Increasing incidence of primary aldosteronism in Western Sweden during three decades – Yet an underdiagnosed disorder

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Disclosure summary: The authors have nothing to declare.

Funding: This work has not received any specific grants.

Keywords: Primary aldosteronism; incidence; prevalence; epidemiology

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Abstract

Context: Primary aldosteronism (PA) is the most common cause of secondary hypertension. Yet, the incidence of PA in the general population has not been studied.

Objective: To estimate the incidence of PA in the general population.

Design and methods: Patients who had received a diagnostic code for PA between 1987 and 2016 were identified in the Swedish National Patient Registry. Assessment of clinical and biochemical data was used to validate the diagnosis. The annual incidence of PA was calculated by using the number of inhabitants in the Västra Götaland County as reference.

Results: Of 570 identified patients, 473 (83%) had confirmed PA. Eligible for the incidence analysis were 416 patients, 248 (60%) men and 168 (40%) women, diagnosed with PA between 1987-2016. The mean (± standard deviation) age at diagnosis was 56±12 years. The median (interquartile range) annual incidence was 2 (1-2) cases per million between 1987 and 1996, 6 (4-9) cases per million between 1997 and 2006 and 17 (12-24) cases per million between 2007 and 2016. At the end of the study (December 31st 2016), 386 patients with confirmed PA were alive and living in the Västra Götaland County, giving a prevalence of 231 cases per million (0.022%).

Conclusions: Despite increasing incidence, the proportion of patients identified with PA is lower than expected. Given the serious consequences of untreated PA, the noticeably low prevalence at the end of the study stresses the need to increase the awareness of PA among health care providers.
Introduction

Primary aldosteronism (PA) affects a significant proportion of the adult hypertensive population, ranging from 4% in patients with stage 1 hypertension, 12% in patients with stage 3 hypertension, and up to 20% in patients with treatment resistant hypertension (1-5). A prevalence as high as 7% in prehypertensive patients (6), and 11% in normotensive patients (7), have also been reported. PA is associated with increased risk of several comorbidities, especially cardiovascular diseases, as well as increased mortality (8,9). Importantly, the outcome improves substantially in patients with PA who receive disease-specific treatment with either adrenalectomy, or mineralocorticoid receptor antagonists, emphasizing the importance of disease detection (9,10).

Unfortunately, PA remains an underdiagnosed disease. In a recent register-based study from northern Italy, only 2% of patients expected to have PA were correctly diagnosed with the disease (11). Similarly, according to a web-based cross-sectional survey, 19% and 36% of general practitioners in Germany and Italy, respectively, have never diagnosed PA among their hypertensive patients (12). Also, in a large cohort of US veterans with treatment-resistant hypertension, only 1.6% were screened for PA (13).

Most epidemiological studies on PA have focused on the prevalence in pre-specified patient populations such as patients with hypertension (2). To the best of our knowledge, the incidence of PA in the general population has not yet been evaluated. The estimation of the current diagnostic rates of PA may be valuable for several reasons, including optimizing health care policies aiming at earlier and more wide-spread detection of the disease.
The objective of this study was to evaluate the incidence of PA in Västra Götaland Country in Sweden from 1987 to 2016. For this purpose, we have used the National Patient Register (NPR) that includes more than 99% of all diagnostic codes provided through hospital visits across Sweden. The reliability of data obtained from the NPR for diseases such as myocardial infarction and hip fracture is high (14), but unknown for PA. Thus, a secondary aim was to validate the diagnosis in patients with presumed PA, identified in the NPR, by review of medical records.

Methods

Design

This was a register study including all patients from Västra Götaland County, Sweden who were registered with a diagnostic code for PA in the NPR between January 1st 1987 and December 31st, 2016. In order to validate the diagnosis, the medical records of the patients were reviewed.

Data sources

The NPR is a population-based registry that collects diagnostic codes from all in-patient hospital visits across Sweden since 1987, and all specialist out-patient visits since 2001. All diseases, as well as external causes of injury and surgical procedures, are registered in the NPR according to the International Classification of Diseases (ICD); the 9th version (ICD-9) between 1987 and 1996, and the 10th version (ICD-10) since 1997. By using a personal identification number, unique for all
residents in Sweden, it is ensured that each patient with PA is taken into account only once.

**Identification of patients**

Patients with PA were identified in the NPR by the following codes: E260 (ICD-10) and 255.B (ICD-9). Every occasion producing a diagnostic code for PA was recorded, providing data on personal identification number, gender, date of diagnosis, and the clinic at which the diagnosis was made. In addition, the presence of adrenal tumor (ICD-9: 227.0 and ICD-10: D350 and/or D441) in a patient with a diagnostic code for PA was also recorded.

**Validation of the diagnosis**

To validate the diagnosis of PA, the medical records of all patients identified in the NPR were reviewed by an experienced endocrinologist. By reviewing the clinical, biochemical, imaging and histopathological data, the patients were assigned to one of the following groups: a) confirmed PA, b) PA probable but not confirmed, c) not PA, or d) medical records not available. Patients with one of the following were considered to have confirmed PA (15): a) a diagnostic test confirming PA b) severe phenotype with high plasma aldosterone concentration [PAC; >555 pmol/L (>20 ng/dL)], low or suppressed direct plasma renin activity (PRA) or plasma renin concentration, and spontaneous hypokalemia, or (c) patients treated medically or surgically for PA after endocrine evaluation, although raw-data on the diagnostic procedures were unavailable.
**Evaluation of coverage in the NPR**

To study the proportion of patients with confirmed PA, who were not registered with the diagnosis in the NPR, we used a cohort of patients with confirmed PA who had undergone adrenal venous sampling (AVS) at our institute since 2006 (16). These patients were identified through a search in the electronic database at the department of radiology by using the specific codes for AVS.

**Statistical analysis**

Descriptive data are presented as mean ± SD or median (interquartile range; range). For comparison between two groups, unpaired t test was used for normally distributed data and Mann-Whitney U test for non-normally distributed data. For proportions, Pearson chi-square or Fisher’s exact test was used. A P-value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 25.

**Calculations of annual notified incidence and prevalence of PA**

After validation of the diagnosis of PA for patients identified in the NPR, the annual notified incidence, and prevalence, for patients with confirmed diagnosis were calculated by using the number of residents in the Västra Götaland County as reference. Information on the number of residents was obtained from the Swedish Total Population Register (17). The Västra Götaland County is the second most populated county in Sweden, with 1.41 million inhabitants at the beginning of the
study (January 1\textsuperscript{st} 1987), and 1.67 million at the end of the study (December 31\textsuperscript{st} 2016).

The annual incidence is presented as the number of patients diagnosed with PA per million inhabitants/year. The date of the first endocrine evaluation due to suspected, and later confirmed, PA was used as the date of diagnosis. Excluded from the incidence analysis were patients diagnosed before 1987, patients with PA not living in the Västra Götaland County and patients diagnosed before they moved to the county. The annual incidence was also calculated for three 10-year periods, 1987-1996, 1997-2006 and 2007-2016, where the first period encompassed patients with PA registered according to ICD-9 and the following two periods encompassed patients registered with an ICD-10 code.

The prevalence of PA at the end of the study was determined by calculating the proportion of inhabitants with PA living in the Västra Götaland County in December 2016. Thus, patients with PA who had died or moved from the county during the study period were excluded from the prevalence analysis.

\textit{Ethics approval}

The study was approved by the local ethics committee of the University of Gothenburg, Göteborg, Sweden (reference number 029-17; approved February 22, 2017). The study was conducted according to the Declaration of Helsinki.
Results

Validation of the diagnosis

In total, 570 patients received a diagnostic code for PA between 1987 and 2016 in the Västra Götaland County (Figure 1). For the validation of the diagnosis, medical records were available for 553 (97%) patients. Of all identified patients, 473 (83 %) had confirmed PA and 17 (3%) had probable PA (Table 1). Sixty-three (11%) patients did not have PA. Of 17 (3%) patients whose medical records were unavailable, 13 had received the diagnostic code for PA during the ICD-9 time period (between 1987 and 1996).

Of 473 patients with confirmed PA, 345 (73%) had a positive confirmatory test (saline infusion test, n=325), and 53 (11%) had a severe phenotype, considered to be confirmative for PA without further testing. Of the remaining 75 (16%) patients, in whom the original biochemical evaluation was unavailable, 68 were considered to have confirmed PA based on administration of disease-specific treatment for presumed PA (i.e., adrenalectomy, n=40 and medical treatment, n=28). The remaining seven patients had undergone AVS due to PA, but clinical data was otherwise lacking.

Of 17 patients with probable PA, 15 had a high plasma aldosterone to renin ratio but were not investigated further due to multiple comorbidities (n=9), unwillingness to proceed with confirmatory testing (n=5), and concomitant pheochromocytoma (n=1). For the remaining two patients, only information from radiological reports were available, stating that they had PA and an "aldosteronoma".
The diagnostic code for PA was incorrectly given in 63 patients without the disease. In 31 of these, PA had been suspected but subsequently ruled out biochemically. Erroneous coding was found in 32 patients (Figure 1).

**Alternative search algorithms**

Of 62 patients registered with a diagnostic code for PA between 1987 and 1996 (ICD-9), 35 (56%) had confirmed PA and three (5%) had probable PA (Table 1). Of 522 patients registered with a diagnostic code for PA between 1997 and 2016 (ICD-10), 452 (87%) had confirmed PA and 14 (3%) had probable PA.

Of 522 patients registered 1997 or later (ICD-10), 393 (75%) were registered with PA on more than one occasion (Table 1). Of these, 368 (94%) patients had confirmed PA. Of 178 patients registered 1997 or later, with a diagnostic code for adrenal tumor, 174 (98%) had confirmed PA.

**Coverage in the NPR**

Of 217 resident patients who had underwent AVS at our institute between 2006 and 2016 due to PA, 7 (3%) were not registered in the NPR with a diagnostic code for PA. In other words, 97% of this subgroup of patients with PA were identified in the NPR.
In total, 416 patients with confirmed PA, diagnosed between 1987 and 2016, 248 (60%) men and 168 (40%) women, were included in the incidence analysis (Figure 1). The median (interquartile range) annual incidence during the whole study period was 6 (2-13) cases per million; 9 (1-17) cases per million for men and 5 (1-11) cases per million for women (p=0.2; Figure 2). The median (interquartile range) annual notified incidence was 2 (1-2) cases per million between 1987 and 1996, 6 (4-9) cases per million between 1997 and 2006 and 17 (12-24) cases per million between 2007 and 2016 (Figure 2).

The mean age at diagnosis was 56±12 years (range 21-86); 54±13 in women and 57±10 in men (p=0.02; Table 2). At diagnosis, 233 (60%) patients were treated with multiple antihypertensive medication and hypokalemia was present in 298 (79%) patients. Of 392 patients, a confirmatory test had been performed in 316 (81%), most commonly the saline infusion test (n=303). AVS had been performed in 282 (68%) patients, of whom 263 were successful (93% success rate). Four hundred (97%) patients had received disease-specific treatment, 176 (43%) with adrenalectomy, and 224 (54%) with MRA. The number of patients operated with adrenalectomy due to PA increased from 7 patients between 1987-1996, to 48 between 1997-2006 and to 121 patients between 2007-2016 (Table 2, Figure 3).
Prevalence

At the end of the study on December 31st, 2016, 386 patients with confirmed PA were alive and living in the Västra Götaland County, with a population of 1,671,783 inhabitants. Thus, the prevalence was 231 cases per million (0.022%).

Discussion

In this register-based study, we found an overall annual incidence of PA to be 6 cases per million. The mean number of notified incident cases increased in a linear fashion over time, from 2 cases per million/year (1987-1996), to 17 cases per million (2007 to 2016). At the end of the study, the prevalence of PA in Västra Götaland was 231 cases per million (0.022%). Dedicated work on PA in the primary health care (18), and quality improvement on AVS (16), corresponding to the dramatic increase of adrenalectomies around 2005 (figure 3), may have contributed to increased awareness of the disease in our region. Still, previous studies on Swedish hypertensive patients have shown a prevalence of PA between 2 and 6% (18-20). Also, in Swedish patients with type 2 diabetes and hypertension, the prevalence of PA was 1% (21). Based on these studies, and given that 27% of the Swedish adult population have hypertension (22), the estimated number of patients with PA in the Västra Götaland County should be between 3,500 and 20,000 cases. Thus, despite an increasing detection rate, PA is obviously still a greatly underdiagnosed disorder.

PA is a serious condition associated with increased risk of cardio- and cerebrovascular diseases. In a recent meta-analysis, patients with PA were found to run a 2-fold increased risk for coronary artery disease and congestive heart failure, 3-fold increased risk for stroke, and 4-fold increased risk for atrial fibrillation,
compared to patients with essential hypertension (8). Mortality is also increased in patients with PA (9). However, when adequately managed with disease-specific treatment, the mortality ratio seems to be comparable to that in patients with essential hypertension (9). It is therefore of utmost importance to identify patients with PA.

Diagnoses such as myocardial infarction (23), hip fracture (24) and pulmonary embolism (25) can be reliably obtained from the Swedish NPR by using diagnostic codes for identification. For other diseases, for example Cushing’s disease, the same approach is not suitable since at least one-third of the patients with a diagnostic code for the disease have diagnoses that are not related to hypercortisolism (26). An important question for the current study, and future epidemiological research, was therefore the reliability of a national health care registry such as Swedish NPR for PA. The accuracy of the diagnostic code for PA between 1987 and 1996 (ICD-9) was low (56%). The accuracy after 1997 (ICD-10) was considerably higher (87%), especially for patients who had received the diagnostic code on more than one occasion (94%). At the same time, however, by applying the diagnostic code for PA on more than one occasion in the ICD-10, 84 of 452 (19%) patients with confirmed PA would not have been captured. Similarly, by using a combination of diagnostic code for PA and adrenal adenoma, 98% of the patients had confirmed PA, but less than 40% would have been identified. Thus, for future epidemiological research on PA in Sweden, including patients who have received the diagnostic code for PA on more than on occasion seems to be a reasonable approach with an acceptable accuracy and sensitivity.
Another important issue for the current and future research is the validity of the results. By using another source to identify patients with PA, the coverage in the NPR could be evaluated. Fortunately, the vast majority (97%) of patients with confirmed PA who underwent AVS at our institute since 2006 were registered in the NPR, strongly suggesting a high external validity.

To our knowledge, this is the first study to evaluate the incidence of PA in the general population. The study provides clear evidence that PA is increasingly being detected. Yet, a large number of patients still remain undiagnosed: The increasing detection rate is most probably explained by increasing awareness of PA, mainly among primary care physicians, together with a simplified diagnostic work-up in patients with suspected PA where “wash out” of anti-hypertensive medications affecting aldosterone and/or renin concentrations are no longer considered necessary. Another possible contributing factor is the widespread use of imaging in general, resulting in increased detection of patients with adrenal incidentalomas that are subsequently screened for PA.

A major strength of this study is that the diagnosis in the vast majority of patients who had received a diagnostic code for PA could be validated. In fact, medical records were unavailable for only 4 of 522 (<1% of patients identified in the NPR since 1997). Also, the Västra Götaland County has a well-defined population, making it possible to provide a reliable calculation of incidence rates of PA. However, the study has limitations, such as the retrospective design, and that the true prevalence and incidence of PA cannot be analyzed, only the notified incidence which is much lower than the true occurrence of the disease (1). Also, due to the retrospective nature of the study, important subjects such as the number of patients with, and the
differentiation between low-renin essential hypertension and idiopathic hyperaldosteronism was not possible (27). Similarly, the majority of the patients in our cohort, especially during the most recent period, were diagnosed with PA based on non-suppressible aldosterone during saline infusion test. This may in fact underestimate the incidence of PA since not all patients with the disease have angiotensin II independent autonomous hyperaldosteronism (28).

In conclusion, the detection rate of PA is increasing. Nevertheless, PA is still greatly underdiagnosed and only a small proportion of hypertensive patients are being diagnosed with PA. Given the serious consequences of untreated PA, the noticeable low prevalence at the end of the study clearly illustrates the need for new and optimized strategies aiming at increasing the awareness of PA among health care providers.

Data availability statement: Access to raw-data is available upon request addressed to the corresponding author.
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Legends to figures

**Figure 1** Flow chart of patient identification

**Figure 2** The annual incidence of primary aldosteronism by calendar year (cases per 1 million inhabitants and year) in the Västra Götaland Country between 1987 and 2016.

**Figure 3** The annual incidence of adrenalectomies for primary aldosteronism by calendar year (operations per 1 million inhabitants and year) in the Västra Götaland Country between 1987 and 2016.
### Table 1. Influence of different search algorithms on the accuracy of the diagnosis of PA.

|                     | Diagnostic code for PA in ICD-9 | Diagnostic code for PA in ICD-9 | Diagnostic code for PA in ICD-10, registered on >1 occasion | Diagnostic code for PA and an adrenal tumor in ICD-10 |
|---------------------|----------------------------------|----------------------------------|-------------------------------------------------------------|------------------------------------------------------|
| **Total number**    | 570                              | 62                               | 522*                                                        | 411                                                  |
|                     | 473 (83%)                        | 35 (56%)                         | 380 (92%)                                                  | 368 (94%)                                            |
| **Confirmed PA**    | 17 (3%)                          | 3 (5%)                           | 5 (1%)                                                     | 5 (1%)                                               |
|                     | 473 (83%)                        | 35 (56%)                         | 380 (92%)                                                  | 368 (94%)                                            |
| **Probable PA**     | 17 (3%)                          | 3 (5%)                           | 5 (1%)                                                     | 5 (1%)                                               |
|                     | 473 (83%)                        | 35 (56%)                         | 380 (92%)                                                  | 368 (94%)                                            |
| **Not PA**          | 63 (11%)                         | 11 (18%)                         | 21 (5%)                                                    | 18 (5%)                                              |
|                     | 473 (83%)                        | 35 (56%)                         | 380 (92%)                                                  | 368 (94%)                                            |
| **Missing data**    | 17 (3%)                          | 3 (5%)                           | 2 (1%)                                                     | 0                                                   |
|                     | 473 (83%)                        | 35 (56%)                         | 380 (92%)                                                  | 368 (94%)                                            |

Abbreviations: ICD-9 - International Classification of Diseases Ninth Revision; ICD-10 - International Classification of Diseases Tenth Revision; PA - primary aldosteronism

*14 patients had received a diagnostic code for PA according to both ICD-9 and ICD-10*
Table 2. Characteristics of patients diagnosed with PA in Västra Götaland County between 1987 and 2016.

|                        | All (n=416) | Men (n=248) | Women (n=168) | P     | 1987-1996 (n=24) | 1997-2006 (n=104) | 2007-2016 (n=288) | P     |
|------------------------|-------------|-------------|---------------|-------|------------------|--------------------|--------------------|-------|
| **Age, mean ± SD**     | 56 ± 12     | 57 ± 10     | 54 ± 13       | 0.02  | 53 ± 10          | 55 ± 10            | 57 ± 12            | 0.13  |
| **No of antihypertensive drugs at diagnosis, median (IQR)** | 2 (1-3)     | 2 (2-3)     | 2 (1-2)       | 0.002 | 2 (1-2)          | 2 (1-3)            | 2 (1-3)            | 0.9   |
| **Potassium supplementation at diagnosis, n (%)** | 298 (79)    | 177 (77)    | 121 (82)      | 0.2   | 8 (100)          | 71 (81)            | 219 (78)           | 0.6   |
| **Saline infusion test, n (%)** | 303 (73)    | 179 (72)    | 124 (74)      | 0.13  | 2 (8)            | 51 (49)            | 250 (87)           | <0.001|
| **Adrenal vein sampling, n (%)** | 282 (68)    | 177 (71)    | 105 (63)      | 0.06  | 4 (17)           | 48 (46)            | 230 (80)           | <0.001|
| **Unilateral disease, n (%)** | 145 (51)    | 87 (49)     | 58 (55)       | 1.0   | 0                | 22 (45)            | 123 (53)           | 0.3   |
| **Bilateral disease, n (%)** | 118 (42)    | 75 (42)     | 43 (41)       | 0.8   | 1 (25)           | 17 (35)            | 100 (43)           | 0.3   |
| **Unsuccessful, n (%)** | 19 (7)      | 15 (8)      | 4 (4)         | 0.13  | 3 (75)           | 9 (19)             | 7 (3)              | <0.001|
| **Treatment, n (%)**   |             |             |               |       |                  |                    |                    |       |
| Adrenalectomy          | 176 (43)    | 100 (41)    | 76 (46)       | 0.3   | 7 (35)           | 48 (46)            | 121 (42)           | 0.5   |
| MRA                    | 224 (54)    | 139 (57)    | 85 (51)       | 0.3   | 10 (50)          | 51 (49)            | 163 (57)           | 0.2   |
| Other treatment        | 12 (3)      | 7 (3)       | 5 (3)         | 0.9   | 3 (15)           | 5 (5)              | 4 (1)              | -     |

Abbreviations: IQR - Interquartile range; MRA - Mineralocorticoid receptor antagonist; SIT - Saline infusion test; SD - Standard deviation

*Data on number of antihypertensive drugs at diagnosis, potassium supplementation, imaging and treatment were not available for 78, 39, 27 and 4 patients, respectively.

**Due to small number of patients diagnosed between 1987-1996, only difference between 1997-2006 and 2007-2016 were compared.
A lateralization index greater than 4.0, or a lateralization index between 3 and 4 together with a contralateral index below 1.0, were considered to be compatible with unilateral disease.

Patients with a lateralization index <3 on adrenal vein sampling, and patients not considered to be candidates for surgery, received treatment with MRA.
Figure 1

Patients registered with a diagnostic code for PA in the NPR between 1987-2015 (n=270)

Not PA (n=63)
- PA suspected but ruled out, n=31
- Other adrenal diagnoses, n=12
- Other endocrine diagnoses, n=10
- Other unrelated diagnoses, n=10

Medical records unavailable (n=17)

PA probable but not confirmed (n=17)

Excluded from the incidence analysis (n=57)
- PA diagnosis before 1987, n=16
- Not resident in VGOC, n=35
- Diagnosed before immigration, n=3
- Year of diagnosis unknown, n=1

Patients with confirmed PA (n=473)

Excluded from the prevalence analysis (n=67)
- Deceased, n=30
- Not resident in VGOC, n=35
- Emigrated, n=14

Patients with confirmed PA eligible for the incidence analysis (n=415)

Patients with confirmed PA eligible for the prevalence analysis (n=386)
Figure 2

Annual incidence of primary aldosteronism (cases per million/year)

- All
- Men
- Women

Year

1987 1992 1997 2002 2007 2012 2017
