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Cardiovascular risk markers in patients with primary aldosteronism: A systematic review and meta-analysis of literature studies

Pasquale Ambrosino [a,1,2], Roberta Lupoli [a,1,2], Anna Tortora [a,2], Marianna Cacciapuoti [a,2], Gelsy Arianna Lupoli [a,2], Paolo Tarantino [a,2], Aurelio Nasto [b,2], Matteo Nicola Dario Di Minno [c,d,*,2]

[a] Department of Clinical Medicine and Surgery, Federico II University, Naples, Italy
[b] Department of Surgery, Unit of General Surgery and Oncology, Andrea Tortora Hospital, Pagani, Italy
[c] Department of Advanced Biomedical Sciences, Division of Cardiology, Federico II University, Naples, Italy
[d] Unit of Cell and Molecular Biology in Cardiovascular Diseases, Centro Cardiologico Monzino, IRCCS, Milan, Italy

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ABSTRACT

Background/objectives: Several studies reported an increased cardiovascular (CV) morbidity and mortality in patients with primary aldosteronism (PA). We performed a meta-analysis on the impact of PA on major markers of CV risk.

Methods: Studies on the relationship between PA and common carotid artery intima-media thickness (CCA-IMT), prevalence of carotid plaques, flow-mediated dilation (FMD), nitrate-mediated dilation (NMD), pulse-wave velocity (PWV), augmentation index (AIx), and ankle-brachial index (ABI) were systematically searched in the PubMed, Web of Science, Scopus and EMBASE databases.

Results: 12 case–control studies (445 cases, 472 controls) were included. Compared to subjects with essential hypertension (EH), PA patients showed a higher CCA-IMT (MD: 0.12 mm; 95% CI: 0.09, 0.16; $P < 0.00001$), and a higher aortic-PWV (272 cases and 240 controls, MD: 1.39 m/s; 95% CI: 0.90, 1.87; $P < 0.00001$). In contrast, non-significant differences were found in AIx and AIx normalized to a heart rate of 75 beats per minute (AIx@75). When compared to normotensive subjects, PA patients showed significantly higher CCA-IMT (MD: 0.16 mm; 95% CI: 0.05, 0.27; $P = 0.004$), aortic-PWV (MD: 3.74 m/s; 95% CI: 3.43, 4.05; $P < 0.00001$), AIx@75 (MD: 8.59%; 95% CI: 0.69, 16.50; $P = 0.03$), and a significantly lower FMD (MD: −2.52%; 95% CI: −3.64, −1.40; $P < 0.0001$). Sensitivity and subgroup analyses substantially confirmed our results. Metaregression models showed that male gender, diabetes, and smoking habit impact on the observed results.

Conclusions: PA appears significantly associated with markers of subclinical atherosclerosis and CV risk. These findings could help establish more specific CV prevention strategies in this clinical setting.

1. Introduction

PA is the most frequent endocrine cause of secondary hypertension that affects 5–13% of hypertensive patients [1] and up to 20% of subjects with resistant hypertension [2]. It is charachterized by autonomous aldosterone overproduction, which is caused in most cases by adrenocortical adenoma or bylateral adrenal hyperplasia [3]. This results in potassium excretion, sodium reabsorption and fluid retention, thus leading to increased systolic and diastolic blood pressure [4].

In addition to these well known effects, it has been reported that patients with PA experience more CV events [3], with increased incidence of myocardial infarction and stroke, and increased prevalence of atrial fibrillation [5]. Moreover, both retrospective and prospective studies suggest that individuals with PA might be at a higher risk of CV mortality than patients with EH [6,7].

However, such an increased CV morbidity and mortality cannot be entirely explained by the increased blood pressure [8] and the

Abbreviations: PA, Primary Aldosteronism; **CV**, Cardiovascular; EH, Essential hypertension; IMT, Intima-media thickness; FMD, Flow-mediated dilation; NMD, Nitrate-mediated dilation; PWV, Pulse-wave velocity; AIx, Augmentation index; ABI, Ankle-brachial index; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; Aortic-PWV, Carotid-femoral PWV; Brachial-PWV, Carotid-radial PWV; ba-PWV, Brachial-ankle PWV; AIx@75, AIx normalized to a 75 beats/min heart rate; NOS, Newcastle–Ottawa Scale; MD, Mean difference; 95% CI, 95% Confidence Interval; OR, Odds Ratio; mm, Millimeters; m/s, Meters per second; cm, Centimeters; BMI, Body-mass index; TC, Total cholesterol; LDLc, LDL-cholesterol; HDLc, HDL-cholesterol; TGs, Triglycerides; SMD, Standardized mean difference.

* Corresponding author at: Department of Advanced Biomedical Sciences, Division of Cardiology, Federico II University, Via S. Pansini 5, 80131 Naples, Italy.
E-mail address: dario.diminno@hotmail.it (M.N.D. Di Minno).

[1] The two Authors equally contributed to this study.
[2] This Author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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underlying mechanisms are not yet clearly understood. It has been suggested that the prolonged exposure to high aldosterone concentrations may result in renal and metabolic sequelae [9], with endothelial dysfunction and myocardial and/or vascular remodeling [10,11]. To further address this issue, a growing attention has been given to the assessment of the association between PA and subclinical atherosclerosis, a recognized marker of CV disease [12].

Carotid IMT assessment is a non-invasive imaging test for subclinical atherosclerosis [13,14], and it has been widely accepted as one of the strongest predictors of major CV events (stroke, myocardial infarction, or CV death) [15,16]. Similarly, FMD, NMD, PWV, AIx, and ABI are considered surrogate markers of subclinical atherosclerosis and independent predictors of CV events [17–20]. FMD and NMD are widely accepted as accurate and non-invasive methods to assess endothelial function in humans [21], while PWV and AIx are measures of peripheral and central arterial stiffness [22]. Thus, these CV risk markers provide important prognostic data over and above traditional CV risk factors.

During recent years, a series of case–control studies reported accelerated atherosclerosis [23,24] impaired endothelial function [25,26], and increased arterial stiffness [27,28] in patients with PA. However, the evidence is limited by small sample size and potential confounding factors and no meta-analytical data providing an overall information about this issue are currently available.

In order to provide a comprehensive overview of the relationship between PA and subclinical atherosclerosis, we performed a systematic review with meta-analysis of literature studies evaluating the impact of PA on the major markers of CV risk.

2. Methods

A protocol for this review was prospectively developed, detailing the specific objectives, the criteria for study selection, the approach to assess study quality, the outcomes, and the statistical methods.

2.1. Search strategy

To identify all available studies, a detailed search pertaining to PA and the markers of CV risk (i.e. IMT, FMD, NMD, PWV, AIx, and ABI) was conducted according to PRISMA guidelines [29]. A systematic search was performed in the electronic databases (PubMed, Web of Science, Scopus, EMBASE), using the following search terms in all possible combinations: *primary aldosteronism*, *hyperaldosteronism*, *Conn syndrome*, *intima-media thickness*, *carotid plaques*, *atherosclerosis*, *flow-mediated dilation*, *nitrate-mediated dilation*, *endothelium-dependent dilation*, *endothelium-independent dilation*, *endothelial dysfunction*, *pulse wave velocity*, *augmentation index*, *arterial stiffness*, *ankle-brachial index*. The last search was performed on 30th October 2015. The search strategy was developed without any language or publication year restriction.

In addition, the reference lists of all retrieved articles were manually reviewed. In case of missing data, study Authors were contacted by e-mail to try to retrieve original data. Two independent Authors (PA and MNDDM) analyzed each article and performed the data extraction independently. In case of disagreement, a third investigator was consulted (RL). Discrepancies were resolved by consensus. Selection results showed a high inter-reader agreement ($\kappa = 0.97$) and have been reported according to PRISMA flowchart (Fig. S1).

2.2. Data extraction and quality assessment

According to the pre-specified protocol, all studies evaluating the impact of PA on the markers of CV risk were included. Case-reports, case-series without a control group, reviews and animal studies were excluded. To be included in the analysis, a study had to provide values (means with standard deviation) of at least one variable among the following: common carotid artery IMT (CCA-IMT), brachial artery FMD or NMD, aortic-PWV, brachial-PWV, ba-PWV, aortic AIx, aortic AIx@75, and ABI. Studies reporting the prevalence of carotid plaques were also included.

In each study, data regarding sample size, major clinical and demographic variables, values of CCA-IMT, FMD, NMD, aortic-PWV, brachial-PWV, ba-PWV, AIx, AIx@75, and ABI, and prevalence of carotid plaques in PA patients and controls were extracted. Controls were represented by patients with EH and/or subjects normal blood pressure.

Given the characteristics of the included studies, the evaluation of methodological quality of each study was performed with the Newcastle–Ottawa Scale (NOS), which is specifically developed to assess quality of non-randomized observational studies [30]. The scoring system encompasses three major domains (selection, comparability, exposure) and a resulting score range between 0 and 8, a higher score representing a better methodological quality. Results of the NOS quality assessment are reported in Table S1.

2.3. Statistical analysis and risk of bias assessment

Statistical analysis was carried out using Review Manager [Version 5.2, The Cochrane Collaboration, Copenhagen, Denmark] provided by The Cochrane Collaboration.

Differences among cases and controls were expressed as MD with pertinent 95% CI for continuous variables, and as OR with pertinent 95% CI for dichotomous variables.

CCA-IMT has been expressed in mm, FMD, NMD, AIx, and AIx@75 as percentage (%), aortic-PWV and brachial-PWV have been expressed in m/s, ba-PWV in cm/s, and ABI as absolute number.

The overall effect was tested using Z scores and significance was set at $P < 0.05$. Statistical heterogeneity between studies was assessed with chi square Cochran's Q test and with I^2 statistic, which measures the inconsistency across study results and describes the proportion of total variation in study estimates, that is due to heterogeneity rather than sampling error. In detail, I^2 values of 0% indicates no heterogeneity, 25% low, 25–50% moderate, and 50% high heterogeneity [31].

Publication bias was assessed by the Egger's test and represented graphically by funnel plots of the standard difference in means versus the standard error. Visual inspection of funnel plot asymmetry was performed to address for possible small-study effect, and Egger's test was used to assess publication bias, over and above any subjective evaluation. A $P < 0.10$ was considered statistically significant [32]. In case of a significant publication bias, the Duval and Tweedie's trim and fill method with the random-effect model was used to allow for the estimation of an adjusted effect size [33].

In order to be as conservative as possible, the random-effect method was used for all analyses to take into account the variability among included studies.

2.4. Sensitivity analyses

We repeated analyses by including only the studies judged as “high quality” according to NOS (i.e. NOS ≥ to the median value found among included studies).

In order to avoid the risk of data overlap, a further sensitivity analysis was performed after excluding studies enrolling patients in the same period time from the same recruitment centers as other included studies.

2.5. Subgroup analyses

Given the potential influence of PA etiology on the outcomes, we planned to perform separate analyses of studies only including patients with aldosterone-producing adenoma.