312431 | 91.8 | 4651 | 85.1 | 0.48 (0.44-0.52) | 0.32 (0.29-0.35) |
| Screening for atrial fibrillation | 273490 | 91.6 | 7028 | 71.2 | 0.18 (0.17-0.19) | 0.26 (0.25-0.28) |
| *Acute therapy and treatment* | | | | | | |
| Antiplatelets ≤48 hours | 182897 | 95.2 | 7342 | 60.4 | 0.07 (0.06-0.07) | 0.18 (0.17-0.19) |
| Intravenous thrombolysis in eligible patients within ≤4 hours from onset | 83413 | 41.4 | 1508 | 54.9 | 1.73 (1.56-1.91) | 0.77 (0.69-0.87) |
| Door-to-needle time ≤1 hour | 55836 | 83.3 | 2867 | 83.4 | 1.02 (0.91-1.13) | 0.99 (0.88-1.11) |
| Treatment on a stroke unit | 236714 | 91.2 | 8596 | 75.0 | 0.26 (0.25-0.28) | 0.39 (0.37-0.42) |

*generalized linear mixed models with logistic link function adjusted for hospital as random effect, age, sex, National Institutes of Health Stroke Scale (score) on admission, living will as fixed effects.

QI not fulfilled is reference

**Table 3.** Univariable and multivariable association between adherence to a set of quality indicators and 7-day in-hospital mortality*

| | Univariable | | Multivariable | |
|---|---|---|---|---|
| | **OR (95% CI)** | **p-value** | **OR (95% CI)** | **p-value** |
| Proportion of QI fulfilled# | | | | |
| 100% | 1 | <0.0001 | 1 | <0.0001 |
| 90%–99% | 0.93 (0.77-1.13) | | 1.10 (0.90-1.34) | |
| 80%–89% | 1.93 (1.83-2.04) | | 1.89 (1.79-2.01) | |
| 70%–79% | 2.40 (2.25-2.57) | | 3.09 (2.87-3.33) | |
| 60%–69% | 3.29 (3.07-3.53) | | 4.13 (3.81-4.47) | |
| 50%–59% | 7.51 (6.99-8.07) | | 6.83 (6.28-7.44) | |
| <50% | 15.40 (14.52-16.34) | | 12.70 (11.81-13.65) | |
| Age group, yr, n (%) | | <0.0001 | | <.0001 |
| 18-64 | 1 | | 1 | |
| 65-74 | 2.19 (2.00-2.40) | | 1.82 (1.65-2.01) | |
| 75-84 | 3.95 (3.64-4.28) | | 2.59 (2.38-2.83) | |
| ≥ 85 | 10.14 (9.36-10.97) | | 4.28 (3.91-4.68) | |
| NIHSS categories | | <0.0001 | | <0.0001 |
| 0-3 | 1 | | 1 | |
| 4-15 | 7.35 (6.76-8.00) | | 6.84 (6.23-7.45) | |
| 16-25 | 62.68 (57.65-68.14) | | 38.04 (34.88-41.39) | |
| 26-42 | 168.67 (152.46-186.60) | | 84.91 (76.23-94.56) | |
| Female sex | 1.89 (1.82-1.96) | <0.0001 | 0.96 (0.92-1.00) | 0.08 |
| Living will | 6.72 (6.46-6.99) | <0.0001 | 2.2 (2.50-2.75) | <.0001 |

*generalized linear mixed models with logistic link function adjusted for hospital as random effect; NIHSS – National Institutes of Health Stroke Scale (score) on admission; #proportion of QI fulfilled was calculated on patient level as the number of QI fulfilled divided through the number of QI the individual patient was eligible for

# 7 Discussion

Reductions, in total stroke mortality and in mortality by stroke subtype, as well as in case-fatality rates in ischemic stroke patients were observed between the late 1990s and 2015[105, 107]. We found a reduction in stroke mortality rates in ischemic and hemorrhagic stroke in Germany between 1998 and 2015[105]. The reduction was more pronounced in ischemic compared to hemorrhagic stroke[105]. Even eight years after the German reunification, differences in ischemic stroke mortality between EG and WG were still present[105]. Beginning in the middle 2000's, the differences started to diminish[105]. In hemorrhagic stroke mortality, no differences between the regions were observed[105]. Additionally, a reduction in case-fatality rates between 1996 and 2015 was observed in all subtypes of ischemic stroke within a large population-based register, except in large-artery atherosclerosis[107]. However, no clear time trends for stroke recurrence were observed[107]. Further, we found that the quality of acute care was high for ischemic stroke patients in Germany[109]. We reported an inverse association between adherence to QI and early in-hospital mortality in the years 2015/2016[109].

In the following sections the results for each WP will be discussed in the presence of the existing literature separately.

## 7.1 Time trends in stroke mortality in Germany

We observed a decline in total, ischemic and hemorrhagic stroke mortality in Germany between 1998 and 2015[105].

This was in line with a globally reported decline of 36% in total stroke mortality from 1990 to 2016, reported by the GBD[2]. Stratified by region, within this comprehensive study, every region in the world, except of Southern sub-Saharan Africa, showed a significant decline in stroke mortality over a 17-year observation period[2]. A significant decrease was also observed for ischemic and hemorrhagic stroke in a similar way in this study[2].

To model the time trends in mortality in Germany, we applied joinpoint regression analysis, which was also the methodology chosen to model stroke mortality in several other countries and to study time trends, such as Northern Ireland, Republic of Ireland and USA, Mexico and Austria[119-122]. Most of these studies reported similar time points of changes in the decline of mortality compared to our finding[119-121]. However, different patterns in time trends between the pathological subtypes of stroke were reported in Mexico[121]. In this study, total stroke mortality, ischemic stroke, hemorrhagic stroke and intracerebral hemorrhagic stroke mortality declined, whereas subarachnoid hemorrhagic stroke mortality increased from 1980 to 2012. Since 1988 mortality rates for ischemic stroke were higher than those for hemorrhagic stroke, whereas we observed lower mortality rates for ischemic stroke[121]. In our analysis, a constant decline with only one change in time trend in women and no change in average annual percentage change in hemorrhagic stroke mortality was observed. Similar, to our findings, no change in average annual percentage in hemorrhagic stroke mortality was found in Mexico. The time points of changes in ischemic stroke mortality rates in Mexico were in line with the time points we observed.

However, not all studies reported a decline in stroke mortality, some countries detected a reversal in the declining trend in the latest years[90, 123, 124]. Two studies from the USA reported a slight increase in mortality rates[123, 124]. A small increase in stroke mortality rates was observed from 2013 to 2015 based on vital statistics and records of death in the USA[123]. Before, from 2000 to 2013, total stroke mortality rates declined with differences between regions and ethnical groups. Changes in the trend were observed in 2003, 2006 and 2012 in men and 2013 in women, which is similar, to our findings. However, from 2013 to 2015 in total and in all groups, except in the youngest age-groups 35-54, a slight increase in stroke mortality was detected. This increase was only statistically significant in the South of the USA and in Hispanics. The authors discussed that the reverse in the time trend might be due to changes in incidence and an unfavorable development of risk factors, such as physical activity and obesity causing hypertension, which is often not controlled adequately in the USA[123]. Additionally, a non-significant increase in stroke mortality was also found in another study from the US, investigating time trends in stroke mortality in the population of Mississippi between 2000 and 2016. In this study, stroke mortality rates decreased at the beginning of the observation period and non-significantly increased from 2009 to 2016 in men and stagnated from 2007 to 2016 in women[124]

In addition, a recent study observed a stagnation of time trends in age-standardized cardiovascular disease mortality since 2015, including stroke mortality based on vital statistics in 23 high-income countries (including Germany, France, Australia, Austria, United Kingdom, USA and Denmark)[90]. The age-standardized cardiovascular disease mortality declined from 2000 to 2015 or 2017, depending on the last point of observation[90]. Shown by the average annual percentage change the decrease was more pronounced in the years 2000 to 2010 and slowed down afterwards. In the latest years of the observation period, annual percentage changes close to zero or above zero - reflecting no change or an increase in stroke mortality over time - were found. Additionally, in the age-group 35-74 years in USA in men and women and Canada in women only, an increase in cardiovascular disease mortality was observed. For Germany, this study reported an average annual percentage change of less than 2% in the years 2010-2015. Similar to these findings, we also estimated slightly decelerating declining mortality rates in total stroke mortality in women. The authors concluded that the effects of public health interventions to reduce cardiovascular risk factors from the last 50 years are no longer effective and that more strategic public-health interventions are needed to further reduce cardiovascular disease mortality, as the mortality is already on a low level[90]. However, the reported increases in the cardiovascular disease mortality might just be due to small fluctuations and must not reflect a true trend, as this was only the annual percentage change of one year to the next (from the next to last to the last year of the observation period). In addition, the observation periods of the included studies were heterogeneous, some ending in 2015 and others in 2017, which hampers valid comparisons.

### 7.1.1 Risk factor development

Several factors might have led to the observed reduction in stroke mortality. Changes in stroke incidence might be one of the major factors driving changes in stroke mortality. Incidence is influenced by the distribution of risk factors for stroke in the general population as well as primary preventive measures addressing these risk factors[125, 126]. In the Tromso Study in Norway based on a Poisson Regression, 57% of the observed decline in incidence of ischemic stroke from 1995 to 2012 could be explained by modifications in cardiovascular risk factors, the two main factors were hypertension and smoking with

26% and 17%[126]. Hypertension and smoking are not only the main risk factors for ischemic, but also for hemorrhagic stroke[127]. Systolic blood pressure declined in the general population in Germany from 1990 to 2011 from 132 mmHg to 120 mmHg in women and from 137 mmHg to 128 mmHg in men[106]. From 1994 to 2012, based on seven population-based studies in Germany, the highest decline in systolic blood pressure (over 10 mmHg) was observed in the age-group 55-74 years[128]. Further the uptake of antihypertensive drugs increased between 1990 and 2011 in men and women from 14.8% to 21.7% in men and from 17.0% to 21.4% in women, which could led to a decline in incidence rates[106]. Smoking prevalence decreased from 1998 to 2015 in Germany based on representative national surveys from 30% to 22% in women and from 39% to 31% in men[129]. Especially in the younger age-groups from 18 to 54 years a significant decrease was observed since 2003, e.g. from 2003 to 2011 smoking prevalence decreased from 39.6% in 2003 to 31.1% in 2011 in women and from 45.9% to 39.8% in men in persons of the age of 30 to 44 years[129, 130]. We observed a joinpoint of the trend in total and ischemic mortality (in WG in men, and in EG in women) in the year 2007. A previous study based on routine data on hospital admission and death certificates in Scotland showed that smoking bans could reduce ischemic stroke incidence immediately[131]. Thus, the observed reduction in stroke mortality in 2007 might be associated with the introduction of smoke-free legislation in Germany in the same year[105].

Another reasons for the decrease in stroke mortality might be healthier lifestyle behaviors, such as a healthy diet, in the general population. These lifestyle factors are associated directly with an increased stroke risk or indirectly via the impact on vascular risk factors being associated with an increased stroke risk and, thus, improving lifestyle factors can lead to a decline in incidence and mortality rates. A previous study showed that all-cause mortality can be reduced by 66% by fulfilling at least four healthy lifestyle factors[132]. Based on three representative national survey from Germany the prevalence of healthy lifestyle was estimated and defined as fulfilling more than four out five healthy behaviors (combination of consumption of fruits and vegetables, sufficient physical exercise, no current smoking, no current risk drinking and normal body weight)[133]. The relative increase of the healthy lifestyle from 1990-92 to 2008 was 58.2% with prevalence rates of 9.3% in 1990-92, 13.5% in 1997-99 and 14.6% in 2008[133]. Time trends in incidence in Germany are only available from ESPro, which reported a

statistically significant decline from 1995 to 2010 in incidence rates of total and ischemic stroke in men, whereas in women no statistically significant decline was observed[11].

Even though some of the risk factors of ischemic stroke showed a favorable development, the prevalence of vascular risk factors was still high in the general population free-of-cardiovascular disease[134]. This was for example shown in the population-based cohort study "Characteristics and Course of Heart Failure Stages A-B and Determinants of Progression" (STAAB), which is a study of over 1,000 randomly chosen inhabitants of Würzburg in Germany between the ages 30-79 years[134]. In this study 32% of the participants between 30-79 years were hypertensive and 25% of the participants were obese[134]. Additionally many vascular risk factors were not identified or not adequately controlled in Germany, e.g. in 36% of all hypertensive participants hypertension was undetected or unknown and 52.7% of the hypertensive participants had a high blood pressure despite the use of antihypertensive drugs [134]. As these risk factors increase the risk of death, an improvement in the identification and control of these risk factors could further reduce mortality[125, 126, 135]. Additionally, a non-optimal control of risk factors and non-adherence to medications such as hypertension and antihypertensive drugs can lead to an increase in mortality rates, as observed in some countries in the recent decade[90, 123, 136] .

### 7.1.2 Treatment and secondary prevention

Improvements in acute stroke treatment can also lead to a decrease in stroke mortality by a reduction of case-fatality rates. The different therapy options for the treatment of acute ischemic and hemorrhagic stroke were improved substantially over the recent years. For example, in 2000 intravenous administration of tPA was approved as therapy of acute ischemic stroke patients in Germany and in 2002 in Europe[71, 137]. The proportion of patients treated with tPA raised constantly in Germany from 3.5% in 2000 to 14.6% in 2012 in patients admitted to a hospital with a certified Stroke Unit[6, 138]. Corresponding to the introduction of tPA in 2000, we observed a change in the decline of total stroke mortality in men in EG and in women in both regions with a steeper decline after 2000.

Improvements in patient management and early secondary prevention, such as antiplatelet therapy within 48 hours after event and physiotherapy might also be associated with a decline in in-hospital

mortality as observed in an analysis of the Northwest German stroke audit from 2000-2011[82]. In this audit, in-hospital mortality declined from 2000 until 2008, afterwards crude in-hospital mortality rates were stable. However, after adjusting for patient characteristics such as age, sex, stroke severity on admission and comorbidities, the rates even increased until the end of the observation period in 2011.

One of the most important improvements in acute stroke management was the introduction of Stroke Units. In the years 1994/1995 the first Stroke Units were implemented in Germany[139]. The number of Stroke Units increased over the years and reached an almost complete coverage in 2012[6]. In 2015 and 2016 based on data from the ADSR, 83.9 % of all ischemic stroke patients were treated on a Stroke Unit[109]. In 1998 the first Stroke Units in Germany were certified with a change in the certification process in 2002[140]. Stroke Unit treatment has shown to reduce the risk of death after stroke significantly by up to 13%[44]. Based on routine data from Germany, collected for reimbursement purposes, the absolute difference in in-hospital mortality rates between patients treated on a general ward and on a Stroke Unit was 1.8% percent[118]. In this data set, in-hospital mortality decreased between 2005 and 2010 in patients treated on either a Stroke Unit or a general ward, with lower mortality rates in patients treated on a Stroke Unit[118]. The wider introduction of Stroke Unit treatment in Germany might be associated with a steeper decline in total stroke mortality in women in both regions and in men in EG and in ischemic stroke mortality in women in EG starting in 2003. Thus, the decrease in stroke mortality might partly be caused by a decrease in case-fatality rates in Germany by an improvement of acute stroke management.

Case-fatality can also be reduced by improving secondary prevention strategies via a lower risk of fatal cardiovascular events such as stroke or heart attack[125, 135, 136, 141, 142]. Uptake and prescription of secondary preventive medications increased in Germany over time. For example, when comparing the two national health interview and examination surveys for adults in Germany (GNHIE98 and DEGS1) uptake of statins in stroke survivors increased from 17.1% in 1997-1999 to 50.1% in 2008-2011[143]. Furthermore, in the federal-state-wide hospital-based stroke registry in Hesse the proportion of patients treated with oral anticoagulants at discharge after stroke increased from 2006 to 2015 up to 24%[72, 82]. Also the uptake

of antihypertensive therapy and antiplatelet therapy within 48 hours increased from 2000 to 2011 or 2007 to 2011, respectively[82].

Improvements in acute treatment and secondary prevention of stroke might have led to a decline in stroke mortality over time. However, as the treatments and therapy options were improved constantly over time, it seems not possible to link these changes to an exact time point corresponding with changes in the time trend of stroke mortality.

### 7.1.3 Regional differences EG and WG

At the beginning of the observation period in 1998, the difference in stroke mortality between EG and WG were huge with up to 1.5 higher rates in EG than in WG[105]. The time trends in ischemic stroke mortality differed, with a steeper decline in EG than in WG. On the other hand, the trends in hemorrhagic stroke developed in parallel. The exact reasons for these regional differences in ischemic stroke mortality remain unknown. The mortality statistic was based on the first cause of death on a death certificate. One of the reasons for the observed regional variations might be methodological differences in the coding of causes of death between EG and WG[97, 144, 145]. Before the German reunification in 1990, different methods to collect the cause of death were used in the two regions, as in WG cause of death was coded from trained staff in the federal statistical offices, based on the death certificate following the rules of the WHO, whereas in EG cause of death was coded directly by the physician or coroner determining the death of the person[144]. We chose to start our analysis in 1998, as this was the year the new coding system ICD-10 was introduced. Even though the same coding system (ICD-10) was used in 1998, there might still be small differences in coding as every federal state uses its own approach of coding the causes of death[145]. For example, sometimes the first cause of death was not clearly indicated by the death certificate and might, therefore, depend on the person's own decision of coding the causes of death[145]. However, these differences might only explain minor changes in the observed mortality rates in our analysis, especially as the differences in stroke mortality started to diminish in 2007.

Another reason for the differences between EG and WG might be disparities in the socioeconomic status. It has been shown that a higher socioeconomic status was associated with a lower stroke risk and

mortality[146, 147]. This is supported by a recent study based on German health insurance data, which found differences in stroke incidence and mortality between income groups. A higher income was associated with a reduced stroke incidence and reduction in the hazard of death after stroke[81]. In Germany even 15 years after the German reunification in 1990, there are still huge differences in income between EG and WG. The income in WG is still higher and the unemployment rates are lower than in the EG[148]. Income itself might not be causal for a higher mortality, rather than the factors that are associated with lower income. A lower income is for example, associated with a less healthy lifestyle and less healthy lifestyle habits[149-152]. For example, the proportion of current smokers was higher and the mean intake of fruits and vegetables was lower in the EG than in the WG[153, 154]. Thus, disparities in socioeconomic status might be associated with the observed differences in stroke mortality between the two regions.

Additionally, a higher rate of diabetes was observed in EG compared to WG[155]. Furthermore, the prevalence of cardiovascular risk factors was higher in EG than in WG[156, 157]. Differences in the distribution of vascular risk factors between EG and WG might have led to differences in incidence, which can lead to differences in mortality rates. Unfortunately, no data on stroke incidence in EG is available, as no population-based stroke register, such as ESPro, exist in EG to estimate the stroke incidence rate. Therefore, the incidence rates between the EG and WG cannot be compared and their influence on the regional differences in stroke mortality in Germany remains unknown.

There might also be differences in the health care systems between EG and WG, that contribute to the observed findings. The medical infrastructure in EG improved over the recent years. For example, from 1990 to 1997 the number of hospital providing specialized cardiac treatments such as catherization increased from five to more than 30 in EG[158].

Interestingly, there were only differences between the regions in total and ischemic stroke mortality, whereas trends in hemorrhagic stroke were in parallel. Differences in mortality trends between the regions in intracerebral hemorrhage and subarachnoid hemorrhage were observed in a sensitivity analysis in men only. In men, subarachnoid hemorrhagic stroke mortality rates were higher in WG compared to EG. This was the only subgroup were this was the case, in all the other subtypes and

subgroups rates in EG were always higher than in the WG. But subarachnoid hemorrhage is a rare cause of stroke, therefore this might also be due to small sample size in this group.

## 7.2 Time trends in case-fatality and recurrence by ischemic stroke etiology

Variations in case-fatality and recurrence rates within the etiological subtypes of ischemic stroke were observed in ESPro. The highest case-fatality rates were observed for cardioembolic strokes and the lowest for stroke due to small artery occlusion. The highest recurrence rates were observed in cardioembolic strokes and strokes of undefined origin. We observed a significant decrease in case-fatality rates from 1996 to 2015 in all etiological subtypes except for large-artery atherosclerosis. However, no statistically significant decrease was observed in recurrence rates over time[107].

### 7.2.1 Case-fatality rates

In ESPro case-fatality rates were still high between 1996 and 2015 with rates of 21% within the first year after the event and 46% within the first five years[107]. However, these figures are in line with the case-fatality rates from the population-based South London Stroke Register, which reported case-fatality rates of 20.4% within the first year after ischemic stroke for the years 2012-2015[159]. In the European Registers of Stroke, a collaboration of six population-based stroke registers, including South London Stroke Register and Dijon Stroke Registry, pooled mean weighted 3-months case-fatality rates of 21.8% were displayed for the years 2004 to 2006[160]. With 13%, the case-fatality rates were lower in ESPro, but still in the range of the reported rates and comparable to the lowest reported rates from the Dijon[160]. In a former analysis of the South London Stroke Register, the 1-year and 5-year case-fatality rates for total stroke were higher compared to our rates[161]. However, as the rates of the South London Stroke Register included also hemorrhagic stroke, they cannot be compared directly to rates from ischemic stroke alone.

We observed a decline in case-fatality rates in ischemic stroke patients from 1996 to 2015. The number of studies, which analyzed time trends in long-term case-fatality, is limited. Overall, a decrease in case-fatality rates have been reported in a recent systematic review, especially in high income countries; early

case-fatality rates (21 days to 1 month) after ischemic stroke declined from 1970 to 2008, even though the decline was not statistically significant[162]. However, in specific countries case-fatality rate declined significantly. For example, in Ontario, Canada a decline in case-fatality rates was observed from 2003 to 2018[163]. In this study, 30-day case-fatality rates after ischemic stroke declined from 16.5% to 10.2% and 1-year case-fatality rates decreased from 28.9% to 20.0%[163]. Declines in case-fatality rates were also reported from different sources in Denmark[80, 164]. Based on a population-based cohort, a decline in 30-day and 5-year case-fatality rates after ischemic stroke was observed between 1994 and 2011[80]. More recently, based on a linkage of four nationwide registries (Danish National Patient Registry, Danish National Prescription Registry, Danish Civil Registration System and the Danish Registry of Causes of Death) a decline in 30-day and 1-year case-fatality rates after first ever in a lifetime ischemic stroke by around 10% and 13% respectively was reported in Denmark between 1996 and 2016[164]. This decline in case-fatality rates is comparable to our data for the same time period. In the Netherlands, also a trend towards declining case-fatality rates were observed[104, 165]. Between 1997 and 2005, a linkage study of different national registries reported a decline in age- and sex-specific 30-day and 1-year case-fatality rates in ischemic stroke patients across most age-groups[104]. In addition, in the population-based Rotterdam study case-fatality rates also decreased after ischemic stroke between 1991 and 2015, whereas no changes in mortality risk were observed in hemorrhagic strokes[165]. A decline in mortality after stroke was also observed in the population-based FINSTROKE study from 1983 to 1997[166]. On the other hand, controversial results have been reported for Sweden[167, 168]. In Risk-Stroke, the Swedish stroke registry, covering Swedish hospitals and providing follow-up data, a rise in 3-months total stroke case-fatality rates was observed between 1995 to 2010, which might be due to variations in severity of hospitalized stroke patients, as a higher proportion of severe strokes was detected[167]. However more recently a decline in 28-days case-fatality rates in Sweden was reported[168].

After stratifying the case-fatality rates by etiological subtypes according to the TOAST classification, we observed the highest 5-year case-fatality rates in patients with stroke due to cardioembolism and the lowest in small artery occlusion. A former analysis of the data of the ESPro up to the year 1998 revealed the same pattern of stratified case-fatality rates of patients with stroke due to cardioembolism having the highest case-fatality rates and patients with small artery occlusion having the lowest rates after 2 years[8].

Our results are also in line with results from a prospective study in the Netherlands with a mean follow-up of 691 days, where the highest case-fatality rates were detected in patients with stroke due to cardioembolism[169]. Data for the 1-year case-fatality rates can be compared to the Chinese Nanjing Stroke Registry, where the probability of dying after stroke within 1-year was lowest in patients with stroke due to small artery occlusion and high in patients with stroke due to cardioembolism and large-artery atheresclorosis[170].

We observed differences in time trends in case-fatality rates stratified by etiological subtype of ischemic stroke[107]. The case-fatality rates of all etiological subtypes expect of large-artery atherosclerosis showed a significant decrease over time. The number of studies reporting trends in case-fatality rates after ischemic stroke stratified by etiological subtypes according to TOAST is limited. The most recent one is from the South London Stroke Register, reporting a decrease in adjusted overall case-fatality rate, 30-days case-fatality rates and 1-year case-fatality rates in ischemic stroke patients between 2000 and 2015[159]. A significant reduction in case-fatality rates was observed for both men and women. However stratified according to etiological subtypes, only a significant decline in mortality in strokes due to cardioembolism was observed[159]. In contrast, we found a decrease in case-fatality rates in all subtypes of ischemic stroke except of the subtype large-artery atherosclerosis in ESPro. These variations might be explained by different adjustment methods between the analyses. The analysis for time trends in case-fatality rates in South London Stroke Register was adjusted for temporal changes in demography, prior risk factors, stroke severity and processes of care, whereas our analysis was only adjusted for age and sex. In addition, variations in the etiological classification systems might also contribute to the observed differences. The Dijon Stroke Registry reported time trends in 28-days case-fatality rates stratified by etiology for the time period 1985-2004. However, etiology was defined slightly different as macroartheroma, microatheroma and cardioembolic[171]. From 1985 to 2004 a significant decrease in case-fatality rates was observed in stroke due to microatheroma only[171]. Even if studies investigating time trends in case-fatality rates stratified by etiological subtype are limited, trends in stroke case-fatality in specific patient subgroups, such as patients with atrial fibrillation, exist. Atrial fibrillation is the most important cause of a cardioembolic stroke, in which we observed high case-fatality rates[16]. In patients with atrial fibrillation age-adjusted hazard of death after stroke decreased in a Danish Cohort[172]. In

addition, in the Athens Stroke Registry, case-fatality rates after stroke in patients with atrial fibrillation decreased from 1993 to 2012 with an average annual percentage change of -7.9%[173].

Case-fatality rates might further be influenced by changes in patient characteristics, such as stroke severity and age at onset[174]. A higher stroke severity and older age were associated with a higher risk of death[174]. Between 2003 and 2011, a significant decrease in stroke severity was observed in all ischemic stroke subtypes in Austria, reflected by an observed reduction of the mean NIHSS from 4 to 3 in men and 5 to 4 in women[175]. However, in this study, the age at stroke onset increased which might be associated with an increased case-fatality[175]. We adjusted our time trend analysis for age, to exclude the effect of age. Unfortunately, we were unable to adjust the time trends for NIHSS, as this information was not collected for the whole time period in ESPro.

### 7.2.2 Recurrence Rates

We reported recurrence rates of 3.1% in men and 3.2% in women within the first 3 months and 20.1% within the first 5 years in ESPro. Our estimates are in the range of the pooled estimated of recurrence rates for ischemic stroke patients of a meta-analysis on population-based studies[22].

Stratified by etiological subtypes according TOAST classification, we observed the highest 5 years recurrence rates in patients with cardioembolic stroke and stroke of undetermined origin with 21.1% and 21.9%[107]. A comparison on the level of the recurrence rates stratified by etiological subtype is difficult as the number of studies reporting ischemic stroke recurrence rates stratified by etiology are limited. The most recent analysis reporting stroke recurrence rates, stratified by etiological subtype, for 3-month, 1-year, 5-years and 10-years was from 1995 to 2018, based on data from South London Stroke Register[27]. Compared to our rates, the reported recurrence rates in the South London Stroke Register were lower for all the subtypes and at any time[27]. We do not know the exact reasons for these differences. One explanation might be differences in effectiveness of secondary prevention measures, as the reported case-fatality rates in South London Stroke Register from 200 to 2015 were in a comparable range to the case-fatality rates in ESPro[76]. However, variations in patient characteristics between the two registers and a smaller sample size in the ESPro could also be potential reasons for the observed differences.

Irrespective of the rates, the patterns between the etiological subtypes were similar. In the South London Stroke Register, also the lowest recurrence rates were observed in patients with small artery occlusions over the whole time period[27, 107]. Furthermore, in the subgroup of patients with large-artery atherosclerosis a high risk of recurrent stroke within the first year after a stroke and a low recurrence risk within 5-years was reported in the South London Stroke Register, comparable to the data from ESPro[27]. Reasons for lower 5-year recurrence rates in patients with large-artery atherosclerosis, could be the high case-fatality rates in this group, as many patients died before they could get a second stroke. Comparable to our findings, a systematic review points towards lower recurrence rates within the first month in lacunar strokes in comparison to non-lacunar strokes[176]. We observed high recurrence rates in patients with cardioembolic or strokes of undefined cause within the first year. Reasons for the high recurrence rates in cardioembolic strokes might be that atrial fibrillation, which is a common cause of cardioembolic strokes, increases the risk of stroke recurrence[177]. This might also be the reason in patients with undefined origin, as the proportion of patients with undetected atrial fibrillation was high in this group with a proportion of 16.1% or even higher[178].

We did not find any trend in stroke recurrence, neither for overall ischemic stroke nor within the etiological subtypes[107]. This was in line with a previous systematic review from 2018, which could also not detect a statistically significant decline in stroke recurrence after ischemic stroke or transient ischemic attack[179]. The review was based on 34 studies, including randomized clinical trials, hospital-based and population-based studies, which were published before December 11, 2016[179].

Our results were in contrast to the recently published results from the South London Stroke Register, where recurrence rates decreased from 1995 to 2005 and stabilized on a lower absolute level after 2005[27]. Additionally, probability of recurrent free survival improved from 1995 to 2015 in the South London Stroke Register[27]. The authors argued with an overall improvement in health care and an increase in life-expectancy, which influences case-fatality rates, but not recurrence rates[27]. As we saw a clear reduction in case-fatality rates and no reduction in recurrence rates in ischemic stroke patients, larger improvements in health care system and less improvements in secondary prevention measures in the setting of the ESPro, might be reasons for that as well. However, in a sensitivity analysis we found

significant decrease in stroke recurrence in stroke of undefined origin by adjusting for competing risks of death[107]. One recently published study also reported improvements in stroke recurrence rates, when taking competing risks into account[180]. In this study from Texas, a decrease in adjusted 1-year and 2-year recurrence rates 2000 to 2013 was observed[180].

We can only speculate, why we did not observe a reduction in stroke recurrence in our main analysis. One of the reasons could be that our sample size was too small to detect a statistically significant time trend, especially in specific subtypes. Another potential reason could be that the recurrence rates did not decrease due to limited adherence to secondary preventive measures[136, 181, 182]. Furthermore, the control of cardiovascular risk factors, such as hypertension and atrial fibrillation, was not optimal in Germany[181]. However, it could also be that a non-linear trend in stroke recurrence rates exists, which we were unable to detect by assuming a linear trend without changes in trends within specific time periods.

## 7.3 Impact of quality of care on early mortality

We saw a decline in stroke mortality and in stroke case-fatality rates after ischemic stroke until 2015, which might be due to improvements in acute treatment. Over the years, the application of evidence-based in-hospital management and treatment options increased in Germany[82, 83]. To investigate the association between the quality of in-hospital care of acute ischemic stroke patients in Germany with early mortality, we analyzed audit data from ADSR for the years 2015 and 2016. Quality of care was operationalized by pre-specified QI, reflecting measures for evidence-based process of care.

In our dataset, only a small percentage of patients fulfilled less than 50% of all the QI, they were eligible for, showing a high quality of care in acute ischemic stroke patients in Germany. Of the investigated QI of processes of care only brain imaging within 30 minutes, antiplatelet within 48 hours and treatment on a Stroke Unit did not reach the predefined target values. Furthermore, an inverse association between adherence to QI and 7-day in-hospital mortality was observed. This association was present for adherence to distinct QI and for the adherence to the combination of several QI. The high quality and

improvements in quality of acute care, might have led to the reduction in case-fatality rates, that we observed in the population-based setting[107].

Most of the QI reached or even outperformed the predefined target values. This was also the case in a former analysis of the stroke registers in ADSR from 2012[55]. However, between 2012 and 2015, quality of care improved substantially, as in comparable QI, hospitals performed on higher levels. For example, the QI that did not met the target value in 2012, such as dysphagia screening or early systematic thrombolysis in eligible patients, were over these values in 2015[55]. Only the QI antiplatelet within 48 hours after stroke did not improve and is still below the target value. However, it is worth noting that the definition of several QI, such as early systematic thrombolysis in eligible patients changed from 2012 to 2015, thus, hampering direct comparisons. The improvement in quality of care of acute stroke patients in Germany is still ongoing, as seen by an updated analysis from ADSR data from 2018 on a register aggregated level[183].

Association between mortality and distinct QI was shown in previous papers[60]. In our analysis 9 out of 11 distinct QI had a significant effect on early in-hospital mortality. Most of them are in line with other studies, for example with a recent systematic review and meta-analysis, covering 30 registers mostly from Europe, investigating the association of key performance measure and outcome after stroke[60]. The review also conducted a meta-analysis of specific performance measures including up to 22 studies reporting a significant association between most of the QI and case-fatality rate up to 1 year, similar to our findings between distinct QI and 7-day in-hospital mortality. The meta-analysis was adjusted for age and stroke severity, however, heterogeneous measures of stroke severity were applied in the included studies. Within the review, also an association for early rehabilitation covering physiotherapy and mobilization (early physiotherapy /mobilization OR 0.78 (95-%-CI 0.67, 0.91) and occupational therapy assessment OR 0.83 (95%-CI 0.75, 0.92)) with early (up to 1 year) case-fatality rates was found[60]. We estimated odds ratios between 0.14 and 0.18 for the association between measures of early rehabilitation and in-hospital mortality, which were larger than the ones in the meta-analysis. This might be due to the heterogeneous follow-up periods ranging from 1 month to 1 years in the meta-analysis and 7-days in our analysis.

From the category “Imaging and screening”, only the two QI brain imaging and dysphagia screening were included in the meta-analysis. Swallow/nutritional assessment was associated with a reduced early-case-fatality (OR 0.78; 95%-CI 0.66, 0.92) in the meta-analysis, which is in line with our results and was also supported by other studies[60, 184, 185]. As dysphagia is a proxy for an increased risk of aspiration pneumonia, early detection and management of dysphagia can, thus, reduce the risk of pneumonia[186-188]. Concerning the QI early vascular imaging, a reduction in in-hospital mortality for patients with early vascular imaging was found. Early vascular imaging is important to detect patients with symptomatic carotid stenosis, so that carotid endarterectomy can be performed to reduce risk of second stroke[189, 190]. The positive effect of early vascular imaging was also found in other studies from routine care[191, 192]. We found a reduction in in-hospital mortality by screening for atrial fibrillation. This might be an indirect effect, as after the detection of newly diagnosed atrial fibrillation oral anticoagulants can be prescribed, which were associated with a reduction in case-fatality as shown in the meta-analysis[60]. In Germany, a non-significant effect on mortality with an odds ratio above 1 was observed for CT / MRI brain imaging. This was in line with results from the meta-analysis were an OR of 1.00 (95%-CI 0.80, 1.25) was reported. The reasons for the absence of an association of brain imaging on mortality might be residual confounding. As brain imaging is the cornerstone of stroke treatment and management to classify patients into the stroke subtypes and to determine the location. Thus, it might be offered to all stroke patients irrespective of their prognosis and individual treatment decision can just start after this diagnostic procedure. Thus, confounding by indication might not play a major role. Door-to needle time also showed no significant association with case-fatality. Reasons for that might be an association between shorter door-to needle time and reduction in disability, but no reduction in the risk of death as shown in recent studies[39].

The positive effect of early antiplatelet therapy on early case-fatality was confirmed by the recent meta-analysis[60]. Effect of Stroke Unit treatment in reduction mortality was also found in the meta-analysis within the registers of The Danish National Indicator Project, Riks Stroke (Sweden), Stroke Improvement National Audit Programme (England), Scottish Stroke Care Audit (Scotland) and within one other observational study in Italy and one in 13 hospitals across 10 European countries, but also in

a large meta-analysis of clinical trials[44, 60]. Early intravenous thrombolysis had a positive effect on good outcome, which was shown before in several studies and in the Danish Stroke Registry[193-195].

For most of the distinct QI we observed a larger effect on early mortality compared to previous studies. This might be due to differences in adjustment methods, differences in patient characteristics and variations in length of follow-up. The effect of QI might be larger on in-hospital mortality than on early case-fatality, as the effect might vanish over time. In addition, there are other factors after hospital discharge, which might influence early case-fatality (within 3 months or later), such as secondary prevention. Furthermore, there might be heterogeneity concerning the inclusion and exclusion criteria for the specific QI.

Additionally, all observed associations between a distinct QI and mortality needs to be interpreted with caution, as confounding by indication might have increased the effect. Confounding by indication means that the factors influencing the decision for selecting a patient for a specific treatment (e.g. age, sex, comorbidities, stroke severity) are also associated with the outcome[196]. Confounding by indication might be present in a number of QI, especially in those with a longer time delay from onset to treatment decision such as early rehabilitation, vascular imaging ≤48 hours, antiplatelet ≤48 hours or screening for atrial fibrillation. The main aims of these procedures are to reduce the risk of recurrent stroke or to reduce long-term case-fatality rates. Hence due to the later time point of these processes, it is easier to predict the prognosis of patient and, therefore, the processes might mainly be performed in patients with a good prognosis.

Furthermore, the investigated QI do not act independent from each other. When one of the QI in the early phase is not fulfilled, chances are high that the other QI in the later phase are also not fulfilled. For example, if in patients eligible for thrombolysis the QI brain imaging ≤30 minutes is not fulfilled, it is most likely that the QI door-to needle time ≤ 1 hour and intravenous thrombolysis ≤ 4 hours are also not fulfilled. Therefore, it is not optimal to study only the impact of a single QI, as the management of acute stroke care is a combination of several process. For example, it was shown that the introduction of quality improvement programs with feedback such as the program “get with the guidelines stroke program”, clinical pathways and treatment from a multidisciplinary team including stroke team,

occupational therapist and physiotherapist, can improve outcome after stroke[197-199]. Therefore, in comparison to the other studies, we tried to reflect the reality by combining all existing evidence-based QI of process of acute care in Germany and by considering the eligibility of patients for one treatment.

Hence, we analyzed not only distinct QI, but also the bundle of several QI reflecting processes of acute stroke care, where we found an inverse dose-response relationship between the adherence to QI and in-hospital mortality. This is in line with results from a systematic review of 30 registers, where fulfilling a combination of QI was associated with a reduced risk of dying after stroke[60]. An inverse dose response relationship between number of QI fulfilled with a maximum number of six QI and early case-fatality and further less complications was observed in a national Danish health study (DNIP)[200, 201], where a combination of QI from early rehabilitation, diagnostic and screening and treatment, comparable to our study, was used. Based on the Stroke Improvement National Audit Programme in England fulfilling minimum five out of six QI reduced the 30-day case-fatality rate significantly[184]. However, the results in the study from the UK were not representative for all ischemic stroke patients, as patients who were not eligible to all of the six QI were excluded, which were for example patients with poor prognosis and illness severity. Additionally, only QI, which were applicable to more than 80% of the patients, were included in the analysis. Therefore, important QI such as thrombolysis could not be included, thus, unmeasured processes of care could mediate the observed effects and might lead to bias[184, 202]. In a previous study from Australia, including patients admitted between September 1998 and October 1999 to one of 8 participating hospitals, a statistically significant effect of level of adherence to a combination of up to 15 indicators of processes of care on mortality was observed for in-hospital mortality only, but not after 28 weeks[203]. Reasons for that might be the small sample size, as the difference between level of adherence and outcome after 28 weeks was not the primary analysis and, therefore, might be underpowered[203].

## 7.4 Strengths and limitations

There are several strengths and limitations in the different data sets and analytical strategies being used within this thesis.

Overall, the strengths of all the WPs are the large national or population-based datasets for the general or the stroke population. For the time trends in stroke mortality, we used the large nationwide data set, which included death certificates of the whole population stratified by region. Therefore, we were able to estimate the mortality rates for the whole population as well as per region. Furthermore, we were able to model time trends using joinpoint regression over a long time period of more than 15 years. By using joinpoint regression, no pre-specification of time periods with constant annual percentage change was needed. Thus, time points of changes were estimated solely based on data and not on knowledge or assumptions, which reduces bias[114]. The data set on which the time trends in case-fatality and recurrence rates were estimated, was a population-based register with a long-term follow-up of over 20 years in Germany[107]. Data collection was standardized across the entire time period. In addition, the TOAST classification of the first event was available from all patients over the whole period in a standardized way[8, 204]. Thus, a stratification of analysis of time trends by etiological subtype was possible. The audit data from the ADSR used to measure the association between QI and in-hospital mortality covers with over 300,000 cases a large sample size[109]. Furthermore, the data set is based on a nation-wide sample of in-hospital stroke patients covering over 80% of all stroke cases and offered, therefore, a representative analysis for stroke care in Germany. Additionally, the available information on hospital characteristics allowed to adjust for possible random effects of hospitals as a cluster.

Our work has several limitations. In the joinpoint analysis of the first WP, the estimated number of joinpoints was based on the smallest p-value. Therefore, not every estimated joinpoint must reflect a true change in the time trends. Mortality rates for the whole German population could only be calculated on an aggregated level based on routine observational data. Therefore, all conclusions of this WP can only be interpreted as hypothesis generating. Furthermore, we could not stratify the primary analysis of the time trends by the pathological subtype of hemorrhagic stroke, as the number of deaths due to

subarachnoid hemorrhage and intracerebral hemorrhage was too small. However, we tried to model these time trends separately in a sensitivity analysis.

In the second WP the proportion of the etiological subtype "undefined causes" according to TOAST classification was remarkably high with 38.5%, however, it was still in the range of other population-based registers[205, 206]. Unfortunately, an analysis of the effect of the etiological subtype of recurrent stroke on the time trends was not possible, as no data on the etiological subtype of recurrent stroke was available. Stroke severity might have influenced the time trends, however, we could not adjust for stroke severity as no standardized scale was collected in ESPro over the whole time period. Although ESPro is population-based, it is worth noting that the source population of Erlangen is relatively small (about 100,000 inhabitants), which might lead to a low statistical power of the derived estimates. However, the Erlangen Stroke Project is unique with its long-term observation period, starting over 20 years ago and it is the largest and longest running population-based stroke register in Germany.

In the third WP, the data set from the ADSR was based on anonymous cases only. Thus, it is possible that patients, who had more than one stroke within the two observed years or patients who were transferred to another hospital, were counted more than once. Therefore, the cases were not strictly statistically independent. However, we tried to reduce the risk of double counting of patients due to the transfer from one hospital to another, by excluding patients, which were transferred to another hospital, which operationalized by documentation of a minimal dataset only. Additionally, adjustment in the multivariable models was only possible for baseline characteristics, which were documented in all registers in a comparable way. Hence, we might have missed some important confounders of the association of quality of care and in-hospital mortality. However, we tried to adjust for as many potential confounders as possible within the data set, such as living will or stroke severity. To calculate the proportion of QI fulfilled, specific pre-defined inclusion and exclusion criteria were used. The observed association between adherence to QI and outcome might be influenced by residual confounding or confounding by indication. However, the observed associations were consistent after stratification by stroke severity as done in a sensitivity analysis. The ADSR data set does not include a follow-up, therefore, only in-hospital mortality could be modeled.

# 8 Conclusion

We saw that stroke mortality across all pathological subtypes and case-fatality across all etiological subtypes of ischemic stroke according to TOAST classification declined from the late 1990s to 2015 in Germany. Regional difference in the time trends in stroke mortality existed between EG and WG. However, these differences almost vanished over the years. Furthermore, the decline in stroke mortality was more pronounced in ischemic than in hemorrhagic stroke. The decline in case-fatality rates was present in all etiological subtypes, except for large artery atherosclerosis. The decline in stroke mortality and case-fatality rates after ischemic stroke might be associated with an improvement in acute treatment and management. This is supported by a high quality in acute stroke care in 2015 and 2016 and an association between performance of health care providers and a reduction in in-hospital mortality in Germany. However, we did not observe a decline in stroke recurrence. This might be an indication for options to improve secondary prevention in stroke patients. There are different ways to improve secondary prevention, such as the implementation of structured ambulatory secondary prevention programs, which might reduce the rate of recurrent strokes, myocardial infarction and death and improve the control of cardiovascular risk factors. These programs were successfully introduced in other countries [207, 208]. However, such structured programs are currently not available for stroke patients in Germany, but complex intervention studies are currently under the way[209, 210].

So far, we can only speculate to what extent the observed decline in stroke mortality and case-fatality is due changes in risk factors, primary and secondary preventive options and improvements in acute treatments. In coronary heart disease, the health policy IMPACT model, calculating the impact of all these factors on mortality, revealed that depending on the population and the time period up to one third of the decline in coronary heart disease mortality could be explained by improvements in acute treatment and secondary prevention and over 50% by changes in risk factors and mostly less than 10% by improvements in primary prevention[142]. However, such a model is still missing for stroke. But the outcomes of such a model would be helpful to guide health care providers and policy makers in planning future effective public health intervention on the population level.

# 9 References


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# 10 Appendix

## 10.1 Abbreviation

| | |
|---|---|
| ADSR | Arbeitsgemeinschaft Deutschsprachiger Schlaganfall Register |
| CI | Confidence Interval |
| CT | Computed tomography |
| EG | Former Eastern Part of Germany |
| ESPro | Erlangen Stroke Project |
| GBD | Global Burden of Disease Study |
| GLMM | Generalized Linear Mixed Models |
| HR | Hazard Ratio |
| ICD-10 | International Statistical Classification of Diseases and Related Health Problems, 10th Revision |
| IS | Ischemic Stroke |
| MRI | Magnetic Resonance Imaging |
| NIHSS | National Institute of Health Stroke Scale |
| OR | Odds Ratio |
| QI | Quality Indicator |
| TOAST | Trial of Org 10172 in Acute Stroke Treatment |
| tPA | Tissue Plasminogen Activator |
| WG | Former Western Part of Germany |
| WHO | World Health Organization |
| WP | Work Package |

## 10.2 Description of contributions

In this section the contribution of the co-authors to the three included publications will be described.

Contributions to the first publication entitled “Decline in Regional Trends in Mortality of Stroke Subtypes in Germany From 1998 to 2015”:

Viktoria Rücker (VR), Peter U. Heuschmann (PUH), Markus A. Busch (MAB), Silke Wiedmann (SW) and Martin O’Flaherty designed the study. Data were provided by the Federal Statistical Office and collected separately in the statistical office of each federal state. VR prepared the data in SAS and analyzed the data using Joinpoint regression and interpreted the results. PUH and MOF consulted VR in analyzing the data. PUH, MAB and SW were involved in the interpretation of the data. VR wrote the first draft of the first publication, including introduction, materials and methods, discussion. VR plotted all the figures and constructed the tables. PUH, SW, MOF and MAB critically revised the manuscript.

Contribution to the second publication entitled “Twenty-year time trends in long-term case-fatality and recurrence rates after ischemic stroke stratified by etiology”:

Peter L Kolminsky-Rabas (PLK-R), PUH, Michael Weingärtner (MW), Stefan Schwab (SS), Manuela Hess (MH), Claudia Sedlak (CS) designed and developed the methods of data collection of the Erlangen Stroke Project over the years. PLK-R, MW, MH, CS and SS collected the data. VR analyzed the data using the software R and interpreted the data. PUH and PLK-R supported VR in the interpretation of the data. VR wrote the whole first draft of the manuscript and plotted the figures and made the tables on her own. PUH, PLK-R, MOF critically revised the manuscript.

Contributions to the third publiction entitled “Association between adherence to quality indicators and 7-day in-hospital mortality after acute ischemic stroke”:

VR, PUH and Kirsten Haas (KH) designed the study and the methods to analysis this data. VR pooled the data of all the nine registers of the ADSR and recoded the variables and prepared the data for the analysis. The data were collected in each register separately. Peter Hermanek (PH) is responsible for the data collection, study design and methods development of the stroke register of the Bavarian Permanent

Working Party for Quality Assurance (BAQ), Björn Misselwitz (BM) is responsible for the data collection, study design and methods development of the stroke register of Institute of Quality Assurance Hesse (GQH). Klaus Berger (KB) is responsible for the data collection, study design and methods development of Quality Assurance in Stroke management in North Rhine-Westphalia. Günter Seidel (GS) is responsible for the data collection, study design and methods development of the stroke register of Externe Qualitätssicherung Hamburg. Alfred Janssen (AJ) is responsible for the data collection, study design and methods development of Quality Assurance Project "Stroke Register Northwest Germany". Susanne Rode (SD) is responsible for the data collection, study design and methods development of the stroke register of Office for Quality Assurance in Health Care Baden-Württemberg (QiG BW GmbH). Christoph Burmeister (CB) is responsible for the data collection, study design and methods development of the stroke register of Quality Assurance Stroke Rhineland-Palatinate. Christine Matthis (CM) is responsible for the data collection, study design and methods development of Quality Association for Acute Stroke Treatment Schleswig-Holstein. Hans-Christian Koennecke (HCK) is responsible for the data collection, study design and methods development of the Berlin Stroke Register.

VR analyzed the data using the software SAS, plotted the figure and constructed all the tables and interpreted the data. KH, PUH also interpreted the data. PH, BM, KB, GS, AJ, SR, CB, CM and HCK critically revised the manuscript and were involved in the interpretation of the data. KH wrote the first draft of the introduction and discussion. VR wrote the first draft of the description of the materials and methods. VR and PUH critically revised the first draft of the manuscript. VR and KH responded to the reviewers and changed the manuscript as proposed by the reviewers. PH, BM, KB, GS, AJ, SR, CB, CM, HCK revised manuscript.

## 10.3 Statement of individual author contributions

**"Dissertation Based on Several Published Manuscripts"**

**Statement of individual author contributions and of legal second publication rights**

| **Publication**:<br>Rücker V, Wiedmann S, O'Flaherty M, Busch MA, Heuschmann PU. Decline in Regional Trends in Mortality of Stroke Subtypes in Germany From 1998 to 2015. Stroke. 2018;49 (11):2577-2583. doi:10.1161/STROKEAHA.118.023193 | | | | | |
|---|---|---|---|---|---|
| **Participated in** | **Author Initials,** Responsibility decreasing from left to right | | | | |
| Study Design<br>Methods Development | VR | PUH | MAB | SW | MOF |
| Data Collection* | | | | | |
| Data Analysis and Interpretation | VR | PUH | MOF | MAB | SW |
| Manuscript Writing | | | | | |
| Writing of Introduction | VR | PUH | SW | MAB | MOF |
| Writing of Materials & Methods | VR | PUH | MOF | SW | MAB |
| Writing of Discussion | VR | PUH | MAB | MOF | SW |
| Writing of First Draft | VR | PUH | MAB | MOF | SW |

Explanations: *Data from the Federal Statistical Office, therefore none of the authors collected the data

| **Publication**:<br>Rücker V, Heuschmann PU, O'Flaherty M, Weingärtner M, Hess M, Sedlak C, Schwab, S and Kolominsky-Rabas, PL. Twenty-year time trends in long-term case-fatality and recurrence rates after ischemic stroke stratified by etiology. *Stroke*. 2020;51:2778-2785 | | | | | |
|---|---|---|---|---|---|
| **Participated in** | **Author Initials,** Responsibility decreasing from left to right | | | | |
| Study Design<br>Methods Development | PLK-R | PUH | VR | MW | MH, CS, SS |
| Data Collection | PLK-R | MW | MH | CS | SS |
| Data Analysis and Interpretation | VR | PUH | PLK-R | | |
| Manuscript Writing | VR | PUH | PLK-R | MOF | |
| Writing of Introduction | VR | PUH | PLK-R | MOF | |
| Writing of Materials & Methods | VR | PUH | PLK-R | MOF | |
| Writing of Discussion | VR | PUH | PLK-R | MOF | |
| Writing of First Draft | VR | PUH | PLK-R | MOF | |

| **Publication**:<br>Haas K*, Rücker V*, Hermanek P, Misselwitz B, Berger K, Seidel G, et al. Association between adherence to quality indicators and 7-day in-hospital mortality after acute ischemic stroke. *Stroke*. 2020;51:3664-3672 | | | | |
|---|---|---|---|---|
| **Participated in** | **Author Initials,** Responsibility decreasing from left to right | | | |
| Study Design<br>Methods Development[1] | VR | PUH | KH | PH, BM, KB, GS, AJ, SR, CB, CM, HCK |
| Data Collection[1] | PH, BM, KB, GS, AJ, SR, CB, CM, HCK | | | |
| Data Analysis and Interpretation | VR | KH | PUH | PH, BM, KB, GS, AJ, SR, CB, CM, HCK |
| Manuscript Writing | | | | |
| Writing of Introduction | KH | VR | PUH | |
| Writing of Materials & Methods | KH<br>VR | VR<br>KH | PUH<br>PUH | |
| Writing of Discussion | KH | VR | PUH | |
| Writing of First Draft | KH | VR | PUH | |

Explanations: *contributed equally. [1] PH, BM, KB, GS, AJ, SR, CB, CM, HCK are equally responsible for data collection in their register, as the data set is based on 9 stroke registers in Germany. Each co-author is responsible for data collection of one register

The doctoral researcher confirms that she/he has obtained permission from both the publishers and the co-authors for legal second publication.

The doctoral researcher and the primary supervisor confirm the correctness of the above mentioned assessment.

Viktoria Rücker

_____

Doctoral Researcher's Name Date Place Signature

Prof. Dr. Peter Heuschmann

_____

Primary Supervisor's Name Date Place Signature

## 10.4 Statement of individual author contributions to figures

**"Dissertation Based on Several Published Manuscripts"**

**Statement of individual author contributions to figures/tables/chapters included in the manuscripts**

| **Publication:**<br>Rücker V, Wiedmann S, O'Flaherty M, Busch MA, Heuschmann PU. Decline in Regional Trends in Mortality of Stroke Subtypes in Germany From 1998 to 2015. Stroke. 2018;49 (11):2577-2583. doi:10.1161/STROKEAHA.118.023193 | | | | | |
|---|---|---|---|---|---|
| **Figure** | **Author Initials,** Responsibility decreasing from left to right | | | | |
| 1 | VR | PUH | MOF | SW | MB |
| 2 | VR | PUH | MOF | SW | MB |
| **Table** | | | | | |
| 1 | VR | PUH | MB | SW | MOF |
| 2 | VR | PUH | MB | SW | MOF |

| **Publication**:<br>Rücker V, Heuschmann PU, O'Flaherty M, Weingärtner M, Hess M, Sedlak C, Schwab, S and Kolominsky-Rabas, PL. Twenty-year time trends in long-term case-fatality and recurrence rates after ischemic stroke stratified by etiology. *Stroke*. 2020;51:2778-2785 | | | | | |
|---|---|---|---|---|---|
| **Figure** | **Author Initials,** Responsibility decreasing from left to right | | | | |
| 1 | VR | PUH | PLK-R | MOF | MW, MH, CS, SS |
| 2 | VR | PUH | PLK-R | MOF | MW, MH, CS, SS |
| **Table** | | | | | |
| 1 | VR | PUH | PLK-R | MOF | MW, MH, CS, SS |
| 2 | VR | PUH | PLK-R | MOF | MW, MH, CS, SS |
| 3 | VR | PUH | PLK-R | MOF | MW, MH, CS, SS |

| **Publication:**<br>Haas K, Rücker V, Hermanek P, Misselwitz B, Berger K, Seidel G, et al. Association between adherence to quality indicators and 7-day in-hospital mortality after acute ischemic stroke. *Stroke*. 2020;51:3664-3672 | | | | |
|---|---|---|---|---|
| **Figure** | **Author Initials,** Responsibility decreasing from left to right | | | |
| 1 | VR | KH | PUH | PH, BM, KB, GS, AJ, SR, CB, CM, HCK |
| **Table** | | | | |
| 1 | VR | KH | PUH | PH, BM, KB, GS, AJ, SR, CB, CM, HCK |
| 2 | VR | KH | PUH | PH, BM, KB, GS, AJ, SR, CB, CM, HCK |
| 3 | VR | KH | PUH | PH, BM, KB, GS, AJ, SR, CB, CM, HCK |

I also confirm my primary supervisor's acceptance.

Viktoria Rücker

| Doctoral Researcher's Name | Date | Place | Signature |
|---|---|---|---|

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Reihs, Blanka Rosenberger), Quality Assurance in Stroke Management in North Rhine–Westphalia – Medical Association North Rhine, Quality Assurance Project ”Stroke Register Northwest Germany”, Quality Assurance Stroke Rhineland-Palatinate – Institute of Quality Assurance Rhineland-Palatinate (SQMed GmbH), Quality Association for Acute Stroke Treatment Schleswig-Holstein

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# 11 Curriculum Vitae

# 12 Affidavit

I hereby confirm that my thesis entitled ***Time trends and determinants of stroke mortality in Germany*** is the result of my own work. I did not receive any help or support from commercial consultants. All sources and/or materials applied are listed and specified in the thesis.

Furthermore, I confirm that this thesis has not yet been submitted as part of another examination process neither in identical nor in similar form.

Würzburg, _____ _____
Date Signature

**Eidesstattliche Erklärung**

Hiermit erkläre ich an Eides statt, die Dissertation ***Zeitliche Trends und Einflussfaktoren auf die Schlaganfall-Sterblichkeit in Deutschland*** eigenständig, d.h. insbesondere selbständig und ohne Hilfe eines kommerziellen Promotionsberaters, angefertigt und keine anderen als die von mir angegebenen Quellen und Hilfsmittel verwendet zu haben.

Ich erkläre außerdem, dass die Dissertation weder in gleicher noch in ähnlicher Form bereits in einem anderen Prüfungsverfahren vorgelegen hat.

Würzburg, _____ _____
Datum Unterschrift

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