Cardiovascular Risk Reduction After Renal Denervation According to Time in Therapeutic Systolic Blood Pressure Range

Felix Mahfoud, MD,[a] Giuseppe Mancia, MD, PHD,[b] Roland E. Schmieder, MD,[c] Luis Ruilope, MD, PHD,[d,e]
Krzysztof Narkiewicz, MD, PHD,[f] Markus Schlaich, MD,[g] Bryan Williams, MD,[h] Flavio Ribichini, MD,[i]
Joachim Weil, MD,[j] Hsien-Li Kao, MD,[k] Oriol Rodriguez-Leor, MD, PHD,[l] Elias Noory, MD,[m] Tiong Kiam Ong, MD,[n]
Thierry Unterseeh, MD,[o] Pedro de Araújo Gonçalves, MD,[p] Andreas Zirlik, MD,[q] Khaled Almerri, MD,[r]
Faisal Sharif, MD, PHD,[s] Lucas Lauder, MD,[a] Marianne Wanten, MS,[t] Martin Fahy, MS,[t] Michael Böhm, MD[a]

ABSTRACT

BACKGROUND Renal denervation (RDN) has been shown to lower blood pressure (BP), but its effects on cardiovascular events have only been preliminarily evaluated. Time in therapeutic range (TTR) of BP is associated with cardiovascular events.

OBJECTIVES This study sought to assess the impact of catheter-based RDN on TTR and its association with cardiovascular outcomes in the GSR (Global SYMPLICITY Registry).

METHODS Patients with uncontrolled hypertension were enrolled and treated with radiofrequency RDN. Office and ambulatory systolic blood pressure (OSBP and ASBP) were measured at 3, 6, 12, 24, and 36 months postprocedure and used to derive TTR. TTR through 6 months was assessed as a predictor of cardiovascular events from 6 to 36 months using a Cox proportional hazard regression model.

RESULTS As of March 1, 2022, 3,077 patients were enrolled: 42.2% were female; mean age was 60.5 ± 12.2 years; baseline OSBP was 165.6 ± 24.8 mm Hg; and baseline ASBP was 154.3 ± 18.7 mm Hg. Patients were prescribed 4.9 ± 1.7 antihypertensive medications at baseline and 4.8 ± 1.9 at 36 months. At 36 months, mean changes were −16.7 ± 28.4 and −9.0 ± 20.2 mm Hg for OSBP and ASBP, respectively. TTR through 6 months was 30.6%. A 10% increase in TTR after RDN through 6 months was associated with significant risk reductions from 6 to 36 months of 15% for major adverse cardiovascular events ($P < 0.001$), 11% cardiovascular death ($P = 0.010$), 15% myocardial infarction ($P = 0.023$), and 23% stroke ($P < 0.001$).

CONCLUSIONS There were sustained BP reductions and higher TTR through 36 months after RDN. A 10% increase in TTR through 6 months was associated with significant risk reductions in major cardiovascular events from 6 to 36 months. (Global SYMPLICITY Registry [GSR] DEFINE; NCT01534299) (J Am Coll Cardiol 2022;80:1871–1880) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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From the [a]Saarland University Hospital, Homburg/Saar, Germany; [b]University of Milano-Bicocca, Milan, Italy; [c]University Hospital Erlangen, Erlangen, Germany; [d]Hospital Universitario 12 de Octubre and Centro de Investigación Biomédica en Red Enfermedades Cardiovasculares, Madrid, Spain; [e]School of Doctoral Studies and Research, Universidad Europea de Madrid, Madrid, Spain; [f]Medical University of Gdansk, Gdansk, Poland; [g]Dobney Hypertension Centre, Medical School—Royal Perth Hospital Unit, The University of Western Australia, Perth, Western Australia, Australia; [h]University College London and National Institute for Health Research University College London Hospitals Biomedical Research Centre, London, United Kingdom; [i]Azienda Ospedaliera Universitaria Integrata Verona, Verona, Italy; [j]Sana Kliniken Lübeck GmbH, Lübeck, Germany; [k]National Taiwan University Hospital, Taipei, Taiwan; [l]Hospital Germans Trias i Pujol, Barcelona, Spain; [m]Universitäts-Herzzentrum Freiburg, Bad Krozingen, Germany; [n]Sarawak General Hospital, Kuching, Malaysia; [o]Institut Hospitalier Jacques Cartier, Massy, France; [p]Centro Hospitalar de Lisboa Ocidental/Hospital de Santa Cruz, Carnaxide, Portugal; [q]Medical University Graz, Graz, Austria; [r]Chest Disease Hospital, Shuwaikh, Kuwait; [s]University Hospital Galway and National University of Ireland Galway, Galway, Ireland; and the [t]Medtronic PLC, Santa Rosa, California, USA.

Renal denervation (RDN) has emerged as a potential treatment for hypertension.[1-3] Patients with uncontrolled hypertension treated with catheter-based radiofrequency RDN experienced clinically meaningful and significant reductions in blood pressure (BP) compared to sham control patients in several randomized trials.[4-6] These trials demonstrated the safety and efficacy of RDN, and data from registries provide additional insights into long-term outcomes in real-world patients.[7] In the GSR (Global SYMPLICTY Registry) significant and sustained BP reductions out to 36 months were documented.[8] Although it is assumed that long-term BP reductions after RDN have an impact on cardiovascular outcomes,[9] this has not been evaluated in a clinical study.

SEE PAGE 1881

Time in therapeutic range (TTR) estimates the proportion of time a patient spends within a specified, targeted BP range.[10-12] Previous analyses identified TTR as an independent predictor of cardiovascular events in patients who are hypertensive[10] and reported higher all-cause mortality with lower TTR in patients with and without hypertension.[11] In this analysis, we evaluate TTR of patients after RDN in the GSR and its association with cardiovascular events.

METHODS

STUDY DESIGN. The study design of GSR has been previously described (NCT01534299).[13,14] GSR is a prospective, multicenter, single-arm, open-label, observational, international registry to assess the safety and efficacy of RDN in an all-comer population. Patients with uncontrolled hypertension were enrolled. All patients provided written informed consent; the study was approved by the Institutional Review Board or ethics committee at each enrolling center; and the study adhered to the Declaration of Helsinki.

STUDY PROCEDURES. Radiofrequency RDN was performed on all patients with the Symplicity Flex or Symplicity Spyral catheter (Medtronic). Patients were followed at in-office visits at 3, 6, 12, 24, and 36 months postprocedure per standard of care. Office BP was measured at discharge and follow-up according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure guidelines.[15] Prescribed antihypertensive and cardiovascular medications were cataloged at each follow-up, but dosages were not reported. Previously in GSR, prescribed antihypertensive medication classes were collected, but the current analysis reflects the number of antihypertensive medications, not classes. Incidence of stroke; myocardial infarction (MI); major adverse cardiovascular events (MACE), defined as cardiovascular death, MI, or stroke; renal artery reintervention; vascular complications; and hospitalization for new onset heart failure, atrial fibrillation, or hypertensive crisis were recorded at each follow-up. Cardiovascular death included unknown deaths. All adverse events were independently adjudicated by the Clinical Events Committee (Cardiovascular Research Foundation, New York, New York).

TIME IN THERAPEUTIC RANGE. To estimate TTR for each patient, successive systolic BP measurements from baseline through follow-up were linearly interpolated as previously described.[10,12] Then, the percentage of time each patient spent within a specified BP range based on the interpolated patient BP was calculated using office systolic blood pressure (OSBP) and 24-hour ambulatory systolic blood pressure (ASBP) measurements, separately. BP target ranges were specified as ≤140 mm Hg for OSBP and ≤130 mm Hg for ASBP. To determine the TTR for each interval, the maximum TTR value using OSBP vs ASBP was selected for each patient and then was averaged across patients in the GSR. For patients with missing follow-up BP measures at a specific interval, TTR was calculated using their BP from the last observation carried forward and imputed to that interval. For example, for a patient with a 3-month follow-up BP measure but without a 6-month follow-up, the TTR value from baseline to 3 months was imputed to 6 months.

The number of days spent in therapeutic range (as opposed to the percentage of time) was determined by multiplying the TTR value by the number of days in the time period. For example, an average TTR of 30.6% at 6 months is calculated in days by multiplying 0.306 by 6 months (30 days per month) equaling approximately 55 days.

TABLE 1 Patient Characteristics, BP, and Number of Medications at Baseline

	All Patients (N = 3,077)	Patients Included in KM Analysis (n = 2,709)	Patients Excluded From KM Analysis (n = 368)	P Value
Age, y	60.5 ± 12.2	60.6 ± 11.9	59.1 ± 13.8	0.047
Female	42.2 (1,297)	41.9 (1,134/2,709)	44.3 (163/368)	0.40
BMI, kg/m^2	31.0 ± 6.2	31.0 ± 5.6	31.1 ± 9.5	0.77
Chronic kidney disease, eGFR <60 mL/min/1.73 m^2	20.8 (638/3,064)	20.0 (540/2,701)	27.0 (98/363)	0.0030
History of cardiac disease	46.8 (1,425/3,048)	46.4 (1,247/2,689)	49.6 (178/359)	0.26
History of vascular disease	24.2 (735/3,034)	23.5 (629/2,678)	29.8 (106/356)	0.010
History of atrial fibrillation	12.3 (375/3,058)	12.0 (324/2,698)	14.2 (51/360)	0.23
Diabetes mellitus (type 2)	37.9 (1,164/3,069)	37.8 (1,023/2,703)	38.5 (141/366)	0.82
Hypocholesterolemia	36.5 (1,120/3,071)	35.9 (973/2,707)	40.4 (147/364)	0.10
Current smoker	10.2 (314/3,071)	9.9 (267/2,707)	12.9 (47/364)	0.080
Number of antihypertensive medications	4.9 ± 1.7	4.9 ± 1.7	4.8 ± 1.9	0.18
Office systolic BP, mm Hg	165.6 ± 24.8	165.7 ± 24.7	164.8 ± 25.7	0.57
Mean 24-h systolic BP, mm Hg	154.3 ± 18.7	154.0 ± 18.3	156.9 ± 21.6	0.063

Values are mean ± SD, % (n), or % (n/N). *P* values comparing patients excluded versus those included in the KM analysis using exact binomial test for categorial data and Student's *t*-tests for continuous tests.

BMI = body mass index; BP = blood pressure; eGFR = estimated glomerular filtration rate; KM = Kaplan-Meier.

STATISTICAL ANALYSIS. Categorical variables are reported as counts and percentages and continuous variables are reported as mean ± SD. Cox proportional hazards models and Kaplan-Meier rate estimates were used to assess the impact of TTR through 6 months on cardiovascular event rates from 6 to 36 months. Patients that had a cardiovascular event between the time of procedure through the first 6 months were excluded from the analysis. Patients with incomplete follow-up (<36 months) were included in the Kaplan-Meier rate estimates and Cox regression analyses and were censored at their last follow-up date. For the Cox proportional hazards regression analyses, the dependent variable is cardiovascular outcome between 6 and 36 months and the independent predictor is TTR through 6 months. HRs are presented corresponding to a 10% increase in TTR. For the Kaplan-Meier categorical TTR analysis, TTR is split into 3 groups: TTR = 0% defines the first group and the remaining subjects are split into 2 equal size groups using a cutoff of TTR = 50%.

SAS for Windows version 9.4 (SAS Institute) was used for all statistical analyses.
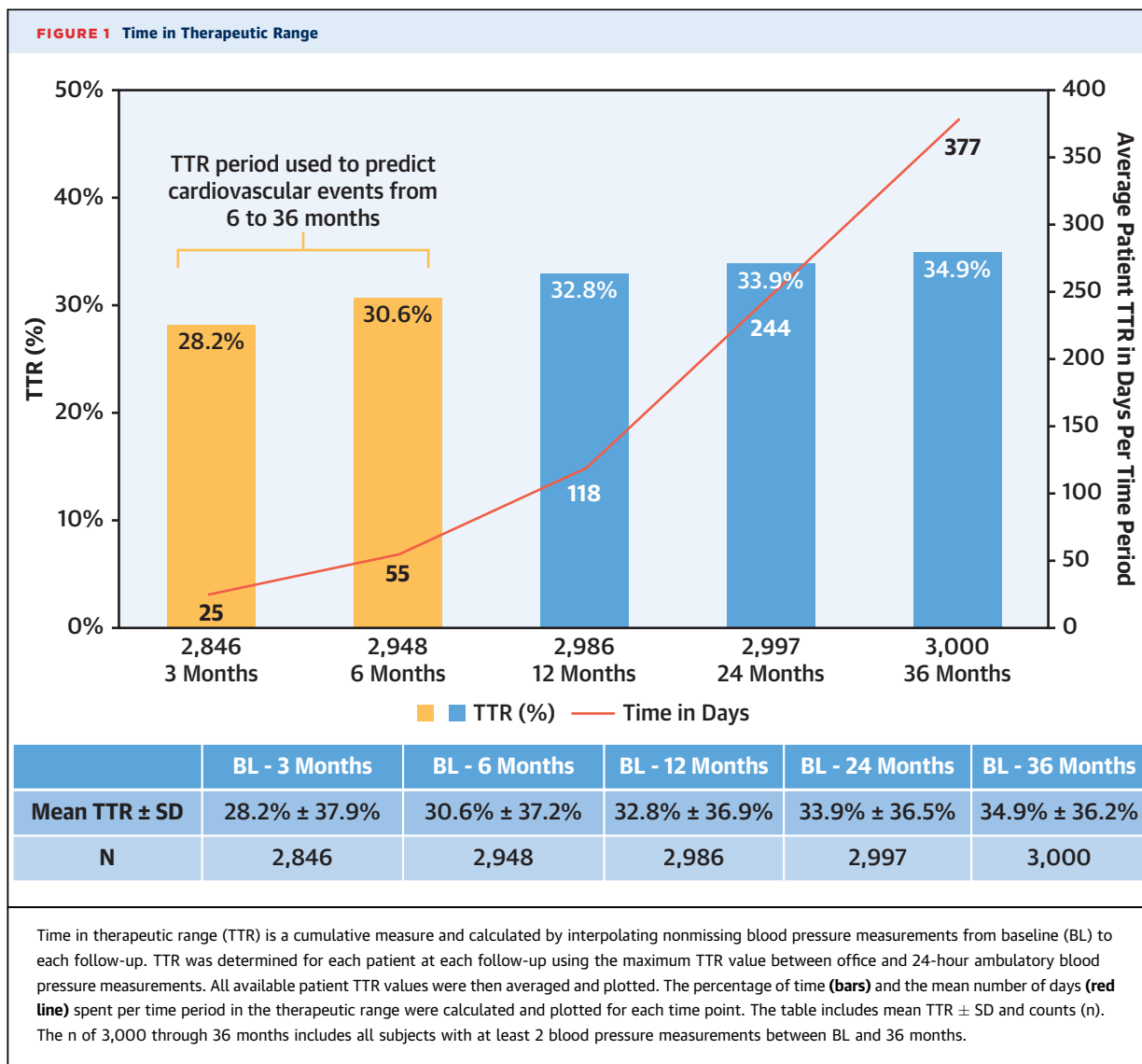
RESULTS

As of March 1, 2022, 3,077 patients were enrolled in the GSR. Baseline characteristics of the cohort included age of 60.5 ± 12.2 years, 57.8 % were male, 46.8% had a history of cardiac disease, 37.9% had type 2 diabetes, 20.8% had chronic kidney disease (estimated glomerular filtration rate <60 mL/min/1.73 m^2), and 12.3% had a history of atrial fibrillation (Table 1).

Mean baseline ASBP was 154.3 ± 18.7 mm Hg and mean OSBP was 165.6 ± 24.8 mm Hg. At baseline, patients were prescribed on average 4.9 ± 1.7 antihypertensive medications.

The mean follow-up time was 845 ± 383 days with a median follow-up time of 1,077 days. TTR, determined by the maximum value between OSBP and ASBP (see the methods), improved from 28.2% through 3 months, to 30.6% through 6 months to 34.9% through 36 months (Figure 1). This corresponded to approximately 25 days spent in therapeutic range from baseline through 3 months (28.2% of 90 days), 55 days through 6 months, and 377 days through 36 months.

Events from baseline through 36 months are shown in Supplemental Table 1 from the 1,896 patients who had an event between baseline and 36 months or had reached 36-month follow-up (Supplemental Figure 1). Kaplan-Meier rate estimates for cardiovascular events from 6 to 36 months for the entire GSR population are shown in Table 2. We assessed the impact of TTR through 6 months on adverse event rates from 6 to 36 months. A 10% increase in TTR through 6 months was associated with significantly lower rates of MACE, MI, cardiovascular death, and stroke from 6 to 36 months (Table 2), resulting in significant risk reductions of 15% for MACE (*P* < 0.001), 11% for cardiovascular death (*P* = 0.010), 6% for all-cause death (*P* = 0.041), 15% for MI (*P* = 0.023), and 23% for stroke (*P* < 0.001). When baseline BP was added to the model, only TTR covariate remained significant (Supplemental Table 2). There was no significant association between TTR and rates of hospitalization

FIGURE 1 Time in Therapeutic Range

Time in therapeutic range (TTR) is a cumulative measure and calculated by interpolating nonmissing blood pressure measurements from baseline (BL) to each follow-up. TTR was determined for each patient at each follow-up using the maximum TTR value between office and 24-hour ambulatory blood pressure measurements. All available patient TTR values were then averaged and plotted. The percentage of time **(bars)** and the mean number of days **(red line)** spent per time period in the therapeutic range were calculated and plotted for each time point. The table includes mean TTR ± SD and counts (n). The n of 3,000 through 36 months includes all subjects with at least 2 blood pressure measurements between BL and 36 months.

	BL - 3 Months	BL - 6 Months	BL - 12 Months	BL - 24 Months	BL - 36 Months
Mean TTR ± SD	28.2% ± 37.9%	30.6% ± 37.2%	32.8% ± 36.9%	33.9% ± 36.5%	34.9% ± 36.2%
N	2,846	2,948	2,986	2,997	3,000

for new onset heart failure, atrial fibrillation, or hypertensive emergency.

Kaplan-Meier rate estimates from 6 to 36 months for MACE, MI, cardiovascular death, and stroke were significantly lower in patients with higher TTR (**Figure 2**). For patients with 0% TTR through 6 months, the event rate for MACE from 6 to 36 months was 8.6%, for patients with TTR >0% to ≤50% it was 5.3%, and for patients with TTR >50% it was 2.3% (*P* < 0.001). Trends in TTR using only OSBP ≤140 mm Hg and associated reductions in events from 6 to 36 months by Kaplan-Meier rate estimates were similar to results presented herein (Supplemental Figures 2 and 3).

Progressive reductions in OSBP and ASBP from baseline to 3, 6, 12, 24, and 36 months are shown in Supplemental Figure 4, and distribution of OSBP at baseline and 36 months is shown in Supplemental Figure 5. At 36 months, change in OSBP was −16.7 ± 28.4 mm Hg (n = 1,270) and change in ASBP was −9.0 ± 20.2 mm Hg (n = 533). Mean number of antihypertensive medications at follow-up visits were 4.9 ± 1.7 at 3 months, 4.9 ± 1.8 at 6 months, 4.9 ± 1.8 at 12 months, 4.8 ± 1.9 at 24 months, and 4.8 ± 1.9 at 36 months. OSBP and ASBP reduction was similar regardless of number of baseline antihypertensive medications (Supplemental Table 3).

DISCUSSION

The main findings from this analysis are: 1) a 10% TTR increase through 6 months post-RDN was associated with significant risk reduction of cardiovascular events from 6 to 36 months (**Central Illustration**);

TABLE 2 Association of a 10% TTR Increase Through 6 Months and Cardiovascular Outcomes From 6 to 36 Months

	KM Event Rates 6-36 mo (%)	HR[a] (95% CI)	P Value
MACE[b]	5.8	0.85 (0.79-0.91)	<0.001
Cardiovascular death[c]	2.6	0.89 (0.81-0.97)	0.010
Myocardial infarction	1.4	0.85 (0.75-0.98)	0.023
Stroke	2.8	0.77 (0.68-0.88)	<0.001
All-cause death	4.2	0.94 (0.88-1.00)	0.041
Hospitalization for new onset heart failure	2.3	0.94 (0.87-1.02)	0.143
Hospitalization for atrial fibrillation	2.1	0.95 (0.88-1.04)	0.251
Hospitalization for hypertensive crisis or emergency	1.5	0.92 (0.82-1.02)	0.114

Target ranges were specified as ≤140 mm Hg for OSBP and ≤130 mm Hg for ASBP. The maximum TTR value between the OSBP and ASBP was selected for each patient. [a]HR refers to a 10% increase in TTR. [b]MACE is defined as cardiovascular death, myocardial infarction, or stroke. [c]Cardiovascular death includes unknown deaths.

ASBP = ambulatory systolic blood pressure; KM = Kaplan-Meier; MACE = major adverse cardiovascular events; OSBP = office systolic blood pressure; TTR = time in therapeutic range.

2) TTR increased over time from 28.2% to 34.9% from 3 to 36 months post-RDN; and 3) continuous reductions in ASBP and OSBP were observed to 36 months after RDN.

A previous analysis from the SPRINT (Systolic Blood Pressure Intervention Trial) identified TTR as an independent predictor of cardiovascular events[10] and a separate analysis of 689,051 patients at Veterans Health Administration hospitals showed an inverse association between TTR and all-cause mortality.[11] Prior research has shown RDN is associated with a significant BP reduction compared to an invasive placebo procedure.[5,6,16] A recently published meta-analysis examined whether RDN improved clinical outcomes across multiple different studies.[9] However, the studies had different inclusion criteria and only a few of the studies were sham-controlled, making the results challenging to interpret. To our knowledge, the present analysis is the first report of an association of improved TTR after RDN and subsequent reductions in cardiovascular events.

The importance of BP control on cardiovascular outcomes has been well documented.[17,18] A 5-mm Hg reduction in systolic BP reduced the risk of MACE, as shown in a recent meta-analysis, specifically the risk of stroke, heart failure, ischemic heart disease, and cardiovascular death by 13%, 13%, 8%, and 5%, respectively.[19] Furthermore, in a multicenter study with blinded core laboratory analysis of cardiac magnetic resonance images, RDN was associated with significant reductions in left ventricular mass index, a recognized surrogate for cardiovascular outcomes.[20]

TTR estimates BP below a specified, targeted value over a period of time as opposed to a single BP measurement. TTR may provide a more accurate assessment of BP for an individual patient, but it can be challenging to implement in clinical practice.[21] In this study, we observed that patients who spent 0% TTR through the first 6 months had a significantly higher rate of cardiovascular events by Kaplan-Meier rate estimate compared with patients who spent >50% TTR (Figure 2). Accordingly, patients who spent >0% TTR but ≤50% through the first 6 months had an estimated cardiovascular event rate in between patients with a TTR of 0% and >50%. These findings are consistent with the observation that a TTR >50% likely achieves an optimal therapeutic benefit.[11] Furthermore, a 10% increase in TTR herein was associated with a 15% risk reduction in MACE (HR: 0.85; 95% CI: 0.79-0.91) and 23% risk reduction in stroke (HR: 0.77; 95% CI: 0.68-0.88). These risk reductions were not caused by increased use of antihypertensive medications, which remained essentially unchanged through 36 months.

Patients in the GSR experienced sustained reductions in mean OSBP (−16.7 mm Hg) and ASBP (−9.0 mm Hg) through 36 months. These results are similar to the long-term SBP reductions reported for the randomized sham-controlled SPYRAL HTN-ON MED (Global Clinical Study of Renal Denervation With the Symplicity Spyral Multielectrode Renal Denervation System in Patients With Uncontrolled Hypertension on Standard Medical Therapy) pilot trial of −20.9 mm Hg and −18.7 mm Hg in OSBP and ASBP, respectively.[16] However, almost one-half of the patients in this study had a TTR of 0%, indicating no time spent with OSBP ≤140 mm Hg or ASBP ≤130 mm Hg. This observation may reflect the difficulties of hypertension management in real-world patients, which is generally poor.[22] Furthermore, patients herein had very high baseline BP (26.3% of patients had baseline OSBP higher than 180 mm Hg) (Supplemental Figure 5) and thus should be considered difficult to control. Patients' inability or unwillingness to tolerate a higher medication burden and/or physicians' inertia to substantially increase antihypertensive medications to achieve BP range may have also contributed.[23] Irrespective of baseline levels, any reduction in BP is associated with improved outcomes.[24] In this cohort, the proportion of patients with an OSBP ≤140 mm Hg or ASBP ≤130 mm Hg increased from 13.5% at baseline to 38.4% at 36 months following RDN.
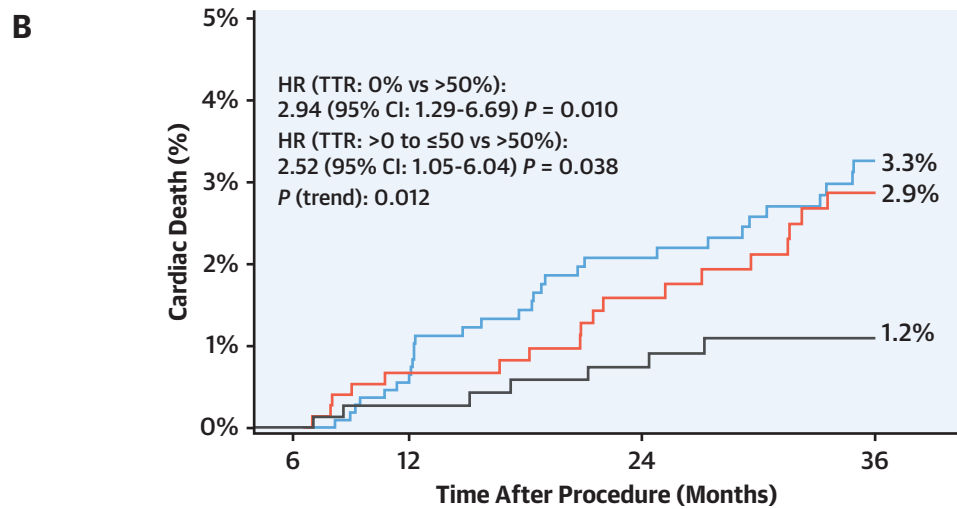
Catheter-based radiofrequency RDN as performed was associated with few safety events out to

**FIGURE 2   Kaplan-Meier Estimates of Cardiovascular Events Based on TTR**
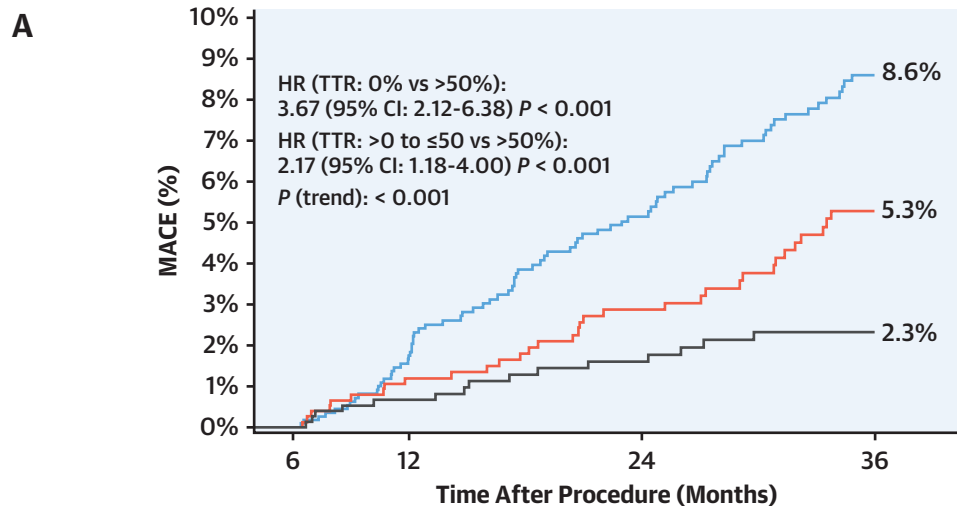
Kaplan-Meier event rates from 6 to 36 months are plotted based on combined time in therapeutic range (TTR) (maximum of office or 24-hour ambulatory blood pressure) from baseline through 6 months. HRs with 95% CIs comparing patients with 0% TTR or >0 to ≤50% TTR vs >50% TTR are listed. A higher TTR through 6 months was associated with a significant reduction in **(A)** major adverse cardiac events (MACE), **(B)** cardiovascular death, **(C)** myocardial infarction (MI), and **(D)** stroke from 6 to 36 months.

FIGURE 2 Continued

C

HR (TTR: 0% vs >50%):
3.10 (95% CI: 1.05-9.16) *P* = 0.041
HR (TTR: >0 to ≤50 vs >50%):
1.97 (95% CI: 0.59-6.54) *P* = 0.269
P (trend): 0.030

MI (%) — 1.9%, 1.4%, 0.6%

Time After Procedure (Months)

At Risk				
TTR: 0%	1,152	1,057	868	586
TTR: >0% to ≤50%	782	720	616	415
TTR: >50%	775	721	599	440

D

HR (TTR: 0% vs >50%):
5.84 (95% CI: 2.31-14.75) *P* < 0.001
HR (TTR: >0 to ≤50 vs >50%):
2.57 (95% CI: 0.92-7.20) *P* = 0.073
P (trend): < 0.001

Stroke (%) — 4.7%, 2.1%, 0.7%

Time After Procedure (Months)

At Risk				
TTR: 0%	1,152	1,053	864	580
TTR: >0% to ≤50%	782	718	611	415
TTR: >50%	775	722	598	440
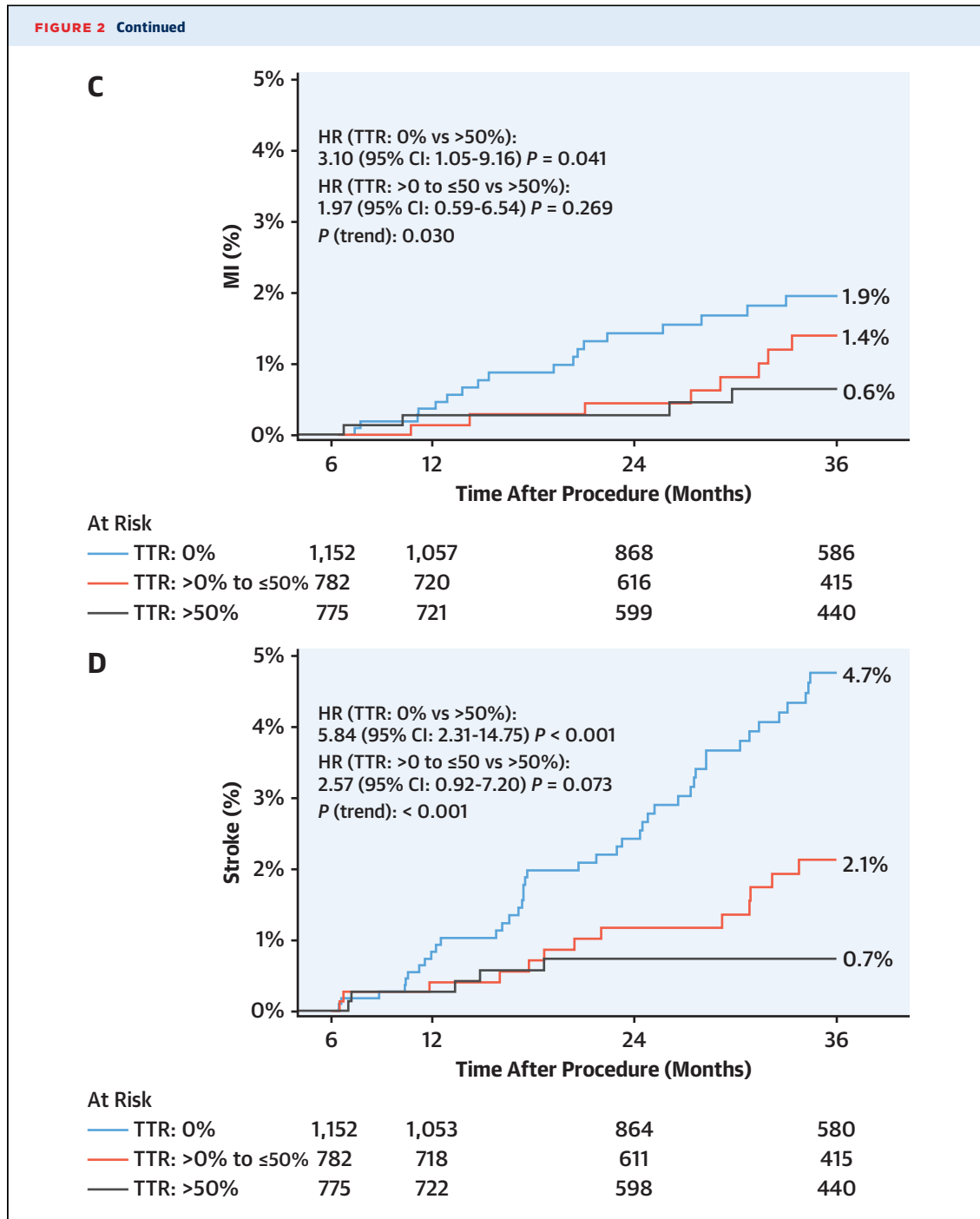
36 months postprocedure. The MACE rate was 9.3% at 36 months (Supplemental Table 1), which is representative of the patients at high risk who are enrolled in the GSR, but the rate of renal artery reintervention or renal artery stenosis (>70%) was only 0.8%. These results suggest that RDN may provide an adjunctive therapy in addition to antihypertensive medications for patients with uncontrolled hypertension.

The impact of visit-to-visit BP variability on cardiovascular events was evaluated in several large trials[25-27] and can be considered a precursor to the TTR analysis described here. A post hoc analysis of the INVEST (International Verapamil SR-Trandolapril Study) with 22,576 patients with hypertension reported a reduction in cardiovascular risk with increased proportion of follow-up visits with BP in

CENTRAL ILLUSTRATION Improved Time in Therapeutic Range Post-Renal Denervation Is Associated With Fewer Cardiovascular Events
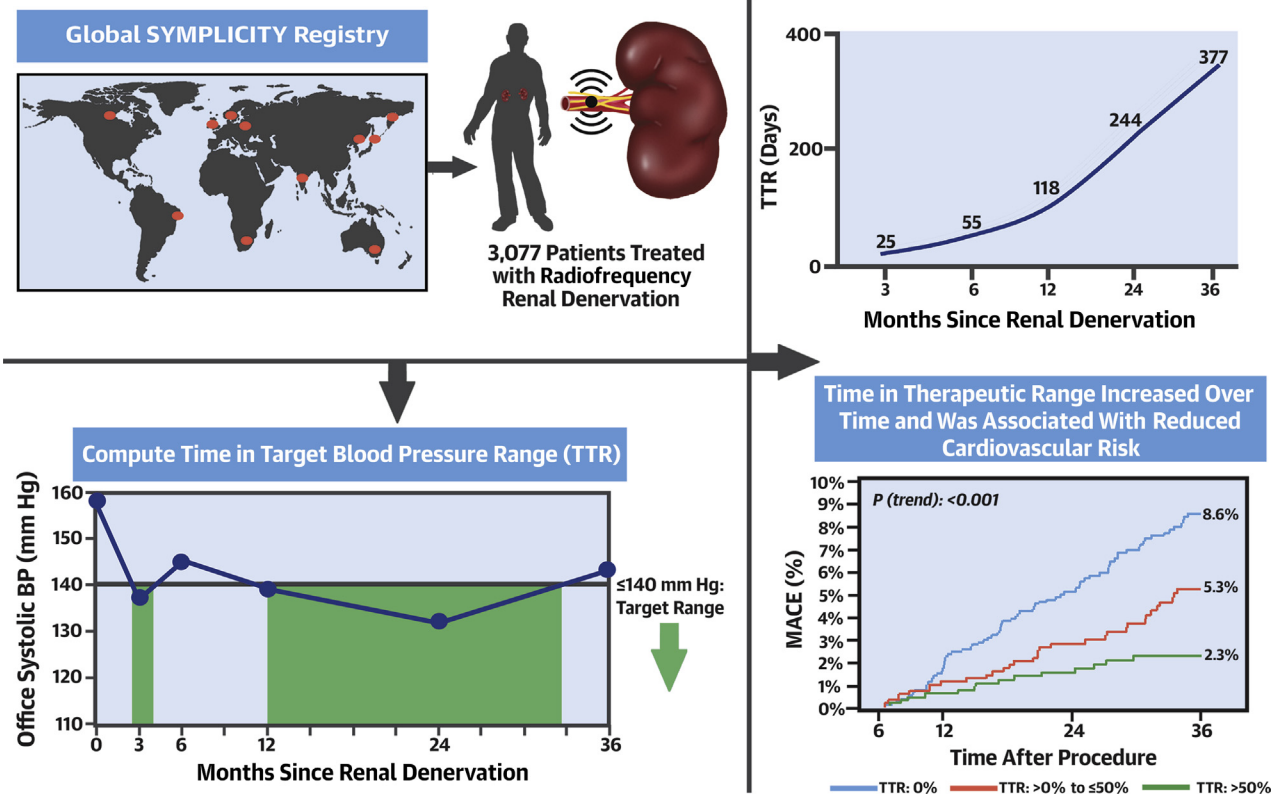
Mahfoud F, et al. J Am Coll Cardiol. 2022;80(20):1871–1880.

Time in therapeutic range (TTR) for systolic blood pressure (BP) improved after renal denervation (RDN) and was associated with a significant reduction in major adverse cardiovascular events (MACE).

control (BP <140/90 mm Hg or BP <130/85 mm Hg for patients with diabetes or renal insufficiency).[26] The VALUE (Valsartan Antihypertensive Long-term Use Evaluation) trial in 13,803 patients found an increased risk of cardiovascular events with higher visit-to-visit BP variability, irrespective of baseline cardiovascular risk.[27] Patient cohorts from 2 randomized studies (ONTARGET [Ongoing Treatment Alone and in Combination With Ramipril Global End Point Trials] and the TRANSCEND [Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease]) were combined to assess the predictive value of visit-to-visit BP variability and mean SBP on cardiovascular events.[25] Results showed mean SBP was a better predictor of cardiovascular risk than visit-to-visit BP variability was, but combining them provided improved prediction of risk.[25]

STUDY LIMITATIONS. Based on the nature of this real-world registry, there is no control group for comparison. Thus, whether reduced cardiovascular events associated with higher TTR was caused by RDN or other contributing factors remains uncertain. However, we observed fewer MACE events in patients with a greater TTR, which is consistent with prior reports. Medication adherence was not assessed using blood or urine testing because this is beyond the scope of the present real-world registry; antihypertensive medication use was documented using prescribed medications. We observed increased TTR despite such probable frequent and dynamic antihypertensive drug nonadherence. Not all patients reached 36-month follow-up at the time of this report, and not all patients had OSBP and ASBP measurements at every follow-up. Linear interpolation may be a limitation of TTR analyses because intermediate BP values may fluctuate. We did not account for changes in lifestyle, such as food/salt intake, which may have influenced BP.

CONCLUSIONS

Long-term OSBP and ASBP reductions were reported out to 36 months after RDN. TTR through 6 months was associated with significant risk reductions in cardiovascular events including MACE, cardiovascular death, MI, and stroke. RDN was associated with an improvement in TTR through 36 months and may represent an attractive adjunctive approach to lower BP in patients with uncontrolled hypertension.

ADDRESS FOR CORRESPONDENCE: Prof Dr Felix Mahfoud, Department of Internal Medicine III, Cardiology, Angiology, Intensive Care Medicine, Saarland University, Kirrberger Strasse 1, IMED, Gebäude 41, 66421 Homburg/Saar, Germany. E-mail: felix. mahfoud@uks.eu.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: A longer time in therapeutic BP range after RDN is associated with a lower incidence of stroke, MI, and cardiovascular death.

TRANSLATIONAL OUTLOOK: Studies with more than 4 years follow-up after renal denervation are needed to better characterize the impact of the procedure on risk of cardiovascular events.

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APPENDIX For supplemental figures and tables, please see the online version of this paper.