Renal denervation for uncontrolled and resistant hypertension: a systematic review and network meta-analysis of randomized controlled trials.

Jonathan Silverwatch, Kristen E. Marti, Mi T. Phan, Hinali Amin, Yuani M. Roman, Vinay Pasupuleti, Maciej Banach, Joshuan J. Barboza, Adrian V. Hernandez

#### **Supplemental Methods: PubMed search strategy**

(renal[All Fields] AND ("denervation"[MeSH Terms] OR "denervation"[All Fields])) AND ((resistant[All Fields] AND ("hypertension"[MeSH Terms] OR "hypertension"[All Fields])) OR (uncontrolled[All Fields] AND ("hypertension"[MeSH Terms] OR "hypertension"[All Fields]))) AND (("randomized controlled trial"[Publication Type] OR "randomized controlled trials as topic"[MeSH Terms] OR "randomized controlled trials"[All Fields]) OR ("randomized controlled trials"[All Fields]) OR ("randomized controlled trials"[Publication Type] OR "randomized controlled trials as topic"[MeSH Terms] OR "randomised controlled trials"[All Fields]) OR (("random allocation"[MeSH Terms] OR ("random"[All Fields] AND "allocation"[All Fields]) OR "random allocation"[All Fields] OR "randomized"[All Fields]) AND ("Trials"[Journal] OR "trials"[All Fields])))

**Table S1.** League Table of the effects of treatments expressed as MD and their 95%CIs on daytime systolic blood pressure (white cells) and daytime diastolic blood pressure (gray cells). For daytime systolic blood pressure the comparison is column vs row (comparator); for daytime diastolic blood pressure the comparison is row vs column (comparator). Effects in bold are statistically significant.

RF MRA + branches	-5.2	-7.6	-1.4	-4.0	-6.7
	(-10.6 to 0.2)	(-15.7 to 0.5)	(-9.5 to 6.6)	(-8.5 to 0.5)	(-13.6 to 0.3)
-5.7	RF MRA	-2.4	3.8	1.2	-1.5
(-12.9 to 1.5)		(-8.4 to 3.6)	(-4.0 to 11.5)	(-2.3 to 5.1)	(-5.9 to 2.9)
-7.7	-7.7	RF MRA +	6.2	3.6	0.9
(-20.2 to 4.8)	(-20.2 to 4.8)	AHT	(-3.6 to 16.0)	(-3.6 to 10.7)	(-3.2 to 5.0)
-0.1	5.6	7.6	US MRA	-2.6	-5.2
(-8.6 to 8.4)	(-2.6 to 13.8)	(-5.5 to 20.7)		(-9.3 to 4.1)	(-14.1 to 3.7)
-4.8	-1.0	2.9	-4.7	Sham	2.6
(-11.3 to 1.9)	(-5.1 to 7.0)	(-8.9 to 14.8)	(-11.8 to 2.5)		(-4.1 to 9.3)
-6.9	-1.2	0.8	-6.9	-2.2	AHT
(-17.2 to 3.3)	(-8.5 to 6.1)	(-6.4 to 7.8)	(-17.9 to 4.2)	(-11.7 to 7.3)	

MD: mean difference; CI: Confidence interval; RF: Radiofrequency. MRA: Main renal artery, US: Ultrasound, AHT: Antihypertensive therapy.

**Table S2.** League Table of the effects of treatments expressed as MD and their 95%CIs on nighttime systolic blood pressure (white cells) and nighttime diastolic blood pressure (gray cells). For nighttime systolic blood pressure the comparison is column vs row (comparator); for nighttime diastolic blood pressure the comparison is row vs column (comparator). Effects in bold are statistically significant.

RF MRA + branches	-5.4	-4.0	-3.2	-3.9	-7.0
	(-11.5 to 0.1)	(-13.5 to 5.4)	(-12.2 to 5.7)	(-9.0 to 1.1)	(-15.2 to 1.4)
-7.6	RF MRA	1.3	2.1	1.4	-1.6
(-14.6 to -0.7)		(-5.8 to 8.5)	(-6.5 to 10.7)	(-3.0 to 5.9)	(-7.2 to 4.1)
-7.3	0.3	RF MRA +	-1.3	0.1	-2.9
(-20.1 to 5.6)	(-10.5 to 11.1)	AHT	(-8.5 to 5.8)	(-8.4 to 8.6)	(-7.3 to 1.5)
-2.3	4.9	-0.3	US MRA	-0.7	-3.7
(-10.9 to 5.3)	(-3.0 to 12.7)	(-11.1 to 10.5)		(-8.1 to 6.7)	(-14.0 to 6.6)
-4.7	2.9	2.6	-2.0	Sham	-3.0
(-11.0 to 1.5)	(-2.9 to 8.9)	(-9.7 to 14.8)	(-8.7 to 4.7)		(-10.2 to 4.2)
-10.4	-2.7	-3.1	-7.6	-5.6	АНТ
(-21.3 to 0.6)	(-11.1 to 5.7)	(-9.8 to 3.7)	(-19.1 to 3.9)	(-15.8 to 4.6)	

MD: Mean difference; CI: Confidence interval; RF: Radiofrequency. MRA: Main renal artery, US: Ultrasound, AHT: Antihypertensive therapy.

**Table S3.** Ranking of renal denervation treatments per outcome. A higher p-score means such a treatment ranks better than others with lower p-scores for a given outcome.

		Outcomes						
Treatment arms	24h ambulatory SBP	24h ambulatory DBP	Office SBP	Office DBP	Daytime SBP	Daytime DBP	Nighttime SBP	Nighttime DBP
RF MRA + branches	0.97	0.95	0.72	0.69	0.83	0.90	0.90	0.88
RF MRA	0.51	0.45	0.39	0.35	0.36	0.40	0.30	0.34
RF MRA + AHT	0.24	0.22	0.84	0.90	0.26	0.17	0.41	0.54
US MRA	0.62	0.68	0.31	0.36	0.81	0.75	0.70	0.56
Sham	0.54	0.53	0.39	0.27	0.43	0.52	0.54	0.50
АНТ	0.12	0.16	0.35	0.43	0.30	0.26	0.14	0.18

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; RF: Radiofrequency; MRA: Main renal artery; AHT: Antihypertensive therapy; US: Ultrasound; NA: Not available.

 Table S4. Meta-analyses of clinical outcomes.

Outcome	Number of studies	Intervention	Control	RR (95%CI)	$I^2$
Heart Failure	2	RF MRA	Sham	1.40 (0.41 to 4.80)	0%
	3	RF MRA	Sham	0.80 (0.22 to 3.00)	0%
Stroke	2	RF MRA + branch	Sham	0.52 (0.04 to 6.13)	0%
	5	RF MRA (+/- branch)	Sham	0.73 (0.23 to 2.33)	0%
	2	RF MRA	Sham	0.98 (0.28 to 3.36)	0%
Myocardial Infarction	2	RF MRA + branch	Sham	1.00 (0.06 to 15.77)	0%
	4	RF MRA (+/- branch)	Sham	0.98 (0.32 to 3.03)	0%
	2	RF MRA	Sham	2.62 (0.51 to 13.56)	0%
Renal Complications	2	RF MRA + branch	Sham	1.00 (0.06 to 15.84)	0%
1	4	RF MRA (+/- branch)	Sham	2.03 (0.49 to 8.36)	0%
	2	RF MRA	Sham	0.55 (0.23 to 1.30)	0%
Hypertensive Crisis	2	RF MRA + branch	Sham	1.93 (0.16 to 22.84)	0%
	4	RF MRA (+/- branch)	Sham	0.63 (0.28 to 1.42)	0%
Serious Adverse	2	RF MRA	Sham	1.69 (0.31 to 9.17)	0%
Events	2	RF MRA + AHT	AHT	1.36 (0.59 to 3.11)	53%
	3	RF MRA (+/- branch)	Sham	1.56 (0.33 to 7.35)	0%

RF: radiofrequency; MRA: main renal artery; AHT: antihypertensive therapy

**Table S5.** Characteristics of previously published systematic reviews compared to our study.

Characteristics	Fadl Elmula et al. 2015	Yao et al. 2016	Coppolino et al. 2017	Dahal et al. 2019	Cheng et al. 2019	Our study
Type of review	Systematic review and	Systematic review and	Systematic review and	Systematic review and	Systematic review and	Systematic review and
	meta-analysis	meta-analysis	meta-analysis	meta-analysis	meta-analysis	network meta-analysis
Primary	To sum up the	To evaluate the	To evaluate the short-	To evaluate the	To assess the efficacy	To assess the
objectives	randomized evidence on	efficiency of RDN on	and long-term effects	efficacy and utility of	and safety of RDN for	comparative efficacy
	the efficacy and safety of	RH.	of RDN in RH on	RDN procedure in RH	the treatment of UH.	and safety of existing
	RDN as treatment		clinical endpoints and	and UH.		RDN interventions for
	modality in treatment-		potential adverse			UH and RH.
	resistant hypertensive		events related to the			
	patients.		procedure.			
Inclusion criteria	RCTs comparing RDN	RCTs comparing RDN	RCTs that compared	Sham controlled trials	RCTs including a study	RCTs in >18 years-old,
	vs no intervention in RH	vs standard medical	RDN to standard	comparing outcomes of	protocol and evaluating	with RH and/or UH
	patients on unchanged or	therapy (≥3 AHT drugs	therapy or sham	RDN in adults with	participants randomly	evaluating RDN
	optimized AHT (≥3 drug	including a diuretic) in	procedure to treat RH,	hypertension reporting	allocated to RDN or	interventions: RF in
	classes, SBP ≥140, 135,	RH patients.	without language	one of the following:	control. SBP of at least	MRA and branches, RF
	or 130 on office,		restriction.	change in 24-h	140, 135, or 130 office,	in MRA, RF in MRA
	daytime, or 24-h			ambulatory BP, office	daytime or 24-h	plus AHT, US in MRA,
	ABPM).			BP, or daytime and	ambulatory	sham, and AHT.
				nighttime ambulatory	measurements	
				BP.	respectively. Sample	
					size of at least 40.	
Databases	PubMed, EMBASE,	PubMed, EMBASE,	The Cochrane	PubMed, EMBASE,	Medline, Cochrane	PubMed, EMBASE,
searched	clinicaltrials.gov	Cochrane Central	Hypertension Group	CINAHL, Cochrane	library, EMBASE	Scopus, Web of Science,
			Specialised Register,	Central Register of		the Cochrane library,
			CENTRAL,	Clinical Trials		clinicaltrials.gov
			MEDLINE, EMBASE,			
			clinicaltrials.gov			
Years of study	January 2009 to	Up to May 2015	Up to February 2016	Up to September 2018	January 2009 to July	Up to May 2020
publication	unspecified month in	• •			2018	
searched	2015					
Number of studies	7 RCTs	9 RCTs	12 RCTs	7 RCTs	12 RCTs	20 RCTs
included						

Sample size	985 randomized (958 analyzed)	1059 randomized (988 analyzed)	1149 randomized (sample analyzed varied according to outcome)	1098 randomized (1055/1047 analyzed for safety and efficacy)	1539 randomized (unspecified sample analyzed)	2152 randomized (sample analyzed varied according to outcome)
Risk of bias assessment	No assessment	2011 Cochrane risk of bias tool	2011 Cochrane risk of bias tool	2011 Cochrane risk of bias tool	2011 Cochrane risk of bias tool	2019 Cochrane risk of bias tool 2.0
Models and methods of meta- analysis	Random effects model; inverse variance method.	Random effects model; no method described.	Mantel-Haenszel fixed effect model primarily; random effects models when statistical heterogeneity was observed.	Random effects model; no method described.	Fixed effect model; random effects model when there was heterogeneity. No method described.	Random effects model; inverse variance method.
Definition of heterogeneity	Cochran's Q test p <0.1. I² statistic (<25%, 25 to 50%, >50% were modest, moderate and substantial, respectively).	I² statistic (<25%, 25 to 50%, >50% were low, moderate and high, respectively).	Chi² test p <0.05; I² statistic (25%, 50%, and 75% were low, medium, and high levels of heterogeneity, respectively).	Cochran's Q and I <sup>2</sup> index, (I <sup>2</sup> >50% defined as significant heterogeneity).	Q-statistic; amount of heterogeneity with I <sup>2</sup> statistic. Heterogeneity of any kind was defined as I <sup>2</sup> >0%.	I <sup>2</sup> statistic (<30%, 30-60%, and >60% were low, medium, and high, respectively).
Blood pressure or other continuous outcome association measure: Effect (95%CI)	MD (control minus RDN): 24-h SBP: -2.81 (-6.46 to 0.83) Office SBP: -4.89 (-20.9 to 11.1) eGFR: 0.81 ml/min/1.73m <sup>2</sup> (-1.69 to 3.3)	MD (RDN minus control): 24-h ambulatory SBP: - 8.23 (-16.86 to 0.39) 24-h ambulatory DBP: - 3.77 (-7.21 to -0.32) Office SBP: -8.23 (-16.86 to 0.39) Office DBP: -3.77 (-7.21 to -0.32)	MD (RDN minus control): 24-h ambulatory SBP: 0.28 (3.74 to 4.29) 24-h ambulatory DBP: 0.93 (-4.50 to 6.36) Office SBP: -4.08 (- 15.26 to 7.11) Office DBP: -1.30 (- 7.30 to 4.69) Serum creatinine: 0.01 mg/dL (-0.12 to 0.14) CrCl: -2.09 mL/min (- 8.12 to 3.95)	MD (RDN minus control): 24-h ambulatory SBP: -3.45 (-5.01 to -1.88) 24-h ambulatory DBP: -1.56 (-2.81 to -0.30) Office SBP: -3.99 (- 8.10 to 0.11) Office DBP: -2.97 (- 4.76 to -1.18)	MD (RDN minus control): 24-h ambulatory SBP: - 4.02 (-5.49 to -2.56) Office SBP: -8.93 (-14.03 to -3.83)	MD (RDN intervention vs RDN intervention) in NMA  RF in MRA and branches vs: 24-hour ambulatory SBP: RF in MRA -7.8 (-15.1 to -0.4), RF in MRA plus AHT -11.9 (-23.4 to -0.4), sham -7.2 (-13.6 to -0.8), and AHT -12.9 (-22.6 to -3.2) 24-hour ambulatory DBP: RF in MRA -4.2 (-8.3 to -0.2), sham -3.7 (-7.1 to -0.2), and AHT -6.8 (-12.7 to -0.8)

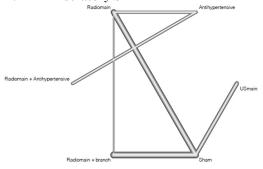
						Nighttime SBP: RF in MRA -7.6 (-14.6 to - 0.7)  RF in MRA plus AHT vs: Office SBP: AHT - 10.1 (-21.4 to -0.6)  Office DBP: AHT -5.4 (-9.6 to -1.1)  Other effects were not significant.
Clinical outcomes association measure: Effect (95%CI)	Not assessed	Not assessed	RR: MI: 1.31 (0.45 to 3.84) Ischaemic stroke: 1.15 (0.36 to 3.72) Unstable angina: 0.63 (0.08 to 5.06) Bradycardia episodes: 6.63 (1.19 to 36.84)  Fatal and non-fatal CV events, all-cause mortality, hospital admissions, and quality of life without effects due to scarce information.	Not assessed	RR: Major adverse events: 1.06 (0.72 to 1.57)  Major adverse events defined as all-cause mortality, vascular complications (acute coronary event, cerebrovascular event or renal artery complications), renal complications, hypertensive crisis and heart failure.	Scarce data. No significant differences between MRA +/- branches or MRA +AHT and Sham or AHT for heart failure, stroke, MI, renal complications, hypertensive crisis, and serious adverse events. Other outcomes (overall mortality, CV mortality, and hospitalization of any cause) did not have data to analyze.

Ranking of best RDN interventions	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	RF MRA and branches: best intervention for 24h ambulatory, daytime, and nighttime SBP and DBP (p scores from 0.83 to 0.97) RF MRA plus AHT: best intervention for office SBP and DBP (p scores 0.84 to 0.90). No NMA possible for clinical outcomes due to scarcity of data.
Conclusion	In RH, RDN with the Symplicity system did not significantly decrease BP but was safe.	RF RDN did not have superiority compared with medical treatment at 6-month follow-up in general population.	Low quality evidence that RDN did not change major CV events and renal function. Moderate quality evidence that RDN did not change BP. Low quality evidence that RDN increased bradycardia events.	RDN reduces ambulatory BP and office DBP in patients with hypertension.	Catheter-based RDN was associated with a significant BP lowering benefit without increasing major adverse events.	RF in MRA and branches was the most efficacious in comparison to other interventions to treat RH or UH. Clinical and adverse events were uncommonly described in existing trials.

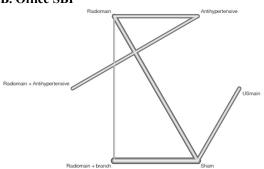
All blood pressures measured as mmHg. HTN: hypertension; US: Ultrasound; MRA: Main renal artery; RDN: Renal denervation; BP: blood pressure; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; AHT: Antihypertensive; RF: radiofrequency; ABPM: Ambulatory blood pressure monitoring; RH: resistant hypertension; UH: uncontrolled hypertension; RCT: randomized controlled trials; CI: confidence interval; MD: mean difference; SMD: standardized mean difference; RR: risk ratio; MI: Myocardial infarction; CV: cardiovascular.

Figure S1. Network geometries for primary and secondary outcomes.

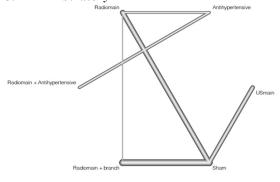
#### A. 24h Ambulatory SBP



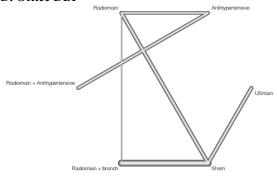
### **B.** Office SBP



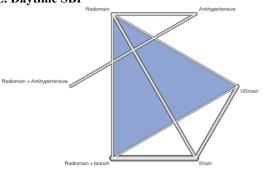
### C. 24h Ambulatory DBP



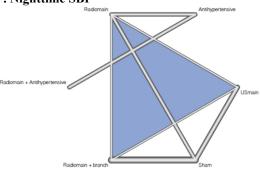
#### D. Office DBP



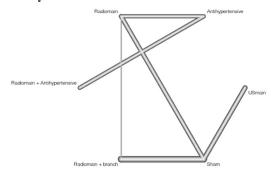
# E. Daytime SBP



## F. Nighttime SBP



## G. Daytime DBP



### H. Nighttime DBP

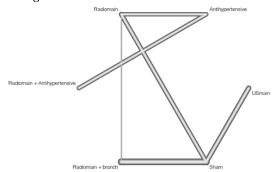
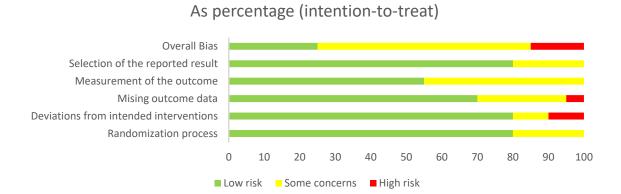
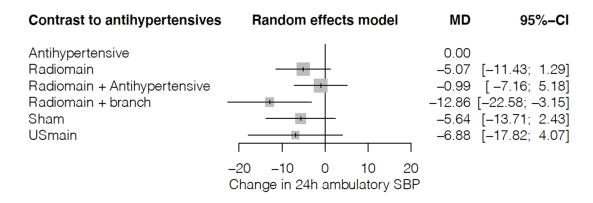


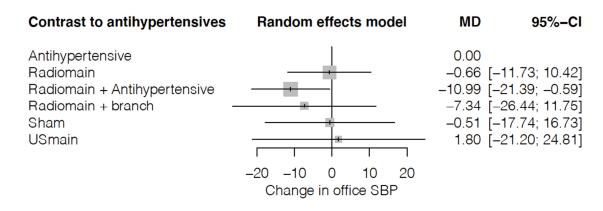
Figure S2. Risk of bias per domain of included randomized trials.



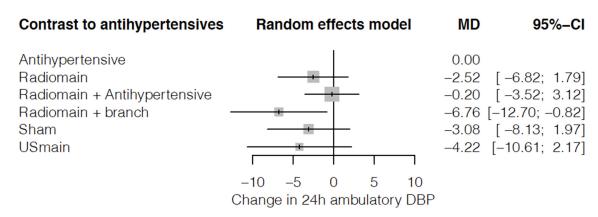
**Figure S3.** Effect of renal denervation interventions on change of 24h ambulatory SBP in comparison to antihypertensive drugs.



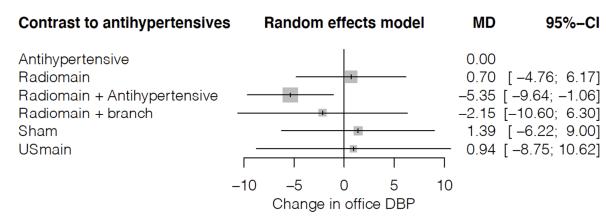
**Figure S4.** Effect of renal denervation interventions on change of office SBP in comparison to antihypertensive drugs.



**Figure S5.** Effect of renal denervation interventions on change of 24h ambulatory DBP in comparison to antihypertensive drugs.



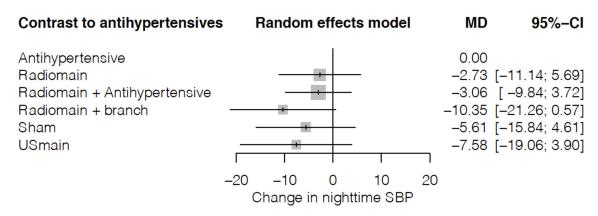
**Figure S6.** Effect of renal denervation interventions on change of office DBP in comparison to antihypertensive drugs.



**Figure S7.** Effect of renal denervation interventions on change of daytime SBP in comparison to antihypertensive drugs.

Contrast to antihypertensives	Random effects model	MD	95%-CI
Antihypertensive Radiomain Radiomain + Antihypertensive Radiomain + branch Sham USmain	-15 -10 -5 0 5 10 15 Change in daytime SBP	0.75 -6.94 -2.20	[-8.54; 6.08] [-6.34; 7.84] [-17.22; 3.34] [-11.69; 7.29] [-17.86; 4.16]

**Figure S8.** Effect of renal denervation interventions on change of nighttime SBP in comparison to antihypertensive drugs.



**Figure S9.** Effect of renal denervation interventions on change of daytime DBP in comparison to antihypertensive drugs.

Contrast to antihypertensives	Random effects model	MD	95%-CI
Antihypertensive Radiomain Radiomain + Antihypertensive Radiomain + branch Sham USmain	-10 -5 0 5 10 Change in daytime DBP	0.94 -6.66 -2.62	[ -5.86; 2.92] [ -3.16; 5.04] [-13.64; 0.33] [ -8.52; 3.27] [-14.12; 3.67]

**Figure S10.** Effect of renal denervation interventions on change of nighttime DBP in comparison to antihypertensive drugs.

Contrast to antihypertensive	s Random effects model	MD	95% <b>-CI</b>
Antihypertensive Radiomain Radiomain + Antihypertensive Radiomain + branch Sham USmain	-15 -10 -5 0 5 10 Change in nighttime DBP	-2.88 -6.93   -2.98	[ -7.21; 4.12] [ -7.29; 1.52] [-15.24; 1.39] [-10.19; 4.22] [-13.98; 6.62]

Figure S11. Effect of RF MRA vs sham on heart failure.

Study	Radiomain Events Total Eve	Sham nts Total	Risk Ratio	RR 95%-	Weight CI (fixed)	Weight (random)
Azizi 2018 Bhatt 2014 Weber2020	0 74 9 352 1 34	0 72 <b>-</b> 3 171 0 17		1.00 [0.02; 49.7 1.46 [0.40; 5.3 — 2.50 [0.06; 98.5	81] 81.1%	8.9% 81.1% 10.1%
Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$ , $\tau$		260	0.1 0.51 2 10	1.49 [0.46; 4.7 1.49 [0.46; 4.7	•	100.0%

Figure S12. Effect of RF MRA vs sham on stroke.

Study	Radiomain Events Total E	Sham Events Total	Risk Ratio	RR	95%-CI	Weight (fixed)	Weight (random)
Azizi2018 Mathiassen2016 Bhatt2014 Weber2020	0 74 0 36 4 352 0 34	0 72 1 33 - 2 171 0 17		0.32 0.97	[0.02; 49.75] [0.01; 7.34] [0.18; 5.25] [0.02; 61.41]	11.3% 17.8% 60.7% 10.2%	11.3% 17.8% 60.7% 10.2%
Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$ , $\tau^2$		293	0.1 0.51 2 10		[0.22; 3.00] [0.22; 3.00]	100.0%	 100.0%

**Figure S13.** Effect of RF MRA + branch vs sham on stroke.

ı	Radiomain + br	ranch	,	Sham				Weight	Weight
Study	Events	Total	Events	Total	Risk Ratio	RR	95%-CI	(fixed)	(random)
Kandazari2018 Bohm2019	0	38 165	0	42 165			0.02; 49.43] [0.01; 8.12]		40.1% 59.9%
Fixed effect mod Random effects Heterogeneity: $I^2 =$	model	<b>203</b>		207	0.1 0.51 2 10		0.04; 6.13] 0.04; 6.13]	100.0%	100.0%

Figure S14. Effect of RF MRA +/- branch vs sham on stroke.

Radio Study	main(+/–brar Events T			ham Total	Risk Ratio	RR	95%-CI	Weight (fixed)	Weight (random)
Azizi2018 Kandazari2018 Mathiassen2016 Bhatt2014 Bohm2019 Weber2020	0 0 0 4 0	74 38 36 352 165 34	0 0 1 2 1 0	72 42 33 - 171 165 -	-	1.00 0.32 0.97 0.33	[]	8.8% 8.9% 13.8% 47.3% 13.2% 7.9%	8.8% 8.9% 13.8% 47.3% 13.2% 7.9%
Fixed effect model Random effects mo Heterogeneity: $I^2 = 0\%$		<b>699</b> 98		500	0.1 0.51 2 10		[0.23; 2.33] [0.23; 2.33]	100.0%	 100.0%

Figure S15. Effect of RF MRA vs sham on myocardial infarction.

Study	Radiomain Events Total Even	Sham ts Total	Risk Ratio	RR 95%	Weight -CI (fixed)	Weight (random)
Azizi 2018 Bhatt 2014 Weber2020	0 74 6 352 0 34	0 72 - 3 171 0 17 -	-	- 1.00 [0.02; 49. 0.97 [0.25; 3. - 1.00 [0.02; 61.	84] 81.0%	10.0% 81.0% 9.0%
Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$ , $\tau^2$		260	0.1 0.51 2 10	0.98 [0.28; 3. 0.98 [0.28; 3.		100.0%

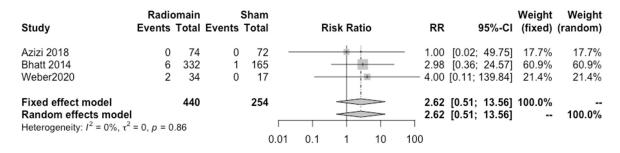
**Figure S16.** Effect of RF MRA + branch vs sham on myocardial infarction.

Radio	main + branch	Sham			Weight	Weight
Study	Events Total E	vents Total	Risk Ratio	RR 95%-	CI (fixed)	(random)
Kandazari 2018	0 38	0 42 -		<b>—</b> 1.00 [0.02; 49.4	3] 50.0%	50.0%
Townsend 2017	0 38	0 42 -	•	— 1.00 [0.02; 49.4	3] 50.0%	50.0%
Fixed effect model	76	84		1.00 [0.06; 15.7	7] 100.0%	
Random effects mode	•			1.00 [0.06; 15.7	7]	100.0%
Heterogeneity: $I^2 = 0\%$ , $\tau^2$	p = 0, p = 1.00		01 051 0 10			
			0.1 0.5 1 2 10			

Figure S17. Effect of RF MRA +/- branch vs sham on myocardial infarction.

Ra Study	diomain(+/–bra Events		Events	Sham Total	Risk Ratio	RR	95%-CI	Weight (fixed)	Weight (random)
Azizi 2018 Kandazari 2018 Townsend 2017 Bhatt 2014 Weber2020	0 0 0 6 0	74 38 38 352 34	0 0 0 3 0	72 42 42 171 17		1.00 1.00 0.97	[0.02; 49.75] [0.02; 49.43] [0.02; 49.43] [0.25; 3.84] [0.02; 61.41]	8.3% 8.4% 8.4% 67.4% 7.5%	8.3% 8.4% 8.4% 67.4% 7.5%
Fixed effect mod Random effects Heterogeneity: $I^2$ =	model	<b>536</b> .00		344	0.1 0.51 2 10		[0.32; 3.03] [0.32; 3.03]	100.0%	 100.0%

Figure S18. Effect of RF MRA vs sham on renal complications.



**Figure S19.** Effect of RF MRA + branch vs sham on renal complications.

Radio Study	main + branch Events Total		Sham Total	Risk Ratio	RR	95%-CI	Weight (fixed)	Weight (random)
Kandazari 2018 Bohm2019	0 38 0 165	0	42 165	*		[0.02; 49.43] [0.02; 50.10]		50.2% 49.8%
Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$ , $\tau$			207	0.1 0.51 2 10		[0.06; 15.84] [0.06; 15.84]		100.0%

Figure S20. Effect of RF MRA +/- branch vs sham on renal complications.

Radiom Study	ain(+/-brai Events T	,	_	Sham Total	R	isk Rati	0	RI	2	95%-CI	Weight (fixed)	Weight (random)
Azizi 2018 Kandazari 2018 Bhatt 2014 Bohm2019 Weber2020	0 0 6 0 2	74 38 332 165 34	0 0 1 0	72 42 165 165 17			<del>-</del>	- 1.00 2.99 - 1.00	0 [0.02; 0 [0.02; 3 [0.36; 0 [0.02; 0 [0.11;	49.43] 24.57] 50.10]		13.1% 13.1% 44.9% 13.0% 15.8%
Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$ , $\tau^2$		<b>643</b>		<b>461</b>	1 0.1	1	10	2.03 2.03 100		8.36] 8.36]	100.0%	100.0%

Figure S21. Effect of RF MRA vs sham on hypertensive crisis.

Study	Radiomain Events Total Ever	Sham nts Total	Risk Ratio	RR 95%-	Weight CI (fixed)	Weight (random)
Azizi 2018 Bhatt 2014 Weber2020	0 74 9 352 1 34	0 72 - 9 171 0 17		1.00 [0.02; 49.7 0.49 [0.20; 1.2 — 2.50 [0.06; 98.5	0] 89.7%	4.8% 89.7% 5.5%
Fixed effect model Random effects mode Heterogeneity: $I^2 = 0\%$ , $\tau^2$		260	0.1 0.51 2 10	0.55 [0.23; 1.3 0.55 [0.23; 1.3	-	 100.0%

Figure S22. Effect of RF MRA + branch vs sham on hypertensive crisis.

Radio Study	omain + branch Events Total Eve	Sham ents Total	Risk Ratio	RR	95%-CI	Weight (fixed)	Weight (random)
Kandazari 2018 Bohm2019	0 38 1 165	0 42 0 165	-	1.00 [0.0 - 3.00 [0.1	2; 49.43] 2; 73.11]		40.1% 59.9%
Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$ , $\tau$		207	0.1 0.51 2 10	1.93 [0.1 1.93 [0.1	6; 22.84] 6; 22.84]	100.0%	100.0%

**Figure S23.** Effect of RF MRA +/- branch vs sham on hypertensive crisis.

Radioma Study	in(+/–branc Events Tot		Sham Total	Risk Ratio	RR	95%–CI	Weight (fixed)	Weight (random)
Azizi 2018 Kandazari 2018 Bhatt 2014 Bohm2019 Weber2020	0 3 9 35 1 16	74 0 38 0 52 9 65 0 34 0	72 42 171 165 17		1.00 [0.02 1.00 [0.02 0.49 [0.2 3.00 [0.12 - 2.50 [0.06	2; 49.43] 0; 1.20] 2; 73.11]	4.3% 4.3% 80.1% 6.4% 4.9%	4.3% 4.3% 80.1% 6.4% 4.9%
Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$ , $\tau^2$	66 = 0, p = 0.76	63	467	0.1 0.51 2 10	0.63 [0.2 0.63 [0.2	,	100.0%	100.0%

Figure S24. Effect of RF MRA vs sham on serious adverse events.

Study	Radio Events		Events	Sham Total		Risk Ratio		RR	95%-CI	Weight (fixed)	Weight (random)
Azizi 2018 Bhatt 2014	1 5	74 361	1 1	72 171		-			.06; 15.26] .28; 20.12]	37.7% 62.3%	37.7% 62.3%
Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$ , $\tau^2$		<b>435</b> .62		243	0.1	0.5 1 2	10	-	).31; 9.17] ).31; 9.17]	100.0% 	 100.0%

Figure S25. Effect of RF MRA + AHT vs AHT on serious adverse events.

Radiomain + AHT AHT											Weight	Weight	
Study	Events	Total	Events	Total		Ris	sk Ra	tio		RR	95%−CI	(fixed)	(random)
De Jager 2017	24	91	12	44		_		_		0.97	[0.53; 1.75]	74.0%	61.1%
Azizi 2015	10	46	5	53			+	•		2.30	[0.85; 6.25]	26.0%	38.9%
Fixed effect model		137		97			4	>		1.21	[0.73; 2.02]	100.0%	
Random effects mo										1.36	[0.59; 3.11]		100.0%
Heterogeneity: $I^2 = 53$	$\%$ , $\tau^{-} = 0.201$	7, p = 0	).14		0.2	0.5	1	2	5				
					0.2	0.0	•	-	Ū				

Figure S26. Effect of RF MRA +/- branch vs sham on serious adverse events.

Radiom Study	ain(+/−branc Events Tot	,	Sham Total	Risk Ratio	RR	95%-CI	Weight (fixed)	Weight (random)
Azizi 2018 Townsend 2017 Bhatt 2014		74 1 38 0 51 1	72 42 - 171		<b>—</b> 1.00	[0.06; 15.26] [0.02; 49.43] [0.28; 20.12]	31.7% 15.8% 52.5%	31.7% 15.8% 52.5%
Fixed effect model Random effects mode Heterogeneity: $I^2 = 0\%$ , $\tau$	•	73	285	0.1 0.5 1 2 10		[0.33; 7.35] [0.33; 7.35]	100.0% 	 100.0%