**Clinical and Economic Benefits of Upper Airway Stimulation**

**for Obstructive Sleep Apnoea in a European Setting**

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**Supplementary Material**

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**S.1 Model structure**

**UAS Treatment or No Treatment**







**Figure S1: Representation of Model structure, showing modeled health states and transitions (top), event tree for well and hypertensive states (2nd from top), and event trees post-MI (2nd to bottom) and post-stroke (bottom).**

MI myocardial infarction; MVC motor vehicle collision; UAS upper airway stimulation

**S.2 Regressions for incidence data input**

Due to the lack of German data on hypertension incidence a regression model was used to calculate the incidence of hypertension based on German prevalence data given in table S1 [[1](#_ENREF_1)].

|  |  |
| --- | --- |
| **Patient age (years)** | **Prevalence of hypertension** |
| **Men** | **Women** |
| 0-29 | 0.084 | 0.013 |
| 30-39 | 0.114 | 0.048 |
| 40-49 | 0.262 | 0.172 |
| 50-59 | 0.417 | 0.346 |
| 60-69 | 0.588 | 0.607 |
| ≥70 | 0.736 | 0.747 |

**Table S1 Prevalence of hypertension by age and gender [**[**1**](#_ENREF_1)**]**

The formula providing the best fitting incidence rate for men was

$$0.0466\*ln\left(age\right)-0.1555$$

and for women it was

$$\left(1\*10^{-7}\right)\* age^{3.0874}$$

where ln is the natural logarithm and age denotes the patient’s age.

The regression-estimated incidence of hypertension for men and women is displayed in figures S2 and S3, respectively.

**Figure S2 Regression on incidence of hypertension for men**

**Figure S3 Regression on incidence of hypertension for women**

To estimate the incidence of acute myocardial infarction for each age group, regressions were run based on German incidence data [[2](#_ENREF_2)] by age group given in table S2.

|  |  |
| --- | --- |
| **Patient age (years)** | **Incidence of acute myocardial infarction** |
| **Men** | **Women** |
| 25-54 | 0.00097047 | 0.000290042 |
| 55-64 | 0.0044298 | 0.001130639 |
| 65-74 | 0.00645076 | 0.003154972 |
| 75,84 | 0.01098006 | 0.006551414 |

**Table S2 Incidence of acute myocardial infarction by age and gender [**[**2**](#_ENREF_2)**]**

The formula resulting in the best fit for estimating acute myocardial infarction incidence for men was

$$0.0003\* age^{3.4556}$$

and for women it was

$$1.167\* e^{0.0788\* age}$$

where e is Euler’s number and age refers to the patient’s age.

The resulting estimated incidence rates of acute myocardial infarction for men and women are shown in figures S4 and S5, respectively.



**Figure S4 Regression on incidence of MI for men.**



**Figure S5 Regression on incidence of MI for women.**

To estimate the incidence of stroke for each age group, regressions based on U.S. stroke incidence data[[3](#_ENREF_3)] given in table S3 were calculated.

|  |  |
| --- | --- |
| **Patient age (years)** | **Rate per 100,000** |
| **estimated** | **1980-84** | **1985-89** |
| 35 | 39.00 | 2.10E+01 | 2.90E+01 |
| 45 | 49.00 | 1.02E+02 | 6.40E+01 |
| 55 | 59.00 | 1.96E+02 | 1.95E+02 |
| 75 | 69.00 | 4.83E+02 | 5.24E+02 |
| 85 | 79.00 | 1.20E+03 | 1.19E+03 |
| 95 | 89.00 | 2.66E+03 | 2.57E+03 |

**Table S3 Incidence of acute stroke [**[**3**](#_ENREF_3)**]**

The formula resulting in the best fit for estimating stroke incidence was

$$min((0.0000000311\*(Age^{5.569})); (0.0000000311\*(85^{5.569})))$$

The resulting estimated incidence rates of stroke for men and women is shown in figure S6



**Figure S6 Regression on incidence of stroke.**

For comparison/external validation: The Ludwigshafen Stroke Study (LuSSt) was a a prospective population-based stroke register in the population of the city of Ludwigshafen am Rhein that started on January 1, 2006 [[4](#_ENREF_4)]; the key figures are reproduced in table S4.

|  |  |
| --- | --- |
| **Patient age (years)** | **Rate per 1,000 (Men and Women)** |
| 25-34 | 0.25 |
| 35-44 | 1.38 |
| 45-54 | 3.04 |
| 55-64 | 5.27 |
| 65-74 | 11.08 |
| 75-84 | 16.72 |

**Table S4 Incidence of acute stroke [**[**4**](#_ENREF_4)**]**

**S.3 Estimation of UAS effectiveness in reducing cardiovascular events**

###### The methodology for estimation of UAS effectiveness in reducing cardiovascular events follows the approach described in the prior UAS analysis (Pietzsch et al, 2015), but uses the data from the German post-market study (Heisler et al, 2016) instead of the STAR Trial data.

###### In the German PMS study, the mean pre-treatment (baseline) AHI was 31.2 events per hour. 12 months’ post UAS implantation, the mean AHI was 13.8 events per hour. Using this information, we estimated the UAS therapy effectiveness in reducing cardiovascular event risk (non-fatal and fatal combined) as follows:

###### We used data from Marin et al.[[5](#_ENREF_5)] that reported long-term cardiovascular outcomes in CPAP-treated vs. untreated male OSA patients. The Marin study included 264 healthy men, 377 simple snorers, 403 with untreated mild-moderate obstructive sleep apnoea-hypopnea, 235 with untreated severe disease, and 372 with the disease and treated with CPAP. Subjects were followed for 10 years to compare incidence of fatal and non-fatal cardiovascular events between cohorts. Table S5 below shows the subset of nonfatal and fatal cardiovascular event rates reported by Marin et al. that are relevant for our study, and the resulting total event rate, which we computed based on the Marin data.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Events** | **Healthy men****(n=264)** | **Simple snorers****(n=403)** | **Mild-moderate OSA****(n=235)** | **Severe OSA****(n=372)** |
| Mean AHI | 1.2 | 3.5 | 18.2 | 43.3 |
| *Non-fatal cardiovascular events* |  |  |
| Numbers of events | 12 | 22 | 36 | 50 |
| Events per 100 person years | 0.45 | 0.58 | 0.89 | 2.13 |
| *Cardiovascular death* |  |
| Numbers of events | 8 | 13 | 22 | 25 |
| Events per 100 person years | 0.3 | 0.34 | 0.55 | 1.06 |
| ***Own computations from Marin et al. [***[***5***](#_ENREF_5)***];data shown above*** |  |
| Total non-fatal or fatal cardiovascular events per 100 person years | 0.75 | 0.92 | 1.44 | 3.19 |

###### Table S5: Overview of subset of data used from Marin et al. study[[5](#_ENREF_5)], and resulting total non-fatal or fatal cardiovascular events per 100 person years.

###### We used the obtained data points to estimate a relationship between AHI and cardiovascular event rates, using a non-linear (polynomial) regression function. Figure S7 shows this resulting regression function, as well as the Marin et al.-derived cardiovascular event rates.



AHI

CV events per 100 person years

###### Figure S7: Regression analysis-based approximation estimating functional relationship between AHI and cardiovascular event risk. Large dots show data reported in Marin et al. (2005).

###### Using this regression function, we then obtained estimates of cardiovascular event rates that could be expected in patients at the AHI levels observed in the German PMS study. For the baseline mean AHI of 31.2, the resulting CV event rate per 100 person years was 2.21. For an AHI of 13.8 (as observed at 12 months under UAS treatment), the resulting event rate was 1.24.

###### Next, we computed hazard ratios (HR), using the simple snorer group (AHI of 3.5) as the reference group. This group was chosen because it more closely resembles the baseline AHI that might be observed in the general population; and the general population in turn used as the basis for a number of event hazard ratios used in our overarching health-economic model. Using this approach, we obtained HRs of 2.40 and 1.34, compared to simple snorers, for the STAR Trial baseline vs. 12 month under UAS treatment.

Using these HRs and the simple snorer baseline (HR 1.0), we obtain an overall estimate of risk reduction of OSA-related CV events of (2.40-1.34)/ (2.40-1.0) = 75.4%.

In the health-economic model we further assumed that only the 81% of patients who reported using UAS on a daily basis (at 3 years’ follow-up in the STAR Trial – Woodson et al., 2016) would benefit from this risk reduction, while the remaining 19% would not achieve any CV event risk reduction. For the full UAS cohort, this led to an assumption of ultimate UAS effectiveness in reducing CV event risk of 71.4% \* 81% = **61.1%.**

**S.4 Detailed computation of UAS Costs**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Item** | **Setting** | **Description** | **Amount** | **Costs** |
| **Preparation** |
| **Anamnesis** | clinic | academic outpatient institution lump sum | 57,50 € | **57.50 €** |
| **Sleep endoscopy** | clinic | DRG E63B (OPS 1-611.0 / G47.31) | case consolidation with implantation | 0 € |
| **Polysomnography screening** | clinic | DRG E63B / EBM30901 | case consolidation with implantation | 0 € |
| outpatient | EBM30901 | 330.30 € | **330.30 €** |
| **Implantation** |
| **Inpatient stay** | inpatient | DRG 902Z | 5,176.62 € | **5,176.62 €** |
| **Implant** | inpatient | additional charge for new examination and treatment methods (NUB) 088 (brutto) | 19,841.20 € | **19,841.20 €** |
| **Activation** |
| **Activation (outpatient)** | clinic | academic outpatient institution lump sum | 57.50 € | **57.50 €** |
| **1. Titration (100%)** | clinic | DRG E63B | 569.66 € | **569.66 €** |
| **2. Titration (13%)** | clinic | DRG E63B | 569.66 € | **74.06 €** |
| **Explantation**  |
| **Due to inflammation (10%)** | clinic | DRG X06C | 2,517.10 € | 251.71 € |
| **Other reason (90%)** | clinic | DRG B17E | 2,589.97 € | 2,330.97 € |
| **Total explantation (2%)**  | **51.65 €** |
| **Revision (1%)** | clinic | DRG B17E | 2.589.97 € | **25.90 €** |
| **Total UAS one-time cost (implant and activation)** | **26.184,39 €** |
| **Annual routine follow-up**  | clinic | academic outpatient institution lump sum | 57.50 € | **57.50 €** |
| **Annual routine follow-up cost** | **57.50 €** |
| **Battery Replacement** |
| **Physician visit** | clinic | academic outpatient institution lump sum | 57.50 € | **57.50 €** |
| **Battery replacement (neurostimulator pulse generator (NPG))**  | clinic | DRG 902Z | 5,176.62 € | **5,176.62 €** |
| clinic | additional charge for new examination and treatment methods (NUB) for NPG (brutto) | 15,263.55 € | **15,263.55 €** |
| **Total battery replacement cost once in 11 years** | **20,497.67 €** |

**Table S6 Overview of UAS cost**

In current German practice the UAS treatment is mainly situated in academic hospitals with attached outpatient clinics because so far there is no specific fee in reimbursement scheme for office-based physicians. Therefore, the anamnesis, the activation and the annual routine follow-up are valued with the according lump sums of these hospitals. Assuming that in regular patients the implantation is scheduled soon after sleep endoscopy and polysomnography there will be no extra fee in the inpatient setting for these diagnostic tests due to case consolidation. Polysomnography in the outpatient setting is refunded according to the outpatient reimbursement scheme. To achieve a conservative estimate of UAS cost polysomnography is assumed to take place in an outpatient setting in all patients. For DRG E63B (titration), only one hospital day is assumed. This means that the length of stay remains below the minimum length of stay and a discount on the DRG fee occurs, which is taken into account in the value given in table S4.

**S.5 Costs of myocardial infarction**

Hospital stay

For the cost of the hospital stay, the DRGs from the year 2008 obtained in Quentin et al. 2012 (DRGs that contain ≥1% of all cases with the corresponding main diagnosis) were tested for validity by the DRG catalogue 2016 [[6](#_ENREF_6), [7](#_ENREF_7)]. The thus identified DRGs are listed in Table S5. The number of cases for each DRG is taken from data of the DRG-accompanying research based on 2014 [[8](#_ENREF_8)]. The relative frequency of each DRG within the identified DRG is used to calculate a weighted average cost. The DRG fees are calculated by applying the cost weights taken from the DRG catalogue [[9](#_ENREF_9)] on the base rate of 2016 (3,311.98 €) [[10](#_ENREF_10)]. The resulting weighted average cost is 5,141.72 € per hospital admission due to myocardial infarction (table S7).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **DRG** | **cases (2014)** | **percentage** | **cost weight (2016)** | **amount (2016)** |
| F24A | 3803 | 1.82% | 2.808 | 9,300.04 € |
| F24B | 23738 | 11.34% | 1.711 | 5,666.80 € |
| F41A | 998 | 0.48% | 2.802 | 9,280.17 € |
| F41B | 21076 | 10.06% | 0.995 | 3,295.42 € |
| F43A | 1383 | 0.66% | 6.484 | 21,474.88 € |
| F43B | 3230 | 1.54% | 4.958 | 16,420.80 € |
| F43C | 11134 | 5.32% | 3.118 | 10,326.75 € |
| F52A | 11330 | 5.41% | 2.522 | 8,352.81 € |
| F52B | 83102 | 39.68% | 1.367 | 4,527.48 € |
| F60A | 10430 | 4.98% | 1.62 | 5,365.41 € |
| F60B | 39186 | 18.71% | 0.798 | 2,642.96 € |
| **Total** | **209410** | **100%** |  | **5,141.72 €** |

**Table S7 Costs of hospital stay due to myocardial infarction**

Medication, physician visits and rehabilitation

The calculation of medication and physician visit costs is based on Dorenkamp et al. 2013 who built a model to analyze the cost-effectiveness of catheter-based renal sympathetic denervation in patients with resistant hypertension [[11](#_ENREF_11)]. Dorenkamp et al. defined medication needs, physician visits and applied German prices which were updated for the present analysis.

For the calculation of medication costs, active ingredients and dosages are derived from Dorenkamp et al. 2013. According to the Coronary Heart Disease (CHD) National Supply Guideline the ACE inhibitor group is added with their recommended dosage [[12](#_ENREF_12)]. Within this group ramipril proved to be the most widely used substance based on the drug prescription report 2016 [[13](#_ENREF_13)]. Prices, package sizes and fixed amounts are taken from the red list [[14](#_ENREF_14)].

To calculate costs per physician visit, 2016 values of published average costs per visit are used for cardiologists (68.84 €) and general practitioners (GP) (21.10 €) [[15](#_ENREF_15)]. In the first year after the acute myocardial infarction (MI) two cardiologist visits and four GP visits are assumed. In all subsequent years one cardiologist visit and four GP visits are considered.

The rehabilitation costs reported by Dorenkamp et al. 2013 are adjusted to reflect 2016 values by the harmonized German general consumer price index. The use of rehabilitation services relevant to the SHI perspective was assumed only for 80% of the population because incidence data implicate that 20% are younger than 65 years and therefore covered by the statutory pension insurance rather than the SHI [[2](#_ENREF_2)].

Table S8 provides an overview of acute and post MI costs used in the model.

|  |  |  |
| --- | --- | --- |
| **Type of Service** | **Acute MI (1st year)** | **Post MI (2nd year+)** |
| **Hospital Stay** | 5,141.72 € | n.a. |
| **Emergency transportation** | 680.00 € [[16](#_ENREF_16)] | n.a. |
| **Medication** | 392.51 € | 220.05 € |
| *Clopidogrel 75 mg/day (Plavix®)* | *172.46 €* | *n.a.* |
| *Acetylsalicylic acid 100 mg/day (Aspirin®)* | *12.40 €* | *12.40 €* |
| *Simvastatin 40 mg/day (Zocor®)* | *87.49 €* | *87.49 €* |
| *Metoprolol 95 mg/day (Beloc zok®)* | *63.25 €* | *63.25 €* |
| *Ramipril 10 mg/ day (Delix ® or Ramiclair ®)* | *56.90 €* | *56.90 €* |
| **Rehabilitation** | 2,169.47 € | n.a. |
| **Physician visits** | 222.09 € | 153.25 € |
| *Cardiologist* | *137.68 €* | *68.84 €* |
| *GP* | *84.41 €* | *84.41 €* |
| **Total annual cost** | **8,605.79 €** | **373.30 €** |

**Table S8: Costs of myocardial infarction.** n.a. not applicable

**S.6 Costs of hypertension**

The cost of hypertension treatment was comprised of medication and physician visits for which resource use was taken from Dorenkamp et al. 2013 [[11](#_ENREF_11)]and valued with 2016 German prices. For physician visits a valuation was undertaken using published unit costs per visit [[15](#_ENREF_15)]and additionally by applying the quarterly consultation fees taken from the German SHI physician tariffs (EBM) [[17](#_ENREF_17)]. Table S9 contains resource use and costs for physician visits per year for hypertensive patients.

|  |  |  |  |
| --- | --- | --- | --- |
| **Resource** | **Units consumed per year [**[**11**](#_ENREF_11)**]** | **Valuation with published unit costs [**[**15**](#_ENREF_15)**]** | **Valuation with SHI physician tariff (EBM) [**[**17**](#_ENREF_17)**]** |
| **Cost per unit** | **Cost per year** | **Cost per unit** | **Cost per year** |
| GP visit | 4 | 21.10 € | 84.41 € | 19.15 € | 76.60 € |
| Cardiologist visit | 1 | 68.84 € | 68.84 € | 22.33 € | 22.33 € |
| *Subtotal GP and cardiologist* |  |  | *153.25 €* |  | *98.93 €* |
| Ophthalmologist visit (fundoscopy) | 1 | 36.59 € | 36.59 € | 14.95 € | 14.95 € |
| Brain imaging (MRI or CT scan) | 0.1 | n.a. | n.a. | 126.59 € | 12.66 € |
| **Total** |  |  | **189.84 €** |  | **126.54 €** |

**Table S9 Resource use and costs for physician visits due to hypertension**

CT computer tomography; MRI magnet resonance imaging; n.a. no unit costs available.

Three different medication regimens were considered[[11](#_ENREF_11)] and valued with prices, dosages and fixed amounts from the red list [[14](#_ENREF_14)] to calculate annual medication cost for hypertension (table S10).

The total costs for hypertension were calculated by summing physician visit costs and medication cost for all combinations. The base case total cost includes the base case medication cost and the total physician visit cost derived from published unit cost calculation. For sensitivity analysis the combinations resulting in minimum and maximum total annual cost were chosen from the range of all calculated costs. The minimum cost includes the alternative three-drug regimen and the physician visits valued with SHI tariff while the maximum cost were comprised of the alternative four-drug regimen and physician visits valued with published unit costs (table S11).

| **Agent, dosage and drug** | **Units in largest package size** | **Fixed amount (refunded by SHI) [**[**14**](#_ENREF_14)**]** | **Cost per year (SHI perspective)** |
| --- | --- | --- | --- |
| ***Base case*** |
| Metoprolol 2 x 95 mg/day (Beloc zok®) | 100 | 17.33 € | 126.51 € |
| Ramipril 10 mg/day (Delix®) | 100 | 15.59 € | 56.90 € |
| Torasemid 10 mg/day (Unat®) | 100 | 16.34 € | 59.64 € |
| **Total**  |  |  | **243.05 €** |
| ***Alternative three-drug regimen*** |
| Amlodipine 10 mg/day (Amlodipin ratiopharm®) | 100 | 13.98 € | 102.05 € |
| Ramipril 10 mg/day (Delix®) | 100 | 15.59 € | 56.90 € |
| Hydrochlorothiazide 25 mg/day (HCT-ratiopharm®) | 100 | 16.02 € | 58.47 € |
| **Total**  |  |  | **217.43 €** |
| ***Alternative four-drug regimen*** |
| Amlodipine 10 mg/day (Amlodipin ratiopharm®) | 100 | 13.98 € | 102.05 € |
| Metoprolol 2 x 95 mg/day (Beloc zok®) | 100 | 17.33 € | 63.25 € |
| Hydrochlorothiazide 25 mg/day (HCT-ratiopharm®) | 100 | 16.02 € | 58.47 € |
| Losartan 100 mg/d (LORZAAR® protect) | 98 | 34.00 € | 126.63 € |
| **Total**  |  |  | **350.41 €** |

**Table S10 Medication cost for hypertension according to different medication schemes**

SHI statutory health insurance

|  |  |  |  |
| --- | --- | --- | --- |
| **Cost scenario** | **Medication regimen** | **Physician visit valuation method** | **Total annual cost** |
| **Base case** | Base case | Published unit costs | **432.89 €** |
| **Minimum cost** | Alternative three-drug regimen | SHI tariff | **343.97 €** |
| **Maximum cost** | Alternative four-drug regimen | Published unit costs | **540.25 €** |

**Table S11 Total annual cost of hypertension in the base case and sensitivity analyses**

**S.7 Clinical Outcomes**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **All-cause death** | **CV death** | **MI events** | **Stroke events** | **MVC events** |
| **Lifetime time horizon** |
| **No Treatment** | N/A | 0.284 | 0.441 | 0.254 | 0.512 |
| **UAS Treatment** | N/A | 0.242 | 0.339 | 0.243 | 0.182 |
| **Absolute Difference** | N/A | -0.042 | -0.102 | -0.011 | -0.330 |
| **Relative Risk** | N/A | 0.85 | 0.77 | 0.96 | 0.36 |
| **NNT** | N/A | 23.8 | 9.8 | 90.9 | 3.0 |
| **Ten-year time horizon** |
| **No Treatment** | 0.195 | 0.082 | 0.173 | 0.076 | 0.246 |
| **UAS Treatment** | 0.165 | 0.053 | 0.111 | 0.058 | 0.083 |
| **Absolute Difference** | -0.030 | -0.028 | -0.062 | -0.018 | -0.162 |
| **Relative Risk** | 0.85 | 0.65 | 0.64 | 0.76 | 0.34 |
| **NNT** | 33.3 | 35.7 | 16.1 | 55.6 | 6.2 |

**Table S12 Clinical Outcomes for lifetime and ten-year time horizon**

CV: Cardiovascular; MI myocardial infarction; MVC: Motor vehicle collision; NNT number needed to treat; UAS upper airway stimulation.



**Figure S8 Clinical outcomes (absolute event rates and numbers needed to treated) ten-year time horizon**

CV: Cardiovascular; MI myocardial infarction; MVC: Motor vehicle collision; NNT number needed to treat; UAS upper airway stimulation.



**Figure S9 Clinical outcomes (absolute event rates and numbers needed to treated) for lifetime horizon**

CV: Cardiovascular; MI myocardial infarction; MVC: Motor vehicle collision; NNT number needed to treat; UAS upper airway stimulation.

**S.8 Complete results of deterministic sensitivity analyses**

Below the key scenarios for sensitivity analyses with resultant ICER as well as the complete health economic outcomes (including costs, effectiveness, and ICER) for all deterministic sensitivity analyses.

|  |  |
| --- | --- |
| **Scenario** | **ICER (€/ QALY)** |
| *Base case* | *44,446* |
| Median instead of mean AHI reduction (28.6 to 9.5 events/hour) | 37,763 |
| No discount rate on costs and effects | 37,040 |
| High discount rate on costs and effects (10%) | 67,245 |
| Male patients | 44,397 |
| Female patients | 46,434 |
| Age 37 (youngest patient treated in underlying study) | 43,083 |
| Age 75 (oldest patient treated in underlying study) | 50,881 |
| UAS adherence (daily use) 100%  | 34,974 |
| UAS adherence (daily use) 66%  | 59,513 |
| UAS CVD event risk-reduction effectiveness 65% (compared to 75%) | 52,078 |
| UAS CVD event risk-reduction effectiveness 50% (compared to 75%) | 68,612 |
| UAS battery replacement every 9 years | 50,250 |
| UAS battery replacement every 13 years | 40,475 |
| UAS implantation cost high (34,040 €) | 52,157 |
| UAS implantation cost low (18,329 €) | 39,234 |
| UAS battery replacement cost high (26,647 €) | 49,634 |
| UAS battery replacement cost low (14,349 €) | 39,234 |
| Total of 8 sleep laboratory assessments considered per ultimately enrolled cohort subject (extreme example of diagnostic work-up cost) | 46,707 |
| High HR stroke from OSA (3.5) | 38,979 |
| Low HR stroke from OSA (1.0) | 48,459 |
| Utility gain for treated vs. untreated OSA only 75% of baseline (0.0675) | 59,261 |
| 50% MI rate | 46,042 |

**Table S13 Results of deterministic sensitivity analysis on cost-effectiveness of upper airway stimulation**

Legend: AHI apnoea-hypopnea index; CVD cardiovascular disease; HR hazard ratio; ICER incremental cost-effectiveness ratio; OAS obstructive sleep apnoea; QALY quality adjusted life year; UAS upper airway stimulation.

| **Scenario** | **Strategy** | **Cost (€)** | **Incremental Cost (€)** | **QALY** | **Incremental QALY** | **ICER €/ QALY** |
| --- | --- | --- | --- | --- | --- | --- |
| Base Case  | No UAS | 54,161 |  | 8.918333 |  |  |
| UAS | 99,357 | 45,196 | 9.9352 | 1.016867 | 44,446 |
| 10 years horizon | No UAS | 24,597 |  | 5.275467 |  |  |
| UAS | 50,189 | 25,592 | 5.700467 | 0.425 | 60,216 |
| Base case for UAS to include total of 8 PSGs for diagnostic workup | No UAS | 54,151 |  | 8.919633 |  |  |
| UAS | 101,660 | 47,509 | 9.9368 | 1.017167 | 46,707 |
| Battery replacement every 7 years | No UAS | 54,151 |  | 8.919633 |  |  |
| UAS | 114,581 | 60,430 | 9.9368 | 1.017167 | 59,410 |
| Battery replacement every 13 years | No UAS | 54,151 |  | 8.919633 |  |  |
| UAS | 95,322 | 41,170 | 9.9368 | 1.017167 | 40,475 |
| UAS 65% CVD effectiveness | No UAS | 54,151 |  | 8.919633 |  |  |
| UAS | 98.944 | 44,793 | 9.779733 | 0.8601 | 52,078 |
| UAS 50% CVD effectiveness | No UAS | 54,151 |  | 8.919633 |  |  |
| UAS | 98,399 | 44,248 | 9.564533 | 0.6449 | 68,612 |
| UAS 75% MVC effectiveness | No UAS | 54,151 |  | 8.919633 |  |  |
| UAS | 99,514 | 45,362 | 9.9299 | 1.010267 | 44,901 |
| UAS 50% MVC effectiveness | No UAS | 54,151 |  | 8.919633 |  |  |
| UAS | 99,679 | 45,527 | 9.923967 | 1.004333 | 45,331 |
| UAS 25% MVC effectiveness | No UAS | 54,151 |  | 8.919633 |  |  |
| UAS | 99,844 | 45,693 | 9.918033 | 0.9984 | 45,766 |
| Same OSA treated and untreated utility | No UAS | 54,151 |  | 8.919633 |  |  |
| UAS | 99,348 | 45,197 | 9.3957 | 0.476067 | 94,937 |
| No cost for replacement | No UAS | 54,151 |  | 8.919633 |  |  |
| UAS | 81,718 | 27,566 | 9.9368 | 1.017167 | 27,101 |
| no discount (0% p.a.) | No UAS | 80,318 |  | 12.1556 |  |  |
| UAS | 138,065 | 57,747 | 13.71467 | 1.559067 | 37,040 |
| high discount (10% p.a.) | No UAS | 27,666 |  | 5.260533 |  |  |
| UAS | 60,854 | 33,179 | 5.753933 | 0.4934 | 67,245 |
| age 30 | No UAS | 55,470 |  | 16.35797 |  |  |
| UAS | 116,524 | 61,054 | 17.76073 | 1.402767 | 43,524 |
| age 40 | No UAS | 58,025 |  | 13.61483 |  |  |
| UAS | 113,775 | 55,750 | 14.8966 | 1.281767 | 43,495 |
| age 60 | No UAS | 52,480 |  | 7.8955 |  |  |
| UAS | 95,386 | 42,907 | 8.835733 | 0.940233 | 45,634 |
| age 70 | No UAS | 46,641 |  | 5.158233 |  |  |
| UAS | 82,905 | 36,265 | 5.904567 | 0.746333 | 48,590 |
| MVC incident rate low (50%) of base case | No UAS | 54,148 |  | 8.919767 |  |  |
| UAS | 99,347 | 45,199 | 9.936867 | 1.0171 | 44,439 |
| MVC incident rate high (200% of base case) | No UAS | 54,186 |  | 8.9184 |  |  |
| UAS | 99,359 | 45,173 | 9.936367 | 1.017967 | 44,376 |
| Probability of death from MVC low (75% of basecase) | No UAS | 54,188 |  | 8.9246 |  |  |
| UAS | 99,366 | 45,178 | 9.9388 | 1.0142 | 44,546 |
| Probability of death from MVC high (125% of basecase) | No UAS | 54,115 |  | 8.9147 |  |  |
| UAS | 99,330 | 45,215 | 9.934833 | 1.020133 | 44,323 |
| Low HR of MVC due to OSA (2.5) | No UAS | 53,984 |  | 8.925567 |  |  |
| UAS | 99,348 | 45,364 | 9.9368 | 1.011233 | 44,860 |
| High HR of MVC due to OSA (3.5) | No UAS | 54,319 |  | 8.9147 |  |  |
| UAS | 99,348 | 45,029 | 9.9368 | 1.0221 | 44,055 |
| Low incidence rate of hypertension (75% of base case) | No UAS | 54,035 |  | 8.975833 |  |  |
| UAS | 99,320 | 45,285 | 9.9921 | 1.016267 | 44,561 |
| High incidence rate of hypertension (125% of base case) | No UAS | 54,256 |  | 8.875567 |  |  |
| UAS | 99,382 | 45,125 | 9.8907 | 1.015133 | 44,453 |
| Low HR of hypertension due to OSA (75% of base case) | No UAS | 54,035 |  | 8.975833 |  |  |
| UAS | 99,332 | 45,297 | 9.964933 | 0.9891 | 45,796 |
| High HR of hypertension due to OSA (125% of base case) | No UAS | 54,256 |  | 8.875567 |  |  |
| UAS | 99,366 | 45,109 | 9.910767 | 1.0352 | 43,575 |
| Low HR for MI from hypertension (1.31, based on weighted average) | No UAS | 56,331 |  | 9.189633 |  |  |
| UAS | 101,720 | 45,389 | 10.1838 | 0.994167 | 45,655 |
| High HR for MI from hypertension (3.5) | No UAS | 52,542 |  | 8.7164 |  |  |
| UAS | 97,434 | 44,892 | 9.733967 | 1.017567 | 44,117 |
| Low HR for stroke from hypertension (2.32, based on Weikert Model 2) | No UAS | 54,042 |  | 8.9329 |  |  |
| UAS | 99,300 | 45,258 | 9.9521 | 1.0192 | 44,405 |
| High HR for stroke from hypertension (4.14, upper 95% CI value from Weikert) | No UAS | 55,590 |  | 8.754933 |  |  |
| UAS | 100,036 | 44,446 | 9.739067 | 0.984133 | 45,162 |
| Low incident rate of MI (50% of base case) | No UAS | 59,037 |  | 9.27474 |  |  |
| UAS | 104,584 | 45,547 | 10.26300 | 0.98824 | 46,042 |
| High incident rate of MI (120% of basecase) | No UAS | 53,227 |  | 8.793033 |  |  |
| UAS | 98,232 | 45,005 | 9.810367 | 1.017333 | 44,238 |
| Low HR for MI from OSA (1.9) | No UAS | 55,626 |  | 9.118267 |  |  |
| UAS | 100,382 | 44,755 | 10.05233 | 0.934067 | 47,914 |
| High HR for MI from OSA (4.3) | No UAS | 51,532 |  | 8.554367 |  |  |
| UAS | 97,190 | 45,658 | 9.691767 | 1.1374 | 40,142 |
| Low HR post-MI for all-cause mortality (1.35) | No UAS | 54,609 |  | 8.9795 |  |  |
| UAS | 99,768 | 45,177 | 9.978033 | 0.998533 | 45,243 |
| High HR post-MI for all-cause mortality (1.54) | No UAS | 53,812 |  | 8.8755 |  |  |
| UAS | 99,023 | 45,211 | 9.905433 | 1.029933 | 43,897 |
| Low incident rate of stroke (80% of basecase) | No UAS | 53,569 |  | 8.992933 |  |  |
| UAS | 99,078 | 45,509 | 10.02313 | 1.0302 | 44,175 |
| High incident rate of stroke (120% of basecase) | No UAS | 54,712 |  | 8.852533 |  |  |
| UAS | 99,619 | 44,908 | 9.8557 | 1.003167 | 44,766 |
| Low HR stroke from OSA (1.0) | No UAS | 52,884 |  | 9.081667 |  |  |
| UAS | 99,046 | 46,162 | 10.03427 | 0.9526 | 48,459 |
| High HR stroke from OSA (3.5) | No UAS | 56,777 |  | 8.621467 |  |  |
| UAS | 100,070 | 43,293 | 9.732133 | 1.110667 | 38,979 |
| Low HR for all-cause mortality from stroke (1.10) | No UAS | 57,213 |  | 9.096067 |  |  |
| UAS | 102,600 | 45,388 | 10.08873 | 0.992667 | 45,723 |
| High HR for all-cause mortality from stroke (2.80) | No UAS | 53,169 |  | 8.861133 |  |  |
| UAS | 98,312 | 45,143 | 9.8865 | 1.025367 | 44,027 |
| UAS implant cost low (70% of base case) | No UAS | 54,151 |  | 8.919633 |  |  |
| UAS | 91,493 | 37,341 | 9.9368 | 1.017167 | 36,711 |
| UAS implant cost high (130% of base case) | No UAS | 54,151 |  | 8.919633 |  |  |
| UAS | 107,203 | 53,052 | 9.9368 | 1.017167 | 52,157 |
| UAS replacement cost low (70% of base case) | No UAS | 54,151 |  | 8.919633 |  |  |
| UAS | 94,059 | 39,907 | 9.9368 | 1.017167 | 39,234 |
| UAS replacement cost high (130% of base case) | No UAS | 54,151 |  | 8.919633 |  |  |
| UAS | 104,637 | 50,486 | 9.9368 | 1.017167 | 49,634 |
| UAS annual visits cost low | No UAS | 54,151 |  | 8.919633 |  |  |
| UAS | 99,096 | 44,945 | 9.9368 | 1.017167 | 44,186 |
| UAS annual visits cost high | No UAS | 54,151 |  | 8.919633 |  |  |
| UAS | 99,600 | 45,448 | 9.9368 | 1.017167 | 44,681 |
| MVC injury cost low | No UAS | 53,580 |  | 8.919633 |  |  |
| UAS | 99,148 | 45,568 | 9.9368 | 1.017167 | 44,799 |
| MVC injury cost high | No UAS | 55,295 |  | 8.919633 |  |  |
| UAS | 99,749 | 44,454 | 9.9368 | 1.017167 | 43,704 |
| MVC death cost low | No UAS | 55,143 |  | 8.919633 |  |  |
| UAS | 99,345 | 45,202 | 9.9368 | 1.017167 | 44,439 |
| MVC death cost high | No UAS | 54,169 |  | 8.919633 |  |  |
| UAS | 99,354 | 45,185 | 9.9368 | 1.017167 | 44,422 |
| Acute MI cost low | No UAS | 53,358 |  | 8.919633 |  |  |
| UAS | 98,766 | 45,408 | 9.9368 | 1.017167 | 44,642 |
| Acute MI cost high | No UAS | 54,945 |  | 8.919633 |  |  |
| UAS | 99,930 | 44,985 | 9.9368 | 1.017167 | 44,226 |
| Acute stroke cost low | No UAS | 53,439 |  | 8.919633 |  |  |
| UAS | 98,701 | 45,263 | 9.9368 | 1.017167 | 44,499 |
| Acute stroke cost high | No UAS | 54,864 |  | 8.919633 |  |  |
| UAS | 99,995 | 45,130 | 9.9368 | 1.017167 | 44,369 |
| Hypertension state cost low | No UAS | 53,291 |  | 8.919633 |  |  |
| UAS | 98,412 | 45,121 | 9.9368 | 1.017167 | 44,360 |
| Hypertension state cost high | No UAS | 55,012 |  | 8.919633 |  |  |
| UAS | 100,284 | 45,272 | 9.9368 | 1.017167 | 44,508 |
| MI state cost low | No UAS | 53,968 |  | 8.919633 |  |  |
| UAS | 99,223 | 45,255 | 9.9368 | 1.017167 | 44,491 |
| MI state cost high | No UAS | 55,984 |  | 8.919633 |  |  |
| UAS | 100,594 | 44,610 | 9.9368 | 1.017167 | 43,857 |
| Post stroke state cost low | No UAS | 53,047 |  | 8.919633 |  |  |
| UAS | 98,459 | 45,384 | 9.9368 | 1.017167 | 44,618 |
| Post stroke state cost high | No UAS | 55,229 |  | 8.919633 |  |  |
| UAS | 100,237 | 45,009 | 9.9368 | 1.017167 | 44,249 |
| No utility decrement for UAS procedure | No UAS | 54,151 |  | 8.919633 |  |  |
| UAS | 99,348 | 45,197 | 9.952833 | 1.0332 | 43,744 |
| High utility decrement for UAS procedure | No UAS | 54,151 |  | 8.919633 |  |  |
| UAS | 99,348 | 45,197 | 9.9208 | 1.001167 | 45,144 |
| Utility untreated OSA low | No UAS | 54,151 |  | 8.571133 |  |  |
| UAS | 99,348 | 45,197 | 9.783933 | 1.2128 | 37,266 |
| Utility untreated OSA high | No UAS | 54,151 |  | 9.705267 |  |  |
| UAS | 99,348 | 45,197 | 10.28083 | 0.575567 | 78,525 |
| Utility treated OSA low | No UAS | 54,151 |  | 8.919633 |  |  |
| UAS | 99,348 | 45,197 | 9.3957 | 0.476067 | 94,937 |
| Utility treated OSA high | No UAS | 54,151 |  | 8.919633 |  |  |
| UAS | 99,348 | 45,197 | 10.23657 | 1.316933 | 34,320 |
| Utility hypertension low | No UAS | 54,151 |  | 8.1587 |  |  |
| UAS | 99,348 | 45,197 | 9.058733 | 0.900033 | 50,217 |
| Utility hypertension high | No UAS | 54,151 |  | 9.009233 |  |  |
| UAS | 99,348 | 45,197 | 10.0403 | 1.031067 | 43,835 |
| Utility post MI low | No UAS | 54,151 |  | 8.587067 |  |  |
| UAS | 99,348 | 45,197 | 9.707633 | 1.120567 | 40,334 |
| Utility post MI high | No UAS | 54,151 |  | 9.023967 |  |  |
| UAS | 99,348 | 45,197 | 10.00863 | 0.984667 | 45,900 |
| Utility post stroke low | No UAS | 54,151 |  | 8.530267 |  |  |
| UAS | 99,348 | 45,197 | 9.6103 | 1.080033 | 41,847 |
| Utility post stroke high | No UAS | 54,151 |  | 9.2256 |  |  |
| UAS | 99,348 | 45,197 | 10.19237 | 0.966767 | 46,750 |
| Utility non-fatal MVC low | No UAS | 54,151 |  | 8.921633 |  |  |
| UAS | 99,348 | 45,197 | 9.936833 | 1.0152 | 44,520 |
| Utility non-fatal MVC high | No UAS | 54,151 |  | 8.779433 |  |  |
| UAS | 99,348 | 45,197 | 9.887467 | 1.108033 | 40,790 |
| UAS Adherence (66%) CVD only | No UAS | 54,151 |  | 8.919633 |  |  |
| UAS | 98,691 | 44,539 | 9.680633 | 0.761 | 58,528 |
| UAS Adherence (76%) CVD only | No UAS | 54,151 |  | 8.919633 |  |  |
| UAS | 99,020 | 44,868 | 9.809733 | 0.8901 | 50,408 |
| UAS Adherence (66%) CVD and MVC | No UAS | 54,151 |  | 8.919633 |  |  |
| UAS | 98,914 | 44,762 | 9.671767 | 0.752133 | 59,514 |
| UAS Adherence (76%) CVD and MVC | No UAS | 54,151 |  | 8.919633 |  |  |
| UAS | 99,178 | 45,026 | 9.8038 | 0.884167 | 50,925 |
| 5-year horizon | No UAS | 13,030 |  | 3.0116 |  |  |
| UAS | 38,890 | 25,860 | 3.2242 | 0.2126 | 121,638 |
| 15-year horizon | No UAS | 34,325 |  | 6.893733 |  |  |
| UAS | 71,877 | 37,552 | 7.513167 | 0.619433 | 60,623 |
| Battery replacement every 10 years | No UAS | 54,151 |  | 8.919633 |  |  |
| UAS | 101,995 | 47,843 | 9.9368 | 1.017167 | 47,036 |
| Battery replacement every 9 years | No UAS | 54,151 |  | 8.919633 |  |  |
| UAS | 105,264 | 51,113 | 9.9368 | 1.017167 | 50,250 |
| Therapy usage 100% | No UAS | 54,151 |  | 8.919633 |  |  |
| UAS | 96,758 | 42,606 | 10.13787 | 1.218233 | 34,974 |
| Median AHI reduction (28.6 to 9.5) | No UAS | 54,151 |  | 8.919633 |  |  |
| UAS | 99,853 | 45,702 | 10.12987 | 1.210233 | 37,763 |

**Table S14 Results of deterministic sensitivity analysis on cost-effectiveness of upper airway stimulation**

AHI apnoea-hypopnea index; CVD cardiovascular disease; HR hazard ratio; ICER incremental cost-effectiveness ratio; MI myocardial infarction; MVC: Motor vehicle collision; N/ A: not applicable; OAS obstructive sleep apnoea; UAS upper airway stimulation.

**References**

1. Neuhauser H, Thamm M, Ellert U. Blutdruck in Deutschland 2008–2011. Ergebnisse der Studie zur Gesundheit Erwachsener in Deutschland (DEGS1) *Bundesgesundheitsblatt* 2013: 56(5-6): 795-801.

2. Robert Koch Institut (RKI). Daten zu Herzinfarkten in der Region Augsburg. Gesundheitsberichtserstattung des Bundes. 14.03.2017 ed, [www.gbe-bund.de](http://www.gbe-bund.de), 2017.

3. Brown RD, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Stroke incidence, prevalence, and survival: secular trends in Rochester, Minnesota, through 1989. *Stroke* 1996: 27(3): 373-380.

4. Palm F, Urbanek C, Rose S, Buggle F, Bode B, Hennerici MG, Schmieder K, Inselmann G, Reiter R, Fleischer R, Piplack KO, Safer A, Becher H, Grau AJ. Stroke Incidence and Survival in Ludwigshafen am Rhein, Germany: the Ludwigshafen Stroke Study (LuSSt). *Stroke* 2010: 41(9): 1865-1870.

5. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet* 2005: 365(9464): 1046-1053.

6. Quentin W, Rätto H, Peltola M, Busse R, Häkkinen U. Acutemyocardial infarction and diagnosis-related groups: Patient classification and hospital reimbursement in 11 European countries. *European heart journal* 2013: 34(26): 1972-1981.

7. Institut für das Entgeltsystem im Krankenhaus InEK. Fallpauschalen-Katalog 2016. 2015 [cited 05.07.2017]; Available from: <http://www.g-drg.de/G-DRG-System_2016/Fallpauschalen-Katalog/Fallpauschalen-Katalog_2016>

8. Institut für das Entgeltsystem im Krankenhaus (InEK). G-DRG-Begleitforschungsbrowser. Datenjahr 2014., [www.g-drg.de](http://www.g-drg.de), 2017.

9. Institut für das Entgeltsystem im Krankenhaus (InEK). Fallpauschalen-Katalog 2016. 2015 [cited 05.07.2017]; Available from: <http://www.g-drg.de/G-DRG-System_2016/Fallpauschalen-Katalog/Fallpauschalen-Katalog_2016>

10. National Association of Statutory Health Insurance Funds (Spitzenverband GKV). Bundesbasisfallwert. 2017 [cited 05.07.2017]; Available from: <https://www.gkv-spitzenverband.de/krankenversicherung/krankenhaeuser/budgetverhandlungen/bundesbasisfallwert/bundesbasisfallwert.jsp>

11. Dorenkamp M, Bonaventura K, Leber AW, Boldt J, Sohns C, Boldt LH, Haverkamp W, Frei U, Roser M. Potential lifetime cost-effectiveness of catheter-based renal sympathetic denervation in patients with resistant hypertension. *European heart journal* 2013: 34(6): 451-461.

12. Bundesärztekammer (BÄK) Kassenärztliche Bundesvereinigung (KBV) Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF). Nationale VersorgungsLeitlinie Chronische KHK – Langfassung. 2016 [cited 05.07.2017]; Available from: <http://www.awmf.org/leitlinien/detail/ll/nvl-004.html>

13. Anlauf M, Weber F. Hemmstoffe des Renin-Angiotensin-Systems. *In:* Schwabe U, Paffrath D, eds. Arzneiverordnungs-Report 2016 Aktuelle Daten, Kosten, Trends und Kommentare. Springer Verlag, Berlin, Heidelberg, 2016; pp. 209-235.

14. Rote Liste® Service GmbH. Rote Liste. Arzneimittelinformationen für Deutschland. 2017 [cited 05.07.2017]; Available from: <https://online.rote-liste.de/>

15. Bock JO, Brettschneider C, Seidl H, Bowles D, Holle R, Greiner W, Konig HH. [Calculation of standardised unit costs from a societal perspective for health economic evaluation]. *Gesundheitswesen (Bundesverband der Arzte des Offentlichen Gesundheitsdienstes (Germany))* 2015: 77(1): 53-61.

16. Berlin Fire Department (Berliner Feuerwehr). Feuerwehrbenutzungsgebührenordnung - Fw BenGebO. 2017 [cited 05.07.2017; Available from: <http://gesetze.berlin.de/jportal/portal/t/ekf/page/bsbeprod.psml?pid=Dokumentanzeige&showdoccase=1&js_peid=Trefferliste&documentnumber=1&numberofresults=1&fromdoctodoc=yes&doc.id=jlr-FeuerwEBenGebOBErahmen&doc.part=X&doc.price=0.0#_XY_d367297e3317_text>

17. Kassenärztliche Bundesvereinigung (KBV). Einheitlicher Bewertungsmaßastab EBM. 2017 [cited 12.07.2017]; Available from: <http://www.kbv.de/html/ebm.php>