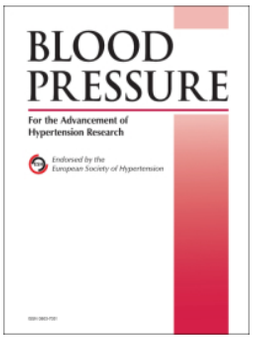

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Management of patients with hypertension and chronic kidney disease referred to Hypertension Excellence Centres among 27 countries. On behalf of the European Society of Hypertension Working Group on Hypertension and the Kidney

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Management of patients with hypertension and chronic kidney disease referred to Hypertension Excellence Centres among 27 countries. On behalf of the European Society of Hypertension Working Group on Hypertension and the Kidney

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ABSTRACT

Objective Real-life management of patients with hypertension and chronic kidney disease (CKD) among European Society of Hypertension Excellence Centres (ESH-ECs) is unclear : we aimed to investigate it. Methods A survey was conducted in 2023. The questionnaire contained 64 questions asking ESH-ECs representatives to estimate how patients with CKD are managed. Results Overall, 88 ESH-ECS representatives from 27 countries participated. According to the responders, renin-angiotensin system (RAS) blockers, calcium-channel blockers and thiazides were often added when these medications were lacking in CKD patients, but physicians were more prone to initiate RAS blockers (90% [interquartile range: 70–95%]) than MRA (20% [10–30%]), SGLT2i (30% [20–50%]) or (GLP1-RA (10% [5–15%]). Despite treatment optimisation, 30% of responders indicated that hypertension remained uncontrolled (30% (15–40%) vs 18% [10%–25%]) in CKD and CKD patients, respectively). Hyperkalemia was the most frequent barrier to initiate RAS blockers, and dosage reduction was considered in 45% of responders when kalaemia was 5.5–5.9 mmol/L. Conclusions RAS blockers are initiated in most ESH-ECS in CKD patients, but MRA and SGLT2i initiations are less frequent. Hyperkalemia was the main barrier for initiation or adequate dosing of RAS blockade, and RAS blockers' dosage reduction was the usual management.

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Chronic kidney disease; hypertension; management; RAS blockers; hyperkalaemia; SGLT2 inhibitors; mineralocorticoid receptor antagonists; guidelines

PLAIN LANGUAGE SUMMARY

What is the context? Hypertension is a strong independent risk factor for development of chronic kidney disease (CKD) and progression of CKD to ESKD. Improved adherence to the guidelines in the treatment of CKD is believed to provide further reduction of cardiorenal events. European Society of Hypertension Excellence Centres (ESH-ECs) have been developed in Europe to provide excellency regarding management of patients with hypertension and implement guidelines. Numerous deficits regarding general practitioner CKD screening, use of nephroprotective drugs and referral to nephrologists prior to referral to ESH-ECs have been reported. In contrast, real-life management of these patients among ESH-ECs is unknown. Before implementation of strategies to improve guideline adherence in Europe, we aimed to investigate how patients with CKD are managed among the ESH-ECs.

What is the study about? In this study, a survey was conducted in 2023 by the ESH to assess management of CKD patients referred to ESH-ECs. The questionnaire contained 64 questions asking ESH-ECs representatives to estimate how patients with CKD are managed among their centres.

What are the results? RAAS blockers are initiated in 90% of ESH-ECs in CKD patients, but the initiation of MRA and SGLT2i is less frequently done. Hyperkalemia is the main barrier for initiation or adequate dosing of RAAS blockade, and its most reported management was RAAS blockers dosage reduction. These findings will be crucial to implement strategies in order to improve management of patients with CKD and guideline adherence among ESH-ECs.

Introduction

Hypertension is a strong independent risk factor for development of chronic kidney disease (CKD) and progression of CKD to end-stage kidney disease (ESKD) [1]. According to guidelines, 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]. These clinical practice guidelines have been widely disseminated for many years and recently re-emphasised [1,3,4]. We recently conducted a survey among European Society of Hypertension excellence centres (ESH-ECs) among 27 countries. This survey indicated numerous deficits regarding CKD screening, use of nephroprotective drugs and it appeared that referral to nephrologists from general practitioners before referral to ESH-ECs was infrequent. However, results varied widely across countries. These deficits were mostly related to low rates of UACR screening and low use of renin-angiotensin system blockers (RASb), glucose co-transporter 2 inhibitors (SGLT2i) and mineralocorticoid receptor antagonists (MRA) [5]. However, how these CKD patients are managed in ESH-ECS has not been reported so far and remains unknown. Wide dissemination of current guidelines is expected in ESH-ECs but whether these guidelines are implemented is also unknown. Physicians in these ESH-ECs are recognised experts in hypertension exploration and management. However, real-life management of patients with hypertension and CKD in these ESH-ECs is unclear. Several issues in patients with hypertension and CKD, including use of antihypertensive medications (especially RASb) when they are lacking, initiation and barriers to use medications such as RASb, MRA, SGLT2i and Glucagon-like peptide-1 receptor agonists (GLP1-RA) [3], the prevalence of uncontrolled hypertension [6], and management of non-severe hyperkalaemia [7]. Before implementation of strategies to improve guideline adherence in Europe, it is crucial to investigate how patients with CKD and hypertension are managed among the ESH-ECs.

In the present study, we assessed how CKD patients are managed among the ESH-ECs and whether ESH-ECs management of these patients markedly differed across centres.

Methods

Design of the survey and participants

A survey was conducted in 2023 among the ESH-ECS network. Briefly, the questionnaire was drafted by the chair (JMH) and vice-chair (LV) of the Hypertension-Kidney Working Group (HT-Kidney-WG) in February 2023, thereafter validated by 3 other members of the ESH (AP, RK, PS), made accessible online and sent by emails between March and June 2023 to all members of the ESH-ECS network. Data-management and analyses were conducted between July and September 2023.

Contents of the survey

The content of the questionnaire has been published (Halimi et al. J Hypertens). Briefly, the questionnaire included ESH-ECS and patient characteristics, including renal diagnosis, use of RASb, SGLT2i and MRA in CKD patients prior to ESH-ECS referral and the specific management of CKD patients in the ESH-ECS (Supplemental Table 1).

Primary CKD was defined as CKD due to primary renal diseases such as glomerulonephritis, polycystic kidney disease, lupus erythematous (i.e. lupus nephritis) not related to cardiovascular and metabolic disorders. Secondary CKD was defined as CKD associated with hypertension, vascular disease or diabetes mellitus.

Variations among 27 countries from Europe and in the Middle East regarding management of CKD in the ESH-ECS

In this analysis, we assessed whether and to what extent to which RASb, SGLT2i, or MRA were added in CKD patients when these drugs were lacking, and whether a significant variability in management of CKD patients was present in ESH-ECS in Europe.

Statistical analyses

Descriptive data are presented as median (IQR, Interquartile Range) for quantitative variables and counts and percentages for categorical variables. Comparisons of parameters among centres were performed using Wilcoxon test, chi^2 test or Fisher's exact test as appropriate. Statistical analysis was performed using SAS (SAS 7.1 SAS Institute Inc., SAS Campus Drive, Cary, NC, USA).

Results

Survey responders among ESH-ECS across European and Middle East countries

Overall, 88 responses were provided from 27 countries (24 from Europe and 3 from the Middle East) (Supplemental Table 2). The survey was fully completed in 66/88 of cases (75.0%). Most of the patients seen in ESH-ECS belonging to the <50 (median: 25% [IQR: 20–30%]) and 50–69-year (40% [30–50%]) age groups. Type 2 diabetes mellitus was present in 33% (25–50%) of cases. Known cardiovascular disease was present in 25% (15–35%) (heart failure: 20% (10–30%)) of patients. Secondary kidney diseases (30% [20–45%]) were more frequent than primary kidney diseases (10% [5–15%])

Management of CKD patients in ESH-ECS

Overall, according to the responses to this questionnaire, RASb, calcium-channel blockers (CCB) and thiazides were often added when these medications were missing (Table 1), and this was especially true for CKD patients (Table 1). Physicians in these ESH-ECs were more prone to initiate ACEI or ARB (90% [70–95%]) than MRA (20% [10–30%]), SGLT2i (30% [20–50%]) or (GLP1-RA (10% [5–15%]) when these medications were missing (Table 2).

After optimisation of treatments, 30% of responders indicated that uncontrolled hypertension was still present in 30% (15–40%) patients with CKD (vs 18% [10%–25%] in all patients) (Table 2).

Interestingly, there was no significant differences in the management of CKD patients among ESH-ECS responders (Tables 1 and 2).

Barriers to RASb optimisation in CKD patients

Physicians were asked to classify potential barriers to RASb use from 1 (the most important or most frequent one) to 4 (the least frequent or least important one) among cough, hyperkalaemia, acute kidney injury (AKI) and low eGFR (usually < 30 ml/min/1.73m^2). Hyperkalemia (32.3%) was usually considered the most frequent one, followed by cough (25%), AKI (15.4%) and low eGFR (12.3%) (Table 3, Figure 1).

Table 1. Initial treatments among all patients and patients with CKD in ESH-ECS.

	n	Median	IQR	Min	Max	*p* Value
Among all patients						
Angiotensin-converting enzyme inhibitors (mono/combination) (%)	67	**40**	30–60	5	90	.6066
Angiotensin-receptor blockers (mono/combination) (%)	66	**50**	35–70	10	95	.4501
Calcium-channel blockers (%)	67	**60**	50–80	10	100	.0600
Thiazides (%)	67	**50**	30–70	15	100	.3372
Loop diuretics (%)	66	**15**	10–25	5	80	.4488
Beta-blockers (%)	67	**25**	15–40	5	80	.6516
Among CKD patients						
Angiotensin-converting enzyme inhibitors (mono/combination) (%)	66	**40**	30–60	10	95	.2877
Angiotensin-receptor blockers (mono/combination) (%)	66	**43**	30–60	10	100	.6526
Calcium-channel blockers (%)	65	**70**	50–80	15	100	.6932
Thiazides (%)	64	**42.5**	20–60	5	100	.1973
Loop diuretics (%)	65	**30**	20–50	5	80	.1829
Beta-blockers (%)	65	**30**	20–40	5	90	.7990

Notes: p Values: comparisons of treatments among all ESH-ECS. ESH-ECS: European Society of Hypertension Excellent Centres.

Table 2. Treatment of CKD patients and proportion of patient with uncontrolled hypertension.

Proportion of CKD patients in whom specific treatments are initiated	n	Median	IQR	Min	Max	*p* Value
Proportion of CKD patients in whom ACEI/ARB are initiated	66	**90**	70–95	5	100	.5293
Proportion of CKD patients in whom MRA are initiated	66	**20**	10–30	5	50	.0686
Proportion of CKD patients in whom SGLT21 are initiated	65	**30**	20–50	5	100	.1397
Proportion of CKD patients in whom GLP1-RA are initiated	63	**10**	5–15	5	35	.0966
Proportion of patients with uncontrolled hypertension after treatment optimization						
CKD patients (%)	63	**30**	15–40	5	90	.4235
All patients (%)	62	**18**	10–25	5	80	.3051

Note: CKD: chronic kidney disease; MRA: mineracorticoid receptor antagonist; SGLT2i: sodium-glucose transporter inhibitors; GLP1-RA: glucagon-like peptide 1 receptor-agonist; IQR: interquartile range.

Table 3. barriers to RAS blockers in CKD patients.

Barriers to RAS blockade optimization (1 to 4) in CKD patients		1	2	3	4[a]	*p* Value
Cough (%)	64	25	12.5	12.5	50	.9766
Hyperkalemia (%)	65	32.3	29.2	27.7	10.8	
Acute kidney injury after RAS blockade challenge (%)	65	15.4	24.6	50.8	9.2	
eGFR considered too low (i.e. usually <30 ml/min) (%)	65	12.3	35.4	26.2	26.2	

Note: RAS: renin angiotensin system; eGFR: estimated glomerular filtration rate.
[a]1 (the most important/frequent) to 4 (least frequent/least important).

Management of non-severe hyperkalaemia

Among patients treated with RASb, 45% of responders indicated that dosage reduction would be considered when kalaemia ranged between 5.5 to 5.9 mmol/L; 30% indicated that they would rather consider the addition of potassium binders, and 10% would not modify treatments. Of note, there were no significant differences among ESH-ECs responders (Table 4).

Potential differences between ESH-EC with versus centres without a nephrologist

We did not find any significant difference regarding any of the studied parameters (initiation of medications: SGLT2i ($p = .4176$), MRA ($p = .5491$), GLP1-RA ($p = .1152$); barriers to the use of RAS blockers: cough ($p = .1251$), eGFR deemed too low ($p = .8651$), acute kidney injury ($p = .5830$), hyperkalaemia ($p = .0649$); management of mild to moderate hyperkalaemia: lowering dose of RASb ($p = .6497$), use of lowering potassium drugs ($p = .4081$), no change in the dose of RASb ($p = .1881$); uncontrolled hypertension among CKD patients ($p = .7933$)).

Discussion

The results of the present study indicate that ACEI/ARB, MRA and SGLT2i were initiated upon referral to ESH-ECS in 90%, 20% and 30%, respectively, according to the responders of this survey. Despite optimisation of treatments, uncontrolled hypertension was still present in 30% in CKD patients compared to 18% in other hypertensive patients without CKD. Hyperkalemia was the main identified barrier to RAAS blockade. For half of responders, management of moderate hyperkalaemia was reduction of RAAS dosage rather than addition of potassium binders or no treatment modification. No significant difference was noted regarding management of CKD patients among the ESH-ECS.

The results of the present study indicate that the initiation of ACEI/ARB was performed in 90% of patients with CKD, according to responders of this survey. The initiation of RAAS blockers by 90% of responders is justified by the results of several clinical trials among diabetic and nondiabetic patients [8–10] and recent European guidelines [1]. RAAS blockers have been shown to reduce proteinuria, the rate of eGFR decline, and the risk of renal failure, especially in protein uric patients [1]. These results are not surprising and correspond to a standard of care for most patients with CKD. It is reassuring that guidelines regarding initiation of ACEI/ARB are respected.

In marked contrast, the initiation of MRA was performed in only 30% of patients with CKD with eGFR > 30 ml/min. According to these recent guidelines, the use of MRA was advocated in patients with CKD, when blood pressure (BP) was uncontrolled despite the use of 3 anti-hypertensive medications (ACEI or ARB, CCB and diuretics) at least when eGFR was > 30 ml/min/1.73m^2 [1]. Only 20% of responders indicated that they consider MRA use in patients with CKD. It is presently unclear whether MRA would be a steroidal MRA such as spironolactone or one such as the non-steroidal MRA

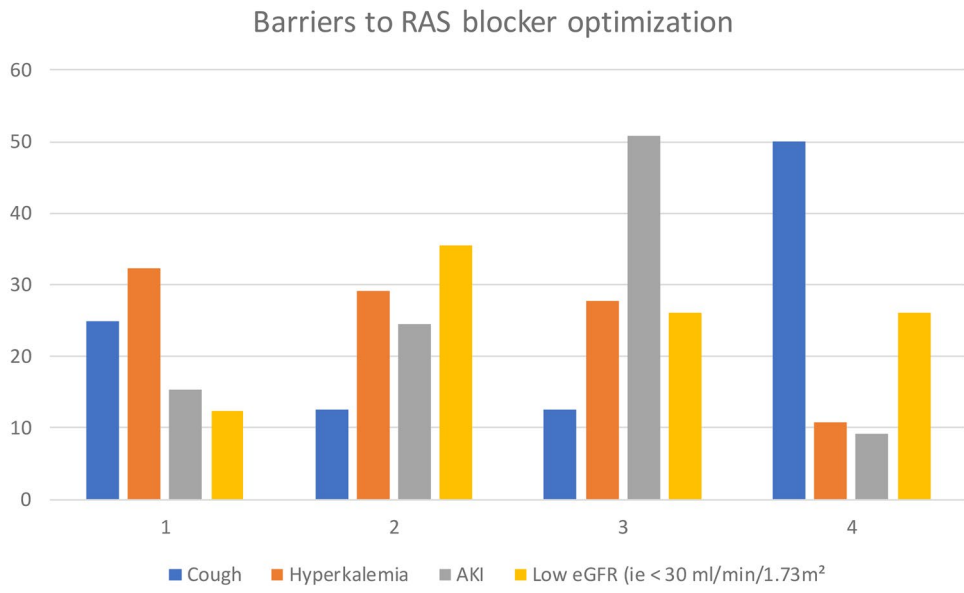

Figure 1. Barriers to RAS blockers' optimisation according to responders (%) (among hyperkalemia, cough, AKI and low GFR).

Table 4. Management of non-severe hyperkalemia.

Non-severe hyperkalemia management	n	Median	IQR	Min	Max	*p* Value
Among patients with hyperkalemia (5.5 to 5.9 mmol/L) treated with RAS blockers						
Proportion of K + lowering treatments considered (%)	65	**30**	10–80	5	100	.5028
Proportion of dosage reduction of RAS blockers (%)	67	**45**	20–80	5	100	.7954
Proportion of patients without treatment modification	56	**10**	5–37.5	5	95	.2477

Notes: p Values for differences among European Society of Hypertension-Excellent Centres; RAS: renin angiotensin system; IQR: interquartile range.

finerenone. A recent meta-analysis of randomised clinical trials showed that spironolactone was superior in lowering BP than other antihypertensive medications, although the BP difference was modest and very few studies were available for analysis [11]. Finerenone reduces BP and has significant beneficial effect vs placebo on the risk of end-stage kidney disease and heart failure among patients with CKD and type 2 diabetes mellitus [12–15]. One of the main barriers for the use of MRA is the risk or at least the fear of hyperkalaemia. Real-world data show that hyperkalaemia is associated with increased mortality [16]. In our study, the fear of hyperkalaemia was also the main barrier for RAAS blockers. Mild to moderate hyperkalaemia (<6.0 mmol/L) can be managed using potassium binders, lowering RAAS blockers dosage, adding thiazide or loop diuretics in patients with uncontrolled hypertension, or one can opt to monitor closely potassium levels. In our study, lowering RAAS blockers dosage was more frequently chosen than the other options [17,18]. In the literature, it was reported that the most frequent reason for dose reduction or discontinuation of RAAS blockers in CKD patients was hyperkalaemia; however, it was also observed that dose reduction or discontinuation of RAAS blockers could result in increased cardiovascular morbidity [19–23]. Our findings that the initiation of MRA was infrequently performed in CKD patients and the discontinuation or dose reduction of RAAS blockers was usually considered, even among ESH-ECs, are in marked contrast with a recent consensus statement [24] and the European guidelines [1]. In the ESH guidelines, it was stated that « a potassium binder can be used to maintain normal or near normal serum potassium levels (<5.5 mmol/L) in order to allow optimal treatment with a RAS-blocker or a MRA to continue » [1]. A potential reason could be the existence of a certain time lag before new recommendations are well applied in routine clinical practice.

Despite optimisation of treatments, uncontrolled hypertension was still present in 30% in CKD patients. In our study, uncontrolled hypertension was confirmed by ambulatory or home BP measurements. Similar numbers were observed in other studies [6,25]. The consequences have been widely identified, including heart failure, progression of renal disease, hypertensive encephalopathy and malignant hypertension [26–28]. Moreover and in accordance with the literature, uncontrolled hypertension was more

frequent in CKD patients than in patients without CKD in the present study [6,29].

Surprisingly, only 30% of the responders indicated that they add SGLT2i in patients with CKD. In marked contrast, recent guidelines recommend adding SGLT2i in diabetic and non-diabetic patients with CKD [1,30–33]. SGLT2i demonstrated significant beneficial effects on cardiovascular morbidity and mortality in addition to large reductions in kidney major events [34–36]. These guidelines are recent but have been largely disseminated [37,38]. Barriers to the prescription of SGLT2i have not been assessed in the present study. However, the low use of SGLT2i is certainly influenced by restrictive health care and reimbursement policies in some countries, that may result in low prescription rates. It is probably true in other countries: it was noted that 'there remain serious challenges to implementation, particularly in the United States where inequities in insurance coverage and high costs limit their use, particularly in vulnerable populations, ultimately widening health care disparities' [39]. In addition, the low reported rate of single RAAS blockade use might have influenced SGLT2i prescription by the ESH-ECS physicians, because RAAS blockade is considered to represent the first line of cardiorenal therapy. It is also important to consider that SGLT2i as well as GLP1-RA are relatively new treatments for nephrologists and hypertension specialists. Further studies to examine the trends in prescription rates in the future are warranted for the aforementioned agents.

Overall, no significant differences were noted in the management of CKD patients among the ESH-ECS but it does mean that difference do not exist, as the number of centres per country was small and heterogenous. In contrast, using the same survey, we observed a high degree of heterogeneity regarding screening and management of hypertensive patients with CKD in the countries of Europe and the Middle East before being referred to the ESH-ECs in our previous study (Halimi JM, in press, J Hypertension). Based on the present results and previous one in ESH-ECs (Halimi JM, in press, J Hypertension), a clearer view of the unmet needs regarding management of hypertensive patients before referral to ESH-ECS and within the ESH-ECS (Table 5): these unmet needs are clearly different: at the GP level, the 3 main unmet needs are: yearly screening (UACR and serum creatinine), increased use or maintenance of ACEI/ARB and introduction of SGLT2i, and reintroduction of these medications if they have been stopped after an acute event in patients with CKD; at the ESH-ECS levels, implementation of BP goals according to current guidelines, addition of SGLT2i and MRA according to local regulations and maintain ACEI/ARB and MRA in patients with mild to moderate hyperkalaemia (Table 5).

The strength of this survey derives from the large number of ESH-ECS and countries involved in this survey. This is the first survey investigating the management of CKD patients referred to Hypertension Excellence centres in Europe.

This study has limitations. Many Excellent centres across Europe responded to this survey, and actually many more than most surveys in Excellence centres [40,41]; however, not all of them responded, and the reasons of non-response are unclear. Within the limits of this survey, it was not possible to obtain real data from patients followed in the same centres. The diagnosis of comorbidities was not rigorously assessed in this survey: it is only assumed that these conditions are defined using the best available guidelines as usually 80% of the responders in such surveys have a professional experience of 10 years or more. Participants willingly participated and therefore a selection bias is possible. It also explains the various number of centres within and across countries. In the present survey, the BP measurement methods and the proportion of ESH-ECs using ambulatory BP monitoring and home blood pressure were not explored.

In conclusion, the results of our survey indicate that RAAS blockers are initiated in 90% of centres in CKD patients but the initiation of other nephroprotective agents such as MRA and SGLT2i is less frequently done, according to responders. Despite optimisation of treatments, uncontrolled hypertension was still present in 30% in CKD patients. The most frequent barrier to RAAS blockade was hyperkalaemia, and for half of responders, management of moderate hyperkalaemia was RAAS blockers dosage reduction rather than addition of potassium binders or no treatment modification, in marked contrast to current guidelines. No significant

Table 5. Major unmet needs at the GP and ESH-ECS levels to improve management of patients with CKD.

Adequate management in hypertensive patients with CKD	
GP level	ESH-ECS level
UACR / eGFR yearly measurement	Implementation of BP goal (pharmacological and non pharmacological aspects)
Add or maintain RAS blockers, introduce SGLT2i	Add SGLT2i and MRA according to local regulations
Increase use of RAS blockers, reintroduce them if stopped	Do not reduce or withdraw RAS blockers/MRA in mild to moderate hyperkalemia (5.5–5.9 mmol/l)

Note: UACR: urinary albumin creatinine ratio; RAS blockers: renin angiotensin system blockers; SGLT2i: sodium-glucose transporter inhibitors; MRA: mineralocorticoid receptor antagonists; GP: general practitioners; ESH-ECs: European Society of Hypertension Excellent Centres.

difference was noted regarding management of CKD patients among the ESH-ECs.

Author contributions

Prof Jean-Michel Halimi had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Concept and design:* Prof Reinhold Kreutz, Prof Jean-Michel Halimi, Prof Liffert Vogt, Alexandre Persu. *Acquisition, analysis, or interpretation of data:* Prof Reinhold Kreutz, Prof Jean-Michel Halimi, Prof Liffert Vogt, Prof Pantelis Sarafidis, Alexandre Persu.

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.

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