Angiotensin Biomarkers for Drug Monitoring and Primary Aldosteronism Screening under Triple Anti-Hypertensive Therapy

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ABSTRACT

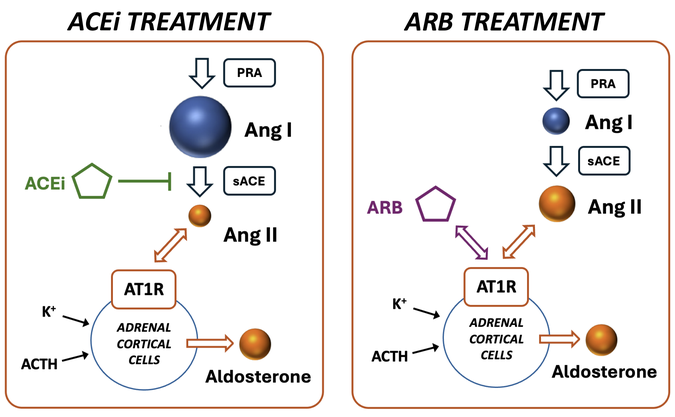
Background: Contemporary guidelines endorse screening for primary aldosteronism (PA) in patients receiving first-line antihypertensive therapy. However, angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) substantially alter renin and angiotensin peptides, complicating interpretation of PA biomarkers and obscuring drug non-adherence. Practical guidance for PA detection under RAAS blockade remains undefined.

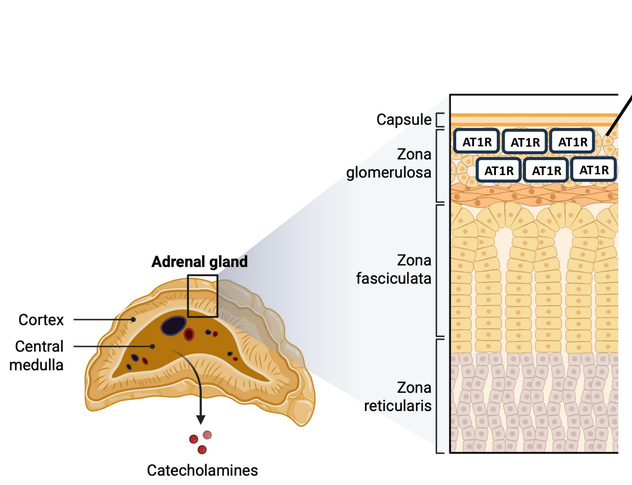
Methods: In the Prospective Cohort: Resistant Hypertension (PRIO) study, patients with uncontrolled or resistant hypertension were transitioned to standardized triple therapy including an ACEi or ARB. At follow-up, standard biochemical screening for PA was performed with referral for adrenal vein sampling as indicated. Patients not meeting diagnostic criteria were classified as uncontrolled hypertension (UHTN). Using a validated LC-MS/MS platform, we retrospectively quantified angiotensin (Ang) peptides and aldosterone to evaluate drug class-specific effects on Ang II, ACE-Q (ratio of Ang II to Ang I), and the aldosterone-Ang II ratio (AA2-R). Drug adherence was determined by direct quantification of antihypertensive agents in serum (reference method). Receiver operating characteristic analyses defined cut-offs for ACE-Q and Ang II to detect ACEi and ARB adherence, respectively. "Clean" adherence thresholds were derived in UHTN patients without PA. Among biomarker-adherent patients, we established ACEi- and ARB-specific AA2-R cut-offs for PA detection and constructed a sequential clinical algorithm integrating drug monitoring and PA screening.

Results: ACEi suppressed ACE-Q, and ARBs increased concentrations of Ang II, confirming mechanistic specificity of these two drug classes. ACE-Q and Ang II robustly identified ACEi and ARB adherence, respectively, with good performance sensitivity and specificity (ACE-Q < 1.0 pM/pM; 100% and 99%; Ang II > 163 pM; 80% and 94%). Drug class – specific AA2-R thresholds for PA differed substantially between ACEi- and ARB-treated patients (20.41 and 2.00 pM/pM with respective sensitivity and specificity of 100% and 82%, and 92% and 98%). The integrated algorithm demonstrated excellent performance for simultaneous adherence assessment and PA detection.

Conclusions: Angiotensin profiling enables mechanism-based drug monitoring and drug class-specific PA screening under triple therapy. This approach reduces ambiguity introduced by RAAS blockade and non-adherence, addresses a critical gap in current guidelines, and advances precision management of resistant hypertension.

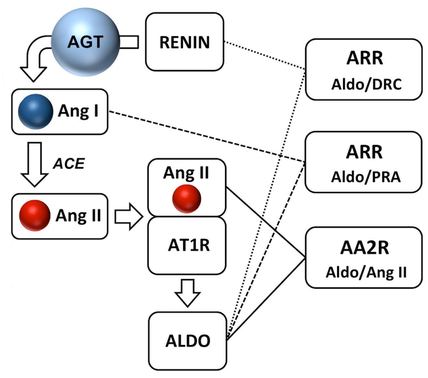
BACKGROUND





Angiotensin II directly binds to highly expressed AT1R on zona glomerulosa cells. **Sinusoidal endothelia** within the adrenal cortex provide **full and direct access access of all solulble RAAS components (Enzymes and Hormones) and anti-hypertensive drugs** to AT1 receptors on ZG-cells. Competition of equilibrium Ang II with ARBs for receptor binding sites directly affects aldosterone synthesis and secretion into the blood stream.

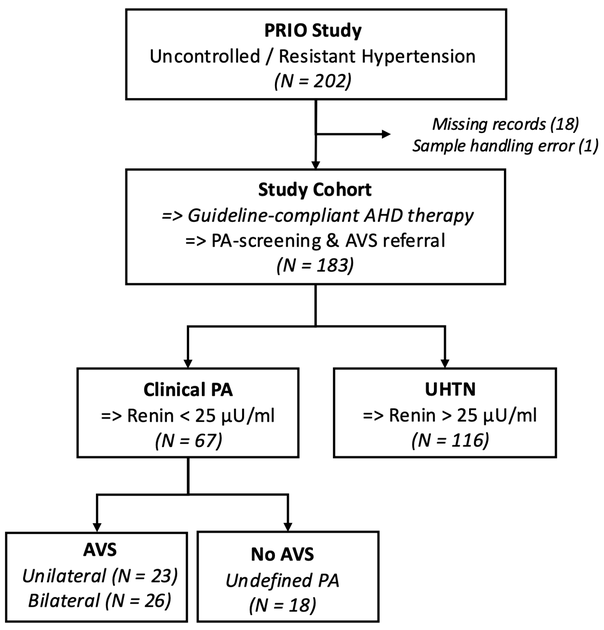
DIAGNOSTIC RATIOS FOR PA



PRIMARY ALDOSTERONISM (PA)

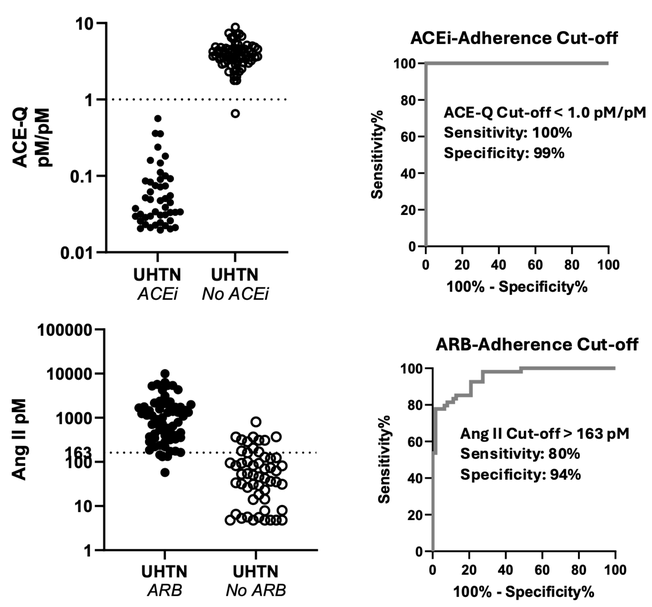
… is a frequent form of hypertension that is characterized by Ang II independent pathologic secretion of Aldosterone, that does not respond to treatment with ACEi or ARBs. The ratio between Aldosterone and Ang II (AA2-Ratio) serves as the only effector hormone based clinically available screening tool for PA. Biomarkers are derived from the levels of the effector hormones Ang I, Ang II and Aldosterone (ALDO+ Test, aTENSION.life) further delivering markers for renin activity (PRA-Q) and angiotensin converting enzyme activity (ACE-Q) allowing for simultaneouys assessment of pharmacologic drug effects. Primary aldosteronism is associated with volume-induced hypertension, renin hyperfiltration and suppression of renin secretion. ACE inhibitors and ARBs interfere with Ang II mediated aldosterone secretion at distinct molecular sites, resulting in specific effects on optimal cut-offs for PA screening during anti-hypertensive therapy.

STUDY COHORT



Clinical work-up of the study cohort. Patients with uncontrolled or resistant hypertension were enrolled in the Prospective Cohort: Resistant Hypertension (PRIO), with 183 patients included in the current study. Medications were adjusted to guideline-compliant therapy including ACE inhibitors or ARBs, after which patients underwent assessment for PA. Patients were initially screened on the basis of low renin (< 25 µIU/mL; n=78), with additional considerations such ARR, serum potassium values, and medical history determining the final clinical diagnosis of PA (n=67) and referral for AVS. There were 52 patients that agreed to undergo AVS, and 49 successful procedures. Patients were subtyped as unilateral or bilateral and those that declined AVS were classified as undefined PA. There was no further diagnostic workup in patients not meeting the clinical diagnosis of PA.

DETECTION OF DRUG EFFECTS/ADHERENCE



Determination of cut-off values of angiotensin-based biomarkers for detection of adherence to ACEi and ARB therapy in UHTN patients. Upper panel: Dot-plot of ACE-Q in UHTN patients with ACEi drug confirmed or absent in serum. Dotted line is the cut-off of ACE-Q < 1 pM/pM derived from B) ROC curve of ACE-Q for the detection of ACEi-adherence in RHTN patients prescribed ACEi and confirmed adherent with serum drug levels (46) versus UHTN patients confirmed to have no detectable serum concentrations of ACEi (70, includes 4 non-adherent to ACEi, and 66 prescribed ARBs). Lower panel: Dot-plot of Ang II concentrations in RHTN patients with ARB drug confirmed or absent (based on serum drug levels). Dotted line is the cut-off of Ang II > 163 pM derived from D) ROC curve of Ang II for the detection of ARB-adherence in UHTN patients prescribed ARB and confirmed adherent with serum drug levels (62) versus UHTN patients confirmed to have no detectable serum concentrations of ARB (55, includes 5 non-adherent to ARB, and 50 prescribed ACEi).

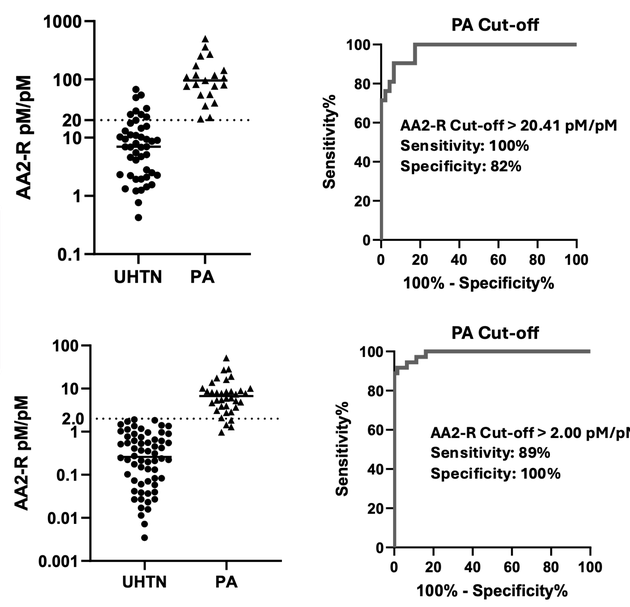
ANGIOTENSIN BIOMARKERS

[Ang I + Ang II] => PRA-Q

[Ang II] / [Ang I] => ACE-Q

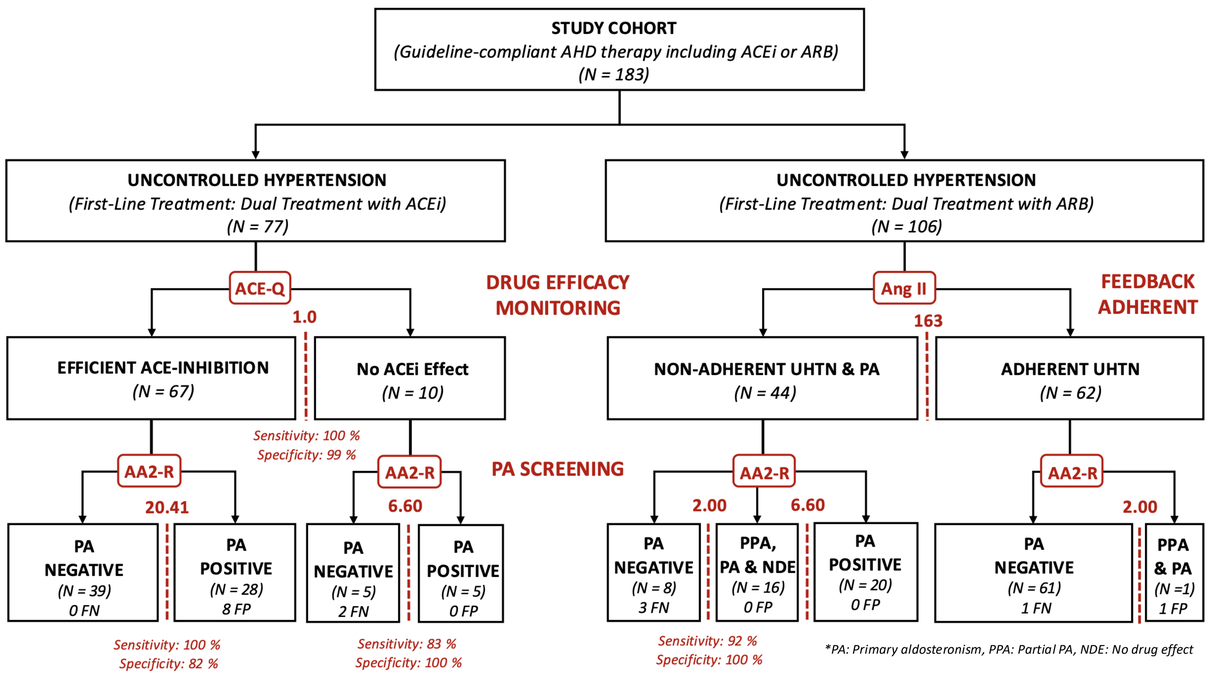
[Aldo] / [Ang II] => AA2-Ratio

DRUG SPECIFIC CUT-OFFS FOR PA-SCREENING



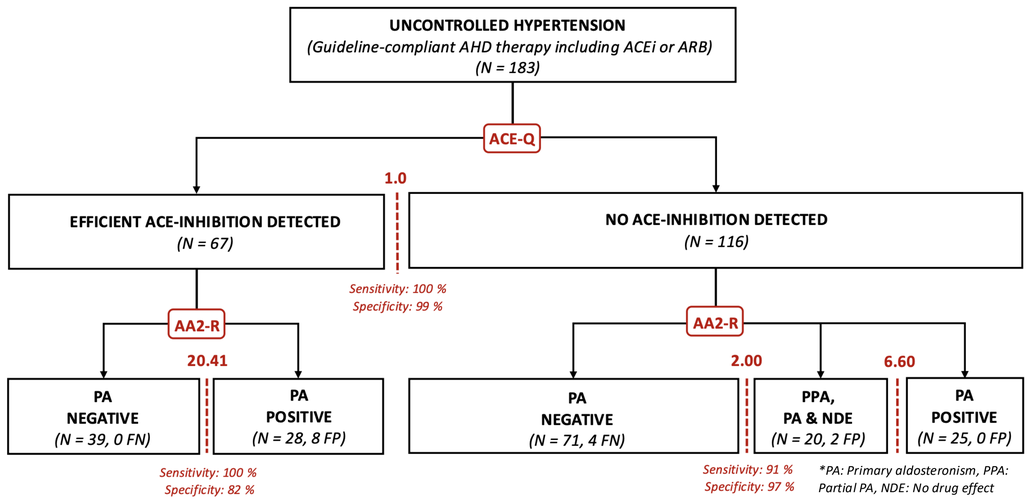
Detection of PA using the AA2-R in medication-adherent patients. A) Dot-plot of AA2-R in UHTN and PA patients adherent to ACEi treatment based on serum drug quantification. Dotted line is the cut-off of 20 pM defined in B) ROC curve of AA2-R for the prediction of PA in ACEi-adherent PA (21) versus RHTN (46) patients. AA2-R > 20 predicted PA with 100% sensitivity and 82% specificity. C) Dot-plot of AA2-R in RHTN and PA patients adherent to ARB treatment based on serum drug quantification. Dotted line is the cut-off of 1.84 defined in D) ROC curve of AA2-R for the prediction of PA in ARB-adherent RHTN (58) versus PA (35) patients. AA2>R 2.0 predicted PA with 88.9% sensitivity and 100% specificity.

PA SCREENING PERFORMANCE (PRESCRIPTION-BASED DRUG ASSIGNMENT)



PA-Screening Performance: 9 FPs & 3 FNs

PA SCREENING PERFORMANCE (ANGIOTENSIN-BASED DRUG ASSIGNMENT)



PA-Screening Performance: 10 FPs & 4 FNs

CONCLUSIONS

- Drug class specific cut-offs for the AA2-Ratio improve PA detection performance in uncontrolled hypertension on potentially interfering drug treatments
- Prescription-based drug class assignment and direct angiotensin-based drug class detection show comparable overall PA-screening performance in a simplified diagnostic process
- Simplified algorithm offers universally applicable clinical approach for simultaneous drug efficacy monitoring and PA screening on anti-hypertensive therapy with drug combinations including ACEi and ARBs
- ACEi treatment enables advantaged and highly simplified diagnostic path for simultaneous drug efficacy monitoring and screening for autonomous aldosterone secretion via Ang II derived biomarkers (ACE-Q, AA2-Ratio)