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Subclinical Primary Aldosteronism and Major Adverse Cardiovascular Events: A Longitudinal Population-Based Cohort Study

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BACKGROUND: Primary aldosteronism (PA), an overt form of renin-independent aldosterone production, leads to a disproportionately high rate of major adverse cardiovascular events (MACEs). Mounting evidence suggests that milder forms of renin-independent aldosterone production (subclinical PA) are highly prevalent; however, the link between subclinical PA and MACE remains uncertain.

METHODS: This prospective study included 2017 Canadian adults 40 to 69 years of age from the randomly sampled, population-based CARTaGENE cohort (Québec, Canada), in which aldosterone and renin concentrations at enrollment (2009–2010) were measured. Follow-up data were obtained via provincial health care administrative database linkage. MACE outcomes consisted of a composite of myocardial infarction, stroke, hospitalization for heart failure, and cardiovascular death. Multivariable linear and nonlinear Cox regression models measured the associations of concentrations of aldosterone, renin, and the aldosterone-to-renin ratio with MACE. Outcome-derived optimal thresholds for these markers were then determined.

RESULTS: The mean (SD) age of participants was 56 (8) years, and 45% were women. Mean blood pressure was 129 (15)/76 (10) mm Hg, with hypertension being present in 27%. Over a median follow-up time of 10.8 years, 57 (3%) MACE outcomes occurred. Lower renin concentration (adjusted hazard ratio [aHR], 2.22 [95% CI, 1.02–4.76]) and higher aldosterone-to-renin ratio (aHR, 2.43 [95% CI, 1.15–5.12]) were associated with a higher risk for MACE, whereas no significant association was found with aldosterone concentration (aHR, 1.57 [95% CI, 0.42–5.90]). Renin concentration exhibited a nonlinear relationship with MACE risk. The outcome-derived optimal thresholds to discriminate a higher MACE risk were renin concentration ≤4.0 ng/L (aHR, 2.12 [95% CI, 1.21–3.72]) and aldosterone-to-renin ratio ≥70 pmol/L per ng/L (aHR, 2.03 [95% CI, 1.09–3.80]). All aforementioned associations were independent of blood pressure.

CONCLUSIONS: Independent of blood pressure, the subclinical PA biochemical phenotype is associated with an increased risk of MACE. Future studies are necessary to determine whether early identification and targeted treatment of subclinical PA mitigates this risk.

Key Words: aldosterone ■ aldosterone-to-renin ratio ■ cardiovascular events ■ cardiovascular health ■ hyperaldosteronism ■ hypertension ■ primary aldosteronism ■ renin ■ subclinical

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Clinical Perspective

What Is New?

- This is the first prospective study to measure the association between subclinical primary aldosteronism (PA) and major adverse cardiovascular events.
- Among a presumably "healthy" adult population, in which individuals had few comorbidities and most had either normal blood pressure or mild hypertension, the subclinical PA phenotype (ie, renin-independent aldosteronism below the diagnostic thresholds traditionally used to define overt PA) was associated with a higher risk for major adverse cardiovascular events independent of blood pressure.
- The biochemical thresholds for subclinical PA beyond which cardiovascular risk was greatest were a renin concentration ≤4.0 ng/L and an aldosterone-to-renin ratio ≥70 pmol/L per ng/L.

What Are the Clinical Implications?

- The presence and magnitude of subclinical PA in the general adult population are associated with a higher risk of clinically relevant hard cardiovascular end points.
- The historical approach to PA fails to capture the expansive severity spectrum of renin-independent aldosteronism that extends across a much broader population base with important clinical implications.
- Future studies should examine whether early identification of subclinical PA (eg, at the timing of the initial diagnosis of hypertension or even prehypertension) and initiation of aldosterone-targeted therapy may serve to mitigate the excess cardiovascular risk associated with this condition.

Nonstandard Abbreviations and Acronyms

aHR	adjusted hazard ratio
ARR	aldosterone-to-renin ratio
BP	blood pressure
HR	hazard ratio
MACE	major adverse cardiovascular event
MR	mineralocorticoid receptor
PA	primary aldosteronism
RAMQ	Régie de l'assurance-maladie du Québec

Primary aldosteronism (PA) is increasingly recognized as the most common and modifiable form of secondary hypertension.[1,2] PA is characterized by renin-independent aldosterone production from one or both adrenal glands, resulting in inappropriate mineralocorticoid receptor (MR) activation. Early diagnosis and implementation of aldosterone-targeted treatment are essential, as PA leads to a disproportionately higher risk for adverse cardiovascular outcomes compared with essential hypertension, independent of blood pressure (BP).[3–5] Traditionally, guideline-recommended testing for PA has been restricted to populations known to be at high risk, including severe or resistant hypertension, hypertension with hypokalemia, and hypertension with an adrenal nodule.[6] However, the Japan Endocrine Society and the European Society of Cardiology were the first to expand their recommendations for PA testing to include all adults with hypertension.[7,8] Testing entails measurement of aldosterone concentration along with renin concentration or activity to determine whether a patient with hypertension meets historically defined biochemical thresholds to apply the diagnostic label of PA.

A rapidly growing evidence base has brought into question this traditional approach of simplifying PA to a categorical diagnosis.[1,9–20] Rather, these studies demonstrate that, when renin concentration or activity is low or suppressed, almost any aldosterone production represents some degree of PA pathophysiology (ie, renin-independent aldosterone production), extending the spectrum of PA well beyond the diagnostic confines employed historically. Approximately one-third of individuals with hypertension have a low renin phenotype, and this continuum also extends to populations with mild hypertension and even normal BP.[1,2,9,21] As these milder forms of renin-independent aldosterone production predominantly go unrecognized in modern-day clinical practice, they are often termed "subclinical PA." Thus, subclinical PA is defined as renin-independent aldosteronism, in which biochemical testing results fall below the diagnostic thresholds traditionally used to define overt PA or in people without a classical clinical phenotype to warrant guideline-recommended screening for PA.[6] Subclinical PA has been demonstrated previously to be associated with inappropriate MR activation, increased kaliuresis, accelerated arterial stiffening, BP elevation, and adverse cardiac remodeling.[1,9–20] However, it remains uncertain whether subclinical PA is linked to a heightened risk of clinically relevant hard cardiovascular end points.

Here, we conducted a prospective cohort study to measure the associations of concentrations of aldosterone, renin, and the aldosterone-to-renin ratio (ARR) with major adverse cardiovascular events (MACEs) in a large, randomly sampled, and population-based cohort of Canadian adults. Participants enrolled in CARTaGENE were investigated to test the hypothesis that the presence and magnitude of subclinical PA is associated with a higher risk for MACEs.

METHODS

Data Availability

Some or all datasets generated or analyzed for the current study are not publicly available but are available from the corresponding author upon reasonable request.

Study Design

Prospective survival analyses were performed to measure the associations of aldosterone and renin concentration profiles with MACEs in a Canadian population-based cohort. The research reported in the paper adhered to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for observational studies (Table S1).[22] All participants provided written informed consent upon enrollment. Study protocols were approved by the Comité d'éthique de la recherche du CIUSSS-NIM (ID 2017-1358) and the Ottawa Health Science Network research ethics board (ID 20200475-01H).

Data Source and Study Cohort

CARTaGENE (https://cartagene.qc.ca) is an ongoing Canadian cohort designed to evaluate determinants of chronic disease among the general adult population. Details of the CARTaGENE design and enrollment have been described previously.[23] In brief, 19 996 adults 40 to 69 years of age were enrolled between August 2009 and October 2010 in 4 metropolitan regions of the province of Québec. Participants were randomly invited using the provincial Régie de l'assurance-maladie du Québec (RAMQ) universal health care administrative database with complex random stratified sampling of 1% of the population base. Participants were selected so that the cohort was representative of the general Québec population of this age group based on sociodemographic characteristics. Baseline data collection was completed at the enrollment visit. Demographic information, medical history, dietary questionnaires, anthropometric measurements, medication lists, and blood samples were collected in a standardized fashion by a research nurse. BP was measured 3 times at 2-minute intervals with the Omron HEM-907XL device (Omron, Lake Forest, IL) using the recommended standardized technique, and the mean was reported.[24] The estimated glomerular filtration rate was calculated using the 2021 Chronic Kidney Disease Epidemiology Collaboration creatinine-based formula. Given the varying thresholds used to define hypertension according to international guidelines, hypertension was classified both by BP ≥140/90 mm Hg and BP ≥130/80 mm Hg along with use of antihypertensive medication.[7,24–26] Diabetes was defined as use of any glucose-lowering medication, hemoglobin A1c ≥6.5%, fasting glucose ≥7.0 mmol/L, or a nonfasting glucose ≥11.1 mmol/L. Previous cardiovascular disease was defined as a history of acute coronary syndrome, stroke, or heart failure ascertained from self-reported questionnaires or the RAMQ provincial administrative database (from 1998 to CARTaGENE enrollment). Daily sodium and potassium dietary intake was determined from the validated Canadian Diet History Questionnaire II.[27] CARTaGENE participants are passively tracked for long-term health outcomes via the RAMQ database. As all Québec residents are provided universal health care coverage and the database captures all insured health care services in the province, the RAMQ database provides comprehensive capture of all outcome events. The end follow-up date for this study was March 31, 2021. All CARTaGENE participants with available baseline aldosterone and renin concentration measurements, along with dietary assessment of 24-hour sodium and potassium intake, were included. The only participants excluded were those without available follow-up data.

Exposures: Aldosterone, Renin, and ARR

At the CARTaGENE enrollment visit, morning nonfasting blood samples were collected on ice with the participant in the seated position (no prespecified seated time) and transferred to the Biobanque Génome Québec – Centre hospitalier affilié universitaire régional de Chicoutimi for processing into serum and plasma aliquots for immediate storage at −176 °C. Sampling was performed without any adjustment to participants' home medications. Frozen EDTA plasma samples were shipped to the accredited Eastern Ontario Regional Laboratories Association Clinical Biochemistry Laboratory (Ottawa, ON, Canada), where samples were thawed immediately before measurement of aldosterone and renin concentrations. Aldosterone (picomoles per liter) and direct renin concentrations (nanograms per liter) were measured by chemiluminescent immunoassay on the Liaison analyzer (DiaSorin Inc, Stillwater, MN). These assays are used for clinical practice and regular quality control testing, as part of laboratory quality assurance practices, confirmed imprecision (coefficient of variation) as ≤10% at clinically relevant concentrations. The lower limit of detection for renin concentration was 1.0 ng/L; to avoid overinflation of the ARR, measures below this were assigned a value of 0.9 ng/L. Although no precise conversion between direct renin concentration and plasma renin activity is available, conversion factors of direct renin concentration 4.9 ng/L ≈ plasma renin activity 1.0 ng/mL per hour and ARR 5.6 pmol/L per ng/L ≈ ARR 1.0 ng/dL per ng/mL per hour have been suggested.[6]

Outcomes: MACEs

Prospective outcome data were obtained from the provincial RAMQ database. MACEs were defined as a composite of myocardial infarction, stroke (ischemic or hemorrhagic), hospitalization for heart failure, and cardiovascular death. Events were identified from the database using validated *International Classification of Diseases, 10th Revision*, diagnostic codes from enrollment through March 31, 2021 (Table S2).[28–31] Only events identified as the principal diagnosis according to the hospitalization discharge summary were included. Recurrent events were not included.

Statistical Analysis

Baseline characteristics are presented as mean (SD) if normally distributed or as median (25th–75th percentile interquartile range) if non-normally distributed. Categorical variables are presented as number (percent). Missing data (<1% for all variables) were handled using multiple imputation. Concentrations of aldosterone, renin, and ARR were log transformed because of highly skewed distributions. Cox proportional hazards regression analyses were performed to evaluate associations (hazard ratio [HR] and 95% CI) of the continuous measures of log-aldosterone, log-renin, and log-ARR with incident MACE outcomes. The proportional hazards assumption was verified by plotting Schoenfeld residuals. Censoring events included noncardiovascular death and end of the follow-up period. Multivariable models were adjusted for the following variables ascertained at the time of CARTaGENE enrollment and selected a priori based upon clinical knowledge, previous literature, and availability within

CARTaGENE: age, sex, mean arterial BP, serum potassium, 24-hour dietary sodium intake, and use of renin-angiotensin-aldosterone inhibitors (angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, renin inhibitors, MR antagonists, or other potassium-sparing diuretics).[6,23] To assess for nonlinear associations of concentrations of aldosterone, renin, and ARR with MACEs, Cox regression analyses were repeated with the addition of restricted cubic spline terms, with the number of knots determined by the Akaike information criterion method.[32] Likelihood ratio testing was used to measure *P* values for nonlinearity. To determine the optimal discriminatory thresholds for the biochemical markers (concentrations of aldosterone, renin, and ARR) within the subclinical PA phenotype based upon MACE risk, 2 different approaches were employed. First, U statistics were calculated using the Contal and O'Quigly method with log-rank tests.[33] Second, time-dependent receiver operating characteristic curves were constructed for each marker, and Youden indices were calculated to identify the maximal difference between true-positive and false-positive rates.[34] Values corresponding to the greatest Youden index were considered as the optimal threshold. Consensus values (among the 2 cutoff selection approaches) for each marker were then selected to dichotomize variables, perform multivariable Cox regression analyses to determine their associations with the composite MACE outcome, and generate adjusted cumulative incidence curves. Statistical significance was defined as 2-sided $P<0.05$ and 95% CIs that did not overlap with 1.0. All statistical analyses were performed using IBM SPSS Statistics software version 29 and R Software version 4.1.0.

Sensitivity Analyses

The following sensitivity analyses were performed: (1) excluding participants taking potassium-sparing diuretics, (2) excluding participants taking any antihypertensive medication, (3) excluding participants taking estrogen therapy, (4) excluding participants with a previous history of cardiovascular disease, (5) excluding participants with an aldosterone concentration >250 pmol/L [9 ng/dL], (6) excluding participants with an ARR >144 pmol/L per ng/L, (7) employing a Fine-Gray subdistribution hazard model to treat noncardiovascular death as a competing (rather than censoring) event, and (8) stratifying by sex.

RESULTS

Baseline Characteristics

A total of 2064 CARTaGENE participants had baseline aldosterone and renin concentration measurements along with dietary assessment of 24-hour sodium and potassium intake at enrollment (Figure 1). The final study cohort included 2017 participants after excluding those with no follow-up data (n=47 [2%]). Baseline characteristics are presented in Table 1. The mean (SD) age was 56 (8) years. There were 914 women (45%) and 1103 men (55%). The majority (1861/2017 [92%]) of participants self-reported as being of White race. The mean systolic and diastolic BPs were 129 (15) and 76 (10) mm Hg, respectively, with 545 participants (27%) having a BP ≥140/90 mm Hg or taking antihypertensive medication. Diabetes and previous cardiovascular disease were uncommon, being present in 135 (7%) and 56 (3%) participants, respectively. The median (25th–75th percentile) concentrations of aldosterone, renin, and ARR were 219 (163–299) pmol/L (7.89 [5.88–10.78] ng/dL), 7.5 (4.5–11.7) ng/L, and 30 (19–50) pmol/L per ng/L (full distributions are displayed in Figure S1). Median estimated 24-hour dietary sodium and potassium intake were 2437 (1629–3285) mg and 3261 (2353–4352) mg, respectively.

Incident MACEs

Over a median follow-up time of 10.8 (10.6–11.0) years, there were a total of 57 (2.8%) participants who developed an incident MACE outcome. This consisted of 41 myocardial infarctions, 6 strokes, 3 hospitalizations for heart failure, and 7 cardiovascular deaths. There were 47 noncardiovascular deaths (2.3%) during follow-up.

Associations of Aldosterone, Renin, and ARR With Incident MACEs

Table 2 displays the crude and multivariable-adjusted associations of continuous linear measures of

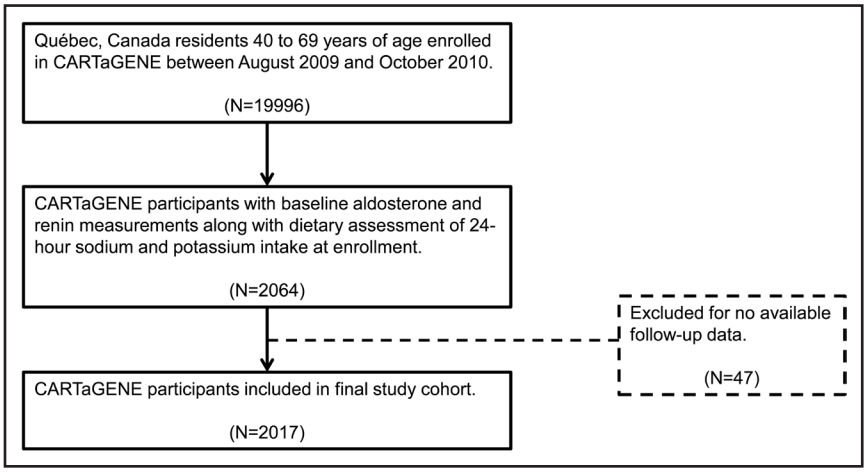

Figure 1. Study cohort flow diagram.

Table 1. Baseline Characteristics of the Study Cohort

Characteristic	Total
Participants	2017
Age, y, mean (SD)	56 (8)
Sex, No. (%)	
Female	914 (45)
Male	1103 (55)
Race or ethnicity (self-reported), No. (%)	
White	1861 (92)
Black	23 (1)
Asian	38 (2)
Middle Eastern	36 (2)
Latino	15 (1)
Aboriginal	15 (1)
Mixed ethnicity	3 (0)
Unknown/other	26 (1)
Vital signs and anthropometrics, mean (SD)	
Systolic blood pressure, mm Hg	129 (15)
Diastolic blood pressure, mm Hg	76 (10)
Heart rate, bpm	71 (11)
Height, cm	168 (9)
Weight, kg	77 (15)
Body mass index, kg/m^2	27 (5)
Comorbidities, no. (%)	
Hypertension	
≥140/90 mm Hg or use of antihypertensive medication	545 (27)
≥130/80 mm Hg or use of antihypertensive medication	1107 (55)
Diabetes	135 (7)
Cardiovascular disease	56 (3)
Active smoking	330 (16)
Laboratory measurements	
Aldosterone concentration	
pmol/L, median (25th–75th percentile)	219 (163–299)
ng/dL, median (25th–75th percentile)	7.89 (5.88–10.78)
Renin concentration, ng/L, median (25th–75th percentile), ng/L*	7.5 (4.5–11.7)
ARR, pmol/L per ng/L, median (25th–75th percentile)*	30 (19–50)
eGFR, mL/min/1.73 m^2, mean (SD)	87 (14)
Sodium, mmol/L, mean (SD)	139 (2)
Potassium, mmol/L, mean (SD)	4.3 (0.4)
Total cholesterol, mmol/L, mean (SD)	5.2 (1.0)
LDL cholesterol, mmol/L, mean (SD)	3.1 (0.9)
Daily Dietary Intake, mg†	
Sodium	
Mean (SD)	2538 (1533)
Median (25th–75th percentile)	2437 (1629–3285)
Potassium	
Mean (SD)	3489 (1803)
Median (25th–75th percentile)	3261 (2353–4352)
Antihypertensive medication use, No. (%)	
Any antihypertensive medication	170 (8)
ACE inhibitor	39 (2)
ARB	85 (4)
Renin inhibitor	1 (0)
Calcium channel blocker	39 (2)
Thiazide diuretic	47 (2)
Loop diuretic	1 (0)
Potassium-sparing diuretic	9 (0)
Beta-blocker	28 (1)
Other medication use, No. (%)	
Aspirin	244 (12)
Statin	336 (17)
Estrogen therapy	152 (8)
Follow-up time, y, median (25th–75th percentile)	10.8 (10.6–11.0)

Missingness of baseline characteristics was as follows: height (n=2, 0.10%), weight (n=2, 0.10%), heart rate (n=2, 0.10%), eGFR (n=1, 0.05%), sodium (n=3, 0.15%), potassium (n=10, 0.50%), total cholesterol (n=1, 0.05%), and LDL cholesterol (n=20, 0.99%). All other baseline characteristics had complete capture with no missingness. ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; ARR, aldosterone-to-renin ratio; bpm, beats per minute; eGFR, estimated glomerular filtration rate; and LDL, low-density lipoprotein.

*Although no precise conversion between direct renin concentration and plasma renin activity is available, conversion factors of direct renin concentration 4.9 ng/L ≈ plasma renin activity 1.0 ng/mL per hour and ARR 5.6 pmol/L per ng/L ≈ ARR 1.0 ng/dL per ng/mL/h have been suggested.[6]

†Assessed via the Canadian Diet History Questionnaire II.[27]

log-aldosterone, log-renin, and log-ARR with the composite MACE outcome. Although higher log-aldosterone was not significantly associated with MACEs (adjusted HR [aHR], 1.57 [95% CI, 0.42–5.90]), lower log-renin (aHR, 2.22 [95% CI, 1.02–4.76]), and higher log-ARR (aHR, 2.43 [95% CI, 1.15–5.12]) were both associated with a higher MACE risk. Figure 2 displays the assessment for nonlinear associations of concentrations of aldosterone, renin, and ARR with MACE risk. Although both aldosterone concentration and ARR demonstrated a linear relationship with MACE risk (*P* values for nonlinearity of 0.57 and 0.90, respectively), renin concentration demonstrated a nonlinear relationship (*P* value for nonlinearity of 0.01).

Outcome-Derived Thresholds for Increased Risk of MACEs in Subclinical PA

Using the U statistic and Youden methods, the consensus renin concentration threshold below which the risk of MACEs increased significantly was determined

Table 2. Associations of Aldosterone, Renin, and Aldosterone-to-Renin Ratio With Major Adverse Cardiovascular Events

Variable*	Crude HR (95% CI) for MACEs	Adjusted HR (95% CI) for MACEs†
Aldosterone concentration, pmol/L	1.33 (0.38–4.70)	1.57 (0.42–5.90)
Renin concentration, ng/L‡	0.42 (0.21–0.85)	0.45 (0.21–0.98)
ARR, pmol/L per ng/L‡	2.49 (1.25–4.96)	2.43 (1.15–5.12)

ARR indicates aldosterone-to-renin ratio; HR, hazard ratio; and MACE, major adverse cardiovascular event.

*Log-transformed variables.

†Models adjusted for age, sex, mean arterial blood pressure, serum potassium, 24-hour dietary sodium intake, and use of renin-angiotensin-aldosterone system inhibitors (angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, renin inhibitors, mineralocorticoid receptor antagonists, or other potassium-sparing diuretics).

‡Although no precise conversion between direct renin concentration and plasma renin activity is available, conversion factors of direct renin concentration 4.9 ng/L ≈ plasma renin activity 1.0 ng/mL per hour and ARR 5.6 pmol/L per ng/L ≈ ARR 1.0 ng/dL per ng/mL/h have been suggested.[6]

to be 4.0 ng/L. In the multivariable Cox regression analysis, a renin concentration ≤4.0 ng/L was associated with a 2.1-fold higher MACE risk (aHR, 2.12 [95% CI, 1.21–3.72]; Figure 3). Among the 2017 included participants, 419 (21%) had a renin concentration ≤4.0 ng/L. The consensus ARR threshold above which the risk of MACEs increased significantly was determined to be 70 pmol/L per ng/L. In the multivariable Cox regression analysis, an ARR ≥70 pmol/L per ng/L was associated with a 2.0-fold higher MACE risk (aHR, 2.03 [95% CI, 1.09–3.80]; Figure 3). Among the 2017 included participants, 299 (15%) had an ARR ≥70 pmol/L per ng/L. Notably, 248/299 (83%) of the participants with an ARR ≥70 pmol/L per ng/L also had a renin concentration ≤4.0 ng/L, whereas 293/299 (98%) had a renin concentration ≤10 ng/L. Having both a renin concentration ≤4.0 ng/L and ARR ≥70 pmol/L per ng/L was associated with a 2.4-fold higher MACE risk (aHR, 2.42 [95% CI, 1.25–6.48]) than having a renin concentration >4.0 ng/L and ARR <70 pmol/L per ng/L. As aldosterone concentration was not significantly associated with MACEs in the aforementioned linear and nonlinear analyses, no outcome-derived threshold was selected for aldosterone concentration.

Sensitivity Analyses

The aforementioned sensitivity analyses yielded results similar to the primary analysis (Table S3). Stratification of the primary analysis by sex showed similar patterns for renin concentration and ARR; however, the effect patterns for aldosterone concentration varied by sex but remained nonstatistically significant for both sexes with a large degree of overlap in the 95% CIs (Table S4).

DISCUSSION

In this large population-based prospective cohort study of Canadian adults, we found that the subclinical PA phenotype (ie, renin-independent aldosteronism, in which biochemical testing results fall below the diagnostic thresholds traditionally used to define overt PA or in people without a classical clinical phenotype to warrant guideline-recommended screening for PA) was associated with a higher risk for MACEs. Notably, the participants that comprised this cohort were overall healthy with few comorbidities, and the majority had normal BP or only

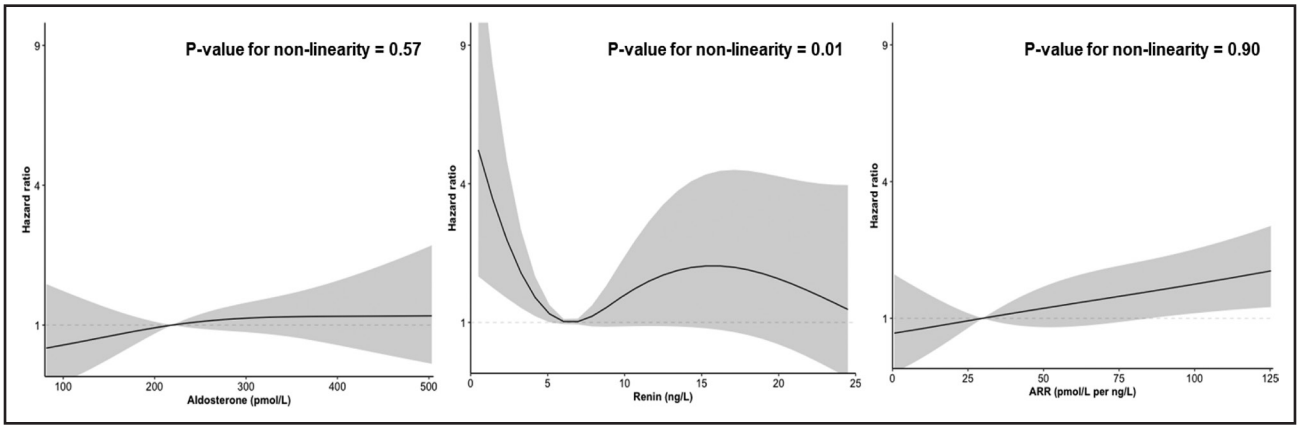

Figure 2. Assessment for nonlinear associations of aldosterone, renin, and aldosterone-to-renin ratio with major adverse cardiovascular events.

Gray-shaded areas represent the 95% confidence bands for the hazard ratio. Likelihood ratio testing was used to measure *P* values for nonlinearity. Models were adjusted for age, sex, mean arterial blood pressure, serum potassium, 24-hour dietary sodium intake, and use of renin-angiotensin-aldosterone system inhibitors (angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, renin inhibitors, mineralocorticoid receptor antagonists, or other potassium-sparing diuretics). Although no precise conversion between direct renin concentration and plasma renin activity is available, conversion factors of direct renin concentration 4.9 ng/L ≈ plasma renin activity 1.0 ng/mL per hour and ARR 5.6 pmol/L per ng/L ≈ ARR 1.0 ng/dL per ng/mL/h have been suggested.[6] ARR indicates aldosterone-to-renin ratio.

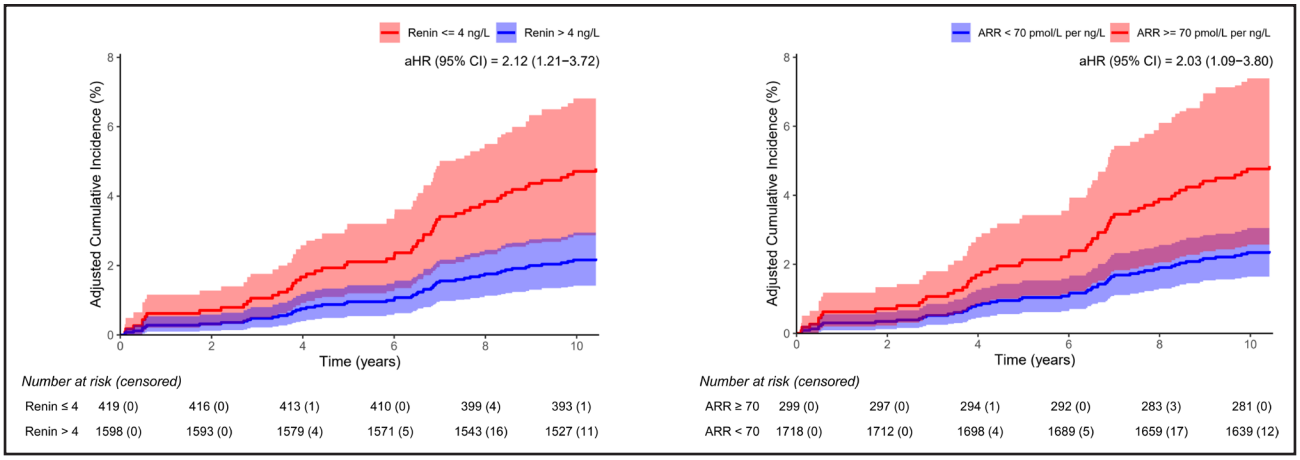

Figure 3. Adjusted cumulative incidence curves using outcome-derived thresholds for increased risk of major adverse cardiovascular events in subclinical primary aldosteronism.

Shaded areas represent the 95% confidence bands. Models were adjusted for age, sex, mean arterial blood pressure, serum potassium, 24-hour dietary sodium intake, and use of renin-angiotensin-aldosterone system inhibitors (angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, renin inhibitors, mineralocorticoid receptor antagonists, or other potassium-sparing diuretics). Although no precise conversion between direct renin concentration and plasma renin activity is available, conversion factors of direct renin concentration 4.9 ng/L ≈ plasma renin activity 1.0 ng/mL per hour and ARR 5.6 pmol/L per ng/L ≈ ARR 1.0 ng/dL per ng/mL/h have been suggested.[6] aHR indicates adjusted hazard ratio; and ARR aldosterone-to-renin ratio.

mild hypertension. Therefore, these findings highlight a clinically significant link between subclinical PA and incident cardiovascular disease risk that exists before the onset, or early in the course, of overt hypertension. Moreover, by adjusting for baseline BP in all analyses, this study demonstrates a BP-independent association between subclinical PA and MACE risk consistent with what occurs in overt and classically defined PA.[4,5]

The results from this study further challenge the traditional approach of employing semiarbitrary biochemical thresholds to define PA exclusively among individuals with hypertension and high-risk clinical features. In particular, the pathophysiology of PA does not require a "high" aldosterone concentration; rather, inappropriate aldosterone production relative to renin and angiotensin II defines the pathophysiology of this condition that imparts increased cardiovascular risk. Milder forms of renin-independent aldosteronism, outside the traditional biochemical thresholds for defining PA, are well known to be highly prevalent in resistant hypertension, which explains why MR antagonists are the most effective add-on therapy for improving BP control for such patients.[35,36] A growing number of studies have extended this subclinical PA phenotype to patients with milder degrees of hypertension and even patients with normal BP,[1,9–20] populations that are not historically considered at high risk for PA and for whom aldosterone and renin testing is not indicated according to the Endocrine Society guidelines.[6] These studies have clearly demonstrated that the subclinical PA phenotype in these populations is associated with inappropriate MR activation and detrimental cardiovascular changes.[1,9–20] In fact, our group demonstrated previously that subclinical PA is associated with accelerated arterial stiffening, adverse cardiac remodeling, and incident hypertension in the present CARTaGENE cohort.[19]

The current study now extends the growing evidence base on subclinical PA by demonstrating its association with clinically relevant hard cardiovascular end points. CARTaGENE is designed to be reflective of the general "healthy" adult Canadian population. The Endocrine Society PA guidelines consider overt PA to be cases in which confirmatory testing is not required.[6] The guidelines specify that this distinction only pertains to individuals with hypertension, spontaneous hypokalemia, undetectable renin, and aldosterone >550 pmol/L. Notably, there were no participants included in this study who met these criteria. Moreover, very few participants met traditional criteria for PA screening, such as resistant hypertension or hypertension plus hypokalemia. For instance, only 5/2017 (0.25%) participants were prescribed ≥4 antihypertensive medications, 4/2017 (0.20%) were prescribed 3 antihypertensive medications and had BP ≥140/90 mm Hg, and 1/2017 (0.05%) had a serum potassium <3.5 mmol/L plus hypertension defined as a BP ≥140/90 mm Hg or being prescribed antihypertensive medication. Nevertheless, we found that the presence and magnitude of subclinical PA in this general population was associated with an increased risk for MACEs. We also identified biochemical thresholds beyond which cardiovascular risk was greatest: a renin concentration ≤4.0 ng/L and ARR ≥70 pmol/L per ng/L. For participants with a low renin concentration or high ARR based on these thresholds, the MACE risk increased by over 2-fold. For comparison, the Endocrine Society PA guidelines suggest an ARR >144–192 pmol/L per ng/L as

the biochemical threshold to indicate a "positive" screen for PA.[6] Notably, only 67/2017 (3%) participants in this cohort had an ARR >144 pmol/L per ng/L, and only 43/2017 (2%) had an ARR >192 pmol/L per ng/L. It is worth mentioning that aldosterone, in itself, is not necessarily deleterious when regulated physiologically, explaining why aldosterone concentration, in isolation, was not associated with an increased risk of MACEs in our analyses.[9] Rather, our findings show that it is only renin-independent aldosterone production, as reflected by an elevated ARR, that is associated with an increased risk of MACEs. Furthermore, the majority of participants with an ARR ≥70 pmol/L per ng/L had a low or "suppressed" renin concentration, with 83% having a renin concentration ≤4.0 ng/L and 98% having a renin concentration ≤10 ng/L (a threshold for renin suppression used in previous studies).[37] This finding supports the pragmatic approach highlighted by previous work, in which a low renin concentration or activity alone (without aldosterone concentration and ARR) is sufficient to identify individuals likely to benefit from MR antagonist therapy.[35,36,38,39] It bears mention that there is great complexity in how renin and aldosterone are associated with cardiometabolic risk. For example, a low renin status has been reported variably to be associated with both increased[40–42] and decreased[43] insulin resistance. Independent of renin, a higher aldosterone concentration has also been reported to increase insulin resistance.[41,44,45]

An important finding from this study is that the increased MACE risk associated with the subclinical PA phenotype occurred in a BP-independent fashion. This BP-independent relationship parallels what is seen in overt and classically defined PA.[3–5] The BP-independent cardiovascular effects have been postulated to be attributable to extrarenal MR expression in tissues such as the myocardium and blood vessels, in which excessive activation promotes a host of deleterious effects, including endothelial damage, oxidative stress, inflammation, tissue remodeling, and fibrosis.[5] Overall, this study suggests that subclinical PA may serve as a major (and potentially modifiable) cardiovascular risk factor beyond just its effect on BP that goes almost completely undetected in modern-day clinical practice.

These findings support a paradigm shift in the approach to hypertension management. Previous work has demonstrated that the population of individuals with normal BP who go on to develop hypertension is enriched for subclinical PA.[9,19] This implies that much of routine hypertension, which has traditionally been labeled as "essential" or "primary," is actually MR-mediated hypertension attributable to subclinical PA. The present study now shows that these individuals with subclinical PA are also at disproportionately high risk for MACEs, independent of BP, similar to what is seen with overt and classically defined PA.[5] As there are proven effective therapies to target renin-independent aldosteronism, early detection of, and intervention for, subclinical PA may serve to mitigate cardiovascular risk for these individuals. For instance, MR antagonist medications along with dietary sodium restriction are effective in improving the clinical and biochemical abnormalities in overt PA, which may carry over to milder cases of PA pathophysiology (ie, subclinical PA) as well.[46] Moreover, the emerging aldosterone synthase inhibitors may provide a novel avenue by which to directly target dysregulated aldosterone production for this patient population.[47] Future interventional studies should focus on whether early diagnosis (eg, at the time of the initial diagnosis of hypertension or even prehypertension) and initiation of aldosterone-targeted therapy for patients with subclinical PA mitigates the excess cardiovascular risk associated with this condition.

The strengths and novelty of this study include a large, randomly sampled, and population-based cohort representative of the general Canadian adult population. Complex random stratified sampling and standardized data collection were employed within the CARTaGENE protocol, thus minimizing selection and ascertainment bias. Furthermore, as opposed to previous studies on subclinical PA that focused on intermediate measures of cardiovascular risk,[1,9–20] the present study showcases a link between subclinical PA and clinically relevant hard cardiovascular end points. Thus, this represents the most concrete evidence to date of the impact of subclinical PA on cardiovascular outcomes.

This study must be interpreted within the context of several limitations. First, the study design was observational. Thus, we were able to determine association but not causation. We adjusted for important factors known to influence aldosterone and renin concentrations along with MACE risk in our multivariable models; however, unmeasured confounding may still have been present. Second, the variables included in our statistical models were only captured at index, which precluded treating them as time-varying variables. Third, despite a large sample size, there were a limited number of outcome events, likely related to the participants being generally healthy with few comorbidities. Based on the low outcome event rate, we restricted the number of variables included in the multivariable models to avoid overfitting. Nevertheless, our various sensitivity analyses showed consistent results. Fourth, MACE end points were captured passively via the provincial RAMQ health care database. Although this has been demonstrated to accurately capture approximately 90% of MACE outcomes, 1 in 10 MACE outcomes may be missed.[31] Therefore, this may have led to a slight underestimation in MACE outcomes, though this would not be expected to vary by aldosterone/renin phenotypes. Fifth, these results may not be generalizable to all populations. For instance, the vast majority of study participants self-identified as being of White race. Given well-established differences

in aldosterone and renin biochemical profiles among Black individuals,[14] generalizability to predominantly Black populations may be limited. Sixth, aldosterone concentration was measured via immunoassay, which may overestimate its concentration relative to liquid chromatography-tandem mass spectrometry.[48] However, as the analyses focused on differences in aldosterone concentrations rather than comparison of absolute values or thresholds, the absolute aldosterone concentrations were less important than the relationship of aldosterone with renin and interindividual comparisons. Seventh, renin concentration may have lower accuracy than renin activity in individuals with low or very low renin, which is hypothesized to relate to some degree of interference from prorenin.[49] This may have attenuated the magnitude of associations between renin concentration (along with ARR) and MACE. Finally, aldosterone and renin concentrations were determined based on single measurements. These measurements are known to display significant intraindividual variability, which may have resulted in some degree of misclassification, likely attenuating the measured associations.[50]

In summary, this prospective population-based study demonstrates that subclinical PA in the general adult population is associated with an increased risk for MACEs. This provides compelling evidence linking the presence and magnitude of subclinical PA to clinically relevant hard cardiovascular end points. The historical approach to PA fails to capture the expansive severity spectrum of renin-independent aldosteronism that extends across a much broader population base with important clinical implications. Pragmatically, a low renin phenotype should serve as a proxy for subclinical PA and heightened risk for MACEs that may benefit from early targeted therapy. Future interventional research studies are necessary to determine whether early initiation of MR antagonists for the subclinical PA phenotype mitigates cardiovascular risk for this large but currently unrecognized population.

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Supplemental Material

Figure S1

Tables S1–S4

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