SUPPLEMENTARY DATA

Model validations

To ensure model projections were in reasonable concordance with real-world outcomes, 2 sets of validations were performed. First, the model was programmed with the cohort characteristics of several landmark HT trials and the model-projected event rates were compared to those reported in the respective trial. Second, model-projected lifetime event incidences were compared to lifetime event incidences reported in large-scale epidemiological studies. Third, model projections were compared to outcome data from a recent large-scale study following hypertensive patients in Spain through ten years of follow-up. The subsections below describe the respective validations, followed by a summary of the overarching validation findings.

1. Model validations with clinical trial data

The model-projected clinical endpoints were compared against published hypertension clinical trial and registry data. Cohort characteristics were compared across all the included trials. Scenarios were explored, relying upon trial-specific inputs, respectively. The projected stroke, MI, and all-cause mortality rates were then compared to study-reported rates. This validation was conducted with respect to the UK, and hence relies upon UK general population lifetable data informed mortality projections.[1] Where lipid levels were not reported, a standard set of lipid levels derived from a hypertension cohort in NHANES were utilized.[2] A summary of cohort characteristics can be reviewed in greater detail in table 2 of the supplementary data.

The trials and registries included in this analysis included a span of over two decades of evidence from hypertension-related therapy and management trials. The trials and registries included the Global SYMPLICITY Registry for renal denervation; pharmacologic intervention and combination trial data from VALUE, ACCOMPLISH, ON-TARGET, TRANSCEND, and HOPE trials; and blood pressure

management trial data from the ACCORD, STEP, and SPRINT trials.[3-13] The results from this analysis informed the adjustment factors relied upon in corresponding sensitivity analyses. Any under- or over-projection of outcomes were absolved with an adjustment factor greater and less than one, respectively.

Overall, results from this validation effort suggest the model to be conservative in its projection of outcomes. The model resulted in under-projected outcomes for six of the trial-informed scenarios, with over-projection only evident for the scenario with SPRINT trial data. The resulting adjustment factors for stroke, MI, and all-cause death ranged from 0.71 to 2.09, 0.70 to 3.08, and 0.23 to 1.46, respectively. Scenarios exploring the effect of adjusting event risks according to the lowest and highest validation study RRs were explored in sensitivity analyses. Results can be reviewed in tables 3 and table 4 of the supplementary data below.

2. Model validation with lifetime incidence data

Furthermore, the model-projected cumulative incidence rates were compared against published epidemiological data. Relevant, large-scale studies specific to stroke, myocardial infarction, cardiovascular disease, heart failure and end-stage renal disease (ESRD) were relied upon in this validation effort. The cohort characteristics for each study again informed the validation scenarios explored, with the study-reported and model-projected incidence values compared. In general, the model-projected and study-reported values were in line with one another.

Data from the 2016 Global Burden of Disease study and estimates from the Framingham study informed the stroke-specific published cumulative incidence comparators. The model-projected values were in line with those reported from both sources – 29.6% in model vs. 26% for age 55, 26.0% vs 24% for age 65, 21.8% vs 22% for age 75 and 15.2% in model vs. 11.5% at 10 years, and 30.5% vs. 23% at lifetime – respectively.[14,15] Thirty-three-year values from the Tromsø trial served as the published

comparator for myocardial infarction incidence. Again, the model-projected outcomes were comparable to those reported in the Tromsø trial (1.1% in model vs 1.2% for males aged 65, 0.6% vs 0.7% for females aged 65, 2.1% vs 2.3% in males aged 75, 1.2% vs 1.3% in females aged 75, 2.8% vs 4.4% in males aged 85, 1.6% vs 2.4% in females aged 85).[16] Cumulative heart failure incidence data from 40,000 participants with on average, 18 years of follow up data, suggest a 21% and 16% lifetime risk of heart failure for 45-year-old males and females, respectively.[17] The model projected values for the same cohort were 20.0% and 12.4%, respectively, again proving the model projections to be quite robust. The lifetime risk of ESRD, for a cohort of 40-year-old males with an eGFR ≥ 60 was 0.99%, compared to a model-projected lifetime risk of 1.20%.[18] Based on the findings from all validation efforts, there were no calibration adjustments made to the multivariate risk equations informing the current analysis.

3. Model validation with Spanish mortality data

The health economic model was also validated against contemporary Spanish hypertension data for cardiovascular and all-cause mortality.[19] This data was sourced from the Spanish Ambulatory Blood Pressure Registry and covered 59,124 patients across all 17 regions of Spain. Patient demographics were inputted into the model. At a 10-year time horizon, cardiovascular death was 4.9% in real-world data compared to 5.0% in the model, while all-cause death was 13.6% in real-world data compared to 13.5% in the model. This indicated high concordance for cardiovascular death and all-cause death between projected and real-world values.

4. Overarching summary of validation findings

Overall, the completed validations found model-projected outcomes to be directionally aligned with those observed in the landmark HT trials (RR study vs. model 0.71-2.09 (mean 1.20) for stroke; 0.70-

3.08 (1.31) for MI; 0.23-1.46 (0.98) for all-cause death), with model-projected lifetime incidences closely resembling those reported in epidemiological studies. On this basis, no calibration adjustments were made to the Framingham and other multivariate risk-equations for the current analysis. Nevertheless, the study also examined the assumptions of halving and doubling the clinical event rates of myocardial infarction, other coronary heart disease and stroke in uncertainty analysis. With an adjustment factor for MI/CHD/stroke of 0.5 and 2.0 – reflecting half or double the event incidence suggested by the original risk equations including Framingham – the ICER was €20 702 and €12 555 per QALY respectively, suggesting no material change in cost-effectiveness findings. See Table 3 in main manuscript for these results.

Cost breakdown by treatment strategy

A reduced number of clinical events were projected in the renal denervation cohort, which helped to in part amortize the cost of renal denervation therapy and provided cost-savings compared to the standard of care. The largest cost-savings was associated with stroke costs, with heart failure and angina pectoris also contributing to cost-savings.

Table 1 of the supplementary data

Mortality transitions. The following table represents the mortality transitions for each primary health state. Secondary health states utilized the higher mortality rate of the two conditions to avoid double-counting

Condition	Range	Source
Hypertension	Variable	Spanish life tables[20]
Stroke (30 Days)	0.0713	Kortazar-Zubizarreta I, et al.[21]
Stroke (annual)	2.3	Geisler B.P., et al.[22]
MI (30 days) (post-admission)	0.071-0.316	Forcadell M.J., et al.[23]
MI (30 days) (Out-of-hospital)	0.20	Sans S, et al.,[24]
MI (annual), relative risk (versus general population)	1.54-2.42	Smolina K, et al.[25]
AP/other CHD (annual)	0.0367	Sánchez Fernández J.J., et al.[26]
Heart failure (annual)	0.0554	Sayago-Silva I, et al.[27]
ESRD (annual)	0.065	Roca-Tey R, et al.[28]

MI, myocardial infarction; AP, angina pectoris; CHD, coronary heart disease; ESRD, end-stage renal disease.

Table 2 of the supplementary data

Summary of cohort characteristics

Variables	GSR R-HT	GSR T2D	VALUE valsartan cohort	VALUE monotherapy	SPRINT standard Trtmt.	ACCOMPLISH	ACCORD	ON-TARGET ramipril subgroup	TRANSCEND	HOPE (placebo)	STEP standard trtmt.	Average
Age (mean)	61	64	67	67	68	61	62	66	67	66	66	65
Gender (% male)	57.5%	59.0%	58.0%	59.0%	65.0%	61.0%	52.3%	72.8%	57.4%	74.2%	46.1%	60.2%
Diabetes (%)	43.0%	100.0%	33.0%	30.0%	0.0%	60.2%	100.0%	36.7%	35.6%	38.0%	19.4%	45.1%
Current Smoker	32.0%	32.0%	22.0%	26.0%	13.0%	11.4%	13.2%	12.4%	9.7%	14.5%		18.6%
Hypertension	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	46.1%	100.0%	95.1%
CHD/CVD	48.0%	28.0%	44.0%	48.0%	20.0%	48.8%	33.7%	74.4%	74.3%	81.4%	6.4%	46.1%
Baseline OSBP	175	165	155	151	140	145.4	139.4	141.8	141.3	139	146	149.0
OSBP (active treatment)	153.5	150	142	137	136	132.5	134	136	141	139	137	139.8
Follow-up (years)	3	3	4.2	3	3.2	3	4.7	5	4.7	4.5	3.3	-
Source	Mahfoud F, et al[13]	Mahfoud F, et al[4]	Julius S, et al.[3]	Julius S, et al.[5]	SPRINT[6]	Jamerson K, et al.[7]	Cushman W.C., et al.[8]	ON-TARGET[11]	TRANSCEND[12]	HOPE[9]	Zhang W, et al.[10]	-

CHD, coronary heart disease; CVD, cardiovascular disease; R-HT, resistant hypertension; OSBP, office-based systolic blood pressure; T2D, type 2 diabetes;

Trtmt, treatment.

Table 3 of the supplementary data

Summary of stroke event validations

Variables	GSR R-HT	GSR T2D	VALUE valsartan cohort	VALUE monotherapy	SPRINT standard Trtmt.	ACCOMPLISH	ACCORD	ON-TARGET ramipril subgroup	TRANSCEND	HOPE (placebo)	STEP standard trtmt.	Av.
Study-observed	4.8%	4.0%	4.2%	2.3%	1.4%	2.3%	2.7%	4.7%	4.6%	6.1%	1.7%	-
Model-projected	2.32%	3.6%	3.7%	2.3%	2.0%	1.5%	3.6%	3.6%	4.1%	3.6%	2.2%	-
RR (study vs model)	2.09	1.11	1.12	0.99	0.71	1.53	0.74	1.32	1.13	1.69	0.78	1.20

Av, average; GSR, Global SYMPLICITY Registry; R-HT, resistant hypertension; RR, relative risk; Trtmt, treatment.

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Table 4 of the supplementary data

Summary of myocardial infarction event validations

Variables	GSR R-HT	GSR T2D	VALUE Valsartan cohort	VALUE Monotherapy	SPRINT Standard trtmt.	ACCOMPLISH	ACCORD	ON-TARGET ramipril subgroup	TRANSCEND	HOPE (Placebo)	STEP Standard trtmt.	Av.
Study-observed	2.3%	4.0%	4.8%	2.7%	2.3%	2.8%	6.4%	4.8%	5.0%	12.3%	1.9%	-
Model-projected	1.9%	3.3%	4.0%	2.6%	2.9%	1.5%	5.2%	3.9%	6.2%	4.0%	2.7%	-
RR (study vs model)	1.21	1.21	1.19	1.04	0.81	1.87	1.23	1.23	0.81	3.08	0.70	1.31

Av, average; GSR, Global SYMPLICITY Registry; R-HT, resistant hypertension; RR, relative risk; Trtmt, treatment.

Table 5 of the supplementary data

Summary of mortality validations

Variables	GSR R-HT	GSR T2D	VALUE valsartan cohort	VALUE monotherapy	SPRINT Standard trtmt.	ACCOMPLISH	ACCORD	ON-TARGET ramipril subgroup	TRANSCEND	HOPE (placebo)	STEP standard trtmt.	Av.
Study-observed	5.7%	7.1%	11.0%	6.2%	4.2%	4.5%	6.0%	11.8%	11.7%	12.9%	1.5%	-
Model-projected	3.9%	6.3%	10.0%	6.4%	6.6%	3.8%	9.3%	9.5%	12.6%	10.0%	6.4%	-
RR (study vs model)	1.46	1.13	1.10	0.97	0.64	1.18	0.64	1.25	0.93	1.29	0.23	0.98
General population per lifetables	2.5%	3.1%	5.9%	3.1%	4.5%	2.4%	4.6%	7.0%	6.7%	6.3%	3.9%	-
HR study vs general population	2.28	2.29	1.86	1.99	0.93	1.88	1.29	1.69	1.75	2.05	0.38	1.67

Av, average; GSR, Global SYMPLICITY Registry; R-HT, resistant hypertension; RR, relative risk; Trtmt, treatment.

Table 6 of the supplementary data

Probabilistic sensitivity analysis distributions

Parameter	Value	SD	SE	Lower bound	Upper bound	Distribution
Age	55.0 years	9.7	0.53	54.0	56.0	Normal
Gender (female)	19.9%		0.02	15.8%	24.3%	Beta
Baseline systolic BP	163 mmHg	7.3	0.40	162.2	163.8	Normal
Treatment effect 1	4.9 mmHg	10	0.54	3.83	5.97	Normal
Treatment effect 2	9.9 mmHg	10	0.54	8.83	10.97	Normal
Costs						
Hypertension (year 1+)	€251	-	25	204	303	Gamma
RF RDN therapy	€7484	-	748	6090	9021	Gamma
Stroke (acute)	€4787	-	479	3895	5770	Gamma
Stroke (remainder of year 1)	€6647	-	665	5408	8011	Gamma
Stroke (year 2+)	€4135	-	414	3365	4984	Gamma
MI (acute)	€7674	-	96	7488	7862	Gamma
MI (year 1+)	€950	-	135	705	1231	Gamma
Stable AP (year 1+)	€615	-	74	478	769	Gamma
Unstable AP (acute)	€2910	-	51	2811	3011	Gamma
Unstable AP (year 1+)	€615	-	74	478	769	Gamma
HF (year 1+)	€5,808	-	300	5,235	6,410	Gamma
ESRD (year 1+)	€25 574	-	2557	20 808	30 824	Gamma
Utilities						
Stroke	0.63	-	0.03	0.57	0.68	Beta
MI (months 1-6)	0.76	-	0.09	0.57	0.91	Beta
MI (months 6+)	0.88	-	0.02	0.85	0.91	Beta
Stable AP	0.84	-	0.02	0.80	0.87	Beta
Unstable AP	0.74	-	0.02	0.70	0.78	Beta
HF	0.71	-	0.07	0.56	0.84	Beta
ESRD	0.63	-	0.06	0.52	0.73	Beta
Adjustment factors						
Stroke risk equation	1.00	-	-	0.80	1.20	Uniform
MI risk equation*	0.90	-	-	0.72	1.08	Uniform
CHD risk equation	1.00	-	-	0.80	1.20	Uniform
HF risk equation	1.00	-	-	0.80	1.20	Uniform
ESRD risk equation	1.00	-	-	0.80	1.20	Uniform
Stroke relative risk from treatment effect	1.00	-	0.05	0.90	1.10	Normal

CHD relative risk from treatment effect	1.00	-	0.03	0.94	1.06	Normal
HF relative risk from treatment effect	1.00	-	0.08	0.83	1.17	Normal

AP, angina pectoris; BP, blood pressure; CHD, coronary heart disease; ESRD, end-stage renal disease; HF, heart failure; MI, myocardial infarction; RF RDN, radiofrequency renal denervation; SE, standard error; SD, standard deviation.
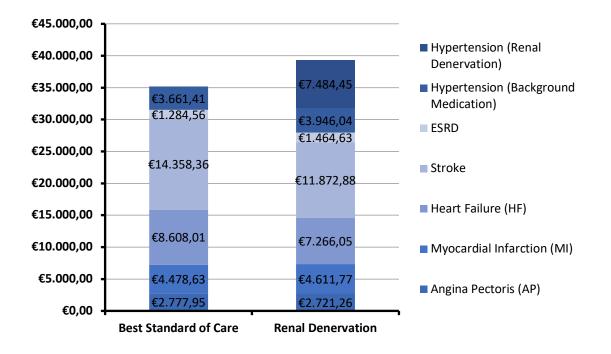
*Note that for the MI risk equation, the male PROCAM equation was adjusted based on the Tromsø study for the mixed-gender HTN-ON MED cohort. As such, the base case value is 0.90 with an upper and lower bound of 0.72-1.08.

Figure 1 of the supplementary data. Cost breakdown by treatment strategy. A reduced number of clinical events were projected in the renal denervation cohort, which helped to in part amortize the cost of renal denervation therapy and provided cost-savings compared to the standard of care. The largest cost-savings was associated with stroke costs, with heart failure and angina pectoris also contributing to cost-savings.

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