Mortality in epilepsy and the influence of comorbid conditions and antiepileptic drugs

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List of publications

Paper I

Aurlien D., Taubøll E., Gjerstad L. (2007) Lamotrigine in idiopathic epilepsy - increased risk of cardiac death? *Acta Neurol Scand* **115**:199-203.

Paper II

Aurlien D., Leren T.P., Taubøll E., Gjerstad L. (2009) New SCN5A mutation in a SUDEP victim with idiopathic epilepsy. *Seizure* **18**:158-60.

Paper III

Aurlien D., Larsen J.P., Gjerstad L., Taubøll E. (2012) Increased risk of sudden unexpected death in epilepsy in females using lamotrigine: a nested, case-control study. *Epilepsia* **53**:258-66.

Paper IV

Svalheim S., Aurlien D., Amlie J.P., Gjerstad L., Taubøll E. (2012) Signal-averaged and standard electrocardiography in patients with newly diagnosed epilepsy. *Epilepsy & Behavior* **25**:543-545.

Paper V

Aurlien D., Larsen J.P., Gjerstad L., Taubøll E. (2012) Comorbid and underlying diseases - major determinants of excess mortality in epilepsy. *Seizure* **21**:573-7.

Abstract

Purpose

Based on a clinical observation, this study was initiated to examine whether treatment with lamotrigine (LTG) is associated with an increased risk of sudden unexpected death in epilepsy (SUDEP) in sub-groups of epilepsy patients, and to explore the underlying causes of the increased mortality rate in the epilepsy population.

Materials and methods

A nested case-control study of SUDEP in Rogaland county, Norway was conducted by review of post mortem reports, data from the Norwegian Cause of Death Registry, and hospital records. We also examined twenty-six newly diagnosed epilepsy patients by signal-averaged and standard electrocardiography. Fifteen patients were treated with LTG and ten with carbamazepine (CBZ). Furthermore the causes of death (COD) of deceased epilepsy patients at Stavanger University Hospital were compared with the COD in the general population.

Results

The incidence of SUDEP was significantly elevated in females on LTG, and a significantly higher proportion of female SUDEP victims were on LTG compared with controls.

No significant electrocardiographic abnormalities were detected in the 25 patients that completed the study.

A significantly lower proportion of deceased epilepsy patients had died from cardiac disease compared with the general population. In a significant proportion of cases, the onset of the disorder leading to death had preceded the onset of epilepsy.

Conclusions

Treatment with LTG in females was significantly associated with SUDEP. However, it remains uncertain whether a causal relationship is present. We found no evidence of cardiac abnormalities caused by LTG or CBZ. Comorbid and underlying disorders were the main determinants of mortality in the epilepsy population.

Contents

Abbreviations

AED	Antiepileptic drug
ARVC	Arrhythmogenic right ventricular cardiomyopathy
BFNC	Benign familial neonatal convulsions
BFNIS	Benign familial neonatal-infantile seizures
CAE	Childhood absence epilepsy
CBZ	Carbamazepine
CI	Confidence interval
cLQTS	Congenital long QT syndrome
COD	Causes of death
CPS	Complex partial seizure
DDD	Defined daily doses
ECG	Electrocardiogram
EEG	Electroencephalogram
GABA	Gamma amino butyric acid
GEFS+	Generalized epilepsy with febrile seizures plus
GTCS	Generalized tonic-clonic seizure
HRV	Heart rate variability
IGE	Idiopathic generalized epilepsy

ILAE	International League Against Epilepsy
JAE	Juvenile absence epilepsy
JME	Juvenile myoclonic epilepsy
LQTS	Long QT syndrome
LTG	Lamotrigine
MR	Mental retardation
MRI	Magnetic resonance imaging
PGES	Postictal generalized electroencephalographic suppression
QTc	Corrected QT interval
SAECG	Signal-averaged electrocardiogram
SMEI	Severe myoclonic epilepsy of infancy
SMR	Standardized mortality ratio
SPS	Simple partial seizure
SUDEP	Sudden unexpected death in epilepsy
VLP	Ventricular late potential

Introduction

Since ancient times people have tried to understand epilepsy. The first known description of epileptic seizures derives from Babylonian tablets from more than 500 years BC (Wilson & Reynolds 1990). Seizures were claimed to be caused by ghosts and demons, and the sufferers were "possessed". Although scientists gradually abandoned these perceptions through the centuries, they are still present in the community to some extent, and not only in developing countries (Chaudhary *et al.* 2011). Even in modern society, there is considerable stigma associated with epilepsy, adding to the burden of living with this condition (McNeil *et al.* 2012).

1.1 Definition of epileptic seizure and epilepsy

According to the 2005 proposal from the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) (Fisher *et al.* 2005) an **epileptic seizure** is a "*transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain*", and **epilepsy** is a "*disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure.*"

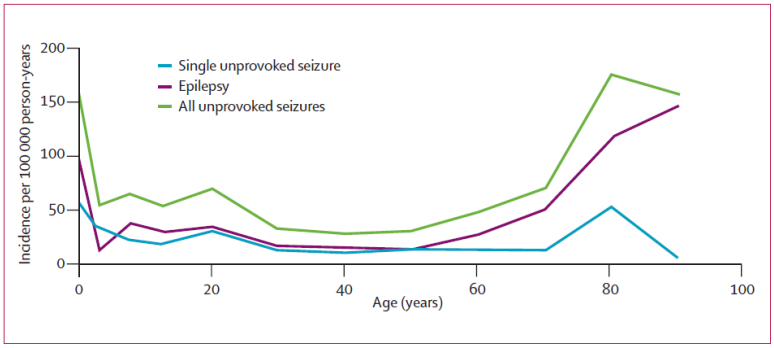
The possibility of diagnosing epilepsy after a single seizure contrasts with the previous definition that required recurrent epileptic seizures (Blume *et al.* 2001).

1.2 Incidence and prevalence

Epilepsy is one of the most common chronic neurological disorders (MacDonald *et al.* 2000) and it has been estimated that 50 million people globally have epilepsy (Brundtland 2001; Leonardi & Ustun 2002; Birbeck 2012). In developed countries the incidence in the general population is about 30 - 50/100.000 per year (Zarrelli *et al.*

1999; MacDonald *et al.* 2000; Kotsopoulos *et al.* 2002; Sander 2003; Olafsson *et al.* 2005) and the prevalence is about 7 per 1000 (Hauser *et al.* 1991; Sander 2003; French & Pedley 2008). In developing countries the reported prevalence is higher; up to 10 per 1000 (Placencia *et al.* 1992; Aziz *et al.* 1994; Sander 2003) . According to a meta-analysis of forty incidence studies, the median annual incidence of epilepsy in developing countries is 68.7 per 100.000, compared with 43.4 per 100.000 in developed countries (Kotsopoulos *et al.* 2002). Although onset of epilepsy may occur at any age, it is more common in children and young people and in the elderly (figure 1) (Olafsson *et al.* 2005).

Figure 1 Age-related incidence of epilepsy and unprovoked seizures



From Olafsson *et al.*(Olafsson *et al.* 2005)

1.3 Classification of epileptic seizures, epilepsies and epileptic syndromes

The 1981 and 1989 proposals from the ILAE for classification of epileptic seizures (ILAE, 1981), epilepsies and epileptic syndromes (ILAE, 1989) have, to date, been widely used in the scientific literature. A revised terminology and classification system for seizures and epilepsies have recently been proposed by the ILAE (Berg *et al.* 2010). However, this new proposal has been debated (Panayiotopoulos 2011; Luders *et al.* 2012; Panayiotopoulos 2012) and is not currently approved by the ILAE and will therefore not be further reviewed here.

Epileptic seizures (ILAE, 1981) are classified according to ictal semiology and electroencephalographic findings as partial, generalized or unclassified. Partial seizures originate in a part of one cerebral hemisphere, whereas generalized seizures have an initial bilateral hemispheric involvement. In simple partial seizures (SPSs) the consciousness is not impaired and the patient has motor, somatosensory or special-sensory, autonomous or psychic symptoms or signs. Complex partial seizures (CPSs) are characterized by impaired consciousness and may be accompanied by similar symptoms as SPSs and sometimes also automatisms. Seizures may start as SPS and evolve to CPS, or they may start directly as CPS. Both seizure types can evolve to a secondary generalized tonic-clonic seizure (GTCS). Generalized seizures include myoclonic, clonic, tonic, tonic-clonic and atonic seizures, and also absences and atypical absences that are characterized by impaired consciousness, sometimes with mild motor signs.

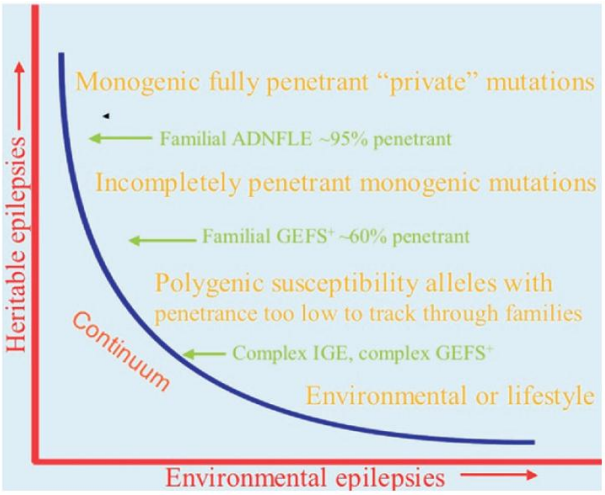
The **epilepsies and epileptic syndromes** (ILAE, 1989) are categorized as localization-related, generalized, undetermined (whether generalized or localization-related) or "special syndromes", which include provoked seizures. The localization-related and generalized epilepsies and epilepsy syndromes are further classified as symptomatic, cryptogenic or idiopathic, depending on aetiology. In symptomatic cases there is an identified acquired cause (e.g. a brain tumour or traumatic brain injury), whereas in the idiopathic epilepsies the aetiology is presumed to be genetic. In cryptogenic epilepsy the cause of epilepsy is unknown, but presumed to be symptomatic.

1.4 Aetiology of epilepsy

A number of diseases or abnormalities affecting the brain have been associated with epilepsy (Hauser *et al.* 1996; Bhalla *et al.* 2011; Shorvon 2011b). The aetiologies may be divided into genetic, developmental (e.g. malformations of cortical development), metabolic, neoplastic, cerebrovascular, infectious, inflammatory, traumatic and degenerative (Bhalla *et al.* 2011). In only a small number of cases a purely genetic cause may be identified (Heron *et al.* 2007; Shorvon 2011a). Likewise, only a very

small proportion of cases are considered to be purely symptomatic or “environmental”, resulting from a known cause and without a genetic component of causality. The majority of epilepsies, however, result from a complex interplay between genes and environment with varying degrees of genetic influence (figure 2) (Heron *et al.* 2007).

Figure 2 The relationship between genetic and environmental aetiologies in epilepsy.



ADNFLE, autosomal dominant nocturnal frontal lobe epilepsy; GEFS+, generalized epilepsy with febrile seizures plus; IGE, idiopathic generalized epilepsy. From Heron *et al.* (Heron *et al.* 2007)

In a population-based study from Rochester, Minnesota, USA a cause of epilepsy was identified in 25 % of prevalent (Hauser *et al.* 1996) and 32 % of incident cases (Annegers *et al.* 1996). Similarly, in a later community-based study from Iceland, the aetiology was identified in 33 % of all incident cases of unprovoked seizures and epilepsy (Olafsson *et al.* 2005). The proportion of cases with an identified cause was lowest in patients younger than 15 years (13 % - 18/134), and highest in those over 64 years of age (59 % - 66/112). In the youngest age group the most common cause was cerebral palsy (5 % - 7/134), whereas among the elderly over 64 years the leading causes were degenerative brain disease (25 % - 28/112) and stroke (23 % - 26/112). Among the 501 cases in the cohort of incident unprovoked seizures and epilepsy, 53.3

% were cryptogenic, 32.1 % symptomatic and 14.6 % idiopathic (71/501 cases) or genetic (2/501).

1.5 Aspects of pathophysiology

Ion channels are macromolecules that are integrated in the membranes of all living cells (Sigworth 2003). By allowing, under certain conditions, ions to pass through their specific channel in the lipid membrane, they are fundamental for the cell's energy production and osmotic stabilization (Hille *et al.* 1999) and also for the normal function of the excitable tissues of the nervous system and muscles (Moody & Bosma 2005; Kullmann 2010). They are *"involved in every thought, every perception, every movement, every heartbeat"* (Hille *et al.* 1999).

Mutations in genes coding for ion channels or their interacting proteins have been detected in many inherited neurological and skeletal muscle disorders and also in cardiac disease (Hedley *et al.* 2009; Ryan & Ptacek 2010). The mutations cause abnormal channel function, and the associated disorders are termed channelopathies. Many of these share the common feature that the patients experience episodes of impaired function that may be provoked by environmental factors like physical or emotional stress (Hanna 2006; Hedley *et al.* 2009; Ryan & Ptacek 2010). Although most of the mutations that have been detected to date are dominantly inherited, the phenotypes of family members with a particular single gene mutation may differ widely. This phenotypic heterogeneity may reflect variable penetrance, the influence of other genes, or environmental factors (Kullmann 2010). In addition, channelopathies may be genotypically heterogeneous, i.e. mutations in different single genes may give rise to the same phenotype (Hirose 2006).

1.5.1 Channelopathies in epilepsy

During the past two decades an increasing number of mutations in single genes coding for sodium-, potassium-, calcium- and chloride channels, and also the nicotinergic

acetylcholine and the gamma amino butyric acid (GABA) receptors, have been detected in different epilepsy syndromes. Among these, mutations in genes coding for different subunits of the sodium channel are the most common (Oliva *et al.* 2012). Mutations in the neuronal sodium channel gene *SCN1A* have been found to cause severe myoclonic epilepsy of infancy (SMEI) (Dravet syndrome) (Claes *et al.* 2001) and generalized epilepsy with febrile seizures plus (GEFS+) (Escayg *et al.* 2000b), mutations in the *SCN1B* gene have been associated with GEFS+ (Wallace *et al.* 1998), and *SCN2A* mutations have been associated with benign familial neonatal-infantile seizures (BFNIS) (Berkovic *et al.* 2004). Familial GEFS+ includes a range of phenotypes, from febrile seizures only to epilepsies with generalized or sometimes focal seizures (Mahoney *et al.* 2009; Scheffer 2011). Mutations in the neuronal potassium channel genes *KCNQ2* (Biervert *et al.* 1998; Singh *et al.* 1998) and *KCNQ3* (Charlier *et al.* 1998) have been shown to cause benign familial neonatal convulsions (BFNC), whereas a mutation in another gene (*KCNA1*) coding for the potassium channel Kv1.1 has been associated with partial epilepsy (Zuberi *et al.* 1999), and a mutation in a calcium-sensitive potassium channel (BK) gene with generalized epilepsy (Du *et al.* 2005). Mutations in the calcium channel genes *CACNB4* (Escayg *et al.* 2000a) and *CACNA1H* (Chen *et al.* 2003) have been detected in idiopathic generalized epilepsy (IGE) and childhood absence epilepsy (CAE), respectively, while mutations in the chloride channel gene *CLCN2* have been associated with IGE (Saint-Martin *et al.* 2009). Furthermore, mutations in genes coding for different subunits of the inhibitory ligand-gated $GABA_A$ receptor have been detected in autosomal dominant juvenile myoclonic epilepsy (JME) (Cossette *et al.* 2002), GEFS+ (Baulac *et al.* 2001), childhood absence epilepsy and febrile seizures (Wallace *et al.* 2001; Maljevic *et al.* 2006; Tanaka *et al.* 2008), and mutations in nicotinergic acetylcholine receptor genes have been shown to cause autosomal dominant nocturnal frontal lobe epilepsy (Steinlein *et al.* 1995; De Fusco *et al.* 2000).

IGE encompasses eight different epilepsy syndromes: GEFS+, benign myoclonic epilepsy of infancy, CAE, juvenile absence epilepsy (JAE), JME, epilepsy with myoclonic-astatic seizures, epilepsy with myoclonic absences and epilepsy with tonic-

clonic seizures only (Nordli 2005). The syndromes show considerable genetic heterogeneity and, although many different single gene mutations causing autosomal dominant epilepsy have been detected, cases of IGE are commonly considered to have a polygenic origin that might also be influenced by environmental factors (Heron *et al.* 2007).

Interestingly, mutations in ion channel genes may be associated with both epilepsy and other neurological diseases. For instance, mutations in the potassium channel gene *KCNA1* have been detected in both episodic ataxia and epilepsy (Zuberi *et al.* 1999), mutations in the potassium channel gene *KCNMA1* in paroxysmal movement disorder and epilepsy (Du *et al.* 2005), and mutations in the sodium channel gene *SCN1A* in familial hemiplegic migraine and epilepsy (Dichgans *et al.* 2005).

1.5.2 Cardiac channelopathies

The long QT syndrome (LQTS) is characterized by a prolonged QT-interval in the electrocardiogram (ECG) and a propensity to develop polymorphous ventricular tachycardia (torsade de pointes arrhythmia) and ventricular fibrillation (Da Costa *et al.* 2000; Hedley *et al.* 2009). Clinical symptoms include hypotensive syncopes and sudden death. While acquired LQTS may be related to electrolyte disturbances, structural heart disease or drugs (Chiladakis *et al.* 2012), congenital LQTS (cLQTS) is caused by mutations which, so far, have been detected in thirteen different genes coding for potassium-, sodium- or calcium channels or their interacting proteins (Hedley *et al.* 2009;Refsgaard *et al.* 2012). Interestingly, however, one study concluded that significant drug-induced prolongation of the terminal part of the QT interval (from the peak to the end of the T-wave) occurred only in first degree relatives of patients with drug-induced LQTS, not in relatives of individuals tolerating QT-prolonging drugs. This indicates that drug-induced LQTS may also be influenced by genetic predisposition (Kannankeril *et al.* 2005).

The prevalence of cLQTS is uncertain, but has been estimated to be around 1:2000 in the general population (Schwartz *et al.* 2009). The genetic penetrance, however, may be low; in one study only 25 % of mutation carriers were symptomatic (Priori *et al.* 1999). In the vast majority of affected cases the LQTS is considered to be the only characteristic, and a Romano-Ward syndrome, which has an autosomal dominant mode of inheritance, is present (Hedley *et al.* 2009). Much more rarely, the LQTS is associated with other organ manifestations. For example, patients with Jervell and Lange-Nielsen syndrome also have congenital deafness (Jervell & Lange-Nielsen 1957); patients with Andersen syndrome may have other cardiac arrhythmias, malformations and periodic paralysis (Plaster *et al.* 2001; Tristani-Firouzi *et al.* 2002) and in some individuals also some cognitive impairment (Yoon *et al.* 2006), and in Timothy syndrome multiple organ manifestations, including cognitive deficit and autism, can occur (Splawski *et al.* 2004).

Mutations in cardiac potassium- , sodium- or calcium channel genes may also cause a diversity of other rare inherited cardiac arrhythmias; (see Morita *et al.* 2008). These include the short QT syndrome, which is characterized by short QT intervals in the ECG and increased risk of atrial fibrillation and sudden death (Hedley *et al.* 2009), and the Brugada syndrome, which is also associated with an increased risk of sudden cardiac death and ECG showing ST-segment elevation in the right precordial leads and right bundle branch block (Vatta *et al.* 2002).

1.5.3 Cardiocerebral channelopathies

It has long been recognized that symptoms associated with cardiac arrhythmias in patients with the LQTS have been erroneously classified as epileptic seizures (Ballardie *et al.* 1983; Moss *et al.* 1991; O'Callaghan & Trump 1993), and a correct diagnosis of LQTS is frequently delayed because of misinterpretation of symptoms (MacCormick *et al.* 2009). Interestingly, however, many of the cardiac ion channel genes that have been associated with the LQTS are also expressed in the brain; (see Nashef *et al.* 2007), and there is emerging evidence that cardiac channelopathies can

cause not only cardiac arrhythmias and hypotensive syncopes, but possibly also genuine epilepsy. More than a decade ago, it was shown that the cardiac sodium channel gene, *SCN5A*, in which mutations cause LQTS type 3 (Refsgaard *et al.* 2012), is expressed in the limbic system of the rat brain (Hartmann *et al.* 1999), and a role in idiopathic seizure disorders was suggested. One year later the same gene was found to be expressed in the human brain (Donahue *et al.* 2000). More direct evidence from animal research was provided when it was shown that the potassium channel gene, *KCNQ1*, in which mutations are associated with the most common form of LQTS, LQTS type 1, is expressed in the forebrain and brainstem (Goldman *et al.* 2009). The authors also showed that animals with mutations in this gene had epileptic seizures with concomitant epileptiform activity in the electroencephalogram (EEG), and they also had malignant cardiac arrhythmias.

Similarly, mutations in the gene encoding for the human ryanodine receptor (hRyR2) have been shown to cause catecholaminergic ventricular tachycardia, which is a potentially fatal cardiac arrhythmia (Priori *et al.* 2001). The ryanodine receptor is a calcium release channel (Imagawa *et al.* 1987) that is involved in the coupling between excitation and contraction (Kondo 1986; McPherson & Campbell 1993), and animal research has revealed that the cardiac isoform of this gene is also expressed widely in the brain (Otsu *et al.* 1990; McPherson & Campbell 1993). Mice with a mutation in the *RyR2* gene have been shown to display GTCSs in the presence of a normal heart rhythm and also exercise-induced ventricular tachycardias and sudden cardiac death (Lehnart *et al.* 2008).

The clinical evidence indicating that cardiac channelopathies may cause epilepsy is limited. However, a mutation in the *SCN5A* gene and a rare variant in the cardiac potassium channel gene, *KCNE2*, in which mutations cause LQTS type 6 (Refsgaard *et al.* 2012), were detected in a patient with neonatal LQTS and epileptic seizures that occurred in the absence of a symptomatic cardiac arrhythmia. These results suggested the possibility that cardiocerebral channelopathies may explain both epilepsy and cardiac arrhythmias (Heron *et al.* 2010). This suggestion was in concordance with

another case report of a patient with a mutation in the potassium ion channel gene *KCNH2* (*hERG*) (LQTS type 2) and a significantly prolonged QT interval in the ECG, syncopal events and torsade de pointes arrhythmia and also a history of tonic-clonic seizures and electroencephalographic abnormalities with paroxysmal slow waves provoked by photic stimulation (Omichi *et al.* 2010). Furthermore, the same mutations in the cardiac potassium channel genes *KCNQ1* and *KCNQ3* have been linked to both LQTS type 1 (Wang *et al.* 1996) and idiopathic epilepsy (Charlier *et al.* 1998).

Studies of paroxysmal events in patients with LQTS have also revealed interesting similarities to epileptic seizures. In nine of 20 individuals with syncope and genetically proven LQTS, motor symptoms, including generalized tonic-clonic movements, were witnessed, and eight had urinary incontinence (MacCormick *et al.* 2011). The authors concluded that symptoms in relation to cardiac syncope might be more difficult to separate from non-cardiac causes than previously anticipated. However, they did not discuss the possibility that some of the seizure-like events may actually have been epileptic, e.g. in patients with generalized tonic-clonic movements and urinary incontinence. Another study on patients with LQTS concluded that a seizure phenotype was significantly more common in individuals with LQTS type 2, which is due to mutations in the cardiac *KCNH2* gene, than in patients with other QT mutations (Johnson *et al.* 2009). This gene is also expressed in the hippocampus, and the authors discussed the possibility that these patients may have had epileptic seizures, although this was not proven as there was no electroencephalographic evidence of epilepsy.

Similarly, in recent years, it has been discussed whether gene mutations that primarily have been associated with epilepsy, may also predispose epilepsy patients to cardiac arrhythmias. Two cases of sudden unexpected death in epilepsy (SUDEP) in a family with GEFS+ and mutations in the *SCN1A* gene were reported (Hindocha *et al.* 2008), and it was argued that the gene product of *SCN1A*, $Na_V1.1$, is also present in the hearts of different mammals and may possibly have predisposed the patients to a fatal cardiac arrhythmia. Two years later a new *SCN1A* mutation was detected in another SUDEP victim with Dravet syndrome (Le Gal *et al.* 2010), and, again, it was discussed

whether an abnormal expression of this gene in the heart may possibly have been involved in the causation of SUDEP.

1.6 Mortality in epilepsy

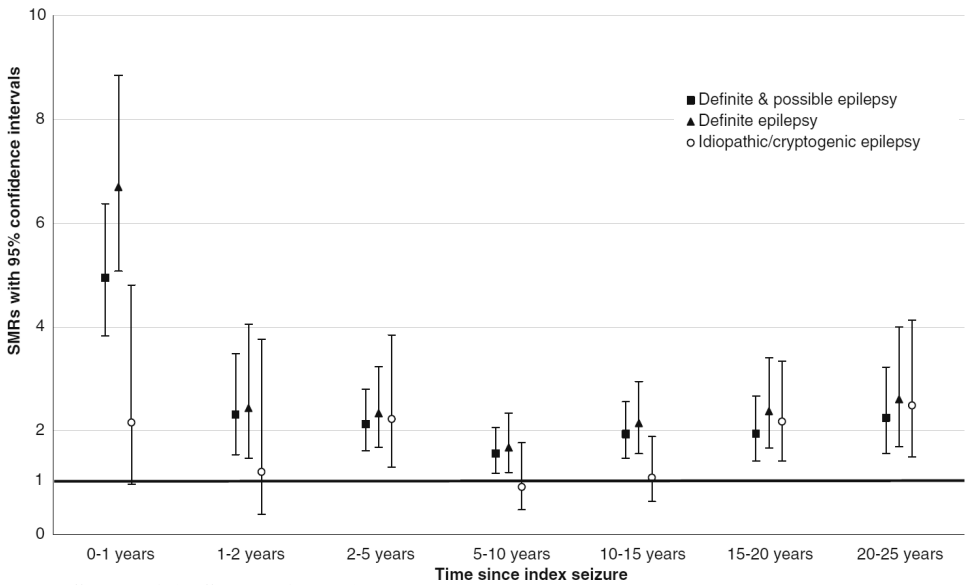
At least since the middle of the Nineteenth Century, scientists have been concerned with the mortality caused by epileptic seizures. G. M. Bacon divided the epilepsy-related causes of death into *"1. Those arising from the long-continued effects of the disease on the body; 2. Deaths after a rapid succession of fits; 3. Sudden deaths in a fit; 4. Accidents due to fits*" (Bacon 1868). Later, over the years, a number of studies have confirmed that a proportion of people with epilepsy die prematurely because of seizures, but also the underlying diseases causing the epilepsy contribute to an increased mortality rate in the epilepsy population.

1.6.1 Standardized mortality ratio

The first published population-based study on mortality in the epilepsy population found that the overall mortality rate in individuals with epilepsy under the age of 50 years was 3.5 times higher than expected, and in those over 50 it was 1.9 times higher than expected (Zielinski 1974). Some of the increased mortality documented in this study could be explained by brain lesions causing the epilepsy, including tumours and cerebrovascular disease. Since then, several population-based studies have confirmed that the mortality rate in epilepsy is significantly increased compared with the general population, commonly by estimating the standardized mortality ratio (SMR) which is the ratio between the observed number of deaths in a cohort over a defined period of time and the expected number of deaths, calculated according to the age and gender-specific mortality rates in the reference population (Forsgren *et al.* 2005; Neligan *et al.* 2011a). In population-based studies with many years of follow-up of incident cases of epilepsy, the SMR has been roughly between two and three (Cockerell *et al.* 1994; Lhatoo *et al.* 2001; Neligan *et al.* 2011a).

However, mortality rate varies with the period since seizure onset and is highest during the first year (figure 3) (Cockerell *et al.* 1994; Neligan *et al.* 2011a), mainly due to a higher proportion of patients with underlying life-threatening brain disorders in newly diagnosed epilepsy (Forsgren *et al.* 2005). Nevertheless, even many years after seizure onset, the mortality rate is significantly higher than in the general population (Neligan *et al.* 2011a). The reasons for this are not completely understood, but may, in part, be explained by underlying brain disorders causing the epilepsy and also seizure-related deaths.

Figure 3 Standardized mortality ratios at different times of follow-up



From Neligan *et al.* (Neligan *et al.* 2011a)

The presence of underlying brain disorders in symptomatic epilepsy may also explain the higher mortality in this sub-group of epilepsy patients compared with those with idiopathic epilepsy (figure 3) (Lhatoo *et al.* 2001; Benn *et al.* 2009). Nevertheless, the mortality rate is also significantly increased in idiopathic epilepsy, with SMRs ranging from 1.6 to 1.8 (Hauser *et al.* 1980; Cockerell *et al.* 1994; Neligan *et al.* 2011a), although some studies report only a slight and statistically insignificant increment in

mortality, with SMRs ranging from 1.1 (Lindsten *et al.* 2000) to 1.3 (Olafsson *et al.* 1998; Lhatoo *et al.* 2001). A possible explanation for the lack of statistically significant findings in the three last studies may be that patients with a single unprovoked seizure were included, and thus a proportion of these may not have developed epilepsy.

In some selected sub-groups of epilepsy patients, the overall SMR has been found to be higher than in studies of population-based incident epilepsy. For example, a Swedish study on people with mental retardation (MR) (Forsgren *et al.* 1996) found significantly increased mortality rates with SMRs of 1.6, 5.0 and 5.8 in individuals with MR only, MR and epilepsy, and MR, cerebral palsy and epilepsy, respectively. Interestingly, mortality rate was highest in patients with only generalized onset seizures. In the patients with epilepsy and MR the mortality rate increased with seizure frequency during the year prior to the prevalence date, and only 6.7 % of the deaths were directly seizure-related. In a study of people with chronic epilepsy in a tertiary outpatient referral centre (Nashef *et al.* 1995b), the SMR was significantly increased at 5.1, and as much as 58 % (14 of the 24 deceased) of the deaths were seizure-related. An even higher SMR of 15.9 (95 % confidence interval (CI) 10.6 – 23.0) was found in a residential school cohort of pupils with severe epilepsy and learning difficulty (Nashef *et al.* 1995a). Again, in this highly selected cohort, the majority of deaths (71.4 %; 20 of 28) were seizure-related. In another cohort of 245 patients with onset of epilepsy in childhood that was followed for 40 years (Sillanpaa & Shinnar 2010), the SMR of incident cases was significantly increased at 5.5, and 6.6 in the overall cohort. In this study too, the authors emphasized the influence of seizures on the mortality rate in the epilepsy population: mortality rate was elevated only in patients that were not seizure-free or had another neurological deficit, and the occurrence of seizures during the past five years was the most important risk factor for all causes of death. Similarly, the previously cited study from UK (Lhatoo *et al.* 2001), found that the mortality rate was increased in patients with generalized tonic-clonic seizures, and that patients with

congenital neurological impairment had a particularly high long-term SMR of 25 (95 % CI 5.1 – 73.1).

1.6.2 Proportionate mortality

The UK study (Lhatoo *et al.* 2001) also reported the number of deaths associated with the leading of causes of death, and among the 195 deaths in individuals with definite epilepsy during the study period, 26 % died from neoplasms, 8 % from ischemic heart disease, and 12 % from cerebrovascular disease. Similarly, data from previous population-based studies (Zielinski 1974; Hauser *et al.* 1980; Annegers *et al.* 1984; Cockerell *et al.* 1994) have enabled calculation of proportionate mortality, which is the percentage of the total number of deceased within each category of causes of death (COD) (Forsgren *et al.* 2005). In these studies 12 – 14 % of the deaths were due to cerebrovascular disease, 8 – 19 % due to heart disease, 9 – 15 % due to brain tumours, and 20 – 35 % due to neoplasms (including brain tumours). Furthermore, 1.3 – 10 % of the deaths were seizure-related, and 0 – 4 % were classified as SUDEP. The diverging results between these studies may possibly be explained by differences in methods and duration (number of years) of follow-up.

1.6.3 Cause-specific mortality

The proportionate mortality ratio *per se* provides no information about the relative risk among people with epilepsy of dying from a specific cause, compared with the general population. However, several studies have estimated cause-specific mortality ratios where SMRs have been calculated for each specific category of COD. Significantly increased SMRs in the epilepsy population have been reported for neoplasms (excluding primary brain tumours), cerebrovascular disease and pneumonia (Nilsson *et al.* 1997; Shackleton *et al.* 1999; Lhatoo *et al.* 2001; Neligan *et al.* 2011a), and, in some studies, also for heart disease (Annegers *et al.* 1984; Nilsson *et al.* 1997; Neligan *et al.* 2011a) and accidents (Hauser *et al.* 1980; Shackleton *et al.* 1999). From at least two cohort studies significantly increased SMR have also been reported for suicide

(Nilsson *et al.* 1997; Rafnsson *et al.* 2001). However, in one of these studies the increased risk was found only in men (Rafnsson *et al.* 2001), and in another cohort study the SMR for suicide was not significantly increased (Shackleton *et al.* 1999). Furthermore, in population-based studies suicide has been found to be very rare (Cockerell *et al.* 1994; Lindsten *et al.* 2000), and at present, to my knowledge, there is no convincing evidence from population-based studies of an increased occurrence of suicide associated with a diagnosis of epilepsy.

As pointed out by Neligan et al. (Neligan *et al.* 2011a), at 20 to 25 years of follow-up the overall mortality rate in the epilepsy population was still significantly increased, and an important explanation for this appeared to be a higher occurrence of malignancy, ischemic heart disease, and pneumonia. However, as also underlined by the authors, a possible influence on mortality from comorbid conditions was not assessed. This may be of importance, since a number of potentially lethal conditions, including cardiovascular disease, chronic lung diseases, diabetes, pneumonia and neurodegenerative diseases, are more prevalent among people with epilepsy than in the general population (Gaitatzis *et al.* 2004).

1.7 Sudden unexpected death in epilepsy (SUDEP)

The directly seizure-related COD include sudden unexpected death in epilepsy (SUDEP), status epilepticus, drownings, and accidents. Of these, SUDEP is the most common (Nashef *et al.* 1995b; Sillanpaa & Shinnar 2010). During recent decades SUDEP has been a topic of considerable scientific interest, and, particularly over the last few years, an increasing number of review articles have focused on this tragic outcome of epilepsy that mainly affects young individuals (Tellez-Zenteno *et al.* 2005; Tomson *et al.* 2005; Tomson *et al.* 2008; Surges *et al.* 2009b; Nei & Hays 2010; Devinsky 2011; Neligan *et al.* 2011b; Shorvon & Tomson 2011; Hesdorffer & Tomson 2012; Surges & Sander 2012).

1.7.1 Definitions of SUDEP

A review of 36 studies of incidence and risk factors revealed that SUDEP was clearly defined in 65 % of the studies, unclear in 29 %, and absent in 6 % (Tellez-Zenteno *et al.* 2005). However, it is claimed (Nashef *et al.* 2012) that in recent years the definitions proposed by Nashef (Nashef 1997) and Annegers (Annegers 1997) have been used in the majority of studies. Nashef (Nashef 1997) defined SUDEP as:

‘‘*Sudden, unexpected, witnessed or unwitnessed, nontraumatic and nondrowning death in patients with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus, in which post mortem examination does not reveal a toxicologic or anatomic cause for death.*’’

whereas, according to Annegers, the criteria for SUDEP are:

“1. The victim suffered from epilepsy, defined as recurrent unprovoked seizures.

2. The victim died unexpectedly while in reasonable state of health.

3. The death occurred “suddenly” (in minutes), when known.

4. The death occurred during normal activities (e.g. in or around bed, at home, at work) and benign circumstances.

5. An obvious medical cause of death was not found.

6. The death was not the direct cause of the seizure or status epilepticus.“

Furthermore, “definite SUDEP” requires that autopsy was performed and all criteria were fulfilled, whereas in “probable SUDEP” post mortem is missing, but otherwise all criteria are met. In “possible SUDEP” an autopsy is lacking and the circumstances of the death are unclear, but SUDEP cannot be excluded.

Recently a new definition of SUDEP was proposed (Nashef *et al.* 2012). This is a synthesis and clarification of the two previously described definitions from 1997.

However, since this new definition has not yet been used extensively in the literature, it will not be further reviewed here.

1.7.2 Incidence

In the epilepsy population, the rates of sudden death have been found to be up to 20 – 40 times that of the general population. In a much-cited U.S. study, the estimated SMR of sudden death in the age group between 20 and 40 years was 23.7 (95 % confidence interval 7.7 – 55.0) (Ficker *et al.* 1998), whereas in another study, among patients between 14 and 21 years of age with epilepsy there were 188.6 cases of sudden death per 100.000 person-years at risk, compared with 4.6 per 100.000 in the general population (Neuspiel & Kuller 1985), and it has been stated that this very high relative risk of 40.2 cannot be disputed (Annegers 1997). SUDEP is very rare in children; a study from Ontario, Canada, found an incidence of 2 per 10.000 person-years among children less than 18 years of age (Donner *et al.* 2001).

However, the incidence of SUDEP varies widely, depending on the population being studied, duration of follow-up, and also on different methods used for case detection. It is lowest in population-based studies, particularly among newly diagnosed and seizure-free patients. In a prospective incidence cohort of patients with epilepsy, the incidence was 0.35 per 1000 person-years (Ficker *et al.* 1998), whereas another prospective population-based study with a shorter follow-up found an incidence of 0.09 per 1000 patient-years (Lhatoo *et al.* 2001). In two other community-based studies of newly diagnosed epilepsy patients with a short follow-up (median 6.9 years) (Cockerell *et al.* 1994) or a low number of patient-years at risk (850) (Lindsten *et al.* 2000), no cases of SUDEP were detected. Similarly, in two studies of epilepsy surgery patients no SUDEP occurred among seizure-free individuals (Sperling *et al.* 1999; Nilsson *et al.* 2003). In a prospective population-based study of a prevalence cohort of epilepsy patients, the incidence of SUDEP was 0.9 – 2.7 per 1000 patient-years (Leestma *et al.* 1989), whereas other community based studies have found an incidence from 0.3 to 1.5 per 1000 patient-years (Terrence *et al.* 1975; Langan *et al.* 1998; Opeskin *et al.* 2000).

In different selected cohorts of epilepsy patients, the reported incidences have been higher. A study of SUDEP in the clinical development programme of the antiepileptic drug (AED) lamotrigine (LTG), which included patients with refractory epilepsy, revealed an incidence of SUDEP of 3.5 cases per 1000 patient-years (Leestma *et al.* 1997), which is very similar to the incidence of 3.4 cases per 1000 patient-years reported from the cohort study of patients with severe epilepsy and learning difficulties (Nashef *et al.* 1995a), and also similar to the SUDEP incidence of 3.6 cases per 1000 patient-years reported in a cohort of epilepsy patients with mental retardation (McKee & Bodfish 2000). Two studies from epilepsy clinics reported incidences of SUDEP of 1.21 (Walczak *et al.* 2001) and 5 (Nashef *et al.* 1995b), respectively, whereas incidences of 6.3 (Nilsson *et al.* 2003) and 9.3 (Dasheiff 1991) per 1000 patient-years have been found among patients in epilepsy surgery programmes.

Community-based studies have found that the proportion of deaths in the epilepsy population due to SUDEP ranges from 0 to 4 % (Zielinski 1974; Cockerell *et al.* 1994; Ficker *et al.* 1998; Lindsten *et al.* 2000; Lhatoo *et al.* 2001). In one of these studies, in which 1.7 % of the deaths were SUDEP, the corresponding percentage in the age group between 15 and 44 years was 8.6 (7 of 81) (Ficker *et al.* 1998). Of a cohort with onset of epilepsy in childhood, after 40 years of follow-up 7 % had died from SUDEP (Sillanpaa & Shinnar 2010). However, in the other more selected cohort studies, the proportions of deaths caused by SUDEP were considerably higher, ranging from 11.7 % to 55 % (Nashef *et al.* 1995a; Nashef *et al.* 1995b; Sperling *et al.* 1999; Walczak *et al.* 2001; Nilsson *et al.* 2003; Hitiris *et al.* 2007). The highest proportion of SUDEP was found among patients with recurrent seizures after epilepsy surgery (Sperling *et al.* 1999).

1.7.3 Pathophysiological mechanisms

Although no clear mechanism, common to all cases of SUDEP, has been identified there is considerable evidence that cardiac or respiratory mechanisms, or a combination of these, are involved. Most cases of SUDEP are unwitnessed (Nilsson *et al.* 1999; Langan *et al.* 2005; Lamberts *et al.* 2012). Nevertheless, evidence of a seizure in relation to the deaths has been reported in 22 % - 88 % of cases (Nashef *et al.* 1998; Kloster & Engelskjon 1999; Opeskin *et al.* 2000), and among documented observed cases, the majority occurred in relation to a GTCS (Terrence *et al.* 1975; Langan *et al.* 2000, 2005). Commonly, these deaths occur in bed or at home (Leestma *et al.* 1989; Nilsson *et al.* 1999; Langan *et al.* 2000; Hitiris *et al.* 2007), and a recent study of 154 SUDEP cases found that 58 % died during sleep (Lamberts *et al.* 2012).

Respiratory dysfunction

Airway obstruction may play a role in a proportion of SUDEP cases. In one retrospective case-control study, 17 of 24 cases (71 %) were found in the prone position (Kloster & Engelskjon 1999), whereas in another study evidence of possibly compromised airways was found in 42 % (11 of 26) of SUDEP cases (Nashef *et al.* 1998). Central apnoea was documented in a case report of a near-SUDEP that occurred during video-electroencephalography (So *et al.* 2000). After a convulsive seizure the patient had prolonged apnoea, without evidence of airway obstruction or pulmonary oedema. During the first 10 seconds of the apnoeic period the ECG showed an unaffected heart rhythm, but thereafter it gradually slowed, before cardiac arrest after 57 seconds. It is well-documented that central apnoea occurs in a significant proportion of epileptic seizures. In a study of individuals with refractory localization related epilepsy, 50 of 100 seizures were accompanied by central apnoea or hypopnoea, and 9 % by obstructive or mixed apnoea (Bateman *et al.* 2008). Pulse oxymetry showed significant reductions in oxygen saturation, in some individuals to below 70 %, and desaturation increased significantly with duration of the seizures.

Patients with oxygen saturation below 85 % also had retention of CO_2. Similarly, another study of patients with complex partial and generalized seizures found that hypoxemia occurred in 25 % of seizures and correlated with seizure duration (Moseley *et al.* 2011). Furthermore, cases of neurogenic pulmonary oedema have been documented in relation to GTCSs and it has been suggested to be a contributory cause of SUDEP (Fredberg *et al.* 1988; Swallow *et al.* 2002; Pezzella *et al.* 2009). Pulmonary congestion and oedema are also common findings in autopsies of SUDEP cases (Terrence *et al.* 1981; Leestma *et al.* 1989).

One documented SUDEP case occurred during ambulatory EEG showing epileptiform activity that was followed abruptly by flattening of the EEG (McLean & Wimalaratna 2007). The authors reviewed two similar, previously published cases (Bird *et al.* 1997; Lee 1998) and suggested that electric cerebral shutdown was the "*primary mechanism*" of SUDEP, although neither respiration nor heart rhythm were monitored in this case report (McLean & Wimalaratna 2007). Nevertheless, the authors argued that the sudden flattening of the EEG was a "*unique phenomenon*" since in cardiac arrest or severe hypotension leading to global cerebral ischemia, flattening of the EEG is not sudden, but gradual. Shortly after this report, the significance of this seizure-related sudden flattening of the EEG was explored in a case-control study in which results from video-electroencephalographic monitoring of individuals that had later died from SUDEP were compared with results from living controls (Lhatoo *et al.* 2010). This study showed that postictal generalized electroencephalographic suppression (PGES) lasting for more than 50 seconds was significantly associated with SUDEP, and it was proposed that this cessation of electrical brain activity could be involved in the causation of SUDEP, possibly by inducing central apnoe. In contradiction to this, another study concluded that the risk of SUDEP was not related to the presence or duration of PGES, but PGES was associated with generalized seizures (Surges *et al.* 2011). Recently it was shown that PGES or postictal bilateral attenuation of the EEG was not associated with central apnoea, but with prolonged and severe oxygen desaturation and retention of CO_2. The authors suggested that these

features were due to intrinsic pulmonary dysfunction (Seyal *et al.* 2012). Interestingly, evidence of underlying seizure-related autonomous dysregulation has recently been provided. In a study of 34 seizures in 11 patients, the degree of sympathetic activation and parasympathetic suppression correlated significantly with the duration of PGES (Poh *et al.* 2012).
Importantly, seizure-induced respiratory and cardiac dysfunction may be related. In a clinical study, the likelihood of seizure-related abnormal prolongation or shortening of the QT interval in the ECG was shown to be significantly higher in the presence of hypoxemia than in its absence, with odds ratio 4.3 (95% CI 2.56 - 7.39) for prolongation of the QT interval and odds ratio 2.13 (95% CI 1.84 - 2.46) for QT interval shortening (Seyal *et al.* 2011).

Animal research has also provided some evidence that respiratory mechanisms may be involved in SUDEP. In a sheep model in which status epilepticus was induced in the animals, severe central hypoventilation occurred in those that died, but not in surviving animals, and evidence of a fatal cardiac arrhythmia was not found (Johnston *et al.* 1995). In a later study using the same animal model, all the sheep displayed central hypoventilation and apnoea, resulting in one death and considered to be contributory in another. One animal died from acute heart failure, but there were no cases of malignant cardiac arrhythmia (Johnston *et al.* 1997). However, death from status epilepticus is, per definition, not SUDEP (Annegers 1997; Nashef 1997), and although interesting, the implications of these findings for the understanding of the mechanisms underlying SUDEP are uncertain.

Cardiac arrhythmia
It has long been suspected that cardiac arrhythmias may underlie cases of SUDEP. Whereas inter-ictally the occurrence of arrhythmias has not been found to be significantly higher among people with epilepsy than in the general population (Blumhardt *et al.* 1986; Massetani *et al.* 1997), several reports have documented seizure-related arrhythmias, some of which have been potentially fatal.

Ictal sinus tachycardia is common and has been reported to occur in up to 99 % of seizures (Nei *et al.* 2000; Opherk *et al.* 2002; Nei *et al.* 2012), whereas sinus bradycardia is rare. A study of 20 patients with refractory localization-related epilepsy reported that sinus bradycardia (less than 40 beats per minute) occurred in eight of 377 events (2.1 %) in seven patients (Rugg-Gunn *et al.* 2004). This finding is very similar to that of a recent study of patients with treatment-resistant epilepsy in which four of 217 (2 %) seizures in four of 75 patients (5 %) were accompanied by sinus bradycardia (Moseley *et al.* 2011). A variety of other abnormalities of heart rhythm and repolarization have been detected in relation to seizures. In a study of 43 patients with refractory epilepsy, 17 (39.5 %) had abnormalities of rhythm and/or repolarization in the ECG in relation to seizures (Nei *et al.* 2000). These included asystole, ventricular premature depolarizations, marked sinus arrhythmia, bundle-branch block, ventricular premature depolarizations and ST-segment elevations. Abnormalities were significantly more frequent in generalized seizures than in partial seizures, but there were no significant differences between pre-ictal and peri-ictal PR or corrected QT interval (QTc). Another study included 41 patients, in which 31 of 102 seizures were generalized (Opherk *et al.* 2002); ictal electrocardiographic abnormalities were found in 15 (37 %) of the patients, and in four patients (10 %) these were potentially serious, with prominent ST-segment depression or T-wave inversion. The electrocardiographic abnormalities were significantly more frequent in generalized seizures than non-generalized seizures.

A near SUDEP caused by ictal cardiac arrhythmia has been reported (Espinosa *et al.* 2009). During video-electroencephalography the patient experienced a partial onset seizure that evolved into a GTCS, during which the patient had sinus tachycardia with 180 beats per minute. At the end of the seizure the patient developed ventricular fibrillation that would have been lethal without cardiopulmonary resuscitation. A cardiac work-up, including heart catheterization and electrophysiologic study, did not reveal any abnormalities that could have predisposed the patient to a life-threatening arrhythmia.

In recent years, several studies have focused on the possible role of alterations in the QT interval in the causation of SUDEP. A study comparing results from video-electroencephalography between 19 patients that later died from SUDEP with those from 19 matched controls concluded that neither peri-ictal prolongation of QTc nor other electrocardiographic abnormalities were significantly associated with SUDEP, as opposed to the frequency of GTCSs (Surges *et al.* 2010a). In another study, among 25 epilepsy surgery patients 17 had abnormally shortened peri-ictal QTc and three had abnormally prolonged peri-ictal QTc (Surges *et al.* 2010b). QTc shortening, but not prolongation, was significantly associated with secondary generalized tonic-clonic seizures.

However, other studies have found further evidence of seizure-related alterations in the QT interval, supporting a possible causative role in some cases of SUDEP. Of 156 seizures that occurred during video-electroencephalography in 39 patients, 21 seizures in nine patients were associated with concomitant significant QTc prolongation (Brotherstone *et al.* 2010). Similarly, the already cited study that included 76 patients with a total of 218 seizures found clinically significantly prolonged QTc in 4.8 – 16.2 % (depending on the method used when correcting the QT interval for heart rate) and QTc shortening in 3.8 – 4.8 % of seizures (Moseley *et al.* 2011).

Abnormalities in the ST-segment and T-waves of the ECG have also gained interest as possible markers for increased risk of SUDEP. Among 19 patients with an implanted loop recorder, detecting a total of 1477 seizures, ictal repolarization abnormalities and cardiac arrhythmias were detected in eight individuals, including T-wave inversion or deepening, or ST-segment depression in four (Nei *et al.* 2012). Again, it was concluded that these ictal cardiac abnormalities particularly occurred during generalized seizures.

Increments of visible alternations from beat-to-beat of the amplitude or morphology of the ST-segment or T-wave (T-wave alternans) are independent predictors of cardiovascular mortality and sudden cardiac death (Rosenbaum *et al.* 1994; Nieminen & Verrier 2010; Strzelczyk *et al.* 2011). In a recent study of 16 patients with

treatment-resistant localization related epilepsy, secondary generalized tonic-clonic seizures preceded an increase in T-wave alternans for 15 minutes, and the authors discussed whether this parameter could possibly have a future role for estimating SUDEP risk in patients (Strzelczyk *et al.* 2011).

In cardiac disease reduced heart rate variability (HRV) has been associated with increased risk of arrhythmias (see Ansakorpi *et al.* 2002). Reduced HRV has also been found in epilepsy patients, reflecting an altered autonomous influence on the heart rhythm (Tomson & Kenneback 1997). Among patients with temporal lobe epilepsy, reduction in HRV was most severe during the night (Ronkainen *et al.* 2005), and this may be of relevance since the majority of SUDEP cases occur during sleep (Lamberts *et al.* 2012). Interestingly, a case has recently been documented in which serial measurements showed increasingly abnormal HRV before SUDEP (Rauscher *et al.* 2011). However, a small study including seven patients that later died from SUDEP and seven controls did not find any significant association between inter-ictal HRV and SUDEP (Surges *et al.* 2009a), and, at present, the role of HRV as a possible parameter in the risk stratification for SUDEP appears uncertain.

Another parameter of potential interest in the evaluation of SUDEP risk is the ventricular late potentials (VLPs) that appear in the terminal part of the QRS complex in the signal-average electrocardiogram (SAECG) of patients with delayed activation of the myocardium. The presence of VLPs has been associated with an increased risk of ventricular tachycardia and fibrillation in patients with arrhythmogenic right ventricular cardiomyopathy (ARVC) (Santangeli *et al.* 2008) and in patients with low ejection fraction after acute myocardial infarction (Breithardt *et al.* 1991). ARVC is among the most common causes of sudden cardiac death in previously healthy young people (Sen-Chowdhry *et al.* 2010). Sudden death may be the first symptom (Sarvari *et al.* 2011), or the deceased may have had recurrent syncopes (Sen-Chowdhry *et al.* 2010). Recently VLPs were detected in 22 of 45 (48 %) patients with chronic epilepsy, and, interestingly, the presence of VLPs correlated with well-known risk factors for

SUDEP: polytherapy, long duration of epilepsy, and frequent seizures (Rejdak *et al.* 2011). However, this study was not sufficiently powered to enable evaluation of a possible influence of individual AEDs.

1.7.4 Risk factors

A diversity of risk factors for SUDEP have been reported from at least 48 studies (Hughes 2009), including studies of different selected epilepsy populations, uncontrolled case series, and studies using non-SUDEP deaths as controls. Different methods have been used in detecting the cases. However, results from studies using living controls with epilepsy are considered to be more reliable in reflecting the risk factors in the general epilepsy population (Tomson *et al.* 2008). There is wide agreement that the most important risk factor is high seizure frequency, and, in particular, frequent GTCSs (Tomson *et al.* 2008; Devinsky 2011; Duncan & Brodie 2011; Shorvon & Tomson 2011; Surges & Sander 2012). Studies using living controls with epilepsy have focused on different risk factors, including different aspects of the influence of seizures. In two studies a high seizure frequency was identified as a risk factor (Nilsson *et al.* 1999; Walczak *et al.* 2001), whereas in another it was not (Timmings 1993). However, in the latter study SUDEP was significantly associated with idiopathic GTCSs. One study found that the occurrence of a seizure during the last year identified patients at a higher risk (Hitiris *et al.* 2007), whereas a high frequency of GTCSs was reported as a risk factor in another study (Surges *et al.* 2010a) and a risk factor only in females in another (Walczak *et al.* 2001). In one study, a history of GTCSs during the last three months identified individuals at higher risk (Langan *et al.* 2005). Young age of onset was associated with a higher occurrence in two studies (Nilsson *et al.* 1999; Hitiris *et al.* 2007), whereas a long duration of epilepsy was a risk factor in two studies (Walczak *et al.* 2001; Hitiris *et al.* 2007), but not in another (Timmings 1993). Two studies found a higher occurrence of SUDEP among individuals with mental retardation (Jick *et al*., 1992;Walczak *et al.* 2001), whereas another study reported that supervision during the night was protective (Langan *et al.* 2005).

With respect to gender, two reports found that SUDEP was more common in males (Timmings 1993; Beran *et al.* 2004). Conversely, a large study including 154 SUDEP cases concluded that gender was not an independent risk factor (Langan *et al.* 2005), and, at present, there is no convincing evidence from population-based studies that the SUDEP risk in males differs from that in females.

Several studies have found an increased risk among patients on polytherapy (Nilsson *et al.* 1999; McKee & Bodfish 2000; Nilsson *et al.* 2001; Beran *et al.* 2004), although this was not found in three other studies (Timmings 1993; Langan *et al.* 2005; Hitiris *et al.* 2007). The association of SUDEP with polytherapy has generally been interpreted as a reflection of poor seizure control (Tomson *et al*. 2008; Hesdorffer *et al*. 2012), although in one study polytherapy remained significantly associated with SUDEP after correction for seizure frequency (Walczak *et al.* 2001). Similarly, frequent changes of AED doses have also been connected with a higher risk of SUDEP (Nilsson *et al.* 1999; Nilsson *et al.* 2001).

Some studies have focused on the possibility that patients that are not compliant with their antiepileptic medication may be at higher risk of SUDEP. One study in which AED concentrations were analysed in hair samples concluded that AED concentrations varied more over time in SUDEP victims than in controls, reflecting lower compliance (Williams *et al.* 2006). However, another report found that compliance of SUDEP victims at their last medical visit did not differ significantly from that of controls (Walczak *et al.* 2001). Results from investigations of psychotropic medication and SUDEP have also been conflicting: in one study the use of antipsychotics and axiolytics in females and males, respectively, was significantly associated with SUDEP (Nilsson *et al.* 1999), whereas in another study the use of psychotropic medication was not found to be a risk factor for SUDEP (Walczak *et al.* 2001).

AEDs that have been shown to affect cardiac function may also have a possible influence on SUDEP risk in some patients. Carbamazepine (CBZ) and intravenous

phenytoin have been associated with cardiac conduction abnormalities with atrioventricular block, sinus bradycardia, and sinus arrest (Barron 1976; Kasarskis *et al.* 1992; Tomson & Kenneback 1997), and CBZ may also reduce heart rate variability (Tomson & Kenneback 1997; Persson *et al.* 2003; Lossius *et al.* 2007). Lacosamide may give rise to atrioventricular block (Ben-Menachem *et al.* 2007). Furthermore, retigabine can increase the QT interval in predisposed patients (Trobalt European Public Assessment Report, EPAR. Committee for Medicinal Products for Human Use (CHMP): www.ema.europa.eu/ema/), whereas the QT interval may be shortened in patients treated with primidone (DeSilvey & Moss 1980) or CBZ (Saetre *et al.* 2009). However, cardiac arrhythmias induced by AEDs have been found to occur mainly in predisposed patients (Kenneback *et al.* 1991; Saetre *et al.* 2009; Sevcencu & Struijk 2010), and among the AEDs mentioned above, only treatment with CBZ (Timmings 1998; Langan *et al.* 2005) or high serum concentrations of this drug (Nilsson *et al.* 2001) have been connected with an increased risk of SUDEP. However, two other studies concluded that patients on CBZ were not at a higher SUDEP risk (Walczak *et al.* 2001; Hitiris *et al.* 2007), and recently the ILAE, Commission on Epidemiology, Subcommission on Mortality concluded their combined analysis of previous research data on SUDEP with a statement that no single AED increases the risk of SUDEP (Hesdorffer *et al*. 2012).

In 2005 a cell experimental study documented that LTG inhibits the cardiac potassium current IKr (Danielsson *et al.* 2005). Previous reports had shown that drugs with a similar potential to inhibit the IKr are associated with prolonged QT interval in the ECG, torsade de pointes arrhythmia, syncope and sudden cardiac death in patients (Witchel & Hancox 2000; Redfern *et al.* 2003). The authors suggested that their finding could be of clinical importance under certain conditions, such as high serum concentrations, concurrent treatment with other IKr blocking drugs or seizure-induced acidosis. At that time, however, no clinical studies had suggested an increased risk of SUDEP in patients being treated with LTG.

Aims of the study

Background

During the 10-year period between August 1 1995 and July 31 2005, four consecutive cases of definite SUDEP were registered among non-hospitalized patients at Neurological Department, Stavanger University Hospital, Stavanger, Norway. All four cases were females with idiopathic epilepsy that had been treated with LTG in monotherapy. These cases did not emerge through systematic study, but were registered as they appeared in the clinical setting. The study described in this thesis was initiated because of the striking similarities between the deceased.

Objectives

Our objectives were to:
1. Evaluate whether our clinical observation could be due an increased risk of SUDEP in sub-groups of epilepsy patients being treated with LTG.
2. Explore the potential underlying causes of the previously described significantly increased mortality among people with epilepsy, even many years after seizure onset.

In order to meet these objectives we:

- Described and discussed the four cases in the light of relevant literature (paper I).
- Performed a post mortem analysis of the long QT syndrome genes of the four deceased patients (paper II).
- Estimated the incidence of SUDEP in our county and investigated whether the use of LTG was associated with an increased risk of SUDEP in females or other epilepsy patient sub-groups (paper III).

- Evaluated the feasibility of using signal-averaged electrocardiography in combination with standard electrocardiography to detect cardiac abnormalities in newly diagnosed epilepsy patients without clinical evidence of heart disease and investigated whether the initiation of therapy with the commonly used antiepileptic drugs LTG or CBZ gave rise to VLPs or significant abnormalities in the standard ECG (paper IV).

- Investigated the distribution of the different COD in an epilepsy population and compared this with the general population in the same catchment area and also with reports from other epilepsy populations. In addition, to evaluate the contribution of comorbid diseases to the mortality, we studied the chronological relationship between the onset of epilepsy and the diseases leading to death (paper V).

Materials and methods

Paper I describes the review of hospital records and post mortem reports of the four SUDEP victims and also provides a review of the literature to evaluate the likelihood of a relationship between the use of LTG and SUDEP in sub-groups of epilepsy patients.

Stavanger University Hospital serves a population of about 300.000 in the southern part of Rogaland County. Data obtained from Farmastat AS (http://www.farmastat.no) showed that LTG during the 10-year period in Rogaland County had a mean market share in defined daily doses (DDD) of 6.7 %, and consequently the accumulation of registered SUDEP cases on LTG did not appear likely to be due to a high proportion of epilepsy patients being treated with the drug.

In **paper II** a post mortem genetic analysis in the four deceased is described, based on our hypothesis that a genetic predisposition to cardiac arrhythmia may have played a role in causing their deaths. The method previously described by Berge et al. (Berge *et al.* 2008) was used for DNA sequencing of the translated exons with flanking intron sequences of the LQTS-associated genes *KCNQ1*, *hERG*, *SCN5A*, *minK* and *MiRP1*.

Paper III describes a systematic study of SUDEP in Rogaland County, Norway during the 10-year period. SUDEP cases were identified by review of autopsy reports and data from the Norwegian Cause of Death Registry, which includes all cases in which epilepsy was listed as a direct or contributory causes of death (N = 136). In addition, from the Norwegian Cause of Death Registry we obtained the direct and contributing COD of all patients that had been registered at Stavanger University Hospital with a diagnosis of epilepsy and had died during the same period (N = 268). Only patients with a permanent address in Rogaland County were included in the analysis. In all cases in which SUDEP was considered to be a possible cause of death, the hospital records were reviewed. Inclusion of cases was based on the Nashef criteria

for SUDEP (Nashef 1997) and cases were classified as definite, probable or possible as previously described (Annegers 1997; Tomson *et al.* 2008). In order to estimate the number of epilepsy patients at risk we multiplied the number of residents each year in the County (Statistics Norway: http://www.ssb.no) by 0.7 %, which is the estimated prevalence of epilepsy in western countries (Hauser *et al.* 1991; Sander 2003; French & Pedley 2008). To estimate the number of patient-years at risk for each AED, the market share in Rogaland of each antiepileptic drug, in DDD, was obtained from Farmastat AS (http://www.farmastat.no).

At least three living controls for each SUDEP case were randomly selected from among patients that had been registered with a diagnosis of epilepsy at Stavanger University Hospital during the same year that the SUDEP had occurred. In order to investigate whether age or gender could be risk factors for SUDEP, a primary unmatched control group of 89 and 120 individuals was selected for definite and probable, and for definite, probable and possible SUDEP, respectively. A further secondary control group, with three to four controls matched by age and gender for each SUDEP victim, was selected for the remaining analyses that included possible risk factors for SUDEP; 63 controls were used for definite and probable SUDEP and 86 controls for definite, probable and possible SUDEP. Since the market share of the different AEDs changed during the period of interest, the clinical data from the medical records of the controls were extracted from the year in which the corresponding SUDEP occurred. Classification of epilepsy syndromes in cases and controls was based on the ILAE 1989 definition (ILAE, 1989). Detailed information on market shares of AEDs and the clinical data that were analysed are available in paper III, tables 1 and 2, respectively.

Paper IV describes a prospective study of 26 individuals (19 females and seven males) with newly diagnosed epilepsy that had not previously been treated with an AED. All patients went through a somatic and neurological examination and also cerebral magnetic resonance imaging (MRI) and standard electroencephalography.

The patients were diagnosed with epilepsy according to the ILAE and the International Bureau for Epilepsy 2005 definition (Fisher *et al.* 2005), and their epilepsy syndromes were classified according to the ILAE 1989 definitions (ILAE, 1989). A prerequisite for inclusion in the study was the absence of clinical evidence of cardiac disease. At inclusion (T0) and three to nine months after initiation of therapy with LTG or CBZ (T1), a routine 12-lead electrocardiography and signal-averaged electrocardiography were conducted, and routine blood tests, including haematologic analyses, electrolytes, creatinine and erythrocyte sedimentation rate were performed. The choice of AED was made according to the clinical judgement of the attending physicians. The signal-averaged electrocardiography was performed as previously described (Sarvari *et al.* 2011). When at least two of the following three criteria were fulfilled, a VLP was considered to be present: 1) Total filtered QRS duration (fQRSd) of > 114 ms; 2) terminal (last 40 ms) QRS root-mean-square voltage (RMS) of < 20 μV; and 3) low amplitude (< 40 μV) late potential duration (HFLA) of > 38 ms.

In **paper V** the hospital records and COD among the 268 deceased epilepsy patients from Stavanger University Hospital during the 10-year period were reviewed. Four patients were excluded because of lack of evidence in the medical records that the patients had been diagnosed with epilepsy. Two additional cases of SUDEP were included; these had died during the 10-year period, but had been registered with a diagnosis of epilepsy only prior to the study period. Thus, a total of 266 deceased were included.

The distributions of age and gender among living epilepsy patients at the end of the study period (N = 2480) were obtained from the database of Stavanger University Hospital, and the corresponding information about the general population of Rogaland County per January 1 2005 (N = 393,104) obtained from Statistics Norway (www.ssb.no). From Statistics Norway, we also obtained the number of deaths within each defined category of age, gender and COD in the county during the study period. The diagnostic categories included ‘‘cerebrovascular’’ (ICD - 9 430 – 438; ICD - 10 I 60 – 69), ‘‘heart disease’’ (ICD - 9 393 – 398, 410 – 414, 415.0 and 420 – 429; ICD -

10 I05 – I09, I 20 – I25, I27 and I30 – I52), ‘‘neoplasm (excluding brain tumours)’’ (ICD - 9 140 – 190, 192.2 – 224 and 225.3 – 239; ICD - 10 C00–C69, C70.1, C72.0, C72.1, C73 – C97, D32.1, D33.4, D34 – D48), ‘‘brain tumours’’ (ICD - 9 191, 192.0, 192.1, 225.0 – 2; ICD - 10 C71, C72.2 – C72.8, C70.0, D32.0, D33.0 – D33.3), ‘‘pneumonia’’ (ICD - 9 480 – 486; ICD - 10 J12–J18), ‘‘suicide’’ (ICD - 9 E950 – E959; ICD - 10 X6n), ‘‘accidents’’ (ICD - 9 E800 – E929; ICD - 10 V0n–V99, W0n – X59, X8n, Y85 – Y89) and ‘‘other’’.

3.1 Statistical analyses

Papers I and II are case reports and did not include statistical analyses.

Paper III: Before conducting the study, a power analysis was performed to evaluate whether data from a population of about 400,000 over a 10-year period could be sufficient for detecting an increased risk of SUDEP in patients that were treated with LTG, compared with epilepsy patients not on this drug. Given a prevalence of epilepsy of 0.7 %, an incidence of SUDEP of 1.4 per 1000 patient-years at risk (Nilsson *et al.,* 1999) and a mean market share in DDD of 6.7 %, an anticipated relative risk of three could be detected with a power of 80 % at significance level of 0.05.

Due to the statistical uncertainty connected with small numbers, statistical analysis was only performed when there were at least five observations. For comparisons of frequencies between cases and matched controls, conditional odds ratios for matched age and sex case–control design were estimated using Epi Info version 3.5.1 (Center for Disease Control, Atlanta, GA, U.S.A.).
The web-based software Open Epi (http://www.openepi.com) was used to estimate rate ratios with 95 % confidence intervals of SUDEP incidence among patients on a particular AED compared with the incidence among those not on this drug.
Mean duration of epilepsy was compared between cases and matched controls using a linear mixed model with a random intercept in SPSS (version 18; IBM Corporation, Armonk, NY, U.S.A.). Analyses were also performed in SPSS when cases were

compared with unmatched controls: Pearson's chi-square tests were used for frequencies and Mann-Whitney tests for means. Because the primary outcome of the case-control study was the proportion of cases on LTG compared with the proportion of controls on this drug, correction for multiple comparisons was not performed.

Paper IV: The parameters in the ECG and SAECG at T0 and T1 were compared using Student's paired samples t-test in SPSS/PASW.

Paper V: Comparisons of proportionate mortality ratios between deceased epilepsy patients and deceased from the general population were performed in SPSS using Pearson's chi-square and Fisher Exact tests.

3.2 Ethical approval

The studies were approved by the Regional Committees of Medical Research Ethics, as described in the articles. Informed consent was obtained from controls (paper III) and patients (paper IV).

3.3 Methodological considerations

The case reports in **papers I and II** are the first published clinical observation suggesting the possibility of an increased risk of SUDEP in sub-groups of patients being treated with LTG, and the first cardiac channelopathy detected in a SUDEP victim. Clearly, our observations could not permit any definite conclusions to be drawn regarding whether or not there is an increased risk of SUDEP connected with the use of LTG or, if present, whether this is due to a possible arrhythmogenic effect of the drug or an insufficient efficacy of the drug in controlling seizures. Nevertheless, in the light of the available literature our findings gave reason to initiate a systematic study to try to address these questions.

In SUDEP victims the reason(s) for the final seizure being lethal, often after several years of living with treatment-resistant epilepsy, remain largely unknown. Since SUDEP is a rare event, a prospective study of incident cases of epilepsy, in which a sufficient number of patients on different AEDs are followed for many years, would be practically impossible to conduct. In searching for risk factors, the aim is to identify factors that differentiate those that died from those that have survived (Hesdorffer & Tomson 2012). Therefore, in order to investigate whether the use of LTG is connected with an increased risk of SUDEP, we used living epilepsy patients as controls (**paper III**) in our nested case-control study.

In addition we used the market share, in DDD, of AEDs to estimate relative risks of SUDEP in individuals being treated with a particular AED compared with those that were not on that drug. In order to obtain a correct reflection of the proportion of individuals on a specific drug, a prerequisite would be a small difference between the DDD, as defined by the World Health Organization, and the mean dose in the study population. Concerning LTG, the DDD is 300 mg (http://www.whocc.no/atc_ddd_index/), which was considerably higher than the mean LTG dose among our cases and controls (197 mg and 158 mg, respectively); a fact of which we became aware during the process of analysis of our data. However, we performed a conservative correction of the estimated number of patient-years at risk on LTG, based on the number of individuals on LTG in 2005, as recorded at www.reseptregisteret.no, and also the assumption that the proportion of females among LTG users did not increase, but was stable at the 2005 level during the course of the 10-year period.

In order to avoid a hypothesis-driven finding of a drug-related SUDEP risk that would not be replicated in future studies because of lack of scientific consistency, we used a conservative approach in inclusion of cases. For example, one female on LTG was found dead in a bath tub, and, because there was no evidence of submersion, could have been classified as a possible SUDEP, according to the recently published proposed definition of SUDEP (Nashef *et al.* 2012). However, we considered

drowning to be the most likely cause of death, and the case was therefore classified as a non-SUDEP. Similarly, another female patient on LTG was found dead with abundant gastric content on the pillow and was therefore classified as a possible SUDEP. However, aspiration of gastric content could also have been considered to be a terminal event, rather than a possible cause of death, and consequently this case could have been classified as a probable SUDEP.

Although our study in Rogaland County documented a statistically significantly increased risk of SUDEP in females on LTG, we were aware that our conclusion was based on a limited number of cases. We therefore acknowledged in the published article that our findings must be confirmed in future studies before definite conclusions are reached.

In the study described in **paper IV,** signal-averaged electrocardiography was performed in combination with standard electrocardiography. To the best of our knowledge among people with epilepsy, this procedure has only been performed in a population with chronic epilepsy (Rejdak *et al.* 2011). Although only a small number of patients were included, the study provided important information supporting the notion that cardiac arrhythmias induced by AEDs occur primarily in predisposed individuals. As no female with idiopathic epilepsy was treated with LTG, it was not possible to investigate whether the drug may give rise to cardiac side effects in this sub-group of epilepsy patients.

The study design described in **paper V** did not permit estimation of cause-specific mortality, which could have provided information on the relative risks among people with epilepsy of dying from a specific cause of death compared with the general population. However, a major strength of this study was the review of the medical records of the deceased, adding new insights into the explanations underlying the

significantly increased mortality rate that has previously been documented in the epilepsy population.

Results

Paper I

The four deceased females were 16 – 37 years of age. They had all been treated with LTG in monotherapy, and diagnosis after post mortem examination was definite SUDEP. In all cases, the medical history and results from neurological examination, electroencephalography and cerebral MRI were consistent with idiopathic epilepsy.

Paper II

Case one was heterozygous for a novel missense mutation, R523C in exon 12 of the *SCN5A* gene (GenBank Accession number: NM_198056.2, which corresponds to XP_001131636 in the published article (paper II)) coding for the cardiac sodium channel, voltage gated, type V, alpha subunit. The mutation changes codon 523 from arginine to cysteine, and was predicted by the prediction program PolyPhen to be pathogenic.
Ictal semiology in this patient had included a feeling of déjà vu, indicating localization-related epilepsy, whereas the electroencephalography showed bilateral synchronous epileptiform activity, which is more consistent with generalized epilepsy. Unfortunately, cardiac disease was not suspected ante mortem and therefore electrocardiography was not conducted.
For the other three cases, genetic analysis did not reveal any abnormalities.

Paper III

We identified 16 definite, three probable and seven possible cases of SUDEP: 15 were female and 11 male. Of these 26 cases, 10 (38.5 %) had been treated with LTG, and nine of these patients were female. Seven of 12 females with definite and probable SUDEP (58.3 %) and 10 of 41 controls matched for age and gender (24.4 %) were on LTG ($p = 0.038$, 95 % CI 1.1 – 28.2).

In females, the incidence of definite and probable SUDEP was estimated as 2.5 per 1000 patient-years among those that were treated with LTG and 0.5 per 1000 patient-years in those that were not treated with LTG ($p = 0.007$, incidence rate ratio 5.0, 95 % CI 1.6–17.3). Mean dose and duration of treatment on LTG did not differ significantly between cases and controls.

The incidence of SUDEP in Rogaland County during the 10-year period was 0.7 per 1000 patient-years for definite and probable SUDEP, and 1.0 per 1000 patient-years when all cases were included.

Concerning other AEDs no significant differences in incidences of SUDEP between cases that were taking/not taking a particular drug were detected, and, similarly, there was no significant difference between the proportion of cases and controls that were on a particular drug.

The proportions of cases and controls with IGE were similar (about 25 %) and also among female SUDEP victims on LTG, the difference between cases and controls was not statistically significant. However, when including the patient with a known *SCN5A* mutation (case one) and also case 11, in which the epilepsy syndrome had primarily been considered unclassifiable, the proportion with idiopathic epilepsy among female SUDEP victims on LTG was significantly higher than in controls.

Neither the distribution of age and gender, nor the proportion with duration of epilepsy for more than 10-years, or onset before 16 years of age differed significantly between cases and controls. However, the proportion of patients between 20 and 40 years of age was significantly higher among cases (13 of 19; 68 %) than controls (30 of 89; 34 %) ($p = 0.005$). Mean duration of epilepsy did not differ significantly between cases (16.25 years) and controls (15.15 years), or, in particular, between cases on LTG (13.25 years) and controls (13.59 years).

Paper IV

In one of the 26 patients, a VLP was present at baseline, whereas the standard ECG was normal. Cardiac MRI showed a reduced thickness of the free part of the right

ventricular wall and possibly some fatty infiltration. This patient was therefore excluded from the remaining part of the study. Twenty-five patients (18 females and 7 males) completed the study; 15 were treated with LTG and 10 with CBZ. At baseline, the total number of GTCSs did not exceed two in any patient. For the 25 patients, both the standard ECG and SAECG were within normal limits at T0 and T1, and no significant abnormalities in the blood parameters were detected. The AED concentrations at T1 were sub-therapeutic in five patients on LTG and in two patients on CBZ, but otherwise they were within range.

Paper V

The distributions of the COD among the 266 epilepsy patients and the 29,332 deceased in the general population are shown in table 2 (paper V). Deaths from brain tumours were excluded from the comparisons between the deceased epilepsy patients and the deceased from the general population. A significantly lower proportion of epilepsy patients died from cardiac disease (39 of 220; 17.7 %) than in the general population (8095 of 29114; 27.8 %) ($p < 0.001$; 95 % CI 0.389 – 0.801). Otherwise there were no significant differences of proportionate mortality between the epilepsy patients and the general population. Onset of cardiac disease or cerebrovascular disease had preceded seizure onset in at least 71.8 % of the patients that died from cardiac disease, and among those that died from cerebrovascular disease the epilepsy was secondary to cerebrovascular disease in 72 %. Similarly, among patients that died from neoplasms, the malignancy had preceded seizure onset in at least 43 %. Furthermore, all the eight deceased from pneumonia had severe underlying and/or comorbid predisposing conditions, and both of the two suicide victims had experienced significant psychosocial distress before onset of epilepsy. 4.5 % of the epilepsy patients died from definite and probable SUDEP, and 6.8 % – 10.2 % of the deaths were seizure-related.

The distribution of age and gender were fairly similar in the epilepsy population at risk compared with the general population (table 3).

Discussion

It is well recognized that the mortality rate in people with epilepsy is significantly higher than in the general population, and that underlying diseases and, in some degree, direct seizure-related deaths, contribute to this increase (Cockerell *et al.* 1994; Shackleton *et al.* 1999; Lhatoo *et al.* 2001; Forsgren *et al.* 2005; Neligan *et al.* 2011a). However, the extent to which this increase in mortality rate is due to the disorder itself or to unrelated conditions that are not caused by epilepsy, is unclear.

SUDEP is the most common of the direct seizure-related causes of death in epilepsy patients, and the majority of victims are young adults. The possibility that the choice of AED treatment may play a role for the SUDEP risk has been discussed for many years. However, a common interpretation of available research data has been that no particular AED appears to be associated with an increased SUDEP risk (Walczak 2003; Tomson *et al.* 2005; Surges *et al.* 2009b; Hesdorffer *et al*. 2012).

5.1 Is treatment with lamotrigine associated with an increased risk of SUDEP in sub-groups of epilepsy patients?

Paper I was the first clinical report suggesting the possibility of an increased risk of SUDEP in sub-groups of epilepsy patients being treated with LTG. Although we acknowledged that one of the possible explanations for our observation could be that LTG was not sufficiently efficacious in controlling seizures, our main hypothesis was that an arrhythmogenic effect of the drug in genetically predisposed individuals may have played a role. This was largely based on the finding of an IKr blocking effect of the drug in an experimental cell-based study (Danielsson *et al.* 2005), despite there being no unequivocal relationship between the demonstration of an IKr blocking effect in the laboratory and an arrhythmogenic effect in patients (Webster *et al.* 2002; Redfern *et al.* 2003). Shortly after our report (paper I) was published, a study of 152 healthy individuals concluded that there was no evidence that LTG increases the QT

interval in the ECG (Dixon *et al.* 2008). These authors also argued that the incidence of SUDEP in the clinical development programme of LTG was 3.5 per 1000 patient-years, which was considered to be no higher than expected (Leestma *et al.* 1997). Nevertheless, whether it is scientifically acceptable to extrapolate from electrocardiographic findings in healthy volunteers to patients with epilepsy or, in particular, patients with idiopathic epilepsy, is open to discussion. Similarly, the clinical development programme only included patients with localization related epilepsy, and therefore the conclusions from this study may not be valid in idiopathic epilepsy.

Although, as we also acknowledged, the finding that all the four cases had idiopathic epilepsy could have been coincidental, another possibility could be that patients with idiopathic epilepsy may be genetically predisposed to drug-induced cardiac arrhythmia, and that patients with this predisposition may be at increased risk when exposed to an IKr blocking drug. The suggestion that the same channelopathy may cause both the long QT syndrome and epilepsy (Hartmann *et al.* 1999) provided an important basis for this hypothesis and, as described in the introduction, in recent years there has been increasing evidence for the existence of cardiocerebral channelopathies and overlapping phenotypes between cardiac and cerebral channelopathies. However, the extent of this overlap is presently unknown, and in idiopathic epilepsy it is not known whether a genetic predisposition for cardiac arrhythmia is present in only a minor proportion of cases or is more common.

The novel *SCN5A* mutation that was detected in one of the four deceased **(paper II)** was the first documentation of a cardiac channelopathy in a SUDEP victim. The ictal semiology of this patient had included episodes of déjà vu, which originates in the limbic system (Wild 2005). Since this gene is also expressed in the limbic system of the rat brain (Hartmann *et al.* 1999), this mutation may possibly have been an underlying cause of both the epilepsy and a susceptibility to cardiac arrhythmia. Interestingly, one study that included analysis of long QT syndrome genes in 48 deceased that were considered to have died from SUDEP revealed a mutation in 6

(12.5 %), and the findings were claimed to provide "*proof-of-principle to conduct a more comprehensive prospective study of SUDEP cases*" (Tu *et al.* 2011). However, in this cases series, for the majority of patients neither classification of seizures and epilepsy syndromes, nor results from electroencephalography were reported, and thus there is a lack of certainty regarding whether these patients had genuine epilepsy. In our patient with an *SCN5A* mutation, because cardiac disease was not suspected ante mortem a cardiac work-up was not conducted, and therefore it could be argued that the mutation may not have been disease-causing. Additionally, as many non-pathogenic mutations have been detected in the region of R523C in the *SCN5A* gene, it has been suggested that the mutation detected in our patient was not likely to be disease-causing (Johnson *et al.* 2010). Importantly, however, it should be mentioned that this particular mutation causes an amino acid substitution - from arginine to cysteine. This implies an alteration in charge, and, based on the analysis by the prediction program PolyPhen, it appears that this mutation is likely to be pathogenic.

Patients with QT mutations may be particularly susceptible to lethal arrhythmia when treated with IKr blocking drugs (Schwartz 2006). Therefore, if the assumption is correct that the mutation in our patient was pathogenic, treatment with LTG could have provided greater potential for inducing cardiac arrhythmia than treatment with this drug in a patient without a cardiac channelopathy.

Paper III describes a population-based study that sought to reveal whether treatment with LTG is associated with an increased risk of SUDEP in sub-groups of epilepsy patients, and also to estimate the incidence of SUDEP in Rogaland County. Whereas the incidence of SUDEP in the general epilepsy population was similar to that which has been documented in previous population-based studies, we found a significantly higher incidence of SUDEP in females that were treated with LTG than in females that were not on this drug. Additionally, a significantly higher proportion of female SUDEP victims were on LTG than matched controls. There was no evidence for an increased risk of SUDEP among males. One possible explanation for this

preponderance of females among SUDEP victims on LTG could be that the drug possesses an IKr blocking ability, since the risk of drug-induced torsade de pointes arrhythmia is higher in females than in males (Makkar *et al.* 1993; Lehmann et al. 1999; Viskin *et al.* 2003).

In a recent combined analysis of data from previous case-control studies of SUDEP, in the crude analysis the risk of SUDEP was significantly higher in patients with IGE that had been treated with LTG compared with controls (odds ratio 2.20; 95 % CI 1.14 - 4.23), whereas the risk was not increased in those without IGE that were treated with LTG (Hesdorffer et al. 2011). The authors stated that their finding was in line with our own report (paper I), in which we suggested an increased risk with treatment with LTG in idiopathic epilepsy. Interestingly, they also found that the risk of SUDEP in patients on LTG was significantly increased when onset of epilepsy was under the age of 16 years, whereas it was not increased in those with a later seizure onset. Whether this could be explained by the fact that onset of idiopathic epilepsy usually occurs in childhood and adolescence (Benbadis 2005), thereby resulting in a higher proportion of patients with idiopathic epilepsy among patients with early onset, was not discussed. We found about the same proportion (about 25 %) of IGE in cases and controls, and also among female SUDEP victims on LTG the difference was not statistically significant. However, as described in the introduction, idiopathic epilepsy encompasses not only IGE, and when including case one with a known *SCN5A* mutation and also case 11, which primarily had been considered to be unclassifiable, the proportion of those with idiopathic epilepsy among female SUDEP victims on LTG was significantly higher than in controls.

We found no evidence of an increased risk of SUDEP connected with any other AED. Taken together, we found a significantly increased risk of SUDEP in female patients on LTG and also some support for the notion that this finding of an increased risk may possibly be explained by an increased SUDEP incidence with LTG only in idiopathic epilepsy, although our findings did not permit any firm conclusions.

5.2 Is there a causal relationship between the use of lamotrigine and a higher occurrence of SUDEP in female patients?

Only months after the identification of LTG use as a potential risk factor for SUDEP in IGE (Hesdorffer *et al.* 2011), the same authors stated that they had provided a consistent message that it is the number of GTCSs that increases SUDEP risk, and not AEDs (Hesdorffer *et al*. 2012). This conclusion was reached after a new analysis showed that when the frequency of primary or secondary generalized tonic-clonic seizures had been controlled for then LTG was not associated with a significantly increased risk of SUDEP. Interestingly, however, and in concordance with our own findings, a similar gender difference was detected, although it was not statistically significant, with an odds ratio for SUDEP in females on LTG of 6.6 compared with 0.4 in males. The lack of statistical significance after controlling for the frequency of GTCSs implies that a causal relationship could not be detected in a mixed epilepsy population with primary and secondary generalized tonic-clonic seizures. However, IGE was not analysed separately, and, given the possibility that the risk is only increased in IGE and not in localization related epilepsy, the definite conclusion that there is a lack of association between LTG use and SUDEP may have been reached too hastily.

Recently the occurrence of SUDEP was examined in 42 randomized controlled LTG trials sponsored by GlaxoSmithKline (Tomson *et al.* 2012). Among patients on LTG, were two male and two female definite and probable SUDEP. In the placebo-controlled studies, the odds ratio for SUDEP in patients on LTG was 0.22 (95 % CI 0.00–3.14), whereas it was 2.18 (95 % CI 0.17 – 117) when an active comparator had been used. Although no evidence was found for a significantly increased risk of SUDEP connected with LTG treatment, the authors emphasized the wide confidence intervals, indicating that "*a clinically important effect cannot be excluded"*. Although the vast majority of patients included in their analysis had localization related epilepsy, there was also a small proportion with primary generalized seizures, and there were no

SUDEP cases among these patients. However, as stated by the authors, the duration of follow-up was limited. Furthermore, as only 647 patients with primary generalized seizures were included in the analysis, the number of patient-years at risk was too low to enable evaluation of risk in this sub-group of patients. Nevertheless, this study provides some evidence that SUDEP risk in patients with localization related epilepsy on LTG therapy is not significantly increased. This conclusion is in concordance with the findings from the clinical development programme of LTG, in which only patients with localization related epilepsy were included (Leestma *et al.* 1997), and is also consistent with our findings in which the majority of female SUDEP victims on LTG had idiopathic epilepsy. Interestingly, however, the finding of an odds ratio of 0.22 when LTG treatment was compared with placebo, although not statistically significant, could give some support in the direction of a protective effect against SUDEP of LTG in localization related epilepsy, compared with no treatment. This is also in line with the conclusion from a recent meta-analysis of randomized trials, including a number of different AEDs, in which add-on treatment with AEDs in efficacious doses was associated with a significantly lower SUDEP risk compared with placebo (Ryvlin *et al.* 2011).

In our study we could not correct for the frequency of GTCSs because information on the frequency of the different seizure types was lacking in several of the hospital records, and this has been used as a basis for arguing against a causal relationship between use of LTG and SUDEP (Pack 2012). Although logistic regression analysis, including seizure frequency totalling more than one per week, identified LTG as an independent risk factor, we have not excluded the possibility that our findings may be due to a higher frequency of GTCSs and have no association with a pro-arrhythmic effect of the drug.

One possible explanation for an increased occurrence of SUDEP in patients with idiopathic epilepsy that have been treated with LTG may be that there is a weaker protective effect against GTCSs with LTG in comparison with other AED treatments.

In a prospective unblinded randomized study (the SANAD study), LTG was significantly less efficacious than valproate in treatment of IGE (Marson *et al.* 2007), although this study did not specify whether this also applied to GTCSs in particular. Similarly, in a study on newly diagnosed epilepsy patients, 39 % of those with juvenile myoclonic epilepsy achieved seizure control with LTG treatment compared with 75 % using valproate ($p = 0.014$) (Mohanraj & Brodie 2005). To the best of my knowledge, no published study on patients with IGE has documented that treatment with LTG is of an equal or higher efficacy than treatment with any other AED.
Another possible explanation for an increased occurrence of SUDEP in patients on LTG could be that despite the lack of efficacy that may be associated with this AED, patients continue to take LTG because it is well tolerated and a lack of effect on seizure control may not have been definitively demonstrated.

It has also recently been suggested that our findings may be explained by low (or absent) serum concentrations of LTG (Hesdorffer & Tomson 2012), although the possibilities of a drug reaction or an arrhythmogenic effect in genetically predisposed patients were also acknowledged. In support of this explanation, are the findings of low or absent serum concentrations of LTG at post mortem examination in four of the seven deceased females that had been treated with LTG. Surprisingly, the argument that post mortem serum concentrations are unreliable (Tomson *et al.* 1998) was not mentioned in the discussion that proposed this explanation. Nevertheless, the possibility of low serum concentrations and consequently an insufficient protective effect against seizures at the time of SUDEP cannot be excluded. In addition, as also inferred (Hesdorffer & Tomson 2012), the serum concentrations of LTG at the time of SUDEP may also have been low in two other cases. However, it seems unlikely that low serum concentrations, resulting in a higher propensity for GTCSs, represent the whole explanation, as this does not address the issue, both from our own data and also information from the combined analysis (Hesdorffer *et al.* 2011), regarding the increased risk of SUDEP apparently only being associated with idiopathic epilepsy.

Furthermore, if a low serum concentration of AEDs is a major explanatory factor in SUDEP in general, then a higher occurrence of SUDEP is less likely to be associated with a particular AED, but with any AED in which clinically relevant serum concentrations are not maintained. It also seems unlikely that female patients on LTG are treated differently to those on other AEDs. Generally, a change in antiepileptic medication is considered when seizure control is unsatisfactory. In a female patient with poor seizure control and a low serum concentration of LTG, the dose would commonly have been increased, regardless of whether the low serum concentration was caused by, for example, co-medication with an oral contraceptive (which has been shown to cause a reduction in serum concentrations of LTG by more than 50 % (Sabers *et al.* 2003)).

A common denominator of the two drugs, CBZ and LTG, which have both been suggested to be associated with an increased risk of SUDEP, is that there is evidence that they may affect cardiac function. At present, however, there is insufficient knowledge regarding whether a drug effect on cardiac rhythmicity may be involved in the causation of SUDEP. **Paper IV** describes a study that sought to reveal whether LTG or CBZ affect cardiac function in newly diagnosed epilepsy patients without clinical evidence of cardiac disease. Furthermore, this study also evaluated the feasibility of using signal-averaged electrocardiography in combination with standard electrocardiography to detect cardiac abnormalities in this patient group. One patient with a VLP at baseline was excluded from the rest of the study, otherwise no electrocardiographic abnormalities were detected at baseline nor after three to nine months on treatment with LTG or CBZ. This lack of findings in patients without evidence of cardiac abnormalities supports the view that cardiac arrhythmias or conduction abnormalities caused by AEDs primarily occur in predisposed individuals. The results are also in line with a previous study on cardiac effects of the same drugs in elderly patients, in which no significant electrocardiographic abnormalities were detected after initiation of AED therapy (Saetre *et al.* 2009). In that study patients with significant atrioventricular conduction defect were excluded from participation.

The reason in SUDEP for the final seizure being lethal, after several years with treatment-resistant epilepsy, is poorly understood. Since SUDEP is very rare in newly diagnosed epilepsy patients (Cockerell *et al.* 1994), whereas a long duration of epilepsy has been identified as a risk factor for SUDEP (Walczak *et al.* 2001; Hitiris *et al.* 2007), it is important to try to understand the underlying mechanisms that might explain why patients with long-standing epilepsy may be at a higher risk. Our finding of a VLP at baseline in only one of twenty-six patients with newly diagnosed epilepsy may therefore be an important observation when compared with the 48 % of patients with chronic epilepsy in which a VLP was detected (Rejdak *et al.* 2011). The patients with a VLP had a significantly longer duration of epilepsy and also a significantly higher seizure frequency compared with those without a VLP. A possible explanation could be that the extensive autonomous activation that occurs during GTCSs may cause fibrosis or vacuolization of the myocardium, which, in turn, may be a substrate for a malignant cardiac arrhythmia (Earnest *et al.* 1992; Natelson *et al.* 1998). In our study no patient had experienced more than two GTCSs, and this may explain why electrocardiographic abnormalities were not detected in any of the twenty-five patients that completed the study. Another possible explanation for the absence of VLPs among our patients may be that they were all on monotherapy, whilst in the patients with a VLP the number of AEDs per patient was significantly higher than in those without a VLP (Rejdak *et al.* 2011). However, whether the VLPs were related to a drug effect or to an anatomic substrate in the myocardium for a potentially malignant arrhythmia could not be determined from that study.

From our findings it appears that electrocardiographic abnormalities induced by LTG or CBZ in the inter-ictal phase are not common in newly diagnosed epilepsy patients without clinical evidence of cardiac abnormalities. However, since in our study only one male patient with IGE was treated with LTG and no female patients, our study did not provide information on the potential effect on the ECG from this drug in these sub-

groups of patients. Furthermore, since the electrocardiographic recordings were conducted inter-ictally, a potential drug effect in the ictal phase has not been excluded. The detection of a VLP in the SAECG in one patient, and the subsequent finding of significant right ventricular pathology, demonstrates that the method may be a useful supplement to standard electrocardiography to detect significant cardiac abnormalities in patients with newly diagnosed epilepsy. However, a general recommendation of using signal-averaged electrocardiography in these patients should not be made on the basis of a single finding.

5.3 What are the most important explanations for the increased mortality in the general epilepsy population?

The most important finding in our study on mortality in the epilepsy population (**paper V**) was that many of the deaths were due to conditions with onset prior to the onset of epilepsy. For more than 70 % of patients that died from cardiac or cerebrovascular disease, the onset of these diseases preceded the onset of epilepsy, and in at least 43 % of the deaths from neoplasms, the onset of malignancy occurred prior to seizure onset. Similarly, all eight deaths from pneumonia occurred in patients with severe underlying or comorbid conditions, and both patients that died from suicide had experienced significant psychosocial distress before seizure onset. That for a high proportion of cases, the ultimately fatal disorders emerged prior to the onset of epilepsy shows that the chronological relationship between onset of epilepsy and onset of the disorders leading to death is highly relevant, and must be taken into consideration when evaluating whether the epilepsy precipitates an elevated risk of dying from a particular specified cause.

When a clinician is faced with a patient with newly diagnosed epilepsy, the question about the risk of premature death may arise. As described in the introduction, several studies have reported a significantly increased mortality rate and cause-specific

mortalities for different causes of death in the epilepsy population compared with a reference population. However, one common denominator of these studies has been that the presence of underlying or comorbid disorders, except brain tumours, has not been accounted for at inclusion into these investigations (Hauser *et al.* 1980; Nilsson *et al.* 1997; Shackleton *et al.* 1999; Lhatoo *et al.* 2001; Neligan *et al.* 2011a). In order to evaluate whether the diagnosis of epilepsy, or its treatment, implies an increased risk of dying from a particular disorder, it is crucial that individuals that already suffer from that disorder at seizure onset are excluded from the analysis. Since this apparently has not been done, the reported increase in standardized mortality ratio for, for example, cancer, may not imply that the risk of dying from a malignant neoplasm is increased in a patient with newly diagnosed epilepsy and without a known malignant disorder than for any other appropriately matched individual.

In our study, there were no significant differences in proportionate mortality compared with the general population, except from a significantly lower proportion of deaths from cardiac disease. Additionally, the distributions of age and gender in the populations at risk were fairly similar in the two populations. Importantly, however, these results do not permit a conclusion to be reached concerning the relative risk in the epilepsy population of dying from a particular cause, since our study design did not allow calculation of SMRs. Several studies have addressed the possibility of a relationship between epilepsy and cardiac disease, but the results have been conflicting. A recent study (Chuang *et al.* 2012) found that treatment with old-generation AEDs was associated with unfavourable alterations in blood lipids and other vascular risk factors, whereas an earlier study on males between 30 and 50 years of age with chronic epilepsy revealed no differences in risk factors for coronary heart disease compared with controls (Nakken & Kornstad 1998). Some studies have also found significantly increased standardized mortality ratios in epilepsy for cardiac disease (Annegers *et al.* 1984; Nilsson *et al.* 1997; Neligan *et al.* 2011a), although in one of these studies statistical significance was not detected before a follow-up of up

to 25 years (Neligan *et al.* 2011a). Furthermore, in another of these studies a significantly higher mortality from heart disease was found only in individuals less than 65 years of age (Annegers *et al.* 1984). Conversely, in our study, only three of the 39 deaths from cardiac disease occurred in individuals under 65 years of age. Given that the majority of those that died from cardiac disease in our study had already developed vascular disease at onset of epilepsy, none of these data provide convincing evidence that the diagnosis of epilepsy *per se* implies an increased risk of dying from cardiac disease. Nevertheless, an increased risk in sub-groups of epilepsy patients may still be possible, e.g. in individuals on long-term therapy with old-generation AEDs.

The proportionate mortality ratios in our epilepsy population were largely similar to those that have been reported from previous studies. However, there were differences for some causes of death, particularly when compared with more selected cohorts from the UK (White *et al.* 1979; Klenerman *et al.* 1993), in which the proportion of deaths due to brain tumours was similar to that in our general population (0.7 %). The proportions with SUDEP (4.5 %) and seizure-related deaths (6.8 % - 10.2 %) were also similar to findings from population-based studies (Zielinski 1974; Hauser *et al.* 1980; Annegers *et al.* 1984). However, in one population-based study (Cockerell *et al.* 1994), there were no cases of SUDEP and only 1.3 % of deaths were seizure-related, probably because of a short follow-up time in a population with newly diagnosed epilepsy.

5.4 Strengths and limitations of the study

Our study provided the first clinical report in which the possibility of an increased risk of SUDEP in epilepsy patients being treated with LTG is discussed. Also, to my knowledge, our study provided the first report suggesting a possible risk connected with treatment with a specific AED may be may depend on gender and epilepsy syndrome. The finding of an *SCN5A* mutation in one of four SUDEP victims also

provided the first evidence of a cardiocerebral channelopathy in a SUDEP victim, indicating the possibility that a genetic predisposition to cardiac arrhythmia might play a role in the causation of SUDEP. However, as a cardiac work-up was not performed in this patient, there was no clinical evidence that the mutation predisposed the patient to cardiac arrhythmia.

In our population-based study, cases of SUDEP were identified by three different methods, and therefore it is unlikely that many cases were missed. In order to ensure reproducible reliability in our results, a conservative approach was used for inclusion of cases. Another strength of our study was that the risk of SUDEP was evaluated both by a nested case-control design, with living epilepsy patients as controls, and by estimation of incidence rate ratios for each AED.

However, the study also had some limitations of which the most important were the relatively low number of observations, and the inability to correct for the frequency of GTCSs. Because of the latter limitation, we were unable to exclude the possibility that the increased occurrence of SUDEP in females on LTG could be due to a higher frequency of GTCSs, rather than as a direct result of an adverse effect of the drug in genetically predisposed individuals.

Further information on the strengths and limitations of the study is described under "Methods" – methodological considerations.

Conclusions

One aim of this thesis was to evaluate whether our clinical observation regarding four consecutive cases of SUDEP in a clinical environment could reflect an increased risk of SUDEP in sub-groups of epilepsy patients being treated with LTG. In addition, the thesis explored the underlying causes of the previously described significantly increased mortality rate among people with epilepsy, even many years after seizure onset.

Among female SUDEP victims, the proportion treated with LTG was significantly higher than in matched controls. Furthermore, whereas the incidence of SUDEP in Rogaland County was similar to that which has been reported from previous population-based studies, the incidence in females on LTG treatment was significantly higher than in females not being treated with this drug.

We found no evidence of an increased risk of SUDEP in male patients treated with LTG or an increased risk of SUDEP connected with any other AED.

Although our findings provided some evidence that an increased risk of SUDEP associated with treatment with LTG occurs only in idiopathic epilepsy patients, no firm conclusions could be reached due to the unavoidable limitations of our study. Nevertheless, in line with our reports, recent studies have confirmed an increased occurrence of SUDEP in patients with IGE that have been treated with LTG and a preponderance of females among SUDEP victims being treated with this drug.

As we were unable to correct for the frequency of GTCSs in our study, it was impossible to ascertain whether the increased occurrence of SUDEP in females being treated with LTG is due to a causal effect, possibly through an arrhythmogenic effect in genetically predisposed individuals, or to insufficient efficacy of LTG at seizure control.

We found no electrocardiographic abnormalities inter-ictally after initiation of treatment with LTG or CBZ in newly diagnosed epilepsy patients without evidence of cardiac abnormalities, suggesting that cardiac abnormalities caused by these drugs are not common in similar cohorts. However, the study did not permit firm conclusions to

be reached about the possible arrhythmogenic potential of these drugs, since the recordings were only conducted in the inter-ictal phase, and there were no female patients with IGE and being treated with LTG in our study cohort.

Of the deaths in the epilepsy population, 4.5 % were caused by definite and probable SUDEP, and 6.8 %, or maximally 10.2 %, were seizure-related. Otherwise, the majority of deaths were due to underlying or comorbid conditions, among which the onset of these conditions preceded the onset of epilepsy in a significant proportion of cases. Apart from the contribution from the directly seizure-related deaths, the significantly increased mortality rate previously described in the epilepsy population may be explained, at least in part, by underlying diseases and comorbid conditions that are not caused by epilepsy.

Future perspectives

Although our study revealed a significant association between treatment with lamotrigine in females and SUDEP, one limitation was that this potentially very important finding was based on relatively few observations. Therefore our results should be confirmed in a larger study before a firm conclusion is reached.

Nevertheless, since an increased occurrence of SUDEP in sub-groups of patients on LTG has been confirmed, at least partly, in other studies, one important future issue may be to explore the underlying reasons for these findings. In particular, there is a need to explore the degree of overlap between cardiac and cerebral channelopathies, as knowledge of a genetic predisposition towards cardiac arrhythmia in individual patients may be of vital importance. Sudden cardiac death in these patients may be preventable by appropriate treatment, e.g. with a β-blocker or implantation of a cardioverter-defibrillator (Garratt *et al.* 2010), and it may be important to avoid IKr blocking drugs in these patients because of their particular vulnerability to drug-induced, potentially fatal cardiac arrhythmia (Schwartz 2006).

Furthermore, whether individual AEDs influence cardiac rhythmicity during the ictal phase, and whether or not gender and epilepsy syndrome is of importance, need to be explored.

Finally, to support the interpretation of blood concentrations of specific AEDs from future post mortem examinations of SUDEP cases, animal research could provide valuable information on the fate of the blood concentrations of various AEDs, including LTG, after death. Studies on genetically modified animals with cardiac channelopathies could also provide valuable information on the potential effects of individual AEDs on cardiac function during and between seizures.

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