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Clinical and Economic Benefits of Upper Airway Stimulation for Obstructive Sleep Apnea in a European Setting

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Keywords
Upper airway stimulation · Implantable pulse generator · Obstructive sleep apnea · Sleep apnea · Markov model · Decision support techniques · Cost-effectiveness analysis · Cost-benefit analysis

Abstract
Background: Upper airway stimulation (UAS) is a treatment approach for patients with moderate-to-severe obstructive sleep apnea who cannot adhere to continuous positive airway pressure therapy. ***Objective:*** The objective was to evaluate added patient benefit and cost-effectiveness of UAS in the German health care system. ***Methods:*** We used a decision-analytic Markov model to project major adverse cardiovascular or cerebrovascular events (myocardial infarction [MI] or stroke), motor vehicle collision (MVC), mortality, quality-adjusted life years (QALYs), and costs. The assumed reduction in the apnea-hypopnea index with UAS compared to no treatment is based on German real-world data. Other input data were derived from the literature, public statistics, and multivariate regression. Cost-effectiveness was evaluated in Euros per QALY gained, both discounted at 3%. ***Results:*** UAS was projected to reduce event risks (10-year relative risk for stroke, MI, cardiovascular death, and MVC: 0.76, 0.64, 0.65, and 0.34, respectively), and to increase survival by 1.27 years. While the UAS strategy incurred an additional 1.02 QALYs within the patient lifetime, there were also additional costs of EUR 45,196, resulting in an incremental cost-effectiveness ratio of EUR 44,446 per QALY gained. ***Conclusions:*** In the present model-based analysis, UAS therapy provides meaningful benefit to patient-relevant endpoints and is a cost-effective therapy in the German setting.

Introduction

Obstructive sleep apnea (OSA) is a condition characterized by frequent interruption in breathing due to collapsing pharyngeal soft tissue while asleep [1, 2]. Gender-

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and age-specific prevalence of moderate-to-severe OSA, as defined by an apnea-hypopnea index (AHI) of ≥15 events/h), has been estimated to range from 3 to 17% [3, 4].

OSA is a risk factor for several cardiovascular, neurologic, as well as metabolic conditions and is associated with increased daytime sleepiness and reduced health-related quality of life [3, 5, 6]. Importantly, OSA-related increases in daytime sleepiness have been shown to be associated with increased risks of motor vehicle collisions (MVCs) and other accidents, which pose particularly high risks for professional drivers and other high-risk professions [5].

To improve quality of life and avoid or reduce adverse consequences of OSA, several therapies are available in routine clinical practice: In mild-to-moderate disease, OSA treatments include dental appliances, positional therapy, and continuous positive airway pressure (CPAP). In moderate-to-severe OSA, CPAP is recommended as first-line therapy and continues to be the mainstay treatment approach [7]. Anatomy-altering surgical interventions can be considered in selected cases. If adhered to, CPAP decreases or even eliminates daytime sleepiness and adverse events associated with OSA. However, nonfitted masks, difficult anatomies, adverse events, or (more commonly) the discomfort of wearing the mask and being ventilated lead to suboptimal adherence, resulting in reduced treatment effectiveness. Previous studies have estimated that adherence to CPAP ranges from 50 to 90% in European countries [8].

For individual patients who are either ineligible for CPAP or mandibular advancement devices or show insufficient treatment efficacy, upper airway stimulation (UAS) has recently emerged as a more viable treatment alternative and has been adopted in clinical practice [7]. This treatment approach involves unilateral respiration-synchronized stimulation of the hypoglossal nerve through surgical placement of an implantable pulse generator, a breathing sensor, and a stimulation electrode placed on the hypoglossal nerve. UAS has been shown to safely and effectively maintain airway patency in controlled clinical trials when certain physiological and anatomical criteria are met [9–11]. One of the major selection criteria for therapy response is the absence of a complete concentric collapse in drug-induced sleep endoscopy [12], which is seen in about a fifth of second-line treatment-seeking patients in a German cohort [13].

In the multicenter prospective observational STAR study conducted in the United States, UAS with the Inspire system (Inspire Medical Systems, Inc., Minneapolis, MN, USA) was shown to reduce the AHI by 68% from 29.3 to 9.0 events per hour at the 12-month follow-up ($p < 0.001$) and to clinically meaningful reductions in daytime sleepiness and increase patients' health-related quality of life [9]. These reductions in disease severity and improvements in quality of life were sustained at the 3- and 5-year follow-ups [10]. Comparable data confirming the safety and effectiveness of the Inspire system at the 12-month follow-up in a real-world setting were recently reported by a prospective German multicenter study (n = 60) [11, 14].

As UAS therapy may involve high upfront investment, long-term outcomes with regard to clinical benefits and cost-effectiveness are of relevance for patients, physicians, and health care systems. A previous health-economic model, projecting costs and outcomes based on the 12-month data from the STAR study, found UAS to be cost-effective in the US context [15].

The objective of the current study was to estimate the long-term clinical benefit as well as the cost-effectiveness of UAS in a German patient cohort.

Materials and Methods

Study Design

A decision-analytic modeling framework projected 10-year and lifetime clinical outcomes and costs of UAS therapy compared to no therapy based on recently published cohort characteristics and effectiveness data from the recent German post-market study [14].

Methods

The model adopted the structure of a previously published Markov model that has been used to investigate the effect of different diagnostic and therapeutic OSA strategies [15]. In brief, this model is comprised of 5 health states and tracks the occurrence of stroke, myocardial infarction (MI), MVC, and death based on multivariate risk equations. To account for different mortality risks and costs after the tracked cardiovascular events, the model includes post-stroke and post-MI states. Schematic representations of the model can be found in Figure 1 and the supplementary material (for all online supplementary material, see www.karger.com/doi/10.1159/000497101).

We populated this model with incidence and prevalence data from the German setting, relying on systematic literature searches to identify parameter data. Wherever available, data for Germany were used; these included lifetables, MI and stroke incidence, prevalence of hypertension, and baseline risks of MVCs. Where German data were not available, inputs from other European or global settings were used to complement the data, as appropriate. Table 1 summarizes key model inputs (see also supplementary material).

Cohort characteristics were based on the German prospective observational study [11] and included a predominantly male population at an average age of 57 years at the time of UAS index treat-

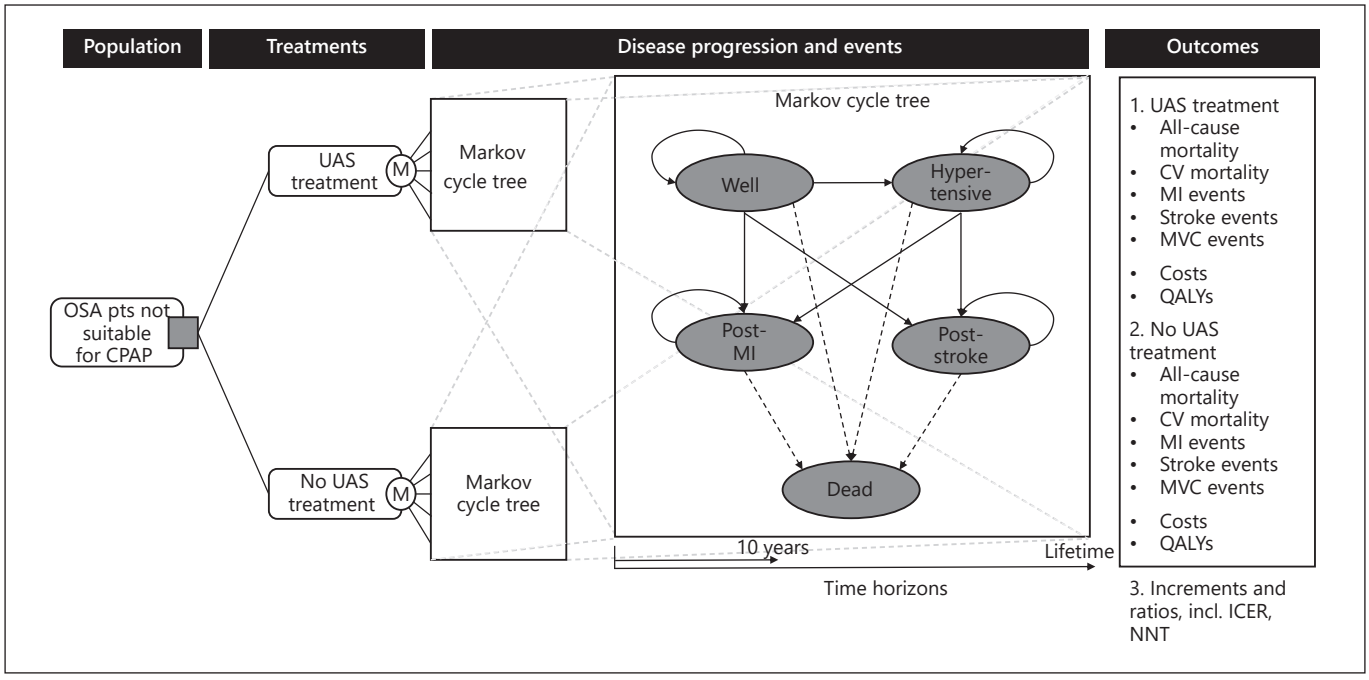

Fig. 1. Schematic representation (simplified) of the model structure, a combination of decision tree and a Markov model. CPAP, continuous positive airway pressure; MI, myocardial infarction; MVC, motor vehicle collision; NNT, number needed to treat; OSA, obstructive sleep apnea; QALY, quality-adjusted life year; UAS, upper airway stimulation.

ment. In that study, the mean baseline AHI of 31.2 events per hour was reduced to 13.8 events per hour within 12 months [14].

In line with the previously published model [15], we performed multivariate linear regression to determine cardiovascular event risks associated with different AHI levels, relying on data from a European cohort study that followed CPAP-treated and non-CPAP-treated patients with different OSA severity over 10 years [16]. AHI was used as it was previously observed that lower AHI levels were associated with a better prognosis. We defined the subset of snorers (AHI of 3.5) as representative for the general population mortality and computed hazard ratios of cardiovascular events associated with AHI rates of 13.8 and 31.2 events per hour, compared to baseline 3.5 [14]. These hazard ratios were multiplied with the baseline event rates for the general population to obtain AHI-adjusted cardiovascular event rates. Based on the regression analysis, we obtained an estimated UAS-associated cardiovascular event risk reduction of 75%. This estimate was further multiplied by the percentage of daily UAS use (81%) reported at the 3-year follow-up in the STAR study [10]. Thus, the estimated effective cardiovascular event risk reduction was 61% (i.e., a 61% reduction in the OSA-associated excess risk) (Table 1; online suppl. material).

MVC event risk in effectively treated patients was assumed to be similar to the general population risk, whereas a threefold increased risk was assumed in untreated patients [17, 18].

For the base case analysis, therapy effectiveness was assumed to be maintained over the patient's remaining lifetime, assuming a constant percentage of daily UAS use. This assumption is supported by the long-term UAS effectiveness observed at the 5-year follow-up in the STAR study [10].

Health state-specific utility estimates were based on values from the published literature and ranged from 0.63 for patients after stroke to 1.0 for patients at non-elevated AHI level without symptoms or other cardiovascular morbidity before age adjustment (Table 1).

The UAS treatment costs included pretreatment examinations, device costs, inpatient hospital stay for device implantation, activation, and titration, as well as annual follow-up outpatient visits (Table 1; online suppl. material). In line with the current product documentation, a mean battery lifetime of 11 years was assumed, at which time replacement of the implantable pulse generator is required.

In the model, acute costs for MI, stroke, and MVC events were considered as well as health state-specific costs which were comprised of age-dependent general health care costs applying to each patient alive and additional condition-specific costs for hypertension and states after MI and stroke. All costs were derived from published literature and public statistics and, if appropriate, adjusted to reflect current German clinical practice (Table 1; online suppl. material). The harmonized German general consumer price index was used to adjust all costs to reflect 2016 Euro values.

Analysis

For both treatment strategies in the model, we computed event rates (MI, stroke, MVC, and cardiovascular disease [CVD] mortality), unadjusted and quality-adjusted survival, and costs. Primary outcomes were 10-year and lifetime-relative event risks, numbers needed to treat (NNT), and unadjusted and quality-adjusted survival gain.

Table 1. Model input parameters

Variable	Base case	Range	Reference
Cohort characteristics			
Age, years	56.8	37–75	[11]
Male gender	96.7%	0–100%	[11]
Risks associated with events and model states			
Annual risk of MVC causing injury or death			
Males	0.0091	±20% rate	German Federal
Females	0.0049	±20% rate	Statistics Office
Probability of death from an MVC with injury or death	0.0087	±20% rate	
Prevalence of hypertension (varies by age, 30–70 years)			
Males	0.114–0.736	±20% rate	[26]
Females	0.048–0.747	±20% rate	
Rate (annual per person, until age 85) for incident hypertension			
Males	0.0466ln(age)–0.1555	±20% rate	[26]; suppl. material
Females	$(1\times10^{-7})\times age^{3.0874}$	±20% rate	
Rate (annual per person, until age 85) for incident MI			
Males	$0.0003\times age^{3.4556}$	±20% rate	Based on [27], see suppl.
Females	1.167ln(age)–0.0788	±20% rate	material
HR for incident MI, with hypertension	2.4	2.0–3.5	[28]
Probability of 28-day mortality (varies by age)			
Males	0.25–0.58	±20% rate	[27]
Females	0.32–0.58	±20% rate	
HR for all-cause mortality, life after MI	1.56	1.35–1.74	[27]
Rate (annual per person, until age 85) for incident stroke	$(3.1\times10^{-13})\times age^{5.569}$	±20% rate	Based on [29–31], validated with Palm et al. [31]; suppl. material
HR for incident stroke, with hypertension	2.44	2.0–4.6	[32]
Probability of 28-day mortality, varies by age	0.09–0.52	±20% rate	[30]
HR for all-cause mortality, life after stroke	2.2	1.1–2.8	[33]
HRs associated with OSA			
HR for MVC causing injury or death	3.0	2.5–3.5	[18, 34]
HR for developing hypertension	1.8	1.3–1.9	[35]
HR for incident MI	2.6	1.9–4.3	[24]
HR for incident stroke	1.7	1.0–3.5	[36]
UAS effectiveness (percent returning to non-OSA risk level [1.0 = 100% effectiveness])			
CVD (hypertension, MI, stroke)	0.754	0.25–1.0	[11, 24]; suppl. material
MVC	1.0	0.25–1.0	[9, 18, 37]
UAS compliance	0.81		[10]
UAS battery life, years	11	8–13	[9], manufacturer-provided estimate (rounded)

Cost-effectiveness was evaluated based on the incremental cost-effectiveness ratio (ICER), measured in terms of cost difference divided by difference in quality-adjusted life years (QALYs), both of which were discounted at 3% p.a., as recommended in current guidelines for cost-effectiveness analysis [19]. In the absence of published willingness-to-pay thresholds for Germany, we followed WHO recommendations, where an intervention with an ICER at <1 time per capita gross domestic product (GDP) is considered highly cost-effective and at <3 times per capita GDP cost-effective [20]. The German per capita GDP in 2016 was EUR 37,866 [21].

One-way deterministic sensitivity analyses were performed based on the parameter ranges given in Table 1 to evaluate the effect of parameter uncertainty on the cost-effectiveness results.

Table 1 (continued)

Variable	Base case	Range	Reference
Costs (2016 EUR)			
UAS treatment, EUR			
UAS implantation (surgery/device) and follow-up (one time)	26,184	±30%	See suppl. material for full details
UAS replacement incl. device/surgery/battery (every 11 years)	20,498	±30%	
Annual office visits	58	±30%	
Acute (one-time) events, EUR			
Nonfatal MVC with injuries	3,083	50–200%	[38–40]
Fatal MVC	5,513	50–200%	[38–40]
Acute MI	8,606	±30%	G-DRG calculation (suppl. material)
Acute stroke	14,218	±30%	[41]
Health state-specific costs (annual), EUR			
Baseline, varies by age	1,198–5,212	N/A	[42]
Health state-specific care costs (additive to baseline cost), EUR			
Well	0	N/A	
Hypertension	433	±30%	[43] (suppl. material)
Post-MI	373	±30%	Estimation based on micro-costing (suppl. material)
Post-stroke, after year 1	3,486	±30%	[41]
Quality-of-life weights			
Baseline, decreases by age (40–80 years)	0.871–0.736		[44]
Health state-specific weights			
Well	1	N/A	
Hypertension	0.96	0.79–0.98	[44]
MI: first year	0.76	0.50–0.87	[45, 46]
Stroke: first year	0.63	0.26–0.92	[47, 48]
Post-MI	0.88	0.67–0.94	[47]
Post-stroke	0.63	0.26–0.92	[47, 48]
Untreated OSA	0.84	0.80–0.93	[49, 50]
Treated OSA	0.93	0.84–0.98	[49, 50]
Nonfatal MVC (lifetime discounted decrement)	0.036	0.031–0.418	[51]
Disutility of UAS implantation	0.016	0–0.032	Assumption

CVD, cardiovascular disease; G-DRG, German Diagnosis-Related Group; HR, hazard ratio; MI, myocardial infarction; MVC, motor vehicle collision; OSA, obstructive sleep apnea; UAS, upper airway stimulation.

Results

The projected event risk reduction for UAS treatment over a 10-year period was 24% for stroke (0.058 vs. 0.076), 36% for MI (0.111 vs. 0.173), and 66% for MVC (0.083 vs. 0.0246). Cardiovascular death and all-cause death were reduced by 35% (0.053 vs. 0.082) and 15% (0.165 vs. 0.195), respectively, in 10 years. Resulting NNTs to avoid 1 event ranged from 6.2 for MVC to 55.6 for stroke (Fig. 2; online suppl. material).

Over the lifetime horizon, relative event risk reduction ranged from 64% for MVC events (0.182 vs. 0.512) to 4% (0.243 vs. 0.254) for stroke. Associated NNTs varied between 3 patients for MVC events and 91 for stroke (Fig. 2; online suppl. material). The survival benefit for UAS-treated patients compared to untreated patients was 1.27 life years with life expectancy increasing from 19.14 to 20.41 years. The undiscounted gain in QALYs is 1.56 QALYs based on an increase from 12.15 to 13.71 QALYs during the patient's lifetime.

For the lifetime projection, UAS treatment was cost-effective compared to no treatment at an ICER of EUR 44,446 per QALY (Table 2). Projecting costs and QALYs over a 10-year period resulted in a slightly higher ICER of

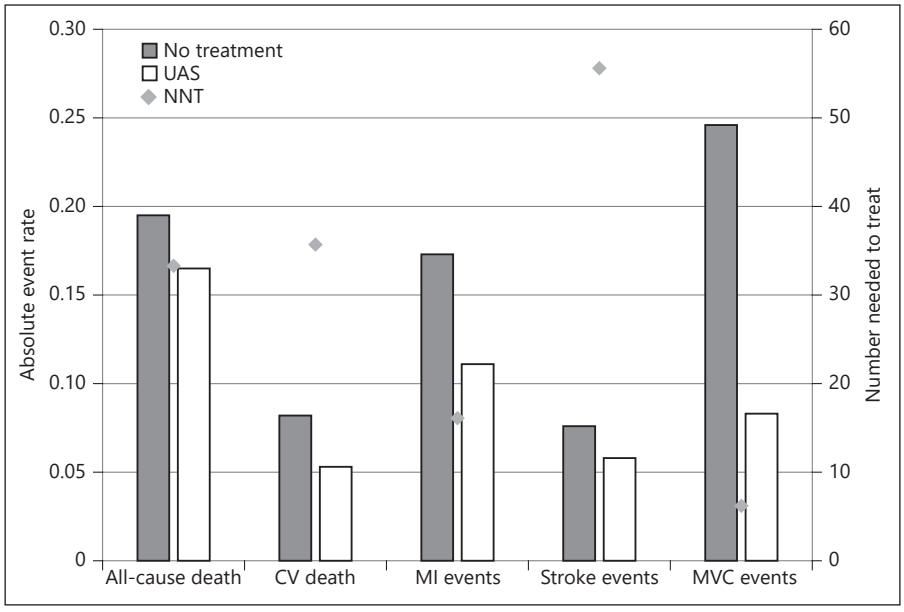

Fig. 2. Absolute event rates and number needed to treat (NNT) of clinical events for a 10-year time horizon (see supplementary material for details as well the for the lifetime analysis). CV, cardiovascular; MI, myocardial infarction; MVC, motor vehicle collision; UAS, upper airway stumulation

Table 2. Total and incremental costs and quality-adjusted life years (QALYs) for a lifetime and 10-year time horizon

Treatment strategy	Total costs[a], EUR	Total QALYs[a]	Difference in costs	Difference in QALYs	ICER, EUR/QALY
Lifetime time horizon					
No treatment	54,161	8.92			
UAS treatment	99,357	9.94	45,196	1.02	44,446
Ten-year time horizon					
No treatment	24,597	5.28			
UAS treatment	50,189	5.70	25,592	0.42	60,216

ICER, incremental cost-effectiveness ratio; UAS, upper airway stimulation.
[a] Discounted at 3% p.a.; all costs are 2016 values.

EUR 60,216/QALY. The total observed cost difference between UAS and no treatment of EUR 45,196 (99,537 vs. EUR 54,161) resulted from UAS index implant costs (EUR 26,184; 58% of total), UAS replacement costs (EUR 17,639, 39% of total), and baseline health care and maintenance costs (EUR 1,373; 3% of total).

Sensitivity analyses showed that assumptions about UAS adherence and cardiovascular event risk reduction based on the study-observed AHI changes had the largest effect on the ICER (Fig. 3; online suppl. material). Under the assumption of 100% therapy adherence, the ICER was reduced to EUR 34,974 per QALY gained. Assuming 50% cardiovascular event risk reduction as the result of UAS therapy, as opposed to the base case assumption of 75%, increased the ICER to EUR 68,612 per QALY gained. Assuming a 50% lower baseline MI risk increases the ICER by EUR 1,596 per QALY gained. An assumed shorter battery lifetime increased the ICER (EUR 50,250 per QALY for assumed 9 years of lifetime), while longer battery lifetime lowered it (EUR 40,475 per QALY for assumed 13 years of lifetime). As none of the tested scenarios led to an ICER that would be considered not cost-effective overall, the cost-effectiveness findings were deemed to be robust. For completeness, we assessed the theoretical adherence threshold under which UAS would not be considered cost-effective and found this value to equate 33%.

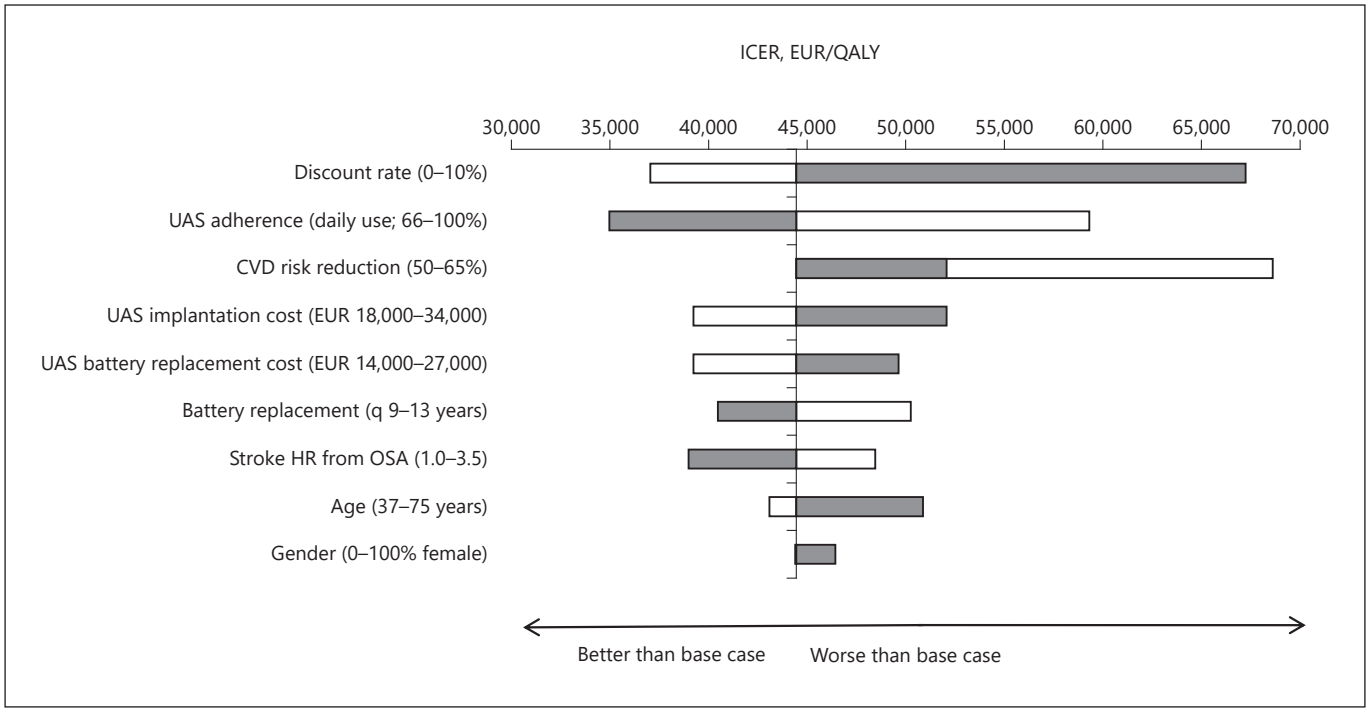

Fig. 3. One-way sensitivity analyses (as tornado diagram) on key model assumptions. The white bar represents the low and the black bar the high value. CVD, cardiovascular disease; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OSA, obstructive sleep apnea; QALY, quality-adjusted life year; UAS, upper airway stimulation.

Discussion

The long-term projections of clinical benefits and costs associated with UAS treatment of patients with moderate-to-severe OSA who do not qualify for CPAP therapy found UAS to provide meaningful benefit to patients at acceptable costs compared to no treatment. Specifically, our analysis found UAS to add more than 1 year of lifetime concomitant with overall improved health-related quality of life.

These findings are generally in line with the earlier cost-effectiveness analysis conducted in the US setting based on the STAR study [15], but add significant new insight. First, our study is based on recent real-world data from a post-market study that reflects practice patterns and patient selection criteria that have been further established in the early years of UAS adoption in clinical practice. Second, our current analysis is based on German incidence and prevalence data of underlying conditions, including hypertension, MI, and stroke incidence, and event rates including MVC incidence, which partly differ from US cohort data. Furthermore, German health care system costs differ substantially from US health care costs, including acute and long-term costs of events that may be avoided or decreased with UAS therapy. It is noteworthy that CPAP adherence over 1 year exceeds 60% in Germany with polysomnographic therapy adjustment [22]. Studying the effect of these changes on cost-effectiveness is hence particularly relevant to German and European decision makers.

In Germany and other European health care systems not adopting a formal willingness-to-pay threshold for decision making, added patient benefit – as measured by differences in mortality, morbidity, and health-related quality of life – is considered an important criterion in the evaluation of the societal value of new therapies. Our findings show that UAS therapy can be expected to add clinically significant benefit to OSA patients who have exhausted first-line therapeutic options.

These reported benefits stem primarily from the expected long-term event reductions and quality of life improvements associated with a maintained reduction in AHI. Our analysis assumes that therapy effectiveness is maintained over the patient's lifetime at levels observed during 12-month follow-up. This assumption is support-

ed by the currently available long-term follow-up data from the STAR study, which showed continued therapy effectiveness at the 5-year follow-up at levels comparable to the 12-month data [14, 23]. As our sensitivity analyses show, potential changes in long-term therapy effectiveness have a direct effect on clinical outcome and associated long-term costs. While any such changes would therefore alter the projected clinical benefit to patients, the effect on cost-effectiveness is less pronounced. This is, in part, explained by the fact that any increases in survival benefit are also associated with increased baseline health care costs incurred during the additional survival, and that any such survival increases also result in additional clinical events the patients might suffer, which in turn add to cost. Similarly, a reduction in UAS-related survival benefit also results in a concurrent reduction in these types of cost, hence limiting the sensitivity of the ICER metric to changes in long-term therapy effectiveness. However, the findings of this model regarding the long-term cost-effectiveness should be interpreted with caution until further trials confirm long-term maintenance of AHI reduction.

One key difference in the baseline event ratios is the higher MI rate compared to the US. We believe that we used the best data available; therefore, we subjected this parameter to extensive sensitivity analyses. However, even when reducing the MI incidence rate by 50%, the ICER did not change by more than EUR 1,600/QALY, which is likely due to this parameter affecting both treatment groups.

The analysis is subject to a number of limitations. First, as described in the prior UAS model publication, our model is a simplified representation of clinical reality and, as such, may not fully capture all possible patient pathways that might be observed in clinical practice [15]. However, this is a typical and well-accepted limitation of any model-based analysis.

Second, cardiovascular event risk reduction, as discussed earlier, needed to rely on a regression-based analysis and, therefore, is hypothesis based, with some degree of uncertainty. While the study by Marin et al. [24] provides data from a European cohort that shares in many aspects characteristics that are similar to the present cohort, effects in UAS-treated patients might differ from those observed in the Marin study, in which reductions in AHI were based on CPAP therapy. In addition, the study by Marin et al. [25] was not an interventional study. Further, a recent study has challenged the significance of clinical event risk reduction that can be induced by CPAP therapy. Some of these challenges might also apply to UAS therapy. Nevertheless, there is still wide agreement that effective OSA treatment, as evidenced by a meaningful reduction in AHI, can be expected to be associated with clinically meaningful reduction in long-term events and an improvement in survival. As cardiovascular event reduction was found to have a strong impact on cost-effectiveness of UAS treatment within the conducted sensitivity analyses, more reliable data on the relation of AHI and cardiovascular event rates will facilitate the assessment of the validity of the projected results. In this context, further elucidation of the potential underlying mechanism by which UAS might lower cardiovascular events would be desirable.

Third, the battery lifetime of the UAS implantable pulse generator is estimated based on laboratory testing and simulations only. A lifetime shorter than the assumed 11 years would negatively affect the cost-effectiveness of the UAS treatment, as shown in our sensitivity analysis. Still, even an approximately 20% shorter battery lifetime would not meaningfully change the cost-effectiveness findings.

Fourth, to calculate QALYs, utility data derived from preference-based quality of life instruments such as the EQ-5D or SF-6D are required. Since both the STAR study and the current German post-market study assessed health-related quality of life using disease-specific non-preference-based instruments, we needed to rely on health state-specific utility estimates from the published literature. However, the employed utility values have been widely used in OSA-related cost-effectiveness analyses, and the variation in these parameters did not lead to meaningful changes in cost-effectiveness results.

Finally, while the analysis is conducted based on cohort and incidence data that are likely representative for a broader European setting, the cost analysis is based on current data from the German health care system. Due to country-specific variations in UAS device and implantation costs, as well as differences in treatment patterns and costs for cardiovascular events and patient follow-up, our current findings may not be readily transferred to other European health care systems without consideration of the potential effect of differences in underlying cost parameters.

In summary, UAS is a therapy that has previously been shown to be clinically efficacious and that in the present model-based analysis added >1 life year or QALY to the remaining life expectancy by reducing, among other events, MIs and MVCs at acceptable costs. Hence, UAS adds meaningful benefit to the health of OSA patients who cannot adhere to CPAP therapy and is a cost-effective treatment strategy in the German health care setting.

Statement of Ethics

Given the study type was a model-based analysis, institutional review board approval and patient consent to participate was not applicable.

Disclosure Statement

The authors maintained the right to publish without approval of the funding source.

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Authors Contributions

J.B.P., A.-K.R., and J.B.-S. conceived of the study, participated in the study design, data collection, model-based analysis, and drafted the manuscript. B.P.G. participated in the model-based analysis and helped with drafting the manuscript. S.L. participated in the model-based analysis. W.R. and A.S. participated in the study design, critically reviewed the model assumptions, and helped with drafting the manuscript. J.W. critically reviewed the model assumptions and projections and helped with drafting the manuscript. All authors read and approved the final manuscript.

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