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Guidelines for primary aldosteronism: uptake by primary care physicians in Europe

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- 1 Guidelines for Primary Aldosteronism: Uptake by Primary Care Physicians in Europe.
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23 Abstract

24 **Context:** Primary aldosteronism (PA) is the most frequent form of secondary hypertension but is still markedly underdiagnosed. In 2008 the Endocrine Society released guidelines for 25 PA diagnosis and management; current indications are that they are not being widely 26 followed. **Objective:** To investigate the level of knowledge and application of the guidelines 27 in a large representative cohort of general practitioners (GPs) in Italy and Germany. Setting 28 29 and Design: The study was carried out by web questionnaire on hypertension and PA management with 500 GPs (250 in Italy and 250 in Germany), stratified by geographical 30 31 area and city size. Results: The mean number of patients seen was 1747 (Germany) and 32 1388 (Italy). Of these, 18% were diagnosed as hypertensive in Italy and 25% in Germany. 33 Renin and aldosterone measurements were ordered by 7% of GPs in Italy and 8% in Germany. GPs in Italy considered 8% of patients eligible for aldosterone and renin 34 35 measurements compared to 13% of GPs in Germany. In Italy, PA prevalence was 1% 36 among hypertensive patients; 36% of the GPs reported no PA patients under their care or diagnosed previously. In Germany, the prevalence of PA was 2% among hypertensive 37 patients; 19% of GPs had no PA patients. **Conclusions**: in Germany and in Italy, PA is not 38 widely recognized by GPs; Endocrine Society guidelines for PA diagnosis are not well known 39 40 or applied, resulting in marked underdiagnosis of the disease.

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48 Introduction

49 In 2008 the Endocrine Society published guidelines for the case detection, diagnosis and treatment of primary aldosteronism (1), co-sponsored by the European Society of 50 51 Endocrinology. These guidelines recommended screening for primary aldosteronism in the 52 \sim 30% of patients with a substantial risk of PA. Hypertension per se is a major driver of cardiovascular morbidity and mortality; the diagnosis of PA is of particular importance given 53 the markedly higher risk profile than that in age-, sex-, and blood pressure-matched 54 55 essential hypertension (2,3). The guidelines published by the Japan Endocrine Society in 2011 recommend screening all hypertensive patients for PA (4); in the revised guidelines 56 recently published by the Endocrine Society in 2016 (5) the previous recommendation has 57 been expanded to ~50% of hypertensives. 58

While such recommendations can be justified in theory, it is difficult to see how in the 59 foreseeable future they might be put into practice. In developed countries it is estimated that 60 61 20-40% of the adult population have high blood pressure (BP). The estimated prevalence of 62 PA currently varies from ~5% of hypertensives to >10%, a range reflecting strict or more 63 relaxed cut-offs for plasma aldosterone concentration (PAC), plasma renin 64 activity/concentration (PRA/PRC) and the aldosterone to renin ratio (ARR). If we take a figure of 30% for the prevalence of adult hypertension, this gives us \sim 70 million 65 hypertensives in the USA, ~30 million in Japan, and ~15 million in Italy. Merely to tread 66 water would require 4 million hypertensives to be screened each year in the US, 2 million in 67 Japan and 1 million in Italy. 68

There is a general consensus that screening rates are in fact very much lower, and the 2016 guidelines are accompanied by a desk regerence module for primary care physicians in an attempt to increase screening of patients at high risk of PA. The present study was undertaken to establish the extent to which primary care physicians (also known as general practitioners) are aware of the guidelines, and secondly their familiarity with the

management of primary aldosteronism. The study took place in Italy and Germany; in both
these countries there are outstanding academic and clinical contributors to the fields of PA.
There is much in common between the two countries' responses, and some differences.
What it shows, in brief, is a yawning gap between theory, as laid down in guidelines, and
practice. It is likely that a similar gap exists throughout the world.

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80 Materials and Methods

The study was directed by the Department of Medical Sciences at the University of Turin, 81 82 approved by the University's Institutional Review Board and supported by an untied grant 83 from Diasorin s.p.a. The questionnaire was posed to 250 physicians in Italy and 250 in Germany by the market research firm Stethos srl using the CAWI (Computer Assisted Web 84 85 Interviewing) methodology. All web interviews were collected between November 2013 and 86 January 2014. The physicians chosen cared for at least one thousand monitored patients, and were stratified on the basis of practice location (village/small town/large town etc.) and 87 geographical area (e.g. North, Centre, South of Italy, plus East and West for Germany). The 88 questionnaire is complex, and physicians were recompensed for lost practice time. Data 89 90 analysis was done by Stethos, specialists in market research in the field of healthcare (Stethos, Milan, Italy) in combination with University personnel. All of the physicians who 91 took part gave their written consent, and a copy of the guestionnaire is included in the 92 93 supplementary materials on-line.

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95 **Results**

A cross sectional comparison of the two countries' responses is shown in Table 1.

97 As might be expected, there are both commonalities and differences between the two

groups of physicians. Among the commonalities are near-identical systolic (SBP) and

diastolic (DBP) levels of blood pressure; the presenting symptoms (headache/dizziness
together comprise 80% in both countries); a female (57-59%) to male (42-43%)
preponderance in both groups; an identical figure for the diagnostician of resistant
hypertension (specialists 54%, primary care physicians 46%); and finally an identical figure
for the percentage (8%) of patients diagnosed with resistant hypertension.

104 Some differences between the two groups may be relevant for the diagnosis of PA, others may not. On average, German physicians were responsible for 1747 patients, their Italian 105 106 counterparts for 1388. The Italians diagnosed hypertension in 18% of their patients, the Germans 25%. Both groups referred patients primarily to cardiologists (Italy 74%, Germany 107 59%) with lesser percentages to Departments of Medicine and specialized Hypertension 108 Centres. The Italians were apparently much more in favour of monitoring renin and 109 110 aldosterone (rating its importance on a scale from 1 to 10, 6.4/10 vs 5.4/10 in Italy and 111 Germany, respectively), but despite this, sent only on average just over half as many (5/4/11) each year for PAC/renin/ARR measurements as their German counterparts (8/8/15). 112 Of the Italian respondents, 36% had no patients with PA, almost double the figure for 113 114 Germany (19%). On average 1% of all the Italian hypertensives were diagnosed with PA, 115 and 2% of German (Figure 1).

At diagnosis of hypertension 50% of GPs in Italy and 43% of GPs in Germany ordered
diagnostic tests. Plasma potassium levels were only requested by 43% (Italy) and 58%
(Germany); renin and aldosterone measurements by 7% (Italy) and 8%(Germany) (Figure
2); of note renin and aldosterone levels were measured in only 3% of patients before starting
pharmacological therapy in both countries. No GP's recognized hyperaldosteronism as a
cause of resistant hypertension, or ordered renin and aldosterone measurements before
changing any therapy.

Notwithstanding the numbers of tests actually requested, 8% of patients were considered
potentially eligible for aldosterone and renin measurement by GPs in Italy compared to 13%
of patients by GPs in Germany.

126 In short, there is widespread acceptance of the existence of resistant hypertension in both 127 countries, although the common figure (8%) is low, even with false diagnosis due to compliance failure factored in. Almost half the physicians in both groups are confident to 128 129 diagnose and manage resistant hypertension: there is no mention of mineralocorticoid 130 receptor antagonists (MRAs) among the list of current therapies, and 'other' is a figure well 131 below 8%. In contrast, recognition of PA seems to vary widely: whereas in Germany 19% of 132 physicians have no PA patients, 11% have >20 and another 20% 10-20 such patients, for example. These latter practitioners thus have a prevalence for PA more or less in the normal 133 134 range for strict cut-offs, or ~5% of hypertensives. However, the figures are overall not reflective of current best practice - \sim 1% of all hypertensives in Italy, and \sim 2% in Germany. 135

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137 **Discussion**

The findings of the survey will be discussed under three headings. The first is a consideration of the results found from the survey. The second is an attempt to address the basis of the physicians' responses, their causes and what these causes might imply. The third is to suggest how the situation might be improved, as simply and as economically as possible.

In terms of study itself, there are a number of inevitable limitations. The data were generated by web interview. The questions are often simple, but often also requiring numeric answers: responses by web are thus likely to be 'ball-park' figures. Secondly, in both countries over 80% of patients presented with headache and /or dizziness, unremarkable given the *average* blood pressure at first visit (Italy 167/97, Germany 170/99). What are remarkable are two issues. First there appear to be no data on incidental finding of raised blood pressure, which

is common in jurisdictions where blood pressure measurement is a routine part of any but the most trivial general practice consultation. Secondly, these *average* values are very high, and in both countries presumably indicate a substantial number of subjects with even higher values. Given the documented increase in prevalence of PA progressively with increased blood pressure (1), the patient cohorts under study are likely to have levels of PA well above the average for unselected primary care patients (6) of ~5%. This makes the finding of only 1-2% even more disappointing.

156 There are, in addition a number of differences between the two cohorts that need to be 157 addressed. The difference in prevalence of hypertension reported (Italy 15%, Germany 25%), taken with the equivalent values for blood pressure at time zero, is not easy to explain 158 159 on the basis of genetics, epigenetics or lifestyle: a possible explanation is that there is a 160 lower rate of consultation in Germany for reasons other than hypertension. While the percentage referral to a specialist is similar (Italy 15.2%, Germany 17.5%), in Italy 74% of 161 referred patients are seen by a cardiologist, while in Germany the percentage is 59%. For 162 the patients that remain in primary care, in Germany appropriately and unsurprisingly 99.5% 163 164 of patients undergo BP monitoring, compared with 78.1% in Italy. In both countries the 165 percentage of patients who appear to have resistant hypertension is the same (8%), and in both countries this seems to be the primary focus. In both countries substantial blood 166 pressure lowering in response to treatment was reported: however calculated, in Germany 167 168 this was 20-21%, and – given clearly less aggressive pharmacotherapy – a surprising figure 169 of 40-42% in Italy. Similarly surprising was that in a substantial minority of patients (Italy 23%, Germany 34%) hypertension was considered secondary to heart disease, rather than 170 the converse. 171

In terms of the basis of the physicians' responses, their causes and what these causes might
imply, there are almost certainly a variety of contributing factors. Many physicians were
taught that primary aldosteronism is a rare (<1%) and relatively benign cause of secondary
hypertension, both of which we now know not to be the case. As previously noted, 36% of

primary care physicians in Italy, and 19% in Germany, profess to have no case of primary
aldosteronism among their hypertensive patients. The questionnaire details average patient
ages, at presentation and at the time of interview: no data were presumed for physicians'
age. If physicians' age data are available, it would also be of interest to look at those who
have >10 and >20 patients with primary aldosteronism under their care.

Secondly, in both countries around half of the respondents knew of the guidelines, but there 181 182 were no data on what percentage were actually conversant with their recommendations. 183 Direct questions on content might have been regarded as too intrusive, but indirect questions ("At what level of presenting blood pressure is it appropriate to test for primary 184 aldosteronism?" "What do you regard as the percentage of hypertensives whose condition is 185 due to primary aldosteronism?") would have been useful, and added to what can only be 186 187 surmised from the number of patients with primary aldosteronism in your practice question. If possible, a finer-grained analysis of those respondents with >10 or >20 primary aldosterone 188 189 patients might also be illuminating - not just age, but practice location, referral patterns and 190 so on.

191 Referral patterns – the major speciality relied upon being cardiology – might also underlie 192 the low discovery rates. In Germany, when patients are referred it is to cardiologists in three fifths of cases, and in Italy three quarters. In most jurisdictions there are far more 193 194 cardiologists than endocrinologists, with the latter largely occupied with diabetes, thyroid disease and reproductive issues. Although primary aldosteronism is primarily an endocrine 195 disorder, with secondary cardiovascular and renal consequences, not all endocrinologists 196 197 are practised in its management: referral for suspected primary aldosteronism should therefore be to an endocrinologist familiar with the condition, or to a specialised hypertension 198 centre with an appropriate track record and personnel. This latter in fact should be the case 199 for all referred patients: although clearly some cardiologists are skilled in managing 200 201 hypertension, it is – as noted previously – a condition in which cardiac effects are secondary,

and more specialised skills – in vascular biology, clinical pharmacology, neuroscience and
 endocrinology – are more suited to identify and rectify the root causes.

204 A fourth possible reason for under-diagnosis is that of the cost to the patient, immediate and 205 future. Ordering of tests at presentation is much more common in Italy than in Germany - for 206 example, the percentage of hypertensives undergoing ECG examination is over 10-fold 207 higher, and creatine levels over 9-fold higher - so no common attitude to testing appears to 208 exist. In fact, the costs of doing a aldosterone to renin ratio are not prohibitive, and easily 209 outweighed by the savings in appropriate management. Probably of less immediate concern 210 are the costs consequent upon confirmation of primary aldosteronism – exclusion testing, 211 imaging, lateralization, and surgery in the case of unilateral disease. As will be further discussed, those are real concerns, but almost certainly a minor contributor to the very low 212 213 level of case detection.

214 Finally, a cause for under diagnosis may be a fear of 'losing the patient', particularly if 215 referral is made to an unfamiliar endocrinologist/ hypertension centre rather than a familiar 216 cardiologist colleague. There are no direct questions in the survey bearing on this: the 217 finding that over 25% of German physicians have >10 patients with primary aldosteronism (10-19 15%, ≥20 11%) compared with Italy (10-19 10%, ≥20 2%) fits with the much higher 218 referral rate to cardiologists. That such patients remain in the primary care physicians 219 220 practice is evidence that not all referred patients are lost; what is not clear is the percentage that may be. What may or may not be relevant is the u-shaped curve for the number (0, 1, 2, 221 3, 4, 5-9, 10-19, \geq 20) of patients in each practice, with a nadir at 4 in both countries (Italy 222 223 4%, Germany 1%), a much lower figure than that for 0/1/2/3.

Given the findings of the survey, broad ranging but inevitably limited, how might the situation be improved, as simply and as economically as possible? First might be the translation and distribution of the Endocrine Society's Guidelines' accompanying desk reference; the cost is relatively trivial, and the distribution might be accompanied by an explanatory letter from the

228 German and Italian members of the Guidelines taskforce. Secondly, in terms of cost, one of 229 the key recommendations of the 2016 guidelines needs to be highlighted, which is that if 230 patients test positive on the case detection step (determining the aldosterone to renin ratio) 231 but are unwilling or unable to proceed they should have a mineralocorticoid receptor 232 antagonist included in their antihypertensive therapy. To the extent that either cost to the 233 patient, or understandable bottlenecks in the optimal patient pathway 234 (confirmation/imaging/lateralization/unilateral adrenalectomy) make entry into the pathway 235 difficult, a low dose mineralocorticoid antagonist is an important addition. Recognition of this 236 course of action for 'low-grade' possible PA (moderate hypertension, normokalemic, modestly elevated ARR, PAC in normal range) may thus encourage primary care physicians 237

to order more ARR testing in their hypertensive patients - or failing that, a simple renin
determination. (7,8)

240 The importance of this, what might be termed an interim strategy, is that there is increasing evidence that 'inappropriate aldosterone secretion' - i.e. primary aldosteronism - might 241 contribute to elevated blood pressure in 30-50% of hypertensive patients, rather than 5-10%. 242 243 The first substantial study to suggest this (9) was published over 30 years ago; more recently, there is clear evidence for mineralocorticoid receptor activation contributing to 244 blood pressure elevation in resistant hypertension (10), low renin hypertension (11) and 245 simple uncomplicated essential hypertension (12). In these latter cases, the ligand activating 246 247 mineralocorticoid receptors may not be aldosterone, but cortisol in the context of tissue 248 damage. On the other hand, recent studies from Athens suggest very strongly that the true 249 prevalence of primary aldosteronism in hypertension may be ~50%, reflecting neglect of ACTH as a secretagogue (13, 14). 250

Whatever the prevalence of primary aldosteronism overall, it is likely that that of aldosterone producing adenomas will remain close to its currently accepted levels, i.e. 3-4% of hypertensives. Patients with APA commonly have more florid disease (higher PAC, ARR, blood pressure and incidence of hypokalemia), and are thus more easily ascertained.

255 Unfortunately the questionnaire did not address the outcomes of diagnosis of primary 256 aldosteronism in either country – whether most or all so diagnosed were patients with 257 aldosterone producing adenoma.

Primary aldosteronism is a rapidly moving field, and the advances of the past couple of 258 259 decades are obviously yet to be appreciated and acted upon by the profession. To the effect 260 that they have been, primary care physicians today may be discouraged in terms of screening, let alone committing a patient to an agreed pathway of ideal treatment, for 261 262 reasons of cost: capacity limitations, particularly of interventionists skilled in adrenal venous sampling, are an additional stumbling block. Over the next decade (perhaps even the next 263 five years) appreciation of the role of mineralocorticoid receptor activation - by 264 inappropriately high aldosterone levels, or by normal levels of cortisol in the context of tissue 265 damage - may begin to increase the use of inexpensive, low dose minimal side-effect 266 mineralocorticoid receptor antagonists as part of first line therapy in hypertension. 267

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315		

316 Figure Legends

Figure 1. Prevalence of primary aldosteronism, other forms of secondary hypertension andessential hypertension in Italy and Germany.

Figure 2. Proportion of patients screened for PA or not, and with a final diagnosis of PA, inItaly and Germany.

Questionnaire for GPs	Italy	Germany 1747	
Number of patients seen by each GP (mean)	1388		
Prevalence of HTN (%)	18	25	
SBP/DBP on diagnosis of HTN (mean, mmHg)	167/97	170/99	
Prevalence of resistant HTN (%)	7.6	7.9	
Patients ordered tests on diagnosis of HTN (%)	50	43	
Plasma [K ⁺] measured on diagnosis of HTN (%)	43	58	
Aldosterone and renin measurement on diagnosis of HTN (%)	7	8	
Aldosterone and renin measurement before drug therapy (%)	3	3	
Awareness of the ES guidelines for PA (%)	53	59	
Patients tested last year for aldosterone alone/renin alone/both	5/4/11	8/8/15	
GPs reporting no patients with PA (%)	36	19	
Overall reported PA prevalence in HTN (%)	1	2	

Table 1. Relevant questions and replies on PA awareness by Italian and German general

325 practitioners.

326 GPs= general practitioners; PA= primary aldosteronism; HTN= hypertension; ES= Endocrine Society.

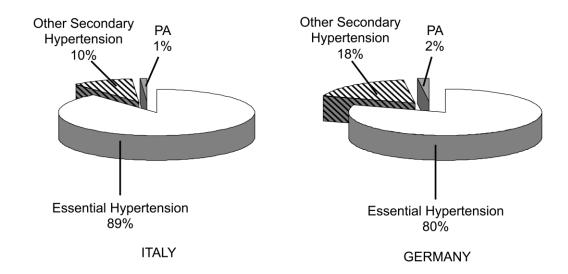


Figure 1

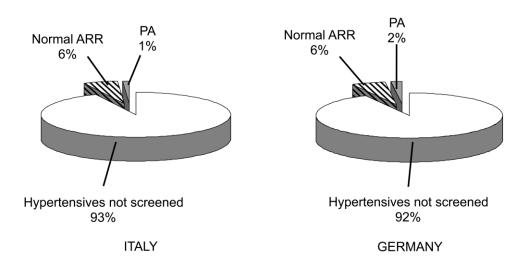


Figure 2