

Screening and management of hypertensive patients with chronic kidney disease referred to Hypertension Excellence Centres among 27 countries. A pilot survey based on questionnaire

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Objective: Real-life management of hypertensive patients with chronic kidney disease (CKD) is unclear.

Methods: A survey was conducted in 2023 by the European Society of Hypertension (ESH) to assess management of CKD patients referred to ESH-Hypertension Excellence Centres (ESH-ECs) at first referral visit. The questionnaire contained 64 questions with which ESH-ECs representatives were asked to estimate preexisting CKD management quality.

Results: Overall, 88 ESH-ECs from 27 countries participated (fully completed surveys: 66/88 [75.0%]). ESH-ECs reported that 28% (median, interquartile range: 15–50%) had preexisting CKD, with 10% of them (5–30%) previously referred to a nephrologist, while 30% (15–40%) had resistant hypertension. The reported rate of previous recent (<6 months) estimated glomerular filtration rate (eGFR) and urine albumin–creatinine ratio (UACR) testing were 80% (50–95%) and 30% (15–50%), respectively. The reported use of renin-angiotensin system blockers was 80% (70–90%). When a nephrologist was part of the ESH-EC teams the reported rates SGLT2

inhibitors (27.5% [20–40%] vs. 15% [10–25], $P=0.003$), GLP1-RA (10% [10–20%] vs. 5% [5–10%], $P=0.003$) and mineralocorticoid receptor antagonists (20% [10–30%] vs. 15% [10–20%], $P=0.05$) use were greater as compared to ESH-ECs without nephrologist participation. The rate of reported resistant hypertension, recent eGFR and UACR results and management of CKD patients prior to referral varied widely across countries.

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Conclusions: Our estimation indicates deficits regarding CKD screening, use of nephroprotective drugs and referral to nephrologists before referral to ESH-ECs but results varied widely across countries. This information can be used to build specific programs to improve care in hypertensives with CKD.

Keywords: albuminuria, chronic kidney disease, glomerular filtration rate, hypertension, management, screening

Abbreviations: BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESH, Euro Society of Hypertension; ESH-EC, Hypertension Excellence Centers; ESKD, End-stage kidney disease; HT-Kidney-WG, Hypertension-Kidney Working Group; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose co-transporter 2 inhibitor; UACR, urinary albumin/creatinine ratio

INTRODUCTION

Hypertension is a strong independent risk factor for development of chronic kidney disease (CKD) and progression of CKD to End-stage kidney disease [1]. The diagnosis of CKD in hypertensive patients is based on evaluation of kidney function (estimated glomerular filtration rate (eGFR)) and the use of the urinary albumin/creatinine ratio (UACR) [1,2]. Moreover, a recent meta-analysis indicated that lowering blood pressure (BP) in CKD patients was associated with reduced mortality [3,4]. Antihypertensive treatment of CKD patients should probably be individualized; however, several randomized clinical trials established that renin angiotensin system blockers should be preferred in diabetic and nondiabetic patients with CKD, especially in the presence of albuminuria [5–8]. All of these clinical practice guidelines have been widely disseminated for many years and recently re-emphasized [1]. Whether these guidelines are really known and respected is still unsure. It is also probable that their

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implementation varies according to many parameters among physicians. Moreover, the recent ESH Guidelines recommend the use of a sodium-glucose co-transporter 2 inhibitor (SGLT2i) for patients with diabetic or nondiabetic CKD, as well as the use of the nonsteroidal mineralocorticoid receptor antagonist (MRA) finerenone for patients with type 2 diabetes mellitus, CKD and albuminuria.

The European Society of Hypertension has made strong efforts to build a network of Hypertension Excellence Centres (ESH-EC) to improve BP control at a population level. Overall, 178 ESH-EC have been approved among 32 European countries and 8 non-European countries (Argentina, Australia, Brazil, Israel, Jordan, Lebanon, China and Venezuela) (<https://www.eshonline.org/communities/excellence-centres>). This network provides a unique opportunity to assess real-life management of patients with CKD and hypertension across countries.

In the present study, we assessed the management of hypertension in respect of current guidelines [1,9] for screening and diagnosis of CKD, referral to nephrologists, management of hypertension, and treatment of CKD patients.

METHODS

Design of the survey and participants

A survey was conducted in 2023 among the ESH-EC network. Briefly, the questionnaire was drafted by the chair (J. M.H.) and vice-chair (L.V.) of the HT-Kidney-WG in February 2023, thereafter validated by three other members of the ESH (A.P., R.K., P.S.), made accessible online and sent by emails between March and June 2023 to all members of the ESH-EC network. Data-management and analyses were conducted between July and September 2023.

Contents of the survey

The questionnaire included ESH-EC characteristics [country, specialty of the ESH-EC chair (cardiologists, nephrologists, internists, pharmacologists, endocrinologists)], whether a nephrologist is part of the ESH-EC, and patient characteristics, as well as availability of recent (<6 months) eGFR and UACR measurements, eGFR category, referral to a nephrologist, use of renin angiotensin system (RAS)-blockers, use of SGLT2is, use of MRAs in CKD patients with eGFR > 30 ml/min/1.73m² and the presence of uncontrolled hypertension despite three or more antihypertensive medications, according to the ESH-EC representatives' opinion. The questions were mainly related to the management of CKD prior to referral to the ESH-EC (Table 1, Supplemental Digital Content, <http://links.lww.com/HJH/C495>).

Primary CKD was defined as CKD due to primary renal diseases such as glomerulonephritis, polycystic kidney disease, lupus. Secondary CKD was defined as CKD associated with hypertension, vascular disease or diabetes.

Variations among 27 countries from Europe regarding screening and management of chronic kidney disease

In this survey, we assessed whether the rate of recent (<6 months) eGFR and UACR measurement, referral to a

nephrologist, use of RAS-blockers, use of SGLT2is, use of MRAs in CKD patients with eGFR >30 ml/min/1.73 m² and no heart failure, and the rate of uncontrolled hypertension differed among the ESH-EC responders.

Statistical analyses

Descriptive data are presented as median (IQR, Interquartile Range) for quantitative variables and counts and percentages for categorical variables. Pearson correlation coefficient between availability of recent eGFR and availability of recent UACR results among CKD patients admitted to ESH-ECs across Europe was calculated. Reported screening and management of CKD patients prior their referral to the ESH-ECs were analysed according to whether the ESH-EC team included or not a nephrologist using Wilcoxon test. Statistical analysis was performed using SAS (SAS 7.1, SAS Institute Inc., SAS Campus Drive, Cary, NC, USA).

RESULTS

Survey responders among European Society of Hypertension- Excellence Centres across European countries

Overall, 88 responses were provided from 27 countries (24 from Europe and 3 from the Middle East) (Fig. 1) (Table 2, Supplemental Digital Content, <http://links.lww.com/HJH/C495>). The survey was fully completed in 66/88 of cases (75.0%). The ESH-EC that responded were chaired by cardiologists (36.4%), nephrologists (36.4%), internists (23.9%) or other specialties (3.4%). A nephrologist was part of the ESH-EC team in 53.4% of centres (Table 1).

Characteristics of patients referred to European Society of Hypertension- Excellence Centres across European countries

According to ESH-ECs representatives' opinion, there was a balanced representation of male and female patients among patients referred to the ESH-ECs (Table 1). With regards to patient age, those who were the most frequently seen were suggested to be patients belonging to the <50 (median: 25% [IQR: 20–30%]) and 50–69-year (40% [30–50%]) age groups. Most frequent reported durations of hypertension were 5–9 (30% [20–35%]) and 10–15 (30% [20–33%]) years (Table 1). Type 2 and type 1 diabetes mellitus were present in 33% (25–50%) and 5% (5–10%) of cases, respectively (Table 1). Known cardiovascular and cerebrovascular diseases were considered to be present in 25% (15–35%) and 20% (10–25%), respectively, whereas heart failure was present in 20% (10–30%) of patients (Table 1). As may be expected, secondary kidney diseases (30% [20–45%]) were more frequent than primary kidney diseases (10% [5–15%]) in patients referred to ESH-EC (Table 1).

Characteristics of patients with chronic kidney disease referred to European Society of Hypertension- Excellence Centres across European countries

Among patients referred to ESH-ECs, 80% (50–95%) were suggested to have had a recent eGFR (<6 months) result

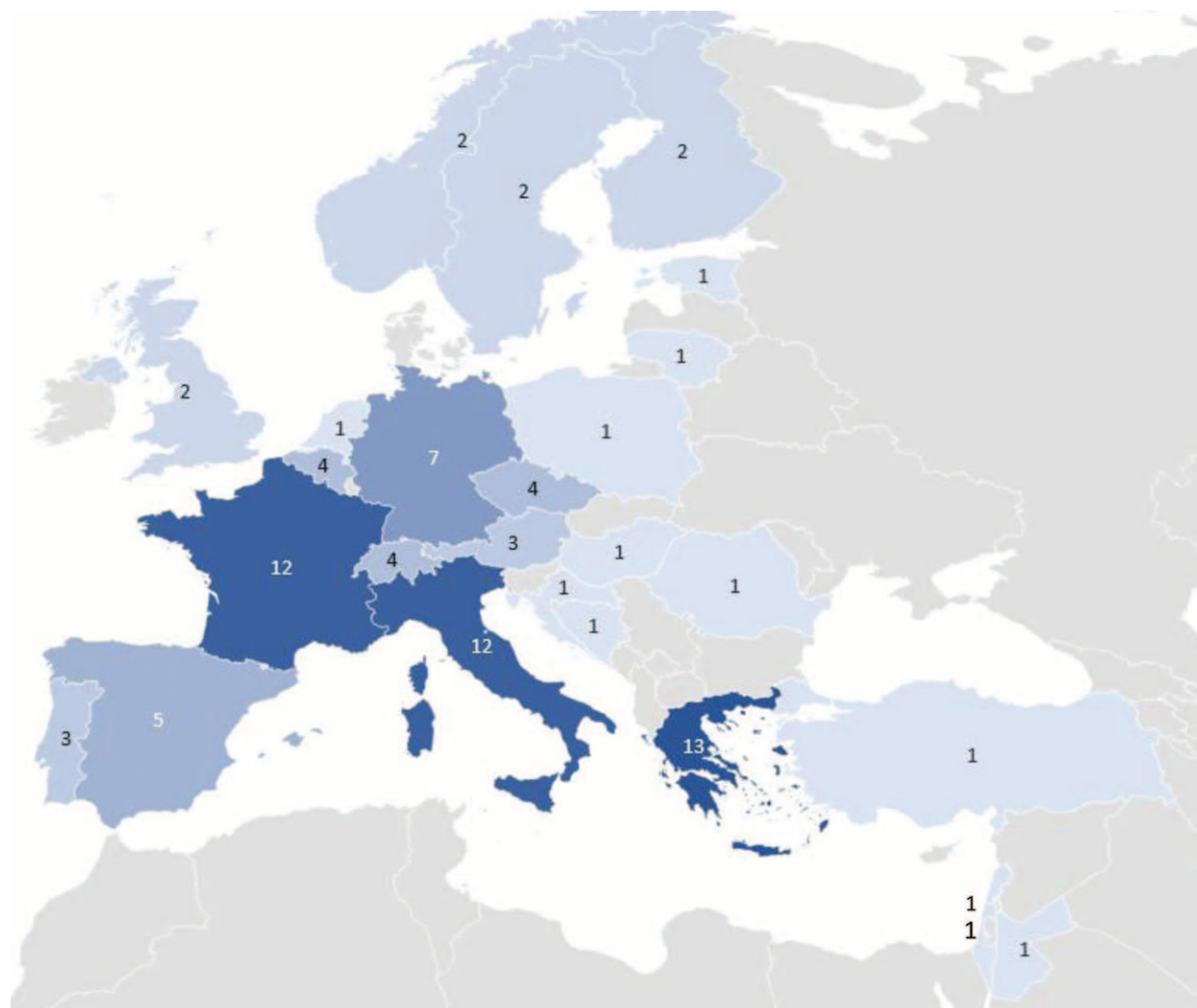


FIGURE 1 ESH-EC responders to the survey. Number of ESH-EC responders in Europe and Middle East (Turkey, Jordan, Israel) per country. The numbers correspond to the numbers of ESH-EC responders. The number of centres for each country was: Armenia: 1, Austria: 1, Belgium: 8, Bosnia-Herzegovina: 1, Croatia: 1, Czech Republic: 7, Estonia: 1, Finland: 2, France: 15, Germany: 16, Greece: 16, Hungary: 6, Israel: 3, Italy: 20, Jordan: 1, Lebanon: 3, Lithuania: 2, Netherlands: 5, Norway: 3, Poland: 11, Portugal: 3, Romania: 1, Spain: 10, Sweden: 2, Switzerland: 6, Turkey: 1, United Kingdom: 15. ESH-EC, European Society of Hypertension-Excellence Centres.

whereas only 30% (15–50%) to have a recent UACR result at presentation (Table 2). There was a modest but significant correlation between availability of recent eGFR result and availability of recent UACR result (Figure 2, Supplemental Digital Content, <http://links.lww.com/HJH/C495>).

Overall, 28% (15–50%) of patients sent to ESH-EC met the definition of CKD (Table 2). Only 10% (5–30%) of them were reported to have seen a nephrologist before referral to the ESH-EC (Table 2). Among ESH-ECs, 41.7% were able to evaluate the CKD stages of the CKD referred patients (Table 2). The distribution of CKD stages was provided based on the responses of participants who were able to evaluate the CKD staging (Table 2). Among the CKD patients, 50% (30–75%) had an eGFR value <60 ml/min/1.73 m² and 30% (20–45%) had UACR value >30 mg/g. The most frequent CKD stage represented was CKD 3a stage (25% [15–30%]) (Table 2).

At presentation, among CKD patients, RAS blockers were estimated to be used in 80% (70–90%) according to ESH-EC representatives' opinion. For mineralocorticoid antagonists (MRA), SGLT2 inhibitors (SGLT2i) and GLP1-RAs,

respective values were 20% (10–30%), 25% (10–40%) and 10% (5–15%), respectively (Table 2). Confirmed resistant hypertension (defined as uncontrolled blood pressure control using HBP/ABPM despite treatment with at least three antihypertensive medications) was present in 30% (15–40%) of CKD patients (Table 2).

Heterogeneity of chronic kidney disease management

Across European Society of Hypertension-Excellence Centres countries

The reported availability of recent results of eGFR varied from 20% (Romania ESH-EC) to 100% (Finland, Hungary, Spain ESH-ECs) (Fig. 2a). Respective figures for UACR were 5% (Poland, Belgium, Jordan ESH-ECs) to 100% (Spain ESH-ECs) (Fig. 2b).

Similarly, the estimated use of RAS blockers varied from 50% (Turkey ESH-EC) to 100% (Spain ESH-ECs), Fig. 3a);

TABLE 1. Characteristics of ESH-EC responders

Countries	
Number of countries involved	27
Centre characteristics	
Number of responder centres	88
Number of responses per country (median (IQR))	4 (2–5)
Speciality of ESH-EC chair (%)	
Cardiologist	36.4
Nephrologist	36.4
Internist	23.9
Other speciality	3.4
Nephrologist present in the ESH-EC	47/88 (53.4%)
Characteristics of patients according to responders	
Male gender (median % (IQR))	50 (43–55)
Age (years) (median % (IQR))	
<50	25 (20–30)
50–69	40 (30–50)
70–79	20 (15–30)
80+	10 (5–10)
Duration of hypertension (median % (IQR))	
<5 years	20 (15–30)
5–9 years	30 (20–35)
10–15 years	30 (20–33)
16+ years	20 (10–25)
Type 1 diabetes mellitus (median % (IQR))	5 (5–10)
Type 2 diabetes mellitus (median % (IQR))	33 (25–50)
Known cardiovascular disease (median % (IQR))	25 (15–35)
Known cerebrovascular disease (median % (IQR))	20 (10–25)
Heart failure (median % (IQR))	20 (10–30)
Primary CKD (glomerulonephritis...) (median % (IQR))	10 (5–15)
Secondary CKD (hypertension, diabetes) (median % (IQR))	30 (20–45)
Vasculitis, lupus or other related diseases (median % (IQR))	5 (5–10)

CKD, chronic kidney disease; ESH-EC, European Society of Hypertension-Excellence Centres; IQR, interquartile range.

TABLE 2. Characteristics of CKD patients admitted to ESH-EC according to responders

CKD patients characteristics	
Patients with CKD (median % (IQR))	28 (15–50)
Known eGFR value (median % (IQR))	80 (50–95)
Known UACR value (median % (IQR))	30 (15–50)
Both and eGFR and UACR value (median % (IQR))	30 (10–50)
CKD patient to referral to nephrologist prior to ESH-EC admission (median % (IQR))	10 (5–30)
eGFR <60 ml/min/1.73 m ² (median % (IQR))	50 (30–75)
UACR >30 mg/g (median % (IQR))	30 (20–45)
Both eGFR <60 and UACR >30 (median % (IQR))	23 (15–40)
Among CKD patients, eGFR <25 ml/min/1.73 m ² (median % (IQR))	60 (20–75)
Among CKD patients, UACR >200 mg/g (median % (IQR))	15 (10–25)
Among CKD patients, both eGFR <25 and UACR >200 (median % (IQR))	15 (5–25)
Known distribution of CKD stages (median % (IQR))	
CKD stage 1 (median % (IQR))	41.7
CKD stage 2 (median % (IQR))	15 (10–30)
CKD stage 3a (median % (IQR))	20 (10–25)
CKD stage 3b (median % (IQR))	25 (15–30)
CKD stage 4 (median % (IQR))	20 (10–30)
CKD stage 5 (median % (IQR))	10 (5–15)
CKD stage 5 (median % (IQR))	5 (5–5)
CKD patient management	
RAS blockers (median % (IQR))	80 (70–90)
MRAs (median % (IQR))	20 (10–30)
SGTL2 inhibitors (median % (IQR))	25 (10–40)
GLP1-RAs (median % (IQR))	10 (5–15)

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESH-EC, European Society of Hypertension-Excellence Centres; IQR, interquartile range; MRA, mineralocorticoid receptor antagonist; UACR, urine albumin-creatinine ratio.

the estimated use of SGLT2is varied from 5% (Poland, Israel ESH-ECs) to 65% (ESH-EC Romania, Fig. 3b); the estimated use of MRAs varied from 5% (Lebanon ESH-EC) to 50% (Sweden, Estonia, Croatia) (Fig. 3c); the estimated use of GLP1-RAs varied from 5% (Poland, Israel, Italy, Hungary, Jordan, UK, Lebanon ESH-ECs) to 25% (Spain, Norway ESH-ECs), Fig. 3d). Before admission to ESH-ECs, referral of CKD patients to a nephrologist varied from 0% (Lithuania, The Netherlands ESH-ECs) to 60% (Jordan ESH-EC) (Fig. 4). Finally, confirmed resistant hypertension despite at least 3 antihypertensive medications also varied widely across ESH-ECs, from 5% (Greece ESH-ECs) to 65% (Croatia ESH-EC) (Fig. 5).

Analysis according to participation of a nephrologist in the European Society of Hypertension-Excellence Centres team

Participation of a nephrologist in the ESH-EC team resulted in no significant difference in the estimated availability of recent results of eGFR (70% (50–90) vs. 85% (60–100), $P=0.07$), UACR (20% (10–40) vs. 30% (20–75), $P=0.09$), prior referral to a nephrologist (15% (5–27.5) vs. 10% (5–30%), $P=0.67$), use of RAS blockers (80% (60–90) vs. 80% (80–90%), $P=0.47$), and reported resistant hypertension (15% (7.5–25) vs. 20 (10–30%), $P=0.31$).

In contrast, the estimated use of SGLT2i (27.5% (20–40%) vs. 15% (10–25), $P=0.003$), GLP1-RA (10% (10–20) vs. 5% (5–10), $P=0.003$) and MRA (20% (10–30) vs. 15% (10–20), $P=0.05$) was more frequent reported when a nephrologist was part of the ESH-EC (vs. when a nephrologist was not part of the ESH-EC).

DISCUSSION

The results of the present study indicates deficits in the management of CKD patients referred to ESH-ECs for hypertension management which affects monitoring of eGFR and ACR, low use of SGLT2i and RAS blockers and low rates of referral to nephrologists previous to the referral to a ESH-EC among 27 mainly European countries. Moreover, this study reveals the wide heterogeneity of management of CKD patients across European countries and ESH-ECs with regards to CKD screening and management, use of antihypertensive and nephroprotective treatments and estimated rate of resistant hypertension.

In the present study, we observed that according to ESH-EC chair estimations around 30% of all patients referred to ESH-EC have CKD (many of them CKD stage 3a) and 33% are patients with type 2 diabetes mellitus. Overall, eGFR determinations were suggested to be present in 80%, but UACR was present in only 30% CKD patients before their referral: both figures indicate that proper use of renal biomarkers is still a matter of concern - especially for UACR. Studies regarding real-life screening of CKD among hypertensive patients are scarce. A few studies reported that UACR is not measured as frequently as recommended among patients with diabetes mellitus or CKD in Europe [10] and other countries [11–13]

It was stated that 20% of individuals with hypertension have increased albuminuria UACR whereas only 7% of patients with hypertension are tested for UACR [14]. Based

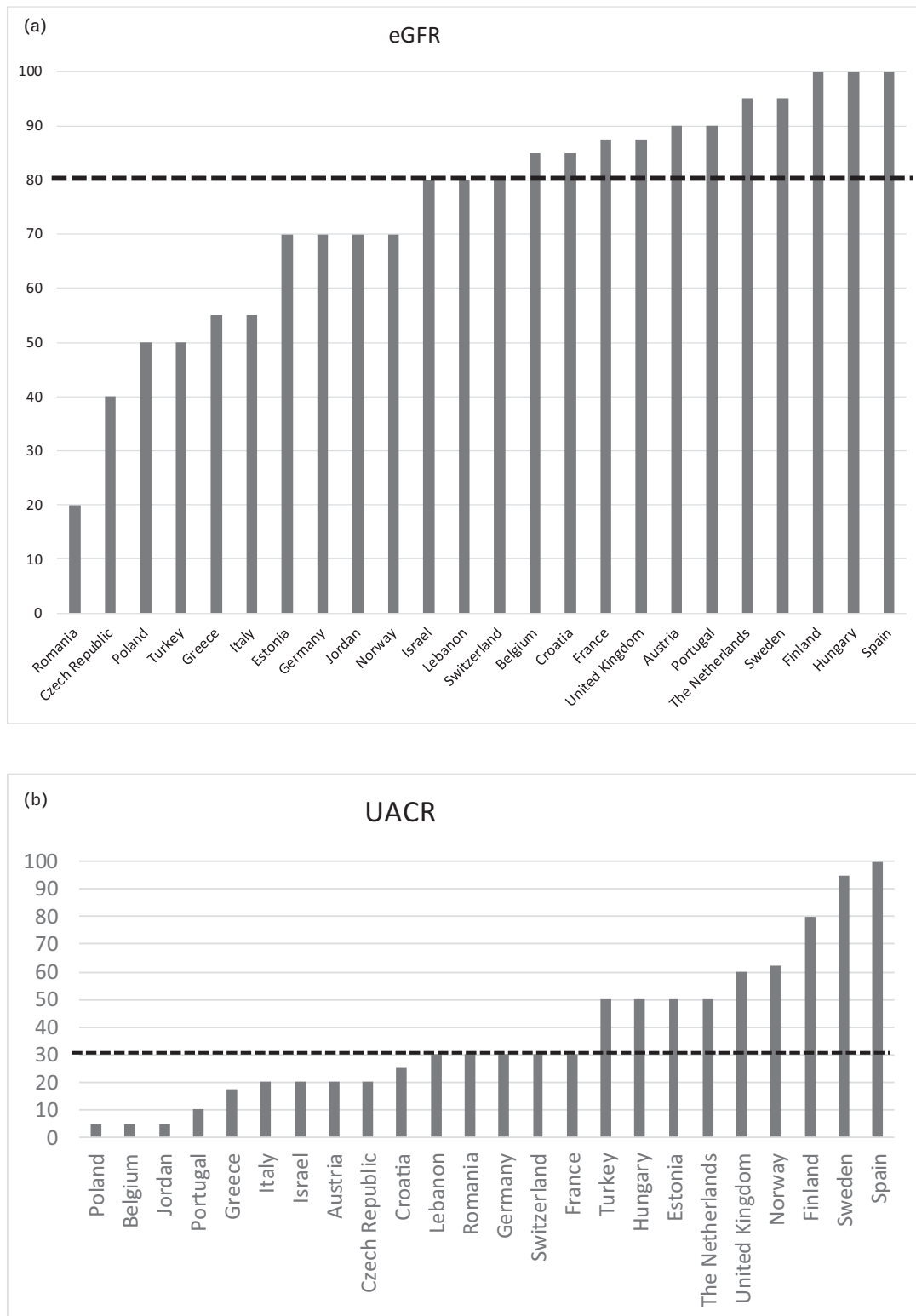


FIGURE 2 Reported rate of availability of eGFR (a) and UACR (b) results in patients referred to ESH-EC. Proportion (median) of patients with recent (<6 months) results of renal biomarkers when they are first seen by ECs per country. The horizontal dotted line indicates the median of all ESH-EC responders. eGFR, estimated glomerular filtration rate; UACR, urine albumin–creatinine ratio.

on these data, one could argue that the diagnosis of CKD may be missed in millions of patients with hypertension or diabetes mellitus, and these findings can be extrapolated to most countries in Europe. Causes of under-testing of UACR

are still unclear. A recent systematic review suggested that a major barrier was the perception that it does not impact patient management [15]. In contrast, numerous studies showed that late referrals, likely a consequence of the

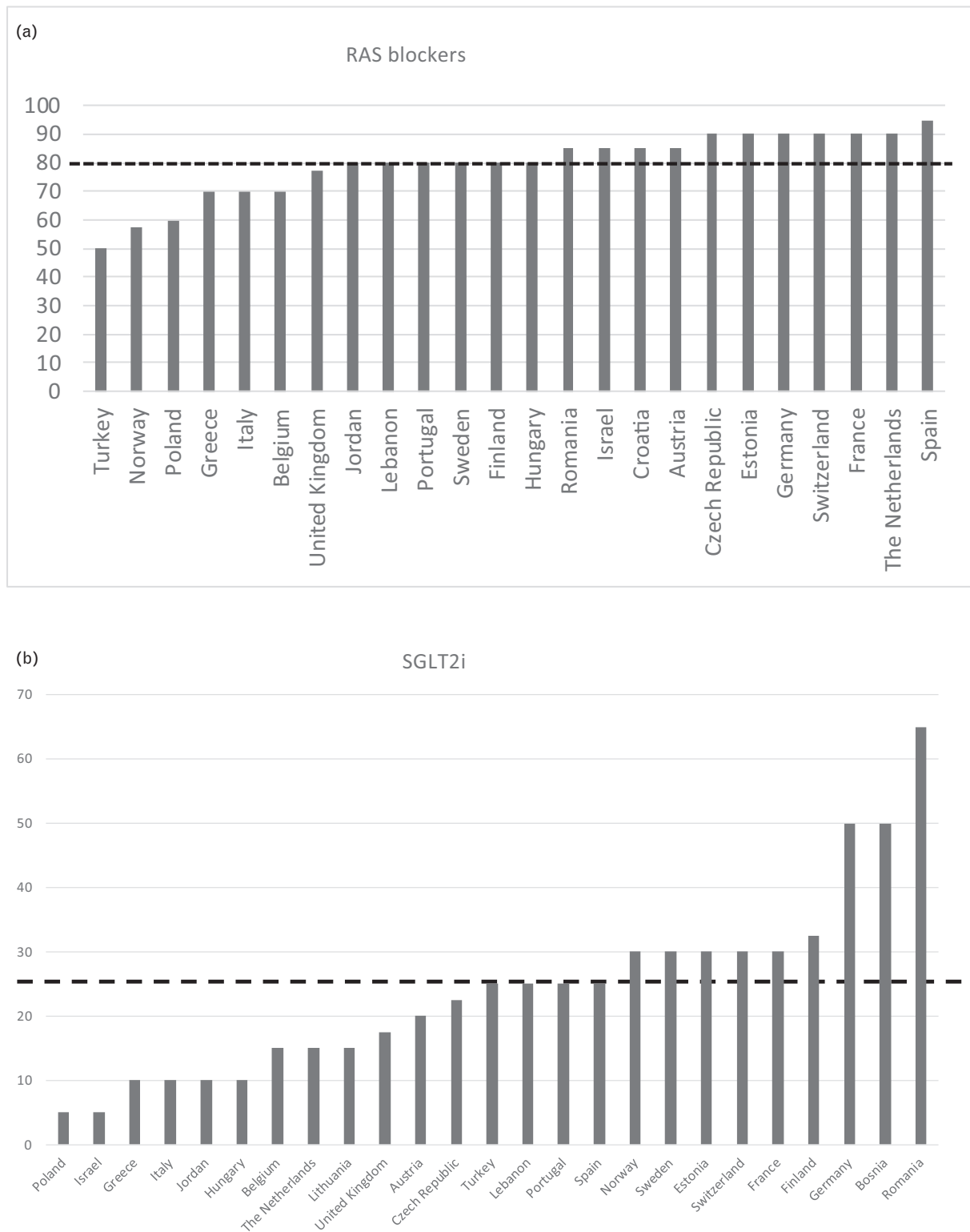


FIGURE 3 Reported treatments among patients with CKD referred to ESH-EC. Proportion (median) of patients treated with RAS blockers (a), SGLT2is (b), MRAs (c) and GLP1-RAs (d). The horizontal dotted line indicates the median of all ESH-EC responders.

under-testing, lead to higher costs and worse outcomes in CKD patients [15,16]. Other hypotheses can be proposed including cost issues in some countries and nonadherence or low acceptance of Guidelines recommendations by GP.

Interestingly, there was a significant correlation between the availability of eGFR value and the availability of UACR values in CKD patients admitted to the ESH-EC. This result suggests that emphasis on eGFR testing could also result in

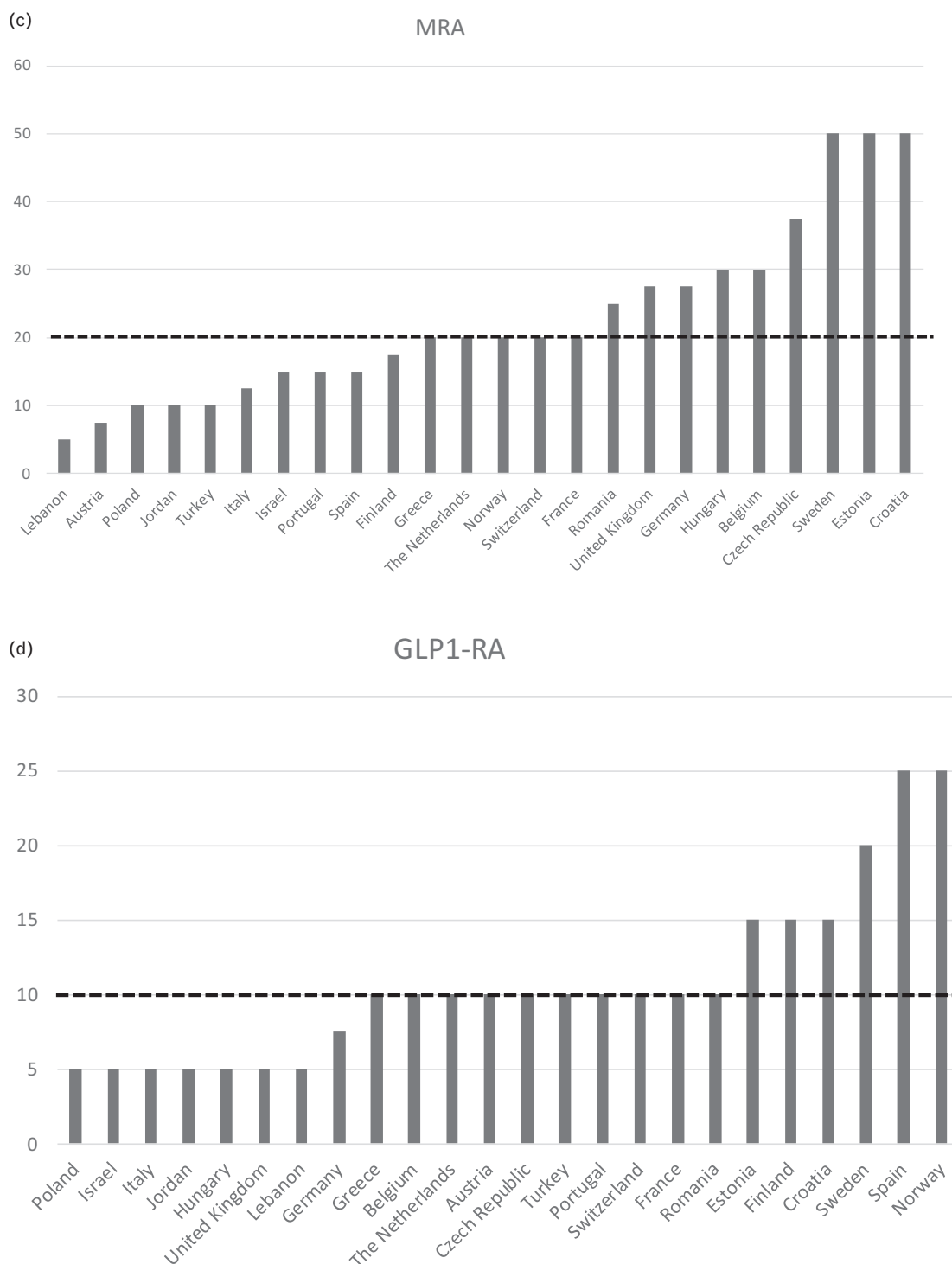


FIGURE 3 (Continued)

improvement of the rate of UACR performed to detect renal dysfunction. However, the weak correlation between these 2 parameters indicates that many other factors are implicated in the fact of prescribing eGFR but not UACR in a given patient, and that specific educational programs dedicated to UACR use must be implemented.

Recent guidelines support the view that the great majority of CKD patients should be treated with RAS blockers and SGLT2is; however, our results indicate that on average 80% and only 20% of CKD patients referred to ESH-EC hypertensive are treated with RAS blockers and SGLT2is, respectively. Other potential cardioprotective and nephroprotective drugs

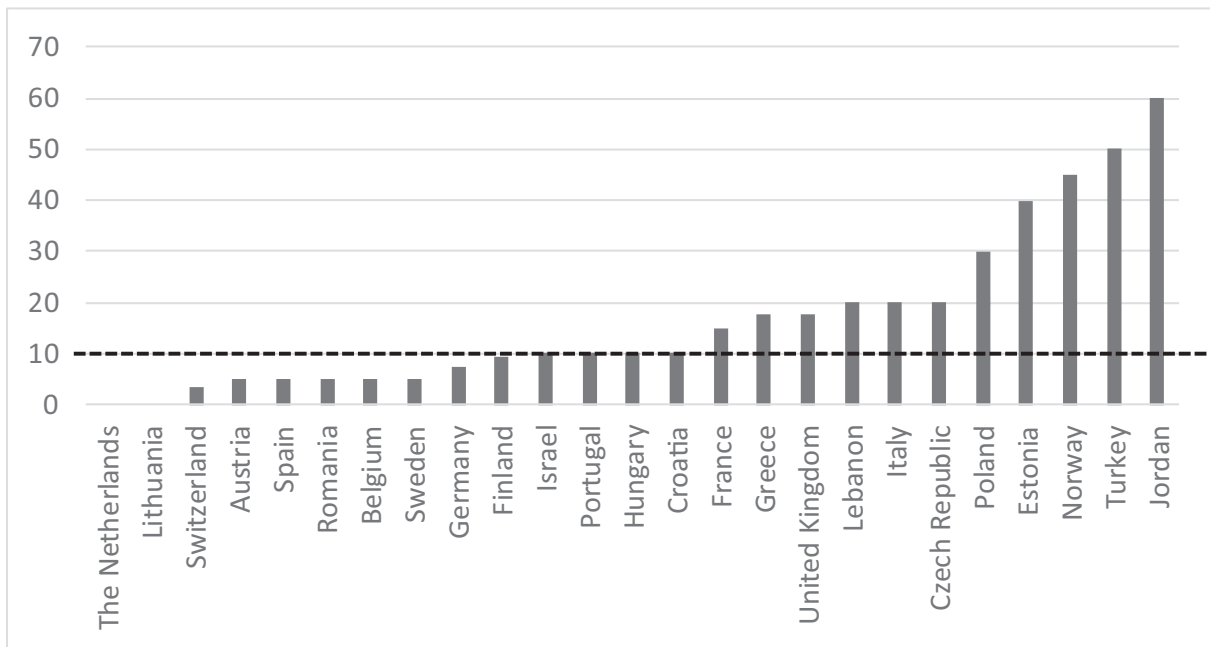


FIGURE 4 Reported referral of CKD patients to a nephrologist prior to ESH-EC admission. Proportion (median) of CKD patients who have been referred to a nephrologist prior to their admission to ESH-EC. The horizontal dotted line indicates the median of all ESH-EC responders. CKD, chronic kidney disease; ESH-EC, European Society of Hypertension-Excellence Centres.

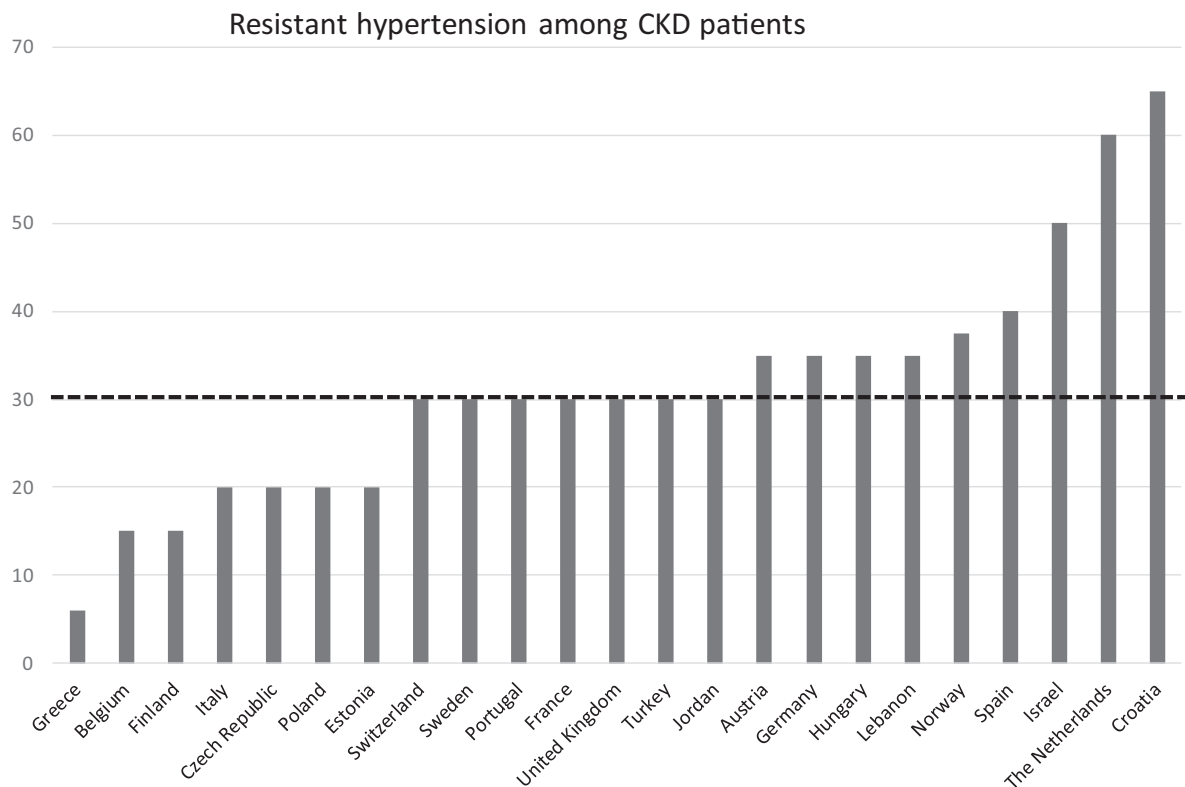


FIGURE 5 Reported confirmed resistant hypertension despite prescription of three or more antihypertensive drugs among CKD patients. The estimated proportion (median) of resistant hypertension confirmed by ambulatory BP or home BP monitoring despite three or more antihypertensive drugs among hypertensive CKD patients in the ESH-EC. The horizontal dotted line indicates the median of all ESH-EC responders. CKD, chronic kidney disease; ESH-EC, European Society of Hypertension-Excellence Centres.

such as MRAs and GLP1-RAs for patients with type 2 diabetes were used even less (20% and 10%, respectively) despite current recommendations [17,18]. This under-prescription has also been observed in the United States [19]. Beside aiming for better blood pressure control among CKD patients, efforts to improve prescription rates of these cardio-nephroprotective drugs seems therefore a logic first step for treatment optimization of hypertensive CKD patients. Before doing so, the reasons for not prescribing these agents should be known, as our survey did not identify them.

Resistant hypertension confirmed by ambulatory or home BP measurements despite treatment of at least three antihypertensive medications was observed in 30% (15–40%) of CKD patients seen in ESH-EC. Similar figures were observed in other studies [20,21]. The consequences have been widely identified, including heart failure, progression of renal disease, hypertensive encephalopathy and malignant hypertension [22–24].

Probably one of the most important findings of this study is the high degree of heterogeneity regarding screening, management, and therapy of CKD hypertensive patients across countries in Europe and the Middle East before they are referred to the ESH-ECs. The reasons for such discrepancies are unclear but the structure of the health system within countries and the financial barriers in some countries probably play an important role. The discrepancies observed among countries in this survey regarding the use of nephroprotective medications are certainly influenced by discrepancies of the different healthcare policies. In some countries, the availability of these drugs and the healthcare policies leading to the reduction of general practitioners' prescriptions may play an important role. This is probably an important issue for newer medications such as SGLT2 inhibitors, GLP1-RA and finerenone. Nevertheless, our results must be taken into account. Indeed, educational programs at the European level appear crucial to improve the care of hypertensive patients but their design and the way they will have to be implemented in specific countries requires to understand their current situation with regard to screening, therapeutic unmet needs, rate of resistant hypertension, and access to innovative therapies. In this respect, our study provides important preliminary insights for such individualized educational programs.

We observed that reported use of SGLT2i, GLP1-RA and MRA was greater when a nephrologist was part of the ESH-EC team. Whether local educational programs of the ESH-EC may be different when a nephrologist is part of the ESH-EC team is probable; however, whether these programs may affect treatment of patients prior to their referral to the ESH-EC is unknown and should be studied.

The strength of this survey derives from the large number of ESH-EC and countries involved in this survey. The questionnaire was first drafted by two physicians then validated by three other experts in the field. To our knowledge, this is the first survey investigating the screening and management of hypertensive patients with CKD referred to Hypertension Excellence centres in Europe. As with most surveys, our study has several limitations. Although 27 countries contributed to the survey and analyses were performed according to countries and presence of absence

of a nephrologist in the ESH-ECs, the survey concerns self-reports by mostly chairs of the ESH-EC and therefore, we do not have any objective data to confirm their perceptions. It would be of interest to complement this study by a survey involving patients followed in the same centres. One of the limitations of the present study is also the fact that not all excellence centres responded to the survey. Nevertheless, in the last 2 reports using the network of ESH Excellence centres [25,26], the number of responders was 67 and 54, respectively. The reasons are unclear but it is possible that not all Excellence Centres have the availability of the data to answer this questionnaire. In addition, it would have been interesting to have not only the percentage of patients but also the actual number of patients referred. Unfortunately, these data are presently unavailable in most Excellence Centres. The diagnosis of diabetes, hypertension and cardiovascular disease has not been clearly defined in this survey; however, it is assumed that these conditions were diagnosed using the best guidelines, as these data were reported by experts in the field. It was reported in a previous paper using the network of the ESH-Excellence Centres that more than 80% of the responders have a professional experience of >10 years. This survey involved 88 centres, but only 27 countries (and only 24 European countries). Participants were free to participate and this explains that the number of participants varied widely across countries and within countries. It is possible that this self-selected sample is affected by a selection bias: participants are probably more interested in CKD management than other physicians working in reference centres.

In conclusion, the results of our survey indicate relevant deficits regarding screening of CKD, insufficient use of RAS blockers and particularly SGLT2is and under-referral to nephrologists before referral to the ESH-EC. In the near future, we wish to plan studies focused on the management of CKD patients in the ESH-EC across Europe, i.e. after referral. There is a huge heterogeneity of management of these patients across European countries, and this information is probably crucial to build specific programs individualized and adapted to local unmet needs and characteristics of health systems. Finally, the greater use of SGLT2is, GLP1-RAs and MRAs in patients referred to ESH-ECs where a nephrologist is present strongly suggests that these ESH-EC may influence the management of hypertensive patients even before referral, probably through their local educational programs.

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Drafting of the manuscript: Prof Jean-Michel Halimi.
Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Prof Jean-Michel Halimi.

Conflicts of interest

The authors report no conflicts of interest relating directly to the contents of this article.

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