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**Risky business: a single-centre cross-sectional analysis of calculated cardiovascular risk in patients with primary aldosteronism and essential hypertension**

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#### ABSTRACT

**Objectives**

Primary aldosteronism (PA), the most common endocrine cause of hypertension, is associated with a higher risk of cardiovascular disease (CVD) than blood pressure (BP)-matched essential hypertension (EH). We aimed to compare the calculated risks of CVD in patients who had hypertension with PA or EH using CVD risk calculators, hypothesising that they will fail to recognise the increased CVD risk in PA.

**Design**

Cross-sectional analysis.

**Setting**

An endocrine hypertension service in Victoria, Australia.

**Participants**

Patients who had hypertension without CVD referred for the investigation of hypertension.

**Outcome measures**

Calculated 5-year or 10-year CVD risk as predicted by the National Vascular Disease Prevention Alliance (NVDPA) algorithm, Framingham Risk Score, Pooled Cohort Equations and QRISK3.

**Results**

Those with PA (n=128) and EH (n=133), did not differ significantly in their calculated CVD risks with the NVDPA algorithm (moderate-to-high 5-year risk 36/100 vs 45/99, p=0.17); the Framingham Risk Score (median 10-year risk 7.72% (4.43%–12.95%) vs 6.84% (3.85%–10.50%), p=0.14); the Pooled Cohort Equations (median 10-year risk 9.45% (4.36%–15.37%) vs 7.90% (2.09%–11.31%), p=0.07); and QRISK3 (median 10-year risk 11.31% (7.22%–20.29%) vs 12.47% (5.10%–19.93%), p=0.51). Similarities persisted on regression analyses accounting for systolic BP.

**Conclusions**

CVD risk algorithms do not reflect the increased risk of CVD in patients with PA, and likely underestimate the true risk of CVD among those with PA. Screening for PA, in addition to using the CVD risk algorithm in patients who had hypertension, may facilitate the targeted treatment of PA and minimisation of cardiovascular risk in affected individuals.

#### STRENGTHS AND LIMITATION OF THIS STUDY

- This study examined clinical participants with hypertension who had rigorous and standardised testing for secondary hypertension.
- Numerous cardiovascular disease risk algorithms that are commonly used across the world were applied.
- Due to retrospective study design, prospective data on actual cardiovascular events were not observed.

#### INTRODUCTION

Cardiovascular disease (CVD) is responsible for significant morbidity and mortality across the global population. To anticipate and manage this risk, the risk of developing CVD among individuals without CVD may be predicted from demographic, blood pressure (BP) and other clinical characteristics using various CVD risk algorithms. However, none of these algorithms consider primary aldosteronism (PA), a syndrome of aldosterone excess (responsible for 3–13% of hypertension in primary care, and up to 30% in specialist clinics) that is associated with higher cardiometabolic risk than BP-matched essential hypertension (EH).

Those with PA experience aldosterone-mediated damage to the heart, kidneys and arterial walls, above and beyond hypertension-mediated injury. One meta-analysis demonstrated greater subclinical atherosclerosis in PA than EH, while another found that, at a median 8.8 years after diagnosis, patients with PA compared with patients with EH had a greater incidence of stroke (OR 2.58, 95% CI 1.93 to 3.45), coronary artery disease (OR 1.77, 95% CI 1.10 to 2.83), atrial fibrillation (OR 3.52, 95% CI 2.06 to 5.99), heart failure (OR 2.05, 95% CI 1.11 to 3.78), diabetes (OR 1.33, 95% CI 1.01 to 1.74), metabolic syndrome (OR 1.53, 95% CI 1.22 to 1.91) and left ventricular hypertrophy (OR 2.29, 95% CI 1.65 to 3.17). PA has also been shown to involve greater interstitial fibrosis and...
arteriosclerosis of renal vasculature than EH.\textsuperscript{11} Despite the known excess of adverse outcomes, screening for PA among patients with hypertension remains very low, such that less than 1\% of people with PA are actually diagnosed.\textsuperscript{12}

If diagnosed, PA is a highly treatable condition using mineralocorticoid receptor (MR) antagonists which specifically block aldosterone action, or, if caused by a unilateral adrenal adenoma, curable by laparoscopic adrenalectomy.\textsuperscript{13} The incidence of adverse cardiovascular events among patients with PA adequately treated with MR antagonists may decrease to that of patients with EH,\textsuperscript{6} although this may depend on the degree of renin suppression\textsuperscript{14}; and it may decrease even lower if PA is surgically cured.\textsuperscript{14} Although these targeted therapies are more effective for treating PA than empirical antihypertensive medications,\textsuperscript{13} PA remains severely underdiagnosed.\textsuperscript{7,8,15} Hence, these individuals may have their CVD risk assessed using the same CVD risk algorithm as the general population.

CVD risk algorithms suggest treatment in accordance with overall CVD risk (as calculated from individual risk factors), with different algorithms used across different countries.\textsuperscript{2-5} The most widely used algorithm in Australia is that outlined in 2012 by the National Vascular Disease Prevention Alliance (NVDPA), scoring Australians as low-risk (<10\%), moderate-risk (10–15\%) or high-risk (>15\%) of developing CVD in the next 5 years.\textsuperscript{2} BP lowering therapy is recommended for those classified as high-risk, as well as those classified as low-to-moderate risk fulfilling additional criteria (eg, BP persistently ≥160/100 mm Hg).\textsuperscript{2} Other algorithms outlined in table 1 include the widely used Framingham Risk Score predicting the risk of coronary heart disease, the Pooled Cohort Equations predicting the risk of ‘hard’ atherosclerotic CVD, and QRISK3 predicting the risk of CVD—all of which predict an individuals’ likelihood of developing CVD in the next 10 years.\textsuperscript{3,5} Two-thirds of Australian general practitioners use at least one CVD risk algorithm,\textsuperscript{16} with evidence indicating that the results of these algorithms significantly influence clinical decision-making (eg, providing a greater level of care to those with increased calculated CVD risk).\textsuperscript{17}

However, the accuracy of these algorithms for predicting CVD risk among patients with PA, who often lack typical cardiovascular risk characteristics,\textsuperscript{9} has only been explored in one previous study.\textsuperscript{18} Using the Framingham Risk Score, Lin et al,\textsuperscript{18} a retrospective cohort study of 461 patients with PA and 553 patients with EH, found only a small although statistically significant difference in 10-year CVD risk in those with PA versus EH (mean 12.8\% vs 10.9\%).\textsuperscript{18} Notably, the actual rate of cardiovascular events over 10 years in patients with PA was much higher at 20.6\%, suggesting CVD risk algorithms may be systematically underestimating cardiovascular risk in patients with PA.\textsuperscript{18}

To further explore the potential gap between calculated and real risk of CVD in patients with PA, we aimed to compare calculated CVD risk (using the NVDPA algorithm; the Framingham Risk Score; the Pooled Cohort Equations; and QRISK3) in patients with PA and EH, hypothesising similar risk predictions despite the known disparity in actual cardiovascular outcomes.

**METHODS**

**Design and participants**

We conducted a cross-sectional study of patients who had hypertension referred for the investigation of suspected secondary causes of hypertension at an outpatient endocrine hypertension service in Victoria, Australia. To evaluate for PA, a screening test for aldosterone and renin was performed twice. If positive, as defined by an aldosterone to renin ratio >70 (pmol/L)/(mU/L), saline suppression testing was performed. Following the infusion of 2 L saline over 4 hours, PA was confirmed if plasma aldosterone remained >140 pmol/L (recumbent position) or >170 pmol/L (seated position) where aldosterone was measured using immunoassay. Once PA was confirmed, adrenal CT and adrenal vein sampling were conducted to subtype the condition as bilateral or unilateral. If further testing was not possible, a small minority of patients with abnormal aldosterone and renin results were diagnosed with PA on strong clinical suspicion.

CVD risk factors from the first appointment for all patients were extracted in June 2021. Patients were excluded from this study if PA could not be confirmed or excluded; if other endocrine causes of hypertension (comprising <1\% of patients) were present; or if pre-existing CVD (myocardial infarction or stroke) was present during the patient’s first consultation. Patients included in the study attended their first appointment between 21 July 2016 and 11 June 2020.

**Patient and public involvement**

Given the retrospective methodology, patients and the public were not involved in this study.

**Data collection**

All data were retrospectively collected from electronic medical records. For systolic BPs (SBPs) and diastolic BPs (DBPs), the mean of two supine BP measurements (Omron automated BP Monitor, HEM-7156) taken during the first appointment was taken as their representative BP. In a small number of patients, only one BP measurement was recorded (in which case measurement was used) or none recorded (in which case a BP measurement documented in the patient’s referral letter was used). Patients’ ethnicities were classified as per the categories used in QRISK3.\textsuperscript{5,19}

**Statistical analysis**

Analyses were performed using R V.4.1.2 for Windows with tidyverse packages. Descriptive statistics of all categorical data were summarised using frequencies (with percentages) for
categorical variables; mean (with SD) for continuous/interval data, or median (with 25th and 75th percentiles (IQR)) if skewness was present. Normality for each variable was assessed using the Shapiro-Wilk test (with p<0.05 indicating non-normality).

Categorical data were compared between groups using \( \chi^2 \) tests and two-tailed Fisher’s exact tests (when there were expected cell frequencies <5). Continuous data were compared between groups using t-tests (for normally-distributed continuous variables), Mann-Whitney U tests (for skewed continuous variables), and Tobit regression.
CVD risk calculations

All risk predictions were calculated according to the published algorithms, and within the sample matching the validated populations (as per table 1). For the NVDPA algorithm, patients ≥45 years old were first classified as high-risk if they met specific criteria as published, following which continuous 5-year percentage risk scores, as per Anderson et al., were calculated for the remaining patients. The scores were then categorised as low-risk (scores <10%), moderate-risk (scores 10–15%) and high-risk (scores >15%). As recommended by the NVDPA guidelines, an age of 74 years was assumed for patients aged over 74 years; moreover, when data on left ventricular hypertrophy on ECG were unavailable, it was inputted into the NVDPA algorithm as unknown. This algorithm was not applied to patients under 45 years, as it has not been validated in this age group.

For the Framingham Risk Score, the β-coefficient, total-cholesterol version of the algorithm was used. For the Pooled Cohort Equations, coefficients differed between sexes and between white and African participants, as described in source literature. For QRISK3, a neutral Townsend deprivation score of 0 was assumed for all participants, since none resided in the UK. All algorithms were coded directly into R as per the source literature, with the exception of QRISK3, for which the validated R package ‘QRISK3’ was used.

DISCUSSION

In this study, patients with PA and EH were found to have similar calculated CVD risks using the NVDPA algorithm, the Framingham Risk Score, the Pooled Cohort Equations and QRISK3. The lack of differences in calculated CVD risk between PA and EH populations persisted even after accounting for differences in SBP. Given the widespread use of CVD risk algorithms and the high prevalence of undiagnosed PA in the community, this underestimation of cardiovascular risk among patients with PA represents a serious public health issue.

It may not be surprising that the calculated CVD risk was similar between patients with PA and EH because they had similar mean age, smoking status, body mass index, SBP, DBP, cholesterol and triglycerides. However, the patients were not matched for these characteristics (for estimated glomerular filtration rate (eGFR), which had a maximum value of 90 mL/min/1.73 m²).

To account for variations in SBP, logistic regression (with NVDPA moderate-to-high risk as the outcome) and linear regression (for the Framingham Risk Score, the Pooled Cohort Equations and QRISK3) were used. Predictor variables in regression models were PA status (0=EH and 1=PA), deviation in SBP (defined as the absolute deviation of the patient’s representative SBP from the sample’s median SBP) and the interaction between PA and deviation in SBP (the two predictors multiplied together). The threshold for statistical significance for all tests was p<0.05.

RESULTS

Following the exclusion of 240 patients without a clear PA or EH diagnosis, and 23 patients with pre-existing CVD (18 with PA and 5 with EH), a total of 261 individuals were included in this study, comprising 128 (49.0%) patients with PA and 133 (51.0%) patients with EH. Of those with PA, 37 (28.9%) had unilateral PA, 61 (47.7%) had bilateral PA and 30 (23.4%) had PA of indeterminate subtype (17 declined further testing; 10 were awaiting tests; 2 had uninterpretable results; and 1 was deemed clinically inappropriate for further testing).

The demographic and clinical characteristics, presented in table 2, were similar for patients with PA and those with EH, with the exception that patients with PA were more likely to have a history of type 2 diabetes mellitus, and use more antihypertensive medications. As expected, patients with PA also had higher aldosterone, lower renin, higher aldosterone/renin ratio, and lower potassium levels than patients with EH.

Calculated CVD risk among patients with PA and EH

The NVDPA algorithm was applied to the n=199 participants aged ≥45 years old (n=100 with PA and n=99 with EH). Of these, n=118 (59.3%) were classified as low risk; n=38 (19.1%) were classified as moderate risk; and n=43 (21.6%) were classified as high risk. The likelihood of being classified as moderate-to-high risk did not significantly differ between patients with PA and EH (n=36 vs n=45, p=0.17). After accounting for SBP on logistic regression, a diagnosis of PA did not significantly alter the likelihood of moderate-to-high risk classification (table 3).

The Framingham Risk Score was applied to the 242 participants aged 30–74 years old (n=121 with PA and n=121 with EH). The median 10-year risk was 7.11% (IQR 4.04%–11.34%), with no statistically significant difference identified between patients with PA and EH (median 7.72% (IQR 4.43%–12.95%) vs 6.84% (IQR 3.85%–10.50%), p=0.14).

The Pooled Cohort Equations were applied to the n=141 Caucasian and African participants aged 40–79 years old (n=78 with PA and n=63 with EH). The median 10-year risk was 8.24% (IQR 3.36%–15.04%), with no significant difference identified between patients with PA and EH (median 9.45% (IQR 4.36%–15.37%) vs 7.90% (IQR 2.09%–14.73%), p=0.07).

The QRISK3 algorithm was applied to the n=217 participants aged 25–84 years old (n=120 with PA and n=97 with EH). The median 10-year risk for CVD was 11.53% (6.56%–20.15%), with no significant difference identified between patients with PA and EH (median 11.31% (IQR 7.22%–20.29%) vs 12.47% (IQR 5.10%–19.93), p=0.51).

After accounting for SBP on linear regression, a diagnosis of PA did not significantly alter the 10-year risk predicted by the Framingham Risk Score, the Pooled Cohort Equations or QRISK3 (table 4).
and the findings reflect the actual lack of difference in the variables that currently determine CVD risk. None of the CVD risk algorithms considered a diagnosis of PA or levels of aldosterone, renin or aldosterone/renin ratio as markers of CVD risk even though they have established associations with cardiovascular risk.6 22 23

Our findings differed to Lin et al18 in two respects. First, our sample had much lower calculated CVD risks among both patients with PA and EH. This is attributable to our sample being younger, having lower BP and including a smaller proportion who smoke or take antihypertensive medications. Taken together with lower aldosterone

| Table 2 | Demographic, clinical and biochemical characteristics of overall sample, patients with PA, and patients with EH |
|---------|------------------------------------------------------------------------------------------------------|
| Overall sample | Patients with PA | Patients with EH | Comparison (PA vs EH) |
| Age, mean (SD) years | 52.5 (12.8) | 53.7 (11.7) | 51.2 (13.8) | p=0.12 |
| Female, n (%) | 148 (56.7) | 67 (52.3) | 81 (60.9) | p=0.16 |
| Caucasian ethnicity, n (%) | 149 (66.8) | 74 (57.8) | 75 (56.4) | p=0.82 |
| Current smoking, n (%) | 19 (7.3) | 11 (8.6) | 8 (6.0) | p=0.42 |
| BMI, median (IQR) kg/m² | 28.7 (25.7–33.1) | 28.6 (25.6–32.7) | 28.9 (25.8–33.2) | p=0.69 |
| Systolic blood pressure, median (IQR) | 148 (134–160) | 148 (136–160) | 147 (134–160) | p=0.36 |
| Diastolic blood pressure, median (IQR) | 91 (84–98) | 92 (85–100) | 90 (82–96) | p=0.09 |
| Number of antihypertensive medications used, median (IQR) | 1 (0–2) | 2 (1–3) | 1 (0–1) | p<0.001 |
| Number using any antihypertensive medication/s, n (%) | 167 (64.0) | 98 (76.6) | 69 (51.9) | p<0.001 |
| Left ventricular hypertrophy on ECG, n (%) | 12/75 (16) | 9/54 (16.7) | 3/21 (14.3) | p=0.08 |
| History of hypercholesterolaemia, n (%) | 56 (21.5) | 32 (25.0) | 24 (18.0) | p=0.17 |
| History of type 2 diabetes mellitus, n (%) | 24 (9.2) | 18 (14.1) | 6 (4.5) | p=0.008 |
| Family history of CAD, n (%) | 12 (4.6) | 6 (4.7) | 6 (4.5) | p=0.95 |
| Aldosterone, median (IQR) pmol/L | 411 (278–584) | 524 (403–738) | 329 (219–444) | p<0.001 |
| Renin, median (IQR), mIU/L | 5.7 (2.7–15.6) | 4.0 (2.0–5.4) | 13.8 (5.4–23.3) | p<0.001 |
| Aldosterone/renin ratio, median (IQR) (pmol/L)/(mIU/L) | 87.9 (23.9–145.7) | 129.1 (92.8–200.5) | 24.3 (13.8–54.8) | p<0.001 |
| Potassium, median (IQR) | 4.2 (3.9–4.5) | 4.1 (3.7–4.3) | 4.4 (4.2–4.6) | p<0.001 |
| eGFR, median (IQR) mL/min/1.73m² | 90 (79–90) | 90 (79–90) | 90 (80–90) | p=0.34 |
| Total cholesterol, mean (SD) | 5.20 (1.04) | 5.18 (0.99) | 5.22 (1.08) | p=0.75 |
| HDL, median (IQR) | 1.39 (1.10–1.70) | 1.34 (1.10–1.70) | 1.40 (1.17–1.70) | p=0.49 |
| LDL, mean (SD) | 3.10 (0.87) | 3.09 (0.82) | 3.10 (0.92) | p=0.95 |
| Triglycerides, median (IQR) | 1.30 (0.90–1.75) | 1.42 (0.90–1.70) | 1.30 (0.90–1.80) | p=0.87 |

Data was missing for aldosterone and renin (one patient), and LDL and triglycerides (two patients). Percentages expressed are relative to the group described in the column (overall sample, patients with PA or patients with EH). BMI, body mass index; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; EH, essential hypertension; HDL, high density lipoprotein; LDL, low density lipoprotein; PA, primary aldosteronism; T2DM, type 2 diabetes mellitus.

| Table 3 | Logistic regression for moderate-to-high risk classification with the National Vascular Disease Prevention Alliance algorithm |
|---------|------------------------------------------------------------------------------------------------------|
| Unadjusted | Adjusted |
| OR (95% CI) | P value | aOR (95% CI) | P value |
| PA status | 0.68 (0.38 to 1.19) | 0.18 | 0.57 (0.22 to 1.46) | 0.25 |
| Absolute deviation of systolic BP from median systolic BP | 1.02 (1.00 to 1.05) | 0.07 | 1.02 (0.98 to 1.05) | 0.32 |
| Interaction term between PA status and absolute deviation of systolic BP from median systolic BP | – | – | 1.01 (0.96 to 1.06) | 0.67 |

Model included n=199 individuals, which included 36/100 patients with PA and 45/99 patients with EH classified as moderate-to-high risk. aOR, adjusted OR; BP, blood pressure; PA, primary aldosteronism.
levels, the data suggest our PA cohort may have been diagnosed earlier in the disease process than study participants in Lin et al.\(^\text{18}\) Second, while Lin et al.\(^\text{18}\) found a significant difference in calculated Framingham Risk Scores between patients with PA and EH, we did not. This may be because our patients with PA and EH had similar clinical characteristics, whereas their patients with PA had significantly higher BP than those with EH. Moreover, our analyses adjusted for SBP, whereas Lin et al.\(^\text{18}\) applied an unadjusted comparison only. Overall, compared with previous literature, our findings are likely more representative of the population of individuals with newly diagnosed hypertension.

With PA being severely underdiagnosed in Australia and worldwide,\(^\text{15}\) it is likely that patients with hypertension, including those with undiagnosed PA, have CVD risk estimated using tools designed for the general population. This is despite the known excess of adverse outcomes in those with PA.\(^\text{6-8}\) Misclassification of risk for patients with PA compromises their immediate treatment and long-term management, given that these tools strongly influence the care provided by many clinicians.\(^\text{16-17}\) Clinicians may decide to neither initiate BP lowering therapy, nor screen for secondary causes of hypertension, in patients with lower calculated CVD risk. Moreover, patients will not receive the targeted treatment necessary to mitigate their actual cardiovascular risk if they have unrecognised PA.\(^\text{13}\)

Since CVD risk algorithms do not reflect the true risk of CVD among those with PA (who remain largely undiagnosed),\(^\text{6-8}\) clinicians should use these algorithms in combination with a detailed clinical assessment, and should consider screening for PA in the majority of newly-diagnosed patients who had hypertension. This will provide valuable additional information about the true risk of CVD in the affected patients and allow for appropriate personalised therapy.

This study had four key limitations. First, the retrospective design meant that prospective data on actual cardiovascular events could not be observed and compared with calculated CVD risks. Nonetheless, there is compelling published evidence demonstrating the higher incidence of cardiovascular events associated with PA.\(^\text{6-9,10}\) Second, the algorithms examined were heterogeneous in their definition of adverse outcomes, validated populations and time frames of prediction (table 1), making them difficult to compare in the absence of prospective outcome data. However, despite this heterogeneity, all algorithms independently reached a similar conclusion regarding CVD risk between the two groups, failing to discriminate the higher risk associated with PA. Third, our sample was from a single centre and therefore smaller than the preceding

| Table 4 | Linear regressions for 10-year risk (continuous %) as per the Framingham Risk Score, Pooled Cohort Equations and QRISK3 algorithm |
|---------|---------------------------------------------------------------|
|         | Unadjusted | Adjusted |
|         | \(\beta\)-coefficient (95% CI) | P value | \(\beta\)-coefficient (95% CI) | P value |
| Framingham Risk Score | | | | |
| PA status | 1.39 (–0.27 to 3.05) | 0.10 | –0.32 (–2.99 to 2.34) | 0.81 |
| Absolute deviation of systolic BP from median systolic BP | 0.07 (–0.003 to 0.14) | 0.06 | 0.01 (–0.09 to 0.11) | 0.82 |
| Interaction term between PA status and absolute deviation of systolic BP from median systolic BP | – | – | 0.12 (–0.02 to 0.27) | 0.09 |
| Pooled Cohort Equations | | | | |
| PA status | 2.89 (–0.72 to 6.51) | 0.12 | 3.27 (–2.62 to 9.16) | 0.27 |
| Absolute deviation of systolic BP from median systolic BP | –0.002 (–0.18 to 0.17) | 0.98 | 0.02 (–0.22 to 0.25) | 0.88 |
| Interaction term between PA status and absolute deviation of systolic BP from median systolic BP | – | – | –0.03 (–0.38 to 0.32) | 0.87 |
| QRISK3 | | | | |
| PA status | 0.48 (–2.44 to 3.39) | 0.75 | –2.57 (–7.24 to 2.09) | 0.28 |
| Absolute deviation of systolic BP from median systolic BP | 0.24 (0.11 to 0.36) | <0.001 | 0.11 (–0.10 to 0.31) | 0.31 |
| Interaction term between PA status and absolute deviation of systolic BP from median systolic BP | – | – | 0.21 (–0.05 to 0.47) | 0.12 |

Each of the models was run independently. The Framingham Risk Score model included 242 participants; the Pooled Cohort Equations model included 141 participants; and the QRISK3 model included 217 participants. BP, blood pressure; PA, primary aldosteronism.
study, but all our patients underwent standardised and rigorous testing for secondary hypertension. Fourth, selection bias has occurred given more patients with PA than patients with EH were excluded because of already having developed CVD; however, this is simply in keeping with the known greater actual CVD risk in PA compared with EH, highlighting the importance of earlier detection of CVD risk in PA.

In conclusion, we found that the heightened cardiovascular risk of PA is not identified by four widely used CVD risk algorithms. Clinicians and patients need to be aware of this limitation of CVD risk algorithms. Clarification of PA status in individuals with hypertension can provide additional information regarding individualised cardiovascular risk. Acknowledging the high prevalence of undiagnosed PA, and the significant rate of cardiovascular complications observed in PA, a more comprehensive approach is needed to ensure those with PA are diagnosed and appropriately managed.

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