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**ORIGINAL ARTICLE**

# Clinical event reductions in high-risk patients after renal denervation projected from the global SYMPLICITY registry

**Roland E. Schmieder [1,*], Felix Mahfoud [2], Giuseppe Mancia [3], Krzysztof Narkiewicz [4], Luis Ruilope [5], David W. Hutton [6], Khoa N. Cao [7], Douglas A. Hettrick [8], Martin Fahy [8], Markus P. Schlaich [9], Michael Böhm [2] and Jan B. Pietzsch [7]**

[1]Department of Nephrology and Hypertension, University Hospital Erlangen, Erlangen, Bavaria 91054, Germany; [2]Internal Medicine and Cardiology, Saarland University Hospital, Homburg/Saar, Saarland 66421, Germany; [3]Department of Medicine, University of Milano-Bicocca, Monza, Lombardia 20126, Italy; [4]Hypertension and Diabetology, Medical University of Gdansk, Gdansk 80-210, Poland; [5]Cardiorenal Investigation, Institute of Research, Hospital Universitario 12 de Octubre and CIBERCV and School of Doctoral Studies and Research, Universidad Europea de Madrid, Madrid 28041, Spain; [6]School of Public Health, University of Michigan, Ann Arbor, MI 48109, USA; [7]Wing Tech Inc., Menlo Park, CA 94025, USA; [8]Coronary and Renal Denervation, Medtronic, Santa Rosa, CA 95403, USA; and [9]Dobney Hypertension Centre, School of Medicine—Royal Perth Hospital Unit, The University of Western Australia, Perth, WA 6009, Australia

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**Aims** Renal denervation has been shown to lower blood pressure in sham-controlled trials and represents a device-based treatment option for hypertension. We sought to project clinical event reductions after radiofrequency renal denervation using a novel modelling approach.

**Methods and results** The Global SYMPLICITY Registry is a global, prospective all-comer registry to evaluate safety and efficacy after renal denervation. For this analysis, change in office systolic blood pressure from baseline was calculated from reported follow-up in the Global SYMPLICITY Registry. Relative risks for death and other cardiovascular events as well as numbers needed to treat for event avoidance were obtained for the respective blood pressure reductions based on previously reported meta-regression analyses for the full cohort and high-risk subgroups including type 2 diabetes, chronic kidney disease, resistant hypertension, and high basal cardiovascular risk. Average baseline office systolic blood pressure and reduction estimates for the full cohort (N = 2651) were 166±25 and −14.8 ± 0.4 mmHg, respectively. Mean reductions in blood pressure ranged from −11.0−−21.8 mmHg for the studied high-risk subgroups. Projected relative risks ranged from 0.57 for stroke in the resistant hypertension cohort to 0.92 for death in the diabetes cohort. Significant absolute reductions in major adverse cardiovascular events over 3 years compared with the projected control (8.6 ± 0.7% observed vs. 11.7 ± 0.9% for projected control; $P < 0.01$) were primarily due to reduced stroke incidence. The robustness of findings was confirmed in sensitivity and scenario analyses.

**Conclusion** Model-based projections suggest radiofrequency renal denervation for patients with uncontrolled hypertension adds considerable clinical benefit across a spectrum of different cohort characteristics.

**Keywords** hypertension • renal denervation • relative risk reduction • outcome assessment • cardiovascular risk

## Introduction

Uncontrolled hypertension remains the leading preventable cause of death globally.[1] Treatment strategies that rely on lifestyle modification and chronic drug therapy have not achieved adequate blood pressure control in populations worldwide[2,3] due to several factors including lack of patient awareness, socio-economic barriers to care, clinical inertia against guideline recommendations, and non-adherence to prescribed medication.[4,5] Percutaneous catheter-based renal denervation has recently been shown to lower both office and 24-hour systolic and diastolic blood pressures in multiple prospective, randomized, sham-controlled trials including nearly 700 patients with

* Corresponding author. Roland E. Schmieder, Department of Nephrology and Hypertension, University of Erlangen-Nürnberg, Ulmenweg 18, 91054 Erlangen, Germany. Fax: 09131 85-36216, Email: roland.schmieder@uk-erlangen.de

uncontrolled hypertension in both the presence and absence of concomitant antihypertensive drug therapy,[6–9] and therefore represents an adjuvant to traditional multiple drug therapy.[10] Procedural safety, long-term preservation of renal function and low incidence of renal vascular complications following the procedure have also been documented.[11–13] Despite the strong correlation between blood pressure and cardiovascular risk,[14–16] questions remain about the magnitude of the effects of renal denervation therapy on cardiovascular outcomes. No large outcome trial of device-based treatments for hypertension has been performed to date.[17] The ongoing prospective open labelled Global SYMPLICITY Registry has enrolled close to 3000 real-world patients treated with radio frequency renal denervation and most have been enrolled to three years post-procedure.[18,19] We previously reported similar blood pressure reduction among various high-risk subgroups of the Global SYMPLICITY Registry.[18] In the present analysis, we estimate clinical event reductions in high-risk groups based on the Global SYMPLICITY Registry-observed data and evidence from a published meta-regression analysis.

# Methods

## Global SYMPLICITY Registry

Details of the design of the international, prospective, single-arm Global SYMPLICITY Registry (NCT01534299) have previously been published.[20] Patients with uncontrolled hypertension or conditions associated with sympathetic nervous system activation were enrolled according to local guidelines. The institutional review board or ethics committee at each enrolling site approved the registry, the study design adhered to the Declaration of Helsinki and all patients provided written informed consent. All patients were treated with the Symplicity renal denervation system (Medtronic, Santa Rosa, CA, USA) using either the single electrode Symplicity Flex™ or the multi-electrode Symplicity Spyral™ catheter to accomplish radiofrequency ablation of the renal nerves. Patients were followed at 3-, 6-, 12-, 24- and 36-months post-procedure. Adverse event occurrence, including death, stroke, myocardial infarction, were recorded at each follow-up and were independently adjudicated by the Clinical Events Committee (Cardiovascular Research Foundation, New York, NY, USA).

## Cohort characteristics and subgroup identification

Analyses were performed on registry follow-up data collected through May 2019. In addition to the full study cohort, the following high-risk subgroups were specified: resistant hypertension, defined as baseline office systolic blood pressure >150 mmHg despite prescription of ≥3 anti-hypertensive medication classes; history of type 2 diabetes mellitus; chronic kidney disease defined as baseline estimated glomerular filtration rate <60 ml/min/1.73 $m^2$; and high atherosclerotic cardiovascular disease risk at baseline >20%, calculated based on each patient's office systolic blood pressure, antihypertensive medications, serum cholesterol, and diabetic and smoking status.[21]

## Risk analysis

A stepwise calculation approach was applied to compare reported events in Global SYMPLICITY Registry to calculated 'control' rates assuming office systolic blood pressure had remained stable at baseline levels (Supplementary material online, *Figure S1*). First, changes in office systolic blood pressure from baseline were averaged from the office systolic blood pressure changes observed at 6-, 12-, 24-, and 36-months follow-up. Observed event rates at 36 months were obtained from Global SYMPLICITY Registry data, including a combined major adverse cardiac events endpoint, defined as the three-point composite of non-fatal stroke, non-fatal myocardial infarction, and cardiovascular death. Next, relative risks for death, cardiovascular death, myocardial infarction and stroke were obtained for the observed average blood pressure reductions from a meta-regression analysis of randomized trials of office systolic blood pressure reductions in hypertensive patients (see supplementary materials).[15] To project 'control' event rates, the observed events in the renal denervation-treated patients were divided by the calculated relative risks. The absolute difference between calculated control group events and observed renal denervation group events was subsequently used to calculate the numbers needed to treat to avoid the respective clinical events over a 3-year follow-up.

For each of these outcomes of interest, we calculated results first via the established deterministic approach. Probabilistic results were then calculated to reflect parameter uncertainty in the observed clinical event rates, blood pressure changes, and the relative risks from the published meta-regression. Distributions of mean event rates and blood pressure changes were obtained by calculating 2500 bootstrap samples of the Global SYMPLICITY Registry patient-level data. For the relative risk functions derived from the published meta-regression, the source report provided distributional information.[15] Distributions for projected control events, events avoided, and numbers needed to treat were then calculated based on these input distributions using second-order Monte Carlo simulation ($n = 5000$ simulations). Using the distributions of mean event rates for the treated and control groups, we calculated the probability that the mean treated event rate would be worse than the mean control event rate—and considered a probability of $<0.05$ as a threshold that renal denervation was significantly better than the control. See supplementary materials for additional details.

## Sensitivity analyses

Several sensitivity analyses were performed to explore the robustness of the study findings. First, results were recalculated for a lower effect size of 10 mmHg, in line with recent data from the ON-MED randomized trial, where this average effect size was reported vs. sham control through 36-month follow-up.[22] Second, risk functions derived from recently analysed data of The Blood Pressure Lowering Treatment Trialists Collaboration (BPLTTC) were obtained and applied to the full cohort analysis to explore the effect of this different set of risk equations onto the analysis outcomes.

For all analyses, actual event rates and predicted distributions of the event parameter means are reported as mean ± standard deviation. All statistical analyses were performed with JMP 15 (SAS Institute, Cary, NC, USA).

# Results

As of May 2019, 2651 patients were enrolled in the Global SYMPLICITY Registry from 196 centers in 45 countries, with a median follow up of 3 years. Median atherosclerotic cardiovascular disease risk score at baseline was 19.8% (Interquartile range: 9%–37%, N = 1485). Baseline demographics for the full registry cohort and for the high-risk subgroups in the supplementary materials are shown in *Table 1*. Patients averaged over 60 years of age, were mostly male and had been diagnosed with hypertension on average 16 ± 12 years prior to enrolment. Most patients had a history of cardiovascular disease and were prescribed an average of 4.6 antihypertensive drug classes at the time of inclusion.

Mean cohort changes in office systolic blood pressure ranged from −11.0 – −21.8 mmHg systolic in the studied high-risk groups. Stroke (4.5%) and all-cause death (5.7%) were the most frequently reported outcome events in the full cohort and event rates varied by subgroup (*Table 2*). The projected relative risk point estimates ranged from 0.57 for stroke in the resistant hypertension cohort to 0.92 for death in the type II diabetes mellitus cohort (*Figure 1*). Probabilistic analysis demonstrated significant absolute reductions in major adverse cardiovascular events over 3 years (8.6 ± 0.7% actual vs. 11.7 ± 0.9% projected control; $P < 0.01$) primarily due to reduced stroke incidence (4.5 ± 0.5% actual vs. 6.9 ± 0.8% projected control; $P < 0.01$; *Figure 2*). Over the three-year horizon, the calculated number of patients needed to treat to avoid one major adverse cardiovascular event (number

**Table 1 Baseline demographics for GSR cohort and sub-groups**

| % or mean ± SD | All Patients (N = 2651)* | rHTN† (*n* = 1821) | Type 2 DM+ (*n* = 1007) | CKD‡ (*n* = 630) | High ASCVD Risk§ (*n* = 737) |
|---|---|---|---|---|---|
| Age (years) | 61 ± 12 | 61 ± 12 | 64 ± 10 | 65 ± 12 | 69 ± 8 |
| Male gender (%) | 57.8 | 57.5 | 59.3 | 52.2 | 64.0 |
| Body Mass Index (kg/m$^2$) | 31 ± 6 | 31 ± 6 | 32 ± 6 | 31 ± 6 | 31 ± 5 |
| eGFR(mL/min/1.73 m$^2$) | 76 ± 25 | 76 ± 25 | 72 ± 25 | 45 ± 13 | 72 ± 24 |
| History of cardiac disease (%) | 46.9 | 47.9 | 57.3 | 56.5 | 57.1 |
| Atrial fibrillation (%) | 12.5 | 11.7 | 13.7 | 17.1 | 16.4 |
| Diabetes, type 2 (%)+ | 38.1 | 40.7 | 100 | 47.9 | 57.8 |
| Obstructive sleep apnea (%) | 11.5 | 11.9 | 15.1 | 12.9 | 13.9 |
| Current smoking (%) | 9.8 | 10.3 | 8.5 | 9.4 | 10.3 |
| Office systolic BP (mmHg) | 166 ± 25 | 175 ± 20 | 165 ± 23 | 164 ± 26 | 167 ± 24 |
| Office diastolic BP (mmHg) | 90 ± 17 | 93 ± 16 | 86 ± 16 | 84 ± 17 | 85 ± 15 |
| 24-hr mean systolic BP (mmHg) | 154 ± 18 | 157 ± 18 | 155 ± 18 | 154 ± 19 | 153 ± 17 |
| 24-hr mean diastolic BP (mmHg) | 87 ± 14 | 88 ± 15 | 83 ± 13 | 82 ± 14 | 82 ± 12 |
| Number of AH meds | 4.6 ± 1.4 | 4.7 ± 1.2 | 4.7 ± 1.3 | 4.8 ± 1.3 | 4.7 ± 1.3 |

* Original dataset[18] included 1 additional patient who subsequently revoked consent and whose data were stricken from the database; Groups are not mutually exclusive.
†rHTN, Resistant hypertension defined as oSBP >150 mmHg and prescription of ≥3 antihypertensive drug classes; +Type 2 DM, Based on physician reporting; ‡CKD: Chronic kidney disease defined as eGFR <60 mL/min/1.73 m$^2$; §High ASCVD risk defined as baseline score >20%.

**Table 2 36-month actual event rates observed**

| | All patients | rHTN | Type 2 DM | CKD | High ASCVD risk |
|---|---|---|---|---|---|
| N (full cohort, baseline) | 2651 | 1821 | 1007 | 630 | 737 |
| N (with event data at 36 months) | 1749 | 1208 | 675 | 408 | 510 |
| Baseline oSBP (mmHg) | 166 ± 25 | 175 ± 20 | 165 ± 23 | 164 ± 26 | 168 ± 24 |
| Mean change in oSBP (mmHg) | −14.8 ± 0.4 | −21.5 ± 0.4 | −14.7 ± 0.5 | −11.0 ± 0.7 | −15.6 ± 0.6 |
| Stroke rate, 36 months (%) | 4.5 | 4.8 | 4.0 | 6.1 | 4.7 |
| MI rate, 36 M (%) | 2.5 | 2.3 | 4.0 | 3.4 | 2.2 |
| CV death rate, 36 M (%) | 2.9 | 2.8 | 4.0 | 5.1 | 4.5 |
| MACE rate, 36 M (%) | 8.6 | 8.7 | 10.4 | 13.0 | 10.2 |
| All-cause death rate, 36 M (%) | 5.7 | 5.7 | 7.1 | 10.0 | 8.4 |

Blood pressure values are mean ± SD. Groups and abbreviations as in *Table 1*; MI, myocardial infarction; CV, cardiovascular; MACE, 3-point major cardiovascular Events; ESRD, end stage renal disease.

needed to treat) ranged from 19–30 in the studied high-risk cohorts (*Figure 3* and supplementary materials online, *Tables S.3.1–S.3.5*).

In sensitivity analysis, the assumed reduction of effect size to 10 mmHg led to a limited reduction in control event rates (projected MACE events 10.9% instead of 11.7% for all GSR and 10.9% instead of 13.2% for resistant hypertension cohorts; see supplementary materials online, *Tables S.4.1–S 4.5* for detailed results of all cohorts). Applying the BPLTTC-derived risk functions led to a projected MACE control event rate for the full cohort of 10.8% instead of 11.7% (vs. 8.6% actual events; $P < 0.01$—see supplementary material online, *Table S.5.1*). The MACE NNTs for the full cohort increased from 33 in the main analysis to 44 for the 10 mmHg effect size scenario and 46 for the BPLTTC risk function scenario.

# Discussion

The results of the current study indicate that radiofrequency renal denervation may lower the occurrence of major adverse cardiovascular events by almost one third within 3-years. This finding is based on a projection of the blood pressure lowering effects observed in the largest real-world registry. This benefit was apparent in a patient population with uncontrolled hypertension despite baseline treatment with greater than four medications on average. The mean calculated number needed to treat to avoid one major adverse cardiovascular event over 3 years was 32 in the full cohort and was lower in the high-risk subgroups with calculated numbers needed to treat of 21, 30, 28, and 27 for resistant hypertension, type II diabetes mellitus, chronic kidney disease, and overall high atherosclerotic cardiovascular disease risk, respectively (*Figure 1*). Therefore, higher risk patients with more comorbidities or higher baseline blood pressure may stand to benefit most from radiofrequency renal denervation treatment, consistent with recommendations promulgated in recent US and European consensus statements.[10,23] The study approach is novel in that relative risks from meta-regression data were not applied to estimate potential events in patients treated with the intervention, but rather were applied to project events in a simulated control group

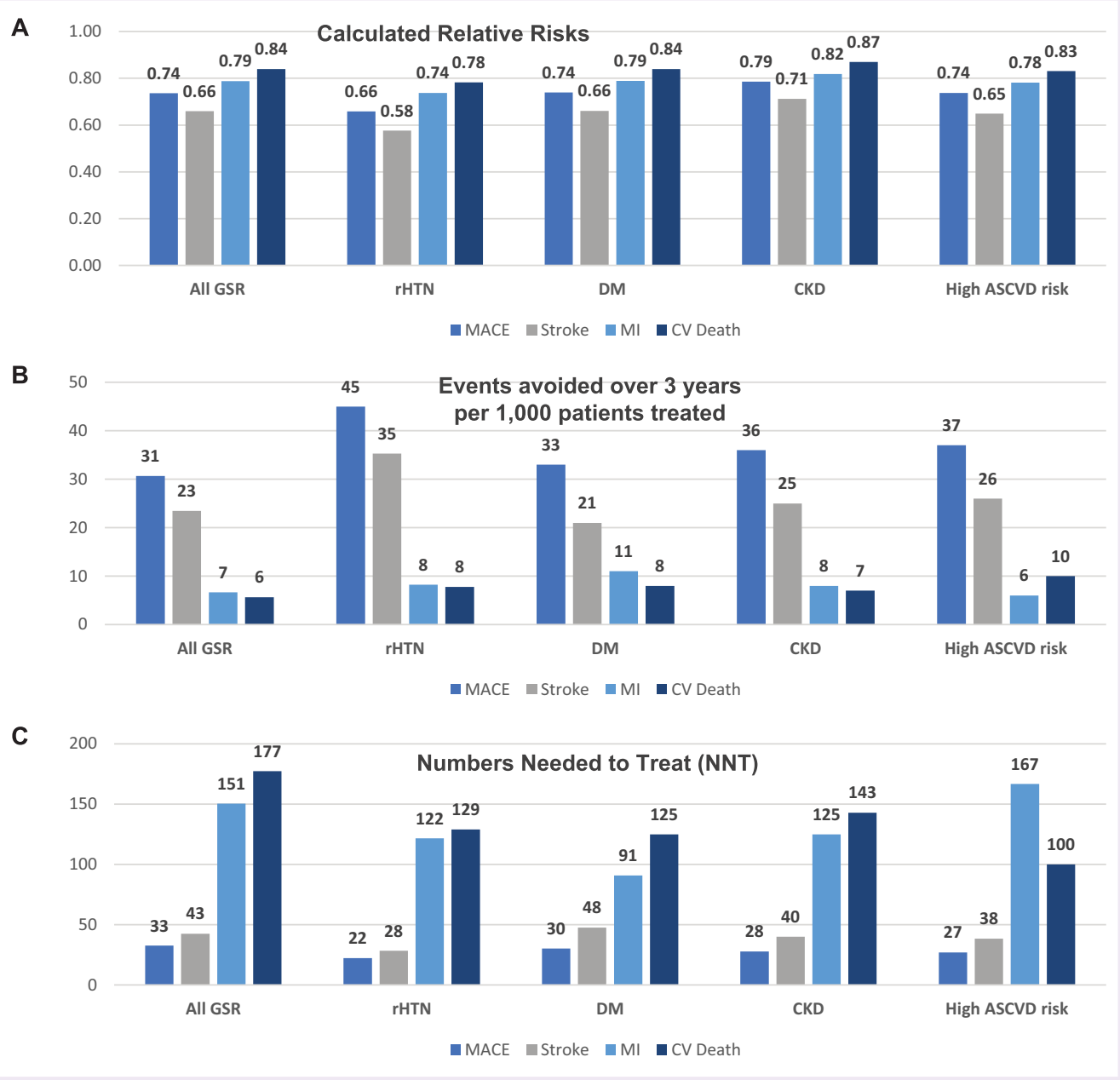


**Figure 1** Deterministic projections for the full, resistant hypertension, diabetes mellitus, chronic kidney disease, and high atherosclerotic cardiovascular disease risk cohorts for: (*A*) relative risks; (*B*) events avoided over 3 years per 1000 treated patients; and (*C*) numbers needed to treat for major adverse cardiac events, stroke, myocardial infarction, cardiovascular death events. MACE, major adverse cardiac events; MI, myocardial infarction; CV, cardiovascular; rHTN, resistant hypertension; DM, type-2 diabetes mellitus; CKD, chronic kidney disease; ASCVD, atherosclerotic cardiovascular disease.

that maintained baseline office systolic blood pressure throughout the follow up period. We believe this approach is innovative in that it can be applied whenever observed event rates in treated patients are available along with observed blood pressure reductions. Modeling projected events in a simulated control group may further enable cost-effectiveness and budget impact evaluations at the observed timeframe and beyond.

Recent randomized, sham-controlled trials included relatively smaller proportions of higher cardiovascular risk patients.[6–8] Prospective evaluation of the effect of the renal denervation procedure on clinical outcomes appears to be impractical because of ethical considerations for potentially under-treated control group patients.[17] Likewise, existing—and imminent—regulatory approvals of renal denervation in many geographies would render randomization of a large-scale population necessary for a prospective outcome trial difficult. Notably, the US Food and Drug Administration have acknowledged that blood pressure reduction is an acceptable surrogate trial endpoint because of the strongly established relationship

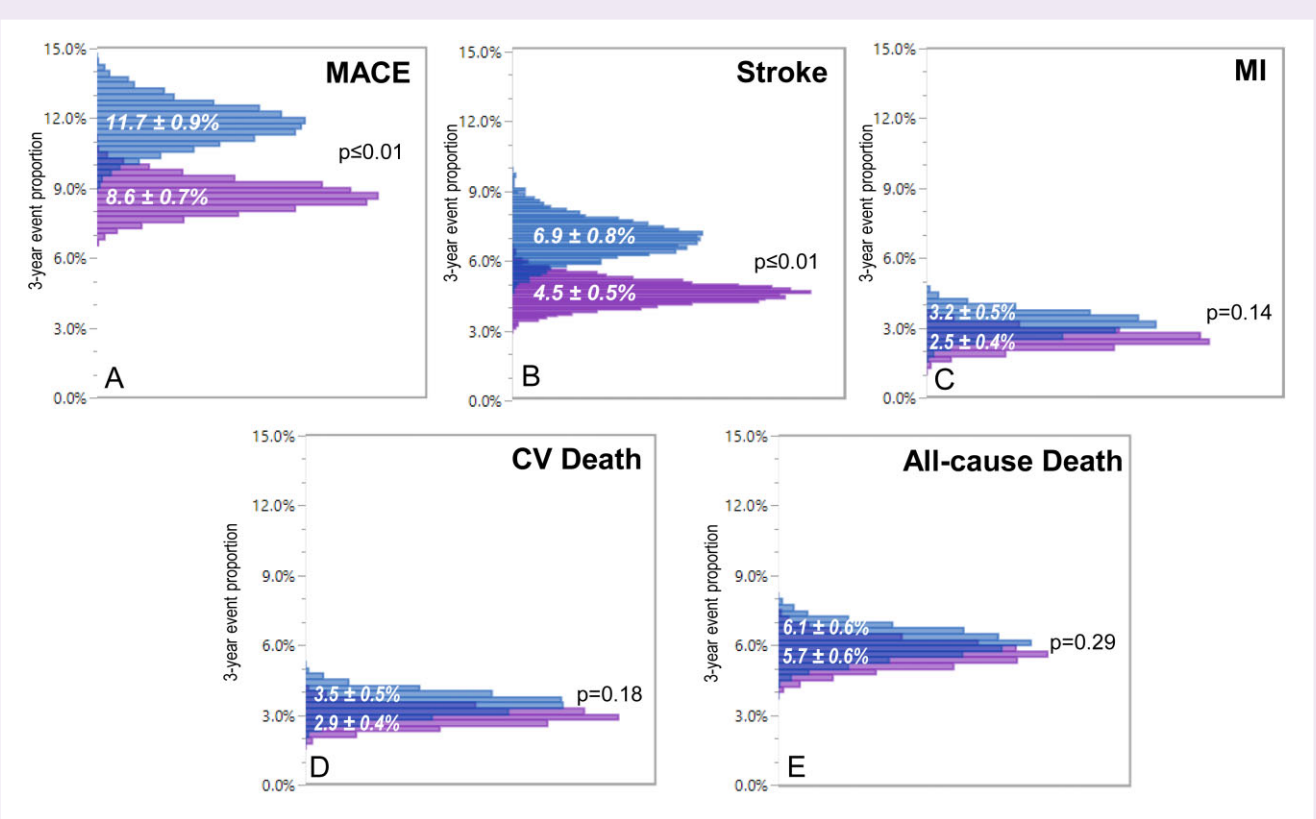


**Figure 2** Distribution of mean rates of (*A*) major adverse cardiac events, (*B*) stroke, (*C*) myocardial infarction, (*D*) cardiovascular death, and (*E*) all-cause death for the actual treated group (purple) vs. calculated control (blue) for the full registry cohort based on simulation results considering parameter uncertainty. MACE, major adverse cardiac events; MI, myocardial infarction.

between blood pressure reduction and improved cardiovascular outcome.[24] Such a relationship has not only been observed in epidemiological studies but also in several meta-analyses reporting a nearly linear relationship between blood pressure lowering and reduction of cardiovascular events, irrespective of the baseline blood pressure.[14–16] Interestingly, a recent retrospective analysis of a large single center cohort (N = 296) of resistant hypertensive renal denervation-treated patients with a median of 4 years follow up demonstrated significantly fewer major adverse cardiovascular events in patients classified as treatment 'responders'.[25] These results suggest that renal denervation-induced blood pressure reductions are indeed associated with major adverse cardiovascular event reduction as assumed in the present analysis. Our projections, based on previously published meta-analysis of cardiovascular risk reduction and blood pressure reduction, may guide estimates of the potential events avoided and the range of numbers needed to treat in the short-term. Such analysis may complement previous[26] and future analysis models extrapolating longer-term clinical effectiveness and associated costs avoided following renal denervation treatment.

Previous investigations besides the Global SYMPLICITY Registry have also demonstrated the safety and efficacy of renal denervation in high risk cohorts of uncontrolled hypertension, including resistant hypertension,[27–29] elderly patients,[30] insulin resistance,[31,32] chronic kidney disease,[33–36] obstructive sleep apnea[37,38] and isolated systolic hypertension.[39] The present analysis focused on high-risk populations associated with hypertension including chronic kidney disease and type II diabetes mellitus. We also examined patients with overall high composite risk. Our modelled projections confirm and extend these previous findings by showing sustained blood pressure reduction vs. baseline in all cohorts and estimating a potential one-third reduction in specific major adverse cardiovascular events associated with observed blood pressure lowering.

The results also compare favorably with prior reports of number needed to treat for various device and drug therapies. For example, the SPRINT trial of intensive vs. standard blood pressure control in patients with uncontrolled blood pressure and increased cardiovascular risk reported an actual risk reduction of 25% for major adverse cardiovascular events, which was associated with a number needed to treat of 61 after an average follow up of slightly over 3 years, although a slightly different definition of major adverse cardiovascular events was applied in that study.[40]

## Study limitations

The present analysis has limitations. First, our findings used blood pressure data from a single-arm registry, with assumptions that blood pressure measurements were not influenced by reporting bias and that control subjects maintained their baseline blood pressure over the study period. However, this assumption appears reasonable since Global SYMPLICITY Registry patients had uncontrolled blood pressure for an average of 16 years prior to receiving the renal denervation procedure. Also, the registry-observed changes in office systolic blood pressure are directionally higher than office systolic blood pressure changes demonstrated in the recent sham-controlled trials. However, these were performed in cohorts with different characteristics and risk profile compared with the real-world population in the Global SYMPLICITY registry. Nevertheless, the conducted sensitivity analysis using an effect size of 10 mmHg derived from recent sham-controlled

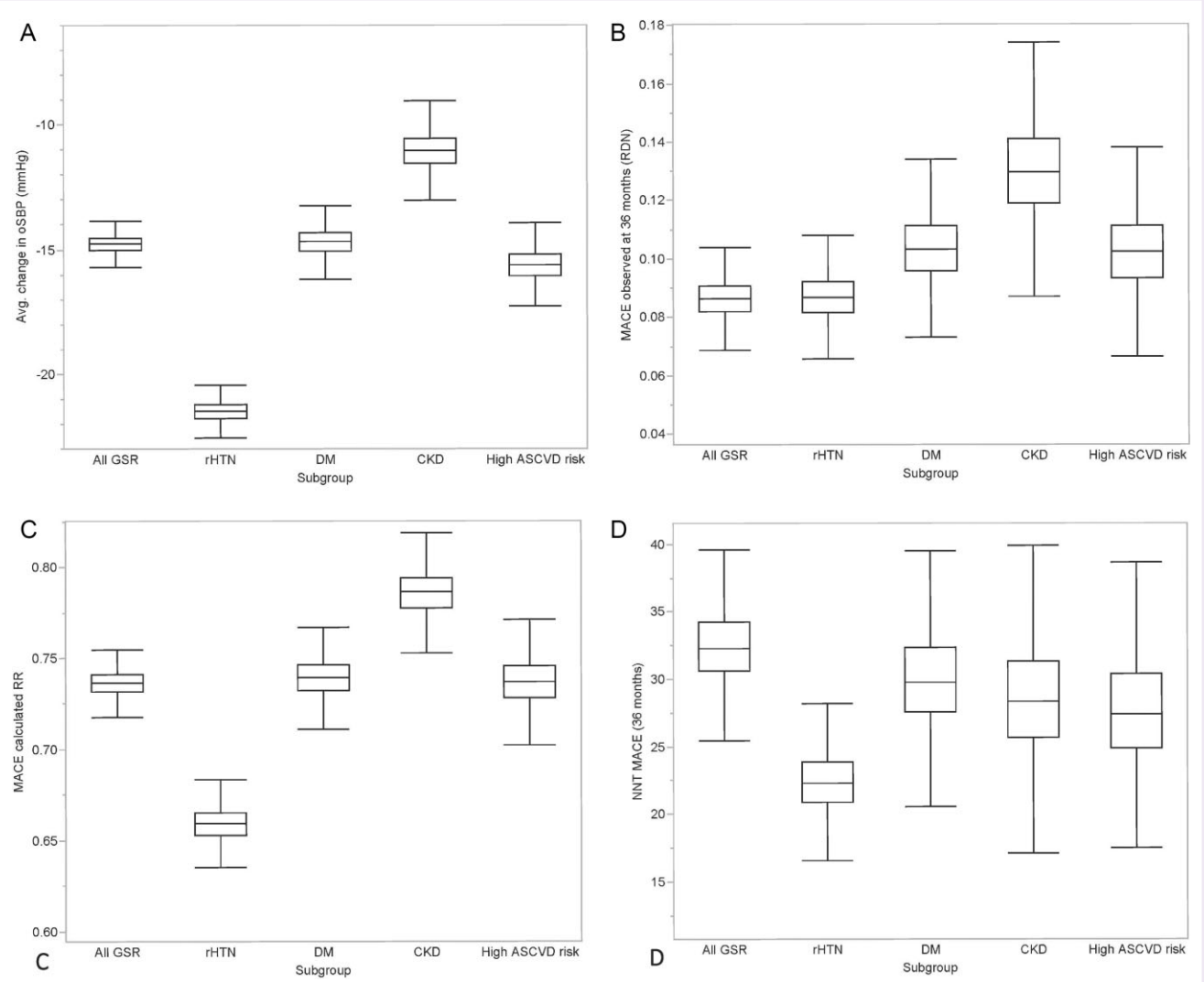


**Figure 3** Sensitivity analysis accounting for sample uncertainty in subgroups analyses is shown. Panels illustrate: (*A*) distribution of actual office systolic blood pressure reductions over 3 years following radiofrequency renal denervation in the full Global SYMPLICITY Registry cohort and high-risk subgroups chronic kidney disease, high basal atherosclerotic cardiovascular disease risk, resistant hypertension, and diabetes mellitus cohorts; (*B*) frequency of actual major adverse cardiac events event occurrence in each group; (*C*) calculated risk reduction distribution for actual BP drops based on meta regression analysis; and (*D*) calculated distribution of numbers needed to treat in each group to avoid one major adverse cardiac events event within the 3-year follow up. oSBP,office systolic blood pressure; RDN, renal denervation; CKD, chronic kidney disease; ASCVD, atherosclerotic cardiovascular disease; rHTN, resistant hypertension; DM, type-2 diabetes mellitus; MACE, major adverse cardiac events; BP, blood pressure; NNT, numbers needed to treat.

trial suggest event reductions and NNTs would remain favorable and directionally comparable. Second, we relied on relative risk estimates derived from a published meta-regression that consider change in blood pressure as the only factor for estimation of risk reduction. This report is the largest meta-regression published to-date and specifically focusing on hypertension interventions, as opposed to associations between point-in-time blood pressure measures and clinical events reported in meta-analyses of broader populations.[41] However, we also performed an additional sensitivity analysis based on data provided by the BPLTTC.[14,16] Again, the calculated risk reductions and event rates, while somewhat smaller, did not materially change the analysis findings and therefore support the robustness of the results. Finally, to complement deterministic analyses, we applied probabilistic simulations to account for uncertainty in the observed clinical event rates, blood pressure changes, and relative risks from the published meta-regression.

## Conclusions

In summary, the meta regression analysis-based projections of clinical events avoided resulted in significant major adverse cardiovascular event reduction and relatively low numbers needed to treat through 3 years follow-up in a real-world uncontrolled hypertension population treated with radiofrequency renal denervation, with consistent results in high-risk sub-cohorts. The relatively even distribution of predicted risk reduction across the full cohort and comorbid groups suggests that renal denervation can benefit all patients with uncontrolled

hypertension, including higher risk uncontrolled hypertensive patients. These shorter-term data might provide useful orientation for clinicians and policymakers interested in extrapolating the potential clinical and economic implications of renal denervation treatment over longer-term horizons.

## Supplementary material

Supplementary material is available at *European Heart Journal—Quality of Care and Clinical Outcomes* online.


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## Data availability

The data, analytical methods, and study materials are owned by the funder and therefore will not be made available to other researchers for the purposes of reproducing the results or replicating the procedure.

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