Supplementary Appendix: Cardiometabolic Outcomes and Mortality in Medically Treated Primary Aldosteronism

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Supplementary Methods:

Detailed Definition of Exposures

Primary aldosteronism (PA) was defined on the basis of inpatient or outpatient ICD-9 or ICD-10 diagnosis codes (ICD-9: 255·10, 255·12; ICD-10: E26·09, E26·9) or text search of the medical records (including notes, diagnoses, communications, and imaging records) indicative of the diagnosis of PA ("primary aldosteronism", "primary hyperaldosteronism", and "Conn's syndrome") (**Figure 1**). Each diagnosis of PA was then confirmed via manual review of the individual medical records and we excluded all patients who had a baseline aldosterone-to-renin ratio < 555 pmol/L per µg/L/h (corresponding to an aldosterone-to-renin ratio of <20 ng/dL per ng/mL/h in conventional units) or a plasma renin activity level ≥ 1 µg/L/h prior to mineralocorticoid receptor (MR) antagonist initiation as the appropriate diagnosis of PA was unclear in these instances.[1] Further, we excluded all patients who underwent confirmatory testing for PA which was not consistent with a diagnosis of PA: oral sodium loading test with 24h urine aldosterone excretion < 33 nmol with 24h urine sodium excretion > 200 mmol or saline infusion testing with post-infusion serum aldosterone levels < 280 nmol/L.[1] Only PA patients who were initiated on MR antagonists for treatment of PA, and who did not undergo surgical adrenalectomy were included.

Essential hypertension was defined on the basis of inpatient or outpatient ICD-9 or ICD-10 diagnosis codes (ICD-9: 401·0, 401·1, 401·9; ICD-10: I10, I11, I12, I13) with exclusions for ICD-9/10 coding or text search terms indicative of PA (see codes and search terms above). Any essential hypertension patient prescribed an MR antagonist on or before the date of study entry was excluded.

Any PA or essential hypertension patient with a prior cardiovascular event (defined as myocardial infarction/coronary revascularization, congestive heart failure hospitalization, or transient ischemic attack/cerebrovascular accident) on or before the date of study entry was excluded. All PA and essential hypertension patients had to have at least 1 follow-up encounter after study entry to be included (**Figure 1**).

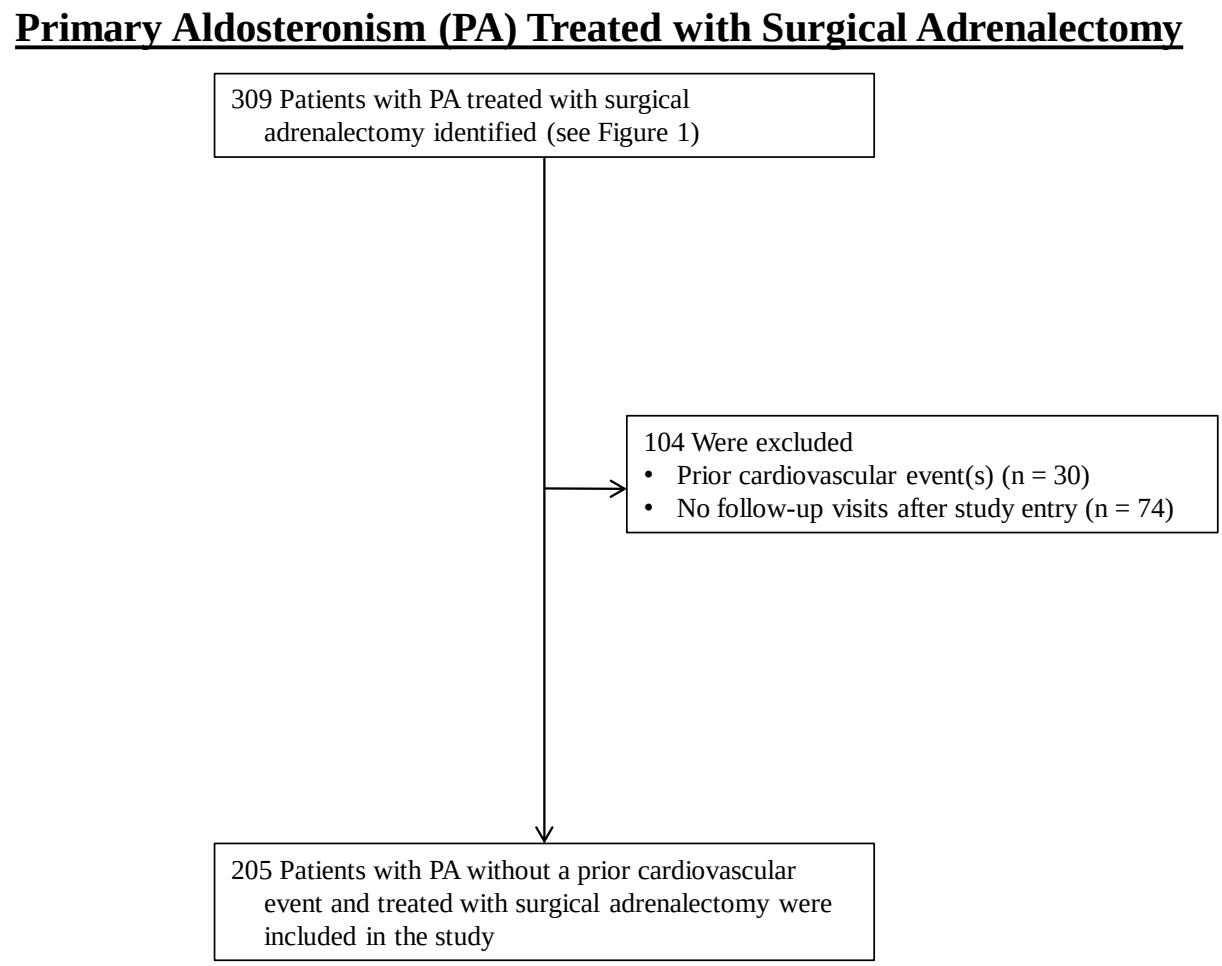
For the secondary analysis of incident cardiovascular outcomes based on renin levels achieved on MR antagonist therapy, the exposure of interest was whether the first renin measurement at least one month after beginning MR antagonist therapy was unsuppressed (≥1 µg/L/h) or suppressed (<1 µg/L/h). For this sub-analysis, study entry for the PA patients treated with MR antagonists occurred on the date of the first renin measurement after initiating MR antagonist therapy.

Detailed Definition of Outcomes

Incident cardiovascular outcomes were defined on the basis of inpatient or outpatient ICD-9 or ICD-10 diagnosis or procedure codes for myocardial infarction/coronary revascularization, congestive heart failure hospitalization, and stroke (transient ischemic attack/cerebrovascular accident). Incident atrial fibrillation and incident diabetes mellitus were also defined in the same fashion (See Table below). Outcomes were independently identified via manual medical record review by two reviewers (G.H. and N.Y.) in the entire PA cohort and via ICD-9 and ICD-10 coding in the essential hypertension cohort. The accuracy of the outcomes identified by ICD-9 or ICD-10 codes was confirmed via manual chart review of a subset (N =1200) of the cohorts by two reviewers (G.H. and N.Y) with a strong agreement of the two methods to identify incident outcomes (kappa = 0·93 [95% CI 0·91, 0·96]). Mortality was identified through the National Death Index which is linked to the research registry utilized for this study.

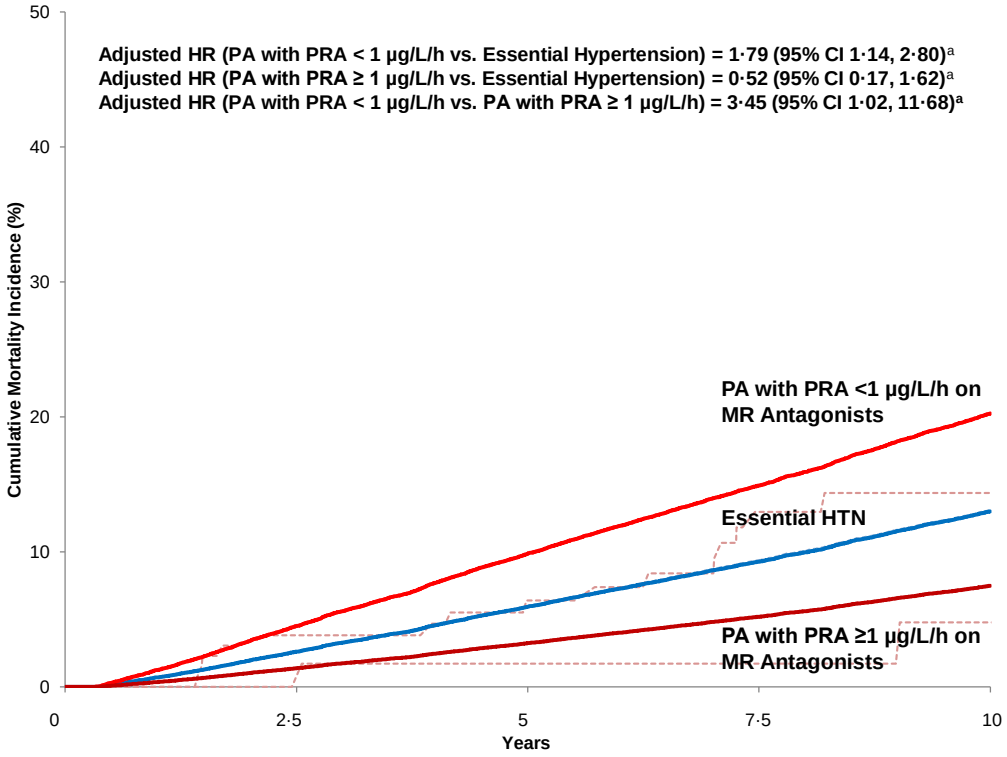
Outcome	ICD-9 Codes	ICD-10 Codes
Myocardial Infarction/Coronary Revascularization	410·0-410·9, 36·0-36·3	I21·0-I21·9, PCS0210-3, PCS0270-04
Congestive Heart Failure Hospitalization	428·0-428·9 (inpatient primary diagnosis only)	I50·0-I50·9
Stroke: Transient Ischemic Attack or Cerebrovascular Accident	434·0-434·9, 435·0-435·9	I63·0-I63·9, G45·0-G45·9
Atrial Fibrillation	427·31	I48·0, I48·1, I48·2, I48·91
Diabetes Mellitus	250·0-250·9	E11·0-E11·9

Figure S1. Eligible Study Patients with PA Treated with Surgical Adrenalectomy.



Study entry for PA treated with surgical adrenalectomy was the first follow-up visit 1-6 months following surgery.
ICD-9/10 = *International Classification of Disease, 9th or 10th Revision*.

Figure S2. Standardized Cumulative Incidence Curve of Mortality in Medically Treated Primary Aldosteronism Stratified by Plasma Renin Activity Achieved with Mineralocorticoid Receptor Antagonists and Essential Hypertension.

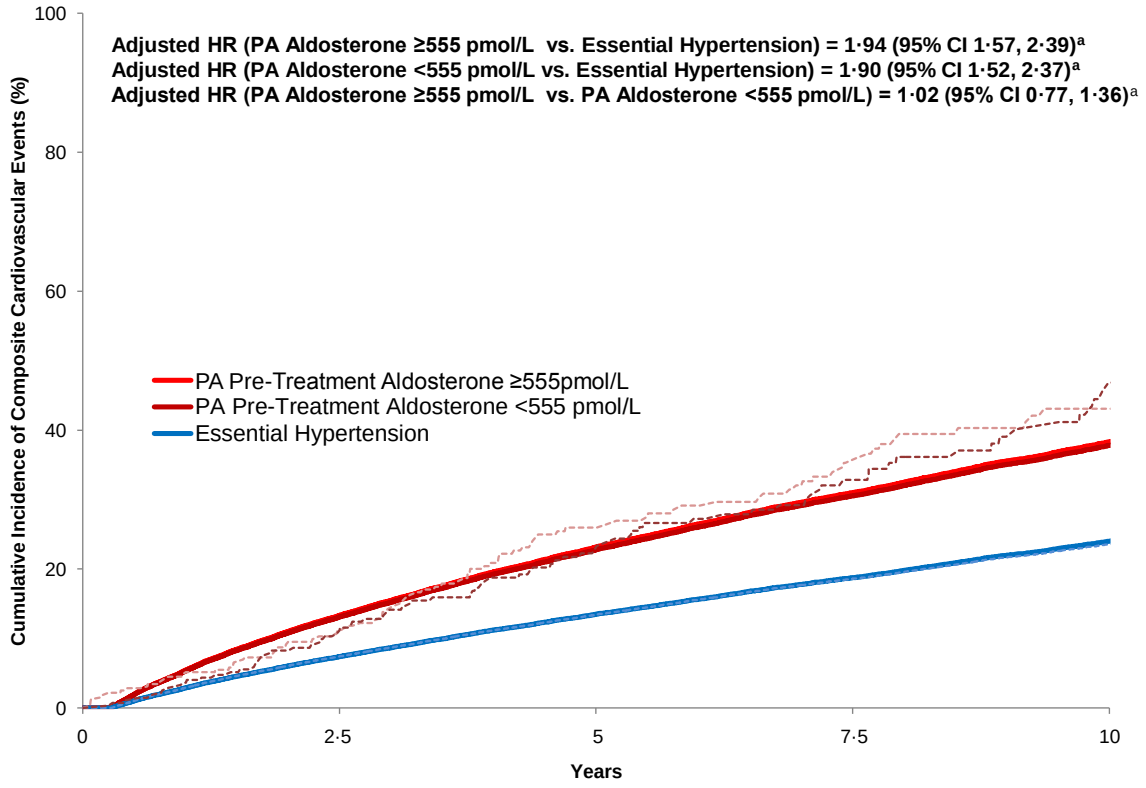


No. at risk					
PA - PRA <1 µg/L/h	134	124	105	75	45
PA - PRA ≥1 µg/L/h	67	58	51	42	25
Essential Hypertension	41,853	40,116	34,090	27,390	20,153

Solid lines = adjusted cumulative incidence; dashed lines = unadjusted cumulative incidence. PA = primary aldosteronism; PRA = plasma renin activity; MR = mineralocorticoid receptor.

[a] Hazard ratios adjusted for, and adjusted cumulative incidence curves standardized to the distribution of, the following variables at the time of study entry in our cohort: age, sex, race/ethnicity, BMI, smoking status, diabetes mellitus, hemoglobin A1C, atrial fibrillation, LDL cholesterol, statin use, daily aspirin use, estimated glomerular filtration rate, systolic blood pressure, diastolic blood pressure, and number of antihypertensive medications.

Figure S3. Standardized Cumulative Incidence Curve of Composite Cardiovascular Events in Medically Treated Primary Aldosteronism Stratified by Pre-Treatment Serum Aldosterone Level and Essential Hypertension.

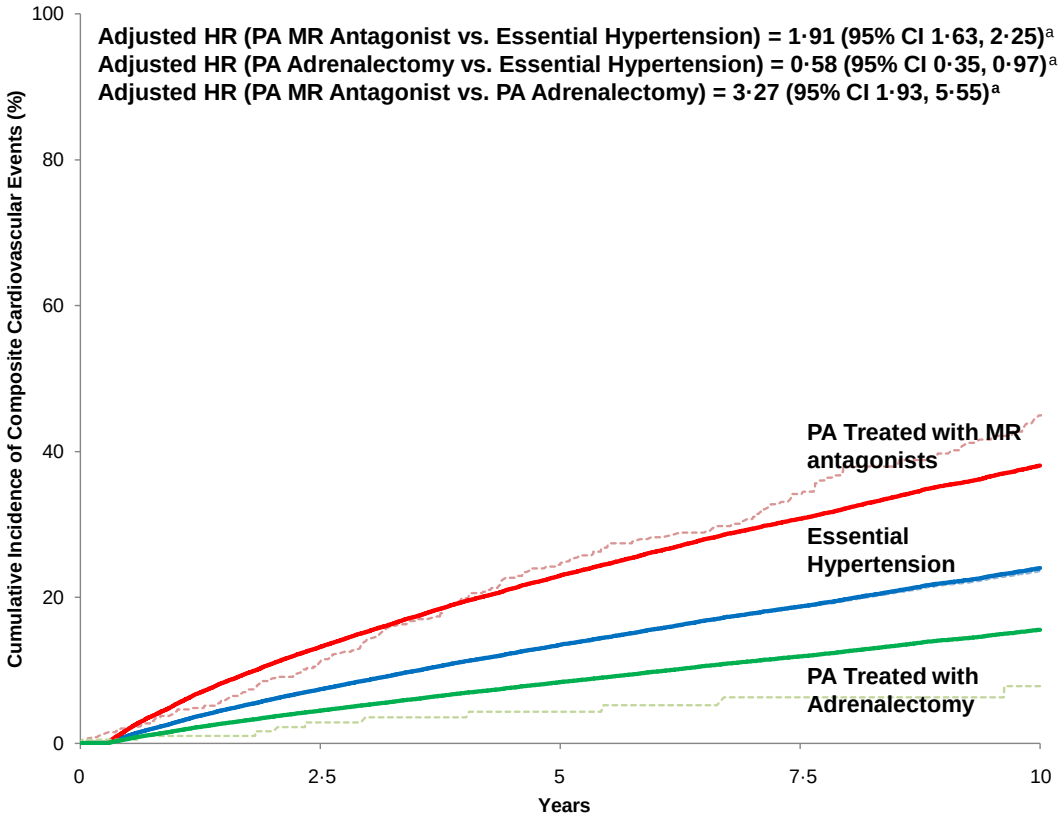


No. at risk					
PA Pre-treatment Aldosterone ≥555 pmol/L	322	227	146	96	49
PA Pre-treatment Aldosterone <555 pmol/L	280	212	145	87	45
Essential Hypertension	41,853	34,423	25,870	18,261	12,453

Solid lines = adjusted cumulative incidence; dashed lines = unadjusted cumulative incidence. Incident composite cardiovascular events defined as a composite of incident myocardial infarction/coronary revascularization, congestive heart failure hospitalization, and transient ischemic attack/cerebrovascular accident. PA = primary aldosteronism.

[a] Hazard ratios adjusted for, and adjusted cumulative incidence curves standardized to the distribution of, the following variables at the time of study entry in our cohort: age, sex, race/ethnicity, BMI, smoking status, diabetes mellitus, hemoglobin A1C, atrial fibrillation, LDL cholesterol, statin use, daily aspirin use, estimated glomerular filtration rate, systolic blood pressure, diastolic blood pressure, and number of antihypertensive medications.

Figure S4. Standardized Cumulative Incidence Curve of Composite Cardiovascular Events in Medically Treated Primary Aldosteronism, Surgically Treated Primary Aldosteronism, and Essential Hypertension.



No. at risk					
PA - MR antagonist	602	439	291	183	94
Essential Hypertension	41,853	34,423	25,870	18,261	12,453
PA - Adrenalectomy	205	148	119	82	55

Solid lines = adjusted cumulative incidence; dashed lines = unadjusted cumulative incidence. Incident composite cardiovascular events defined as a composite of incident myocardial infarction/coronary revascularization, congestive heart failure hospitalization, and transient ischemic attack/cerebrovascular accident. PA = primary aldosteronism; MR = mineralocorticoid receptor.

[a] Hazard ratios adjusted for, and adjusted cumulative incidence curves standardized to the distribution of, the following variables at the time of study entry in our cohort: age, sex, race/ethnicity, BMI, smoking status, diabetes mellitus, hemoglobin A1C, atrial fibrillation, LDL cholesterol, statin use, daily aspirin use, estimated glomerular filtration rate, systolic blood pressure, diastolic blood pressure, and number of antihypertensive medications.

Table S1. Longitudinal Blood Pressure Trends in the Study Cohort.

	Primary Aldosteronism	Essential Hypertension
Baseline Blood Pressure Prior to Study Entry[a]		
Systolic Blood Pressure (mm Hg) – mean (SD)	148 (18)	138 (19)
Diastolic Blood Pressure (mm Hg) – mean (SD)	86 (13)	81 (11)
Baseline Blood Pressure at Time of Study Entry[b]		
Systolic Blood Pressure (mm Hg) – mean (SD)	137 (19)	135 (18)
Diastolic Blood Pressure (mm Hg) – mean (SD)	81 (13)	80 (11)
Blood Pressure at Follow-Up Year 3[c]		
Systolic Blood Pressure (mm Hg) – mean (SD)	135 (19)	133 (18)
Diastolic Blood Pressure (mm Hg) – mean (SD)	79 (12)	79 (11)
Blood Pressure at Follow-Up Year 5[c]		
Systolic Blood Pressure (mm Hg) – mean (SD)	134 (20)	133 (18)
Diastolic Blood Pressure (mm Hg) – mean (SD)	78 (13)	79 (11)
Blood Pressure at Follow-Up Year 10[c]		
Systolic Blood Pressure (mm Hg) – mean (SD)	135 (19)	133 (17)
Diastolic Blood Pressure (mm Hg) – mean (SD)	77 (12)	77 (11)

[a] Refers to the last blood pressure recorded prior to study entry (i.e. just prior to starting MR antagonist [PA] or just prior to ICD-9/10 coding for essential hypertension).
[b] Refers to the first blood pressure recorded 1-6 months after starting MR antagonist therapy (PA) or initial ICD-9/10 coding for essential hypertension.
[c] Blood pressure measurements recorded are the measurements closest to each specified time interval +/- 1 year.

Table S2. Hazard Ratios for Incident Composite Cardiovascular Events in Primary Aldosteronism Patients on Mineralocorticoid Receptor Antagonists (Stratified by Plasma Renin Activity Achieved) and Essential Hypertension. Results reflect the risk for composite cardiovascular events based on renin activity achieved using definitions of the renin exposure based on the first, second, and third meaurements obtained following at least one month of mineralocorticoid receptor antagonist therapy.

First Plasma Renin Activity (PRA) Measurement[a]	**Suppressed PRA (<1 μg/L/h)**	**Unsuppressed PRA (≥1 μg/L/h)**	**Essential Hypertension**
# Eligible Patients without cardiovascular events	134	67	41853
Years to PRA Measurement – Median (IQR)	0·56 (0·21 – 2·08)	0·62 (0·21 – 2·58)	--
Hazard Ratio (95% CI) for Incident CVE vs. Essential Hypertension	2·83 (2·11 – 3·80)	1·09 (0·56 – 2·10)	1.00
Hazard Ratio (95% CI) for Incident CVE (PRA < 1 μg/L/h vs. PRA ≥ 1 μg/L/h)	2·60 (1·27 – 5·32)	Reference	--
Second PRA Measurement[ab]			
# Eligible Patients without cardiovascular events	86	63	41853
Years to PRA Measurement – Median (IQR)	0·73 (0·42 – 3·07)	0·88 (0·48 – 3·56)	--
Hazard Ratio (95% CI) for Incident CVE vs. Essential Hypertension	3·16 (2·02 – 4·95)	1·27 (0·63 – 2·55)	1.00
Hazard Ratio (95% CI) for Incident CVE (PRA < 1 μg/L/h vs. PRA ≥ 1 μg/L/h)	2·50 (1·09 – 5·69)	Reference	--
Third PRA Measurement[ab]			
# Eligible Patients without cardiovascular events	46	52	41853
Years to PRA Measurement – Median (IQR)	1·13 (0·67 – 3·60)	1·30 (0·75 – 5·06)	--
Hazard Ratio (95% CI) for Incident CVE vs. Essential Hypertension	3·33 (1·83 – 6·05)	1·86 (0·92 – 3·74)	1.00
Hazard Ratio (95% CI) for Incident CVE (PRA < 1 μg/L/h vs. PRA ≥ 1 μg/L/h)	1·79 (0·72 – 4·47)	Reference	--

CVE = composite cardiovascular events

[a] Excludes any patients with incident cardiovascular event prior to specified PRA measurement.
[b] If any PRA level up to the specified measurement was ≥ 1 μg/L/h, the patient was included in the "Unsuppressed PRA" category.

Table S3. Longitudinal Blood Pressure Trends in Medically Treated Primary Aldosteronism Patients Stratified by Renin Activity Level Achieved while on Mineralocorticoid Receptor Antagonists.

	PA Achieving Unsuppressed PRA (≥ 1 µg/L/h)	PA with Persistent Suppressed PRA (< 1 µg/L/h)
Baseline Blood Pressure Prior to Study Entry[a]		
Systolic Blood Pressure (mm Hg) – mean (SD)	146 (16)	149 (19)
Diastolic Blood Pressure (mm Hg) – mean (SD)	87 (11)	86 (12)
Baseline Blood Pressure at Time of Study Entry[b]		
Systolic Blood Pressure (mm Hg) – mean (SD)	136 (16)	140 (21)
Diastolic Blood Pressure (mm Hg) – mean (SD)	79 (11)	83 (14)
Blood Pressure at Follow-Up Year 3[c]		
Systolic Blood Pressure (mm Hg) – mean (SD)	134 (14)	136 (24)
Diastolic Blood Pressure (mm Hg) – mean (SD)	82 (12)	80 (15)
Blood Pressure at Follow-Up Year 5[c]		
Systolic Blood Pressure (mm Hg) – mean (SD)	135 (17)	138 (22)
Diastolic Blood Pressure (mm Hg) – mean (SD)	82 (12)	80 (13)
Blood Pressure at Follow-Up Year 10[c]		
Systolic Blood Pressure (mm Hg) – mean (SD)	136 (21)	138 (18)
Diastolic Blood Pressure (mm Hg) – mean (SD)	78 (14)	79 (12)

PA = primary aldosteronism; PRA = plasma renin activity.

[a] Refers to the last blood pressure recorded prior to study entry (i.e. just prior to starting MR antagonist).
[b] Refers to the first blood pressure recorded 1-6 months after starting MR antagonist therapy.
[c] Blood pressure measurements recorded are the measurements closest to each specified time interval +/- 1 year.

Table S4. Mineralocorticoid Receptor Antagonist Dosing Stratified by Renin Activity Level Achieved.

	Mean Spironolactone Total Daily Dose (mg) (n=161)		Mean Eplerenone Total Daily Dose (mg) (n=40)		Mean MR Antagonist Equivalent Potency Total Daily Dose (mg)[a] (n=201)	
	PRA < 1 µg/L/h (N=106)	PRA ≥ 1 µg/L/h (N=55)	PRA < 1 µg/L/h (N=28)	PRA ≥ 1 µg/L/h (N=12)	PRA < 1 µg/L/h (N=120)	PRA ≥ 1 µg/L/h (N=105)
Initial MRA Dosing	43 (28)	50 (27)	53 (48)	65 (27)	79 (55)	94 (52)
Max Dose Over Study Period	71 (63)	84 (60)	165 (172)	108 (55)	148 (139)	158 (113)

Doses reported as mean (SD). MR= Mineralocorticoid Receptor; PRA = Plasma Renin Activity.

[a] The mean MR antagonist equivalent potency dose is a metric to allow consolidation of spironolactone and eplerenone doses into a single MR antagonist potency. Spironolactone is considered to be twice the potency of eplerenone for this calculation; therefore, the dosing was calculated by multiplying spironolactone total daily dose by two and eplerenone total daily dose by one.

Table S5. Baseline Characteristics of Study Patients Including Surgically Treated Primary Aldosteronism.

	PA treated with MR Antagonists (N = 602)	PA treated with surgical adrenalectomy (N = 205)	Essential Hypertension (N = 41853)
Age - yr	58 (12)	50 (11)	57 (12)
Sex – Female (n/%)	271/45	86/42	21484/51
Race or Ethnic Group (n/%)			
White	336/56	131/64	27544/66
Black	153/25	31/15	6775/16
Hispanic	54/9	23/11	2693/6
Other[a]	59/10	20/10	4841/12
Body Mass Index – kg/m^2	31·1 (6·0)	30·6 (6·5)	29·8 (6·4)
Follow-up Time - yr	7·0 (4·7)	7·6 (6·1)	8·8 (5·6)
Primary Aldosteronism Characteristics[b]			
Serum Aldosterone – pmol/L	638 (472-943)	1165 (583-1276)	--
Plasma Renin Activity[c] (n/%)			
≤ 0·60 µg/L/h	548/91	191/93	--
0·61 – 0·99 µg/L/h	54/9	14/7	--
≥ 1·00 µg/L/h	0/0	0/0	--
Aldosterone-to-Renin Ratio – pmol/L per µg/L/h	1689 (987-4239)	2413 (1221-5631)	--
Serum Potassium – mmol/L	3·6 (0·5)	3·6 (0·6)	4·1 (0·5)
Potassium Supplementation (n/%)	275/46	49/24	442/1
CT or MRI Imaging (n/%)	581/97	205/100	--
Unilateral Adrenal Abnormality (n/%)	220/38	186/91	--
Bilateral Adrenal Abnormalities (n/%)	65/11	10/5	--
Normal Appearing Adrenal Glands (n/%)	296/51	9/4	--
Adrenal Vein Sampling (n/%)	344/57	167/81	--
Lateralization (n/%)	54/16	162/97	--
No Lateralization (n/%)	239/69	0/0	--
Unsatisfactory/Indeterminate (n/%)	51/15	5/3	--
Baseline Blood Pressure Prior to Study Entry[d]			
Systolic Blood Pressure – mm Hg	148 (18)	145 (17)	138 (19)
Diastolic Blood Pressure – mm Hg	86 (13)	87 (15)	81 (11)
Baseline Blood Pressure at Time of Study Entry[e]			
Systolic Blood Pressure – mm Hg	137 (19)	133 (18)	135 (18)
Diastolic Blood Pressure – mm Hg	81 (13)	76 (11)	80 (11)
Antihypertensive Medication Use			
MR Antagonist Use (n/%)	602/100	0/0	0/0
Spironolactone	500/83	--	--
Eplerenone	102/17	--	--
Mean Spironolactone Total Daily Dose (mg)	45 (30)	--	--
Mean Eplerenone Total Daily Dose (mg)	54 (36)	--	--
Mean Number of Non-MR Antagonist Antihypertensives	2·9 (1·4)	2·4 (1·3)	2·7 (1·4)
ACE Inhibitor/Angiotensin II Receptor Blocker (n/%)	407/68	121/59	30396/73
Calcium Channel Blocker (n/%)	405/67	131/64	17247/41
Beta Blocker (n/%)	395/66	111/54	23743/57
Diuretic			

Thiazide (n/%)	243/40	43/21	21864/52
Loop (n/%)	42/7	3/1	6767/16
Potassium-sparing (non-MR Antagonist) (n/%)	112/19	33/16	3857/9
Other[f] (n/%)	137/23	57/28	7227/17
Other Cardiovascular Risk Factors			
Daily Aspirin (n/%)	213/35	43/21	12689/30
LDL – mmol/L	2·80 (0·85)	2·85 (0·85)	2·87 (0·96)
Statin (n/%)	204/34	45/22	17492/42
Diabetes Mellitus (n/%)	118/20	27/13	8364/20
Hemoglobin A1C – proportion of total hemoglobin	0·060 (0·011)	0·060 (0·011)	0·061 (0·010)
Serum Creatinine – µmol/L	80·8 (44·2)	80·1 (29·0)	78·5 (57·2)
Estimated Glomerular Filtration Rate – mL/s/1·73m^2	1·32 (0·38)	1·37 (0·38)	1·35 (0·37)
Atrial Fibrillation (n/%)	24/4	4/2	1761/4
Smoking Status (n/%)			
Never	330/55	112/55	19478/47
Former	176/29	49/24	9683/23
Current	34/6	13/6	3935/9
Not known	62/10	31/15	8757/21

Unless otherwise specified, normally distributed continuous variables are reported as mean (SD); non-normally distributed continuous variables are reported as median (25^{th} – 75^{th} percentile IQR); categorical variables are reported as percentages. MR = mineralocorticoid receptor.

[a] Other race includes Asian, Native American, other, and unknown.
[b] Laboratory values most recent prior to study entry.
[c] For the majority of the study period, the hospital-affiliated laboratories reported a minimum plasma renin activity of < 0·60 µg/L/h. For study purposes, these minimum values were recorded as 0·59 µg/L/h.
[d] Refers to the last blood pressure recorded prior to study entry (i.e. just prior to starting MR antagonist [PA] or just prior to ICD-9/10 coding for essential hypertension).
[e] Refers to the first blood pressure recorded 1-6 months after starting MR antagonist therapy (PA) or initial ICD-9/10 coding for essential hypertension or after surgery.
[f] Other antihypertensive medication includes hydralazine, clonidine, alpha blockers, nitrates, minoxidil, methyldopa, and direct renin inhibitors.

REFERENCES:

1. Funder JW, Carey RM, Mantero F, Murad MH, Reincke M, Shibata H, et al. The Management of Primary Aldosteronism: Case Detection, Diagnosis, and Treatment: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016;101(5):1889-916.