Full-length Original Research

Long-term surveillance of SUDEP in drug-resistant epilepsy patients treated with VNS therapy

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Summary
Objective: Limited data are available regarding the evolution over time of the rate of sudden unexpected death in epilepsy patients (SUDEP) in drug-resistant epilepsy. The objective is to analyze a database of 40 443 patients with epilepsy implanted with vagus nerve stimulation (VNS) therapy in the United States (from 1988 to 2012) and assess whether SUDEP rates decrease during the postimplantation follow-up period.

Methods: Patient vital status was ascertained using the Centers for Disease Control and Prevention’s National Death Index (NDI). An expert panel adjudicated classification of cause of deaths as SUDEP based on NDI data and available narrative descriptions of deaths. We tested the hypothesis that SUDEP rates decrease with time using the Mann-Kendall nonparametric trend test and by comparing SUDEP rates of the first 2 years of follow-up (years 1-2) to longer follow-up (years 3-10).

Results: Our cohort included 277 661 person-years of follow-up and 3689 deaths, including 632 SUDEP. Primary analysis demonstrated a significant decrease in age-adjusted SUDEP rate during follow-up (S = −27 P = .008), with rates of 2.47/1000 for years 1-2 and 1.68/1000 for years 3-10 (rate ratio 0.68; 95% confidence interval [CI] 0.53-0.87; P = .002). Sensitivity analyses confirm these findings.

Significance: Our data suggest that SUDEP risk significantly decreases during long-term follow-up of patients with refractory epilepsy receiving VNS Therapy. This finding might reflect several factors, including the natural long-term dynamic of SUDEP rate, attrition, and the impact of VNS Therapy. The role of each of these factors cannot be confirmed due to the limitations of the study.

Keywords
epilepsy, mortality, sudden unexpected death in epilepsy patients, vagus nerve stimulation
INTRODUCTION

Sudden unexpected death in epilepsy (SUDEP) is the second leading neurological cause of years of potential life lost in the United States. Recent practice guidelines of the American Academy of Neurology indicate that the risk of SUDEP is 1.2/1000 patient-years (95% confidence interval [CI] 0.64-2.32) in adults with epilepsy, and 0.22/1000 patient-years in children. Comparable figures were recently reported in a Swedish population-based study with a SUDEP rate of 1.2/1000 patient-years (95% CI 0.93-1.52). This risk increases up to 5.9/1000 patient-years in patients with chronic refractory epilepsy. However, the majority of epidemiological studies have been cross-sectional, thereby lacking information on the evolution of SUDEP rate over time. A long-term, prospective, follow-up study of an unselected cohort of Finnish patients with childhood-onset epilepsy, showed a cumulative SUDEP incidence rate of 22% (95% CI, 14%-30%) over a 40-year follow-up period among patients who were not in 5-year terminal remission. However, the sample size was too limited to reliably estimate changes in SUDEP rates over time. Exploring SUDEP incidence in large datasets of patients with refractory epilepsy and long-term follow-up might thus provide important information on the evolution of SUDEP incidence over time, as well as on potential preventive intervention.

VNS Therapy (Cyberonics, Inc./LivaNova, Houston, TX, USA) implants are recorded by the manufacturer in its Device Tracking Database when information is provided by the implanting facilities. Using data through 31 December 2012, information was available on a large dataset of 40 443 patients in the United States with 277 661 person-years (PY) of follow-up. Here we report the results from our analysis of this database to understand the evolution of SUDEP risk over time.

METHODS

The study protocol (see Data S1) and data collection methods were developed by the study coauthors in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement. Although the protocol was designed to assess all-cause mortality rates and several specific causes of death, the current study focuses only on SUDEP-related analyses. Institutional Review Board approval was received prior to receiving vital status from the Centers for Disease Control and Prevention’s National Death Index (NDI).

Key Points

- A total of 40 443 patients with VNS Therapy were followed up to 10 years postimplantation, accumulating 277 661 person-years of follow-up
- There were 3689 deaths, including 632 SUDEP, with 84% classified as possible and 16% as probable or definite
- Age-adjusted SUDEP rates decreased significantly over time (by over 30%) from years 1 to 2 (2.47/1000 person-years) to years 3 to 10 (1.68/1000 person-years)
- Several mechanisms could account for these findings including attrition and natural evolution, aging, changes in medications or medical practice over time, or VNS Therapy; the respective impacts cannot be disentangled due to study limitations

2.1 Study population

The VNS Therapy Device Tracking Database is maintained by the manufacturer and includes information on patients who are implanted with the VNS Therapy device. The population included in this analysis were implanted for epilepsy between 16 November 1988 and 31 December 2012. The database includes the patient name, date of birth, US Social Security Number, indication treated, and the dates of implantation surgery, explantation surgery, and death (if applicable).

Patients were included in the study analysis if they met the following criteria: (1) implanted with VNS Therapy by December 31, 2012 (ie, the study end date) based on a diagnosis of epilepsy, (2) were a US citizen or resided in the United States at the time of implant, (3) had a US Social Security Number, and (4) had a known date of birth.

2.2 Ascertainment of deaths and SUDEP

The study was based on data collected by the National Center for Health Statistics with the causes of death in the United States classified in accordance with the International Classification of Diseases (ICD) Ninth Revision (ICD-9; for data prior to 1999) and Tenth Revision (ICD-10; for data starting from 1999). Using the available unique patient identification information from the VNS Device Tracking Database, data on all study patients were submitted to the NDI for ascertainment of vital status and cause of death. The latter included an underlying cause of death (UCD).
and up to 20 contributory causes of death (CCDs). Other information available in all deceased patients were gender, age at VNS implant (corresponding to the time of onset of follow-up within the study), and age at death.

When a death was reported to Cyberonics by the patient’s family or physician, the company collected information regarding the details surrounding the death and autopsy findings, when available, as part of their US Food and Drug Administration (FDA)–mandated complaint-handling process. Such information was transcribed into narratives by Cyberonics at the time of each report and reviewed by an expert panel as part of this study.

It is important to note that no further clinical information was available in this study, such as age at epilepsy onset, epilepsy duration, and seizure frequency and its evolution under VNS therapy.

SUDEP was defined according to criteria published by Annegers (1997),\(^\text{10}\) that is, the victim had epilepsy, defined onset, epilepsy duration, and seizure frequency and its evolution by Cyberonics at the time of each report and handled process. Such information was transcribed into – and Drug Administration (FDA) autopsy findings, when available, as part of their US Food and Drug Administration (FDA)–mandated complaint-handling process. Such information was transcribed into narratives by Cyberonics at the time of each report and reviewed by an expert panel as part of this study.

SUDEP was defined according to criteria published by Annegers (1997),\(^\text{10}\) that is, the victim had epilepsy, defined as recurrent unprovoked seizures; the victim died unexpectedly while in a reasonable state of health, the death occurred “suddenly” (in minutes), when known; the death occurred during normal activities (eg, in or around bed, at home, at work) and benign circumstances; and an obvious medical cause of death was not found. SUDEP was considered definite when all criteria were met, and postmortem data were available, probable when all criteria were met without postmortem data, and possible when SUDEP could not be ruled out but there was insufficient evidence regarding the circumstances of the death and no postmortem report was available. Unlikely/Not SUDEP was considered when the cause of death was clearly established, or the circumstances make SUDEP highly improbable.

SUDEP cannot be directly extracted from NDI data, since there is no corresponding ICD code in the ICD-9/ICD-10 classification. Thus adjudication of SUDEP required a specific procedure that was developed by the SUDEP expert panel of the study and included all available data, in particular, age at death, UCD and CCD recorded in the NDI, and death narratives as collected by Cyberonics in a subset of patients. This procedure included the following 3 steps.

The first step consisted of the development and processing of an algorithm that identifies combinations of UCD and CCD likely compatible with the diagnosis of SUDEP. The expert panel (DF, DH, ES, MS, OD, and PR) in charge of developing this algorithm was exposed to the list of UCD recorded in the database, from which it selected 41 UCD pooled into 3 groups (see Table 1 for details) reflecting the main situations encountered in NDI transcription of SUDEP: (1) group 1, epilepsy or seizure is considered as the UCD. In this group, an exclusion criterion was the presence of status epilepticus among CCD; (2) group 2, UCD is quoted as “other ill-defined and unspecified causes of mortality” or as an acute cardiac or respiratory disorder such as “cardiac arrest, unspecified,” “anoxic brain damage, not elsewhere classified,” or “unspecified threat to breathing.” In this group, an exclusion criterion was the presence of another well-defined life-threatening cardiorespiratory disorder such as ischemic heart disease or asthma; (3) group 3: UCD is a congenital brain disorder, primarily cerebral palsy and mental retardation, although such conditions are usually not directly responsible for death. In this group, an additional inclusion criterion was that epilepsy or seizure should be listed among CCDs. This algorithm was run automatically among all deceased patients to select the per-protocol population used for the next steps of SUDEP adjudication.

The second step consisted of exploring the subset of patients with a death narrative and evaluating the correspondence between these narratives and combinations of UCD and CCD, to increase the accuracy of SUDEP adjudication based on UCD/CCD alone in patients without death narrative.

The third step was the adjudication of all cases selected through step 1, based on all available information and knowledge gained from step 2. A panel of 2 neurologists (DF and PR) independently performed this task, blinded to the duration of follow-up in the study. In all cases where the first 2 neurologists did not agree exactly on the SUDEP classification level, a third neurologist (ES) performed a final independent adjudication. Finally, the 3 investigators discussed during teleconferences all cases where they initially disagreed in order to better understand reasons for disagreement and see whether they could reach a consensus.

### 2.3 Sensitivity analyses

Because of the level of uncertainty of SUDEP ascertainment in patients without a death narrative, an alternative adjudication “by extrapolation” was used, whereby the rate of adjudicated SUDEP of cases with a narrative within each year of follow-up was prescribed to the cases without a narrative in the same year of follow-up. Furthermore, all analyses were repeated for the subset of patients who were 10 to 54 years old with the view to exclude younger patients whose risk of SUDEP is very low, and older patients who often have coexisting, competing medical causes of death. The same analyses were also performed on the subset of definite and probable SUDEP.

### 2.4 Statistical analysis

Patient exposure was calculated from date of implantation until death, device explantation, known date at which the device was disabled, or the last follow-up date of 31...
December 2012. Both crude and directly standardized (ie, age-adjusted) SUDEP rates were reported per 1000 PY of follow-up along with 95% CI. The directly standardized rates used the U.S. Standard Population for 2000 and age ranges of 0-4, 5-9, 10-14, 15-19, 20-24, 25-34, 35-44, 45-54, 55-64, 65-74, and 75+ years to match the census data. For each patient, we calculated the number of years of follow-up that were spent in each age group. Deaths were

| Underlying cause of death (UCD) as recorded in the national death index (NDI) | N  | %   |
|------------------------------------------------------------------------------|----|-----|
| Epilepsy and seizure                                                        | 578| 60.7|
| Epilepsy, unspecified [G40.9, 345.9]                                         | 266| 27.9|
| Other and unspecified convulsions [R56.8]                                   | 242| 25.4|
| Grand mal seizures, unspecified (with or without petit mal) [G40.6]        | 28 | 2.9 |
| Generalized idiopathic epilepsy and epileptic syndromes [G40.3]             | 19 | 2.0 |
| Other generalized epilepsy and epileptic syndromes [G40.4]                  | 16 | 1.7 |
| Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes [G40.1; G40.2] | 5  | 0.5 |
| Other epilepsy [G40.8]                                                      | 2  | 0.2 |
| Ill-defined and cardiorespiratory                                           | 61 | 6.4 |
| Other ill-defined and unspecified causes of mortality [R99]                 | 49 | 5.1 |
| Anoxic brain damage, not elsewhere classified [G93.1]                       | 46 | 4.8 |
| Cardiac arrest, unspecified [I46.9]                                         | 25 | 2.6 |
| Cardiac arrhythmia, unspecified [I49.9]                                     | 22 | 2.3 |
| Unspecified threat to breathing [W84]                                       | 11 | 1.2 |
| Sudden cardiac death, so described [I46.1]                                  | 7  | 0.7 |
| Sleep apnea [G47.3]                                                         | 4  | 0.4 |
| Accidental suffocation and strangulation in bed [W75]                       | 3  | 0.3 |
| Other specified threats to breathing [W83]                                  | 3  | 0.3 |
| Asphyxia [R09.0, 799.0]                                                     | 2  | 0.2 |
| Respiratory arrest [R09.2]                                                  | 2  | 0.2 |
| Ventricular fibrillation and flutter [I49.0]                                | 2  | 0.2 |
| Ventricular tachycardia [I47.2]                                             | 2  | 0.2 |
| Cardiac arrest [427.5]                                                      | 1  | 0.1 |
| Cardiac dysrhythmias, unspecified [427.9]                                   | 1  | 0.1 |
| Preexcitation syndrome [I45.6]                                              | 1  | 0.1 |
| Instantaneous death [R96.0]                                                 | 1  | 0.1 |
| Cerebral palsy/mental retardation                                           | 193| 20.3|
| Infantile cerebral palsy, unspecified [G80.9, 343.9]                        | 121| 12.7|
| Unspecified mental retardation [F79]                                        | 34 | 3.6 |
| Severe mental retardation [F72]                                             | 9  | 0.9 |
| Childhood autism [F84.0]                                                   | 6  | 0.6 |
| Other infantile cerebral palsy [G80.8]                                      | 4  | 0.4 |
| Profound mental retardation [F73]                                           | 4  | 0.4 |
| Rett’s syndrome [F84.2]                                                     | 4  | 0.4 |
| Disorder of brain, unspecified [G93.9]                                      | 3  | 0.3 |
| Spastic cerebral palsy [G80.0]                                              | 2  | 0.2 |
| Mild mental retardation [F70]                                               | 2  | 0.2 |
| Unspecified disorder of psychological development [F89]                    | 2  | 0.2 |
| Infantile hemiplegia [G80.2]                                                | 1  | 0.1 |
| Other specified disorders of brain [G93.8]                                  | 1  | 0.1 |
assigned to the patient’s age group at the time of death. All analyses were performed after pooling definite, probable, and possible SUDEP, except sensitivity analyses focusing on definite and probable SUDEP only.

The hypothesis that SUDEP rates decrease with time on VNS Therapy was first assessed by testing for a decreasing SUDEP hazard rate over follow-up time and applying the Mann-Kendall nonparametric trend test to the SUDEP rates by year of follow-up. In addition, the CI was calculated for the ratio of the last 8 years postimplantation divided by the first 2 years postimplantation with the view to compare our findings to those of the 2 previous reports of SUDEP in patients undergoing VNS that used that methodology.

The Barlow-Campo test was performed by counting the number of times the total time on test (TTT) plot crosses a 45-degree line; a small number of crossings indicates that the hazard rate is nonconstant and is either decreasing (the TTT plot lies below the 45-degree line) or increasing (the TTT plot lies above the 45-degree line).

We performed additional analyses to test the potential impact of changes in calendar year and aging on our findings. First, we calculated and compared the average date of follow-up for patients at years 1 and 2, vs years 3 to 10 post-VNS implant. Secondly, the age-adjusted SUDEP rates during the first full year of VNS Therapy were tested for a decreasing hazard rate over calendar years to detect changes in SUDEP rate over time independent of the duration of VNS Therapy. Finally, we calculated the theoretical number of cases of SUDEP that should have occurred in our cohort during years 3 to 10 of follow-up, provided that the risk of SUDEP would remain the same in each age group as that observed during years 1 and 2. The duly observed number of deaths was divided by the expected number of deaths to calculate a standardized mortality ratio (SMR) per the indirect standardization method, with 95% CI calculated using the Byar approximation.

Statistical analyses were performed using JMP Version 9, Minitab 17, and SAS Version 9.3 (SAS Institute Inc., Cary, NC, USA).

3 | RESULTS

3.1 | Study participants

According to implant registrations, 57 551 patients were implanted with VNS Therapy systems in the United States between 16 November 1988 and 31 December 2012. Of these patients, 40 443 (70%) met the inclusion criteria for this analysis. The average age at implantation was 30.8 years (range, 0-89) with 15% of the patients under 12 years of age. Fifty percent of the patients were male.

There were 277 661 PY of follow-up with a median duration of follow-up of 7.6 years. Of the 40 443 patients, 12 037 (30%) had completed at least a 10-year follow-up period, 21 853 (54%) were implanted after 2002 and were alive and receiving VNS Therapy as of the analysis cutoff date, 2864 (7%) had their device explanted or known to be turned off prior to the cutoff date, and 3689 (9%) died within the study analysis period. The all-cause mortality rate was 13.3 per 1000 PY of follow-up (95% CI, 12.9-13.7), translating into an age- and gender-adjusted SMR of 4.58 (95% CI, 4.43-4.73).

3.2 | SUDEP adjudication

Step 1: of the 3689 deaths, 953 (25.8%) were associated with UCD and CCD considered compatible with SUDEP and selected by our algorithm, including 578 (61%, 95% CI [57%-64%]) in group 1 (epilepsy/seizure), 181 (19%, 95% CI [16%-22%]) in group 2 (ill-defined and cardiorespiratory UCD), and 194 (20%, 95% CI [18%-23%]) in group 3 (congenital brain disorders) (see Table 1).

Step 2: A death narrative was available in 408 of these 953 patients (43%), including 263 in group 1 (65%, 95% CI [60%-69%]), 74 in group 2 (18%, 95% CI [14%-22%]), and 71 in group 3 (17%, 95% CI [14%-21%]). Among these 408 patients with a death narrative, one or several potentially life-threatening CCDs that would exclude SUDEP were recorded in 56 patients (14%). The most frequent CCD, accounting for 36 of these 56 cases (64%), were related to aspiration and/or pulmonary infection with the following axis codes: “pneumonitis due to food and vomit,” “foreign body in respiratory tract” usually associated with “inhalation and ingestion of other objects causing obstruction of respiratory tract,” and “pneumonia.” These were primarily encountered in patients from group 3 with cerebral palsy and severe mental retardation (22 of 36 such CCD). The second most frequent CCD was drowning encountered in 8 patients (14%), primarily in bathtub. The remaining CCD each occurred only once in 11 patients, and included various axis codes such as “Acute renal failure,” “Hyperkalemia,” “Asthma, unspecified,” “Cachexia,” “Chronic renal failure,” “Edema of larynx,” “Hemorrhage, not elsewhere classified,” “Pneumothorax,” “Pulmonary edema,” “Status epilepticus,” “Fracture of neck,” and “Acute myocardial infarction.” The death narratives of these 56 patients confirmed the relevance of the above CCDs in most instances, with only 3 cases (5%; 95% CI [0%-12%]) where the CCD was disproved by the detailed description of the circumstances of death available for all 3 patients and autopsy findings in 1 patient, leading to adjudication of SUDEP in all cases (one definite, one probable, one possible). In the 352 patients with a death narrative and no CCDs that would exclude SUDEP, the proportion...
of cases where the narrative permitted the adjudication of SUDEP. Dramatically varies between groups, with 87% (95% CI [82%-91%]) in group 1, 81% (95% CI [71%-91%]) in group 2, but only 49% in group 3 (95% CI [34%-64%]). In the latter group, many patients with cerebral palsy and severe mental retardation would be described as dying in-hospital or in a specialized institution following aspiration or end-stage respiratory infection, even though these conditions were not listed among CCDs.

Overall, step 2 suggested that the following statements could be used to help adjudicate cases without death narrative, based on UCD and CCD alone: (1) the presence of CCDs representing potentially life-threatening conditions that would exclude SUDEP permits the adjudication of such cases as Not SUDEP with a level of confidence of 95%; (2) patients whose UCD falls into groups 1 and 2 categories (epilepsy, seizure, cardiac arrest or dysrhythmia, threat to breathing, ill-defined cause of death) with no CCDs excluding SUDEP, are very likely to have SUDEP (above 80%); (3) patients whose UCD corresponds to nondirectly lethal congenital brain disorders, such as cerebral palsy and mental retardation, and in whom no CCDs exclude SUDEP, have <50% of chances to have had SUDEP.

Step 3: Among the 953 potential SUDEP selected at step 1, the 2 reviewers disagreed on adjudicating death as SUDEP or not SUDEP in 79 cases (8.3%) for a Cohen’s kappa value of 0.81 (95% CI, 0.76-0.85). They also disagreed in another 94 cases (9.7%) on the classification level of SUDEP. Following the evaluation of these 173 discordant cases by the third reviewer, adjudication per-protocol resulted in 632 SUDEP (66.3%) classified as definite (n = 38; 4%), probable (n = 63; 7%), and possible (n = 531; 56%) (Table S1), with an overall crude SUDEP rate of 2.28/1000 PY of follow-up (95% CI, 2.10-2.46). Following discussions of all cases with disagreements between the 3 adjudicators, most disagreements appeared to result from failures to identify important information in the death narrative or among CCDs. The 3 experts eventually reached a consensus conclusion in all cases, resulting in a total of 638 SUDEP (66.9%), almost identical to that of the per-protocol adjudication.

Adjudication by extrapolation used for sensitivity analysis resulted in a total of 667 SUDEP (70.0%) and 286 not SUDEP (30.0%).

3.3 | SUDEP rates during follow-up period

The annual age-adjusted SUDEP rates in our per-protocol population significantly decreased with the duration of follow-up (nonparametric Mann-Kendall trend test, S = –27, P = .008) (Table 2). Nonparametric tests based on survival analysis confirmed that the hazard rate of SUDEP including all patient ages decreases with duration of follow-up (Barlow-Campo L = 1, P = .001). This was graphically observed from year 1 (2.73/1000 PY) to year 9 (1.23/1000 PY), with a rebound at year 10 (2.09/1000 PY) (Figure 1). Comparable findings were observed for crude SUDEP rates (S = –27, P = .008) and sensitivity analyses restricted to the 10-54 age range, except for the lack of rebound at 10 years in the latter age range (S = –35, P < .001) (Table 2 and Figure 2). Accordingly, the crude and age-adjusted SUDEP rates during years 3 to 10 of follow-up (2.10/1000 PY, 1.68/1000 PY) were significantly lower than those observed during the first 2 years of follow-up (2.74/1000 PY; 2.47/1000 PY), with rate ratios of 0.77 (95% CI, 0.65-0.91, P = .002) and 0.68 (95% CI 0.53-0.87, P = .002), respectively (Table 2).

Adjudication by extrapolation provided comparable results with significant outcomes for all 4 rate ratios and 3 of the 4 Mann-Kendall trend tests with the exception of a nonsignificant decreasing trend for one age-adjusted analysis (S = –17, P = .078) (Table 2 and Figures S1 and S2).

Similarly, when only considering definite and probable SUDEP, both crude and age-adjusted Mann-Kendall trend tests, and the rate ratio comparing years 3 to 10 to the first 2 years of follow-up, showed a highly significant decreased SUDEP rate over time (see Table 2).

SUDEP rates during the first year of VNS Therapy as a function of calendar year did not decrease significantly between 1999 and 2012 (S = –25, P = .96) (Figure 3). Furthermore, because new patients entered the cohort during the entire study period, the average date of follow-up for patients at years 1 and 2 post-VNS implantation (December 2004) was only 3 years earlier than for patients at years 3 to 10 post-VNS implantation (December 2007). We calculated that 566 SUDEP cases should have been observed during years 3 to 10 of follow-up if the risk of SUDEP per age group would remain the same as that observed during the first 2 years of follow-up. This translated into an SMR of 0.75 (95% CI, 0.68-0.82) in comparison with the 423 SUDEP duly observed during years 3 to 10 of follow-up (Table 3).

To better understand the pace of reduction in SUDEP rate over time, we investigated the crude and age-adjusted SUDEP rates by trimester during the first 2 years post-VNS implantation. As illustrated in Figure S3, these rates appear to remain relatively stable during this period.

4 | DISCUSSION

The primary finding from this large longitudinal long-term cohort study is the observation that SUDEP rates decrease over time in patients with drug-resistant epilepsy being treated with adjunctive VNS Therapy. The decrease in SUDEP rate appears to be sustained until the ninth year of follow-up postimplantation, translating into an overall 25%
| Adjudication per protocol | Crude SUDEP rates 1000 PY | Age-adjusted SUDEP rates 1000 PY |
|--------------------------|--------------------------|---------------------------------|
|                          | Mann-Kendal trend test   | Years 1-2 | Years 3-10 | Rate ratio (95% CI) | Mann-Kendal trend test | Years 1-2 | Years 3-10 | Rate ratio (95% CI) |
| Adjudication by extrapolation |                          |            |            |                  |                          |            |            |                  |
| All ages (N = 632)       | $S = -27 \, P = .008$    | 2.74       | 2.10       | 0.77 (0.65-0.91) $P = .002$ | $S = -27 \, P = .008$    | 2.47       | 1.68       | 0.68 (0.53-0.87) $P = .002$ |
| Aged 10-54 (N = 560)     | $S = -37 \, P < .001$    | 3.02       | 2.19       | 0.73 (0.61-0.87) $P < .001$ | $S = -35 \, P < .001$    | 3.00       | 2.16       | 0.72 (0.64-0.81) $P < .001$ |
| Probable and definite SUDEP |                          |            |            |                  |                          |            |            |                  |
| All ages (N = 101)       | $S = -29 \, P < .001$    | 0.67       | 0.25       | 0.37 (0.25-0.55) $P < .001$ | $S = -31 \, P < .001$    | 0.56       | 0.19       | 0.34 (0.23-0.51) $P < .001$ |
| Aged 10-54 (N = 89)      | $S = -37 \, P < .001$    | 0.67       | 0.28       | 0.41 (0.27-0.62) $P < .001$ | $S = -37 \, P < .001$    | 0.67       | 0.27       | 0.41 (0.31-0.54) $P < .001$ |
reduction in the number of SUDEP events expected to occur in this cohort under the hypothesis of stable age-adjusted SUDEP rate during follow-up. The information that individual risk of SUDEP might decrease over time in patients with refractory epilepsy has not been previously reported in the literature and would be of value for patients at risk of SUDEP.

The paucity of individual data available in our cohort is responsible for several limitations. Thus one major shortcoming of this study is that only 16% of SUDEP could be ascertained as definite or probable. In most other cases adjudicated as possible SUDEP, description of the circumstances of death was not sufficiently detailed to support a more robust diagnosis, although death certificate or narrative did not suggest any other clear-cut cause of death. Although based on weaker evidence, adjudication of possible SUDEP was consolidated by the independent assessment of 3 experts who, when invited to discuss disagreed cases, reached a consensus in all cases. Most important to note is that, our goal was not to provide precise epidemiological figures of SUDEP, but to select deaths likely to be due to SUDEP and of sufficient number to test the impact of duration of follow-up on such deaths. From a patient perspective, this latter finding might be more relevant than observations based on restricted cases of probable and definite SUDEP assessed in much smaller populations.
Another limitation of our findings is the interpretation of the decreased rate of SUDEP over time. In particular, the direct role of VNS Therapy cannot be assessed due to the lack of preimplantation baseline, lack of a control group, and lack of information on individual responses to VNS Therapy. In fact, it could be that the risk of SUDEP during first 2 years of VNS treatment differs, in one direction or the other, from the preimplantation baseline. One might also challenge whether the level of antiepileptic efficacy demonstrated in pivotal randomized trials of VNS\textsuperscript{15,16} could explain the reduction in SUDEP rate observed in our cohort. In fact, a meta-analysis of randomized controlled trials (RCTs) of add-on antiepileptic drugs (AEDs) in drug-resistant epilepsy, with an effect size on seizure frequency comparable to that of VNS, showed that the risk of SUDEP was decreased by 7-fold in patients receiving an add-on AED as compared to those allocated to placebo.\textsuperscript{17}

Several other mechanisms could account for our findings including attrition and natural evolution, aging, or changes in medications or medical practice over time. Indeed, one might hypothesize that patients at highest risk of SUDEP might preferentially die during the first 2 years following VNS.

**TABLE 3** Impact of aging on SUDEP rate and number

| Age group | SUDEP rate per age group in years 1-2 | Number of SUDEP expected in years 3-10 | Number of SUDEP observed in years 3-10 | SUDEP rate per age group in years 3-10 |
|-----------|----------------------------------------|----------------------------------------|----------------------------------------|----------------------------------------|
| 0-4       | 0                                      | 0                                      | 0                                      | 0                                      |
| 5-9       | 1.80                                   | 12.5                                   | 3                                      | 0.43                                   |
| 10-14     | 2.10                                   | 32.6                                   | 12                                     | 0.77                                   |
| 15-19     | 1.67                                   | 30.8                                   | 38                                     | 2.06                                   |
| 20-24     | 3.50                                   | 68.9                                   | 42                                     | 2.14                                   |
| 25-34     | 3.51                                   | 134.1                                  | 84                                     | 2.20                                   |
| 35-44     | 3.54                                   | 147.1                                  | 118                                    | 2.84                                   |
| 45-54     | 2.75                                   | 100.4                                  | 78                                     | 2.14                                   |
| 55-64     | 1.91                                   | 35.2                                   | 46                                     | 2.50                                   |
| 65+       | 0.72                                   | 4.1                                    | 2                                      | 0.35                                   |
| Overall   | 2.81                                   | 565.7                                  | 423                                    | 2.10                                   |

**FIGURE 3** SUDEP rate adjudicated according to protocol during the first year post-VNS implantation. The age-adjusted SUDEP rates per 1000 person-years of follow-up are shown for calendar years 1999 to 2012.
implantation. Cross-sectional epidemiological data rather suggest that SUDEP rate increases with epilepsy duration >15 years as compared to ≤15 years (odds ratio [95% CI] 1.95 [1.45-2.63]). However, we have no information regarding the natural evolution of SUDEP rates for longer epilepsy duration, and do not know the duration of epilepsy in our cohort. The role of aging in driving our main finding appears unlikely according to our age-adjusted analyses and simulation of the effect of aging on the individual risk of SUDEP during years 3-10 of VNS Therapy. The censored group of 2864 patients who had their device explanted or turned off prior to the cutoff date is also unlikely to influence the SUDEP trends over time, as this group represented a small and consistent 1% of patients each year post VNS implantation. The possibility that new AEDs made available during this study could have influenced our findings also seems unlikely according to a difference of only 3 calendar years between the average follow-up dates of years 1 and 2 and years 3 to 10 postimplantation and lack of a significant reduction in SUDEP rate during the first year of post VNS implantation over a 13-year period.

Our finding of a sustained reduction in SUDEP rate in patients undergoing VNS Therapy is consistent with one of the 2 small-scale studies previously published. A SUDEP rate of 5.5/1000 PY of follow-up (95% CI, 2.8-9.8) was observed during the first 2 years postimplantation, which decreased to 1.7/1000 PY of follow-up (95% CI, 0.2-6.1) thereafter. However, another single-center study with 10 SUDEP cases reported no difference between the first 2 years of VNS Therapy (3.4/1000 PY [95% CI, 0.7-10]) and the following years (3.3/1000 PY [95% CI, 1.3-6.8]).

Our data fall into the confidence intervals reported in these 2 series (Figure S4). However, the value of such comparison is hampered by the fact that our cohort includes a majority of possible SUDEP, whereas the other studies only considered definite and probable SUDEP. There might be several mechanisms by which VNS could participate to decrease SUDEP rate over time. Open-label series suggest that VNS reduces the frequency of generalized tonic–clonic seizure, the main SUDEP risk factor in focal and generalized epilepsies, and that the time-frame increase in seizure reduction is consistent with that of SUDEP reduction reported herein. VNS stimulation may also reduce the duration and severity of the ictal and postictal phases, which could mitigate some of the mechanisms contributing to seizure-induced SUDEP.

An intriguing, yet unexplained, finding is the apparent rise in the risk of SUDEP at year 10 of follow-up. It appeared to be primarily driven by the very rare cases of SUDEP occurring in children younger than 10, and was not observed in the population aged 10-54, suggesting the possibility of a random fluctuation of SUDEP rate in very young patients.

Overall, long-term follow-up of patients with drug-resistant epilepsy undergoing VNS Therapy suggests that the risk of SUDEP significantly decreases over time for reasons that remain uncertain and deserve to be further explored. However, according to the 25% reduction of SUDEP rate observed in the study, a 3-year-long RCT would need to enroll a minimum of 28 000 patients in each arm of adjunctive VNS vs treatment-as-usual, which is not feasible. Novel biomarkers highly predictive of SUDEP will be needed to make prospective studies of SUDEP prevention feasible in an enriched population. Until then, only large retrospective cohorts, such as the study presented here, can help us make progress in SUDEP prevention, an issue that one should acknowledge when weighing the limitations and value of currently available data.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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