Hyperkalaemia and hypokalaemia outpatient management: a survey of 500 French general practitioners (93)

L'objectif principal de l'enquête était de décrire les seuils de prise en charge et la gestion des dyskaliémies par les médecins généralistes français, et plus particulièrement chez les patients insuffisants cardiaques et/ou rénaux chroniques.

Nous avons ainsi réalisé une enquête téléphonique auprès de 500 médecins généralistes français répartis sur l'ensemble du territoire. Le questionnaire comprenait 4 questions fermées et 8 questions ouvertes amenant des réponses qualitatives. Ces questions ouvertes représentaient un atout important de notre étude, puisqu'elles ont permis de recueillir l'avis des médecins sans qu'ils soient influencés par un choix fermé, parmi une liste de réponses proposées. La première partie du questionnaire comportait des questions socio-démographiques ; la seconde partie était axée sur les seuils des dyskaliémies connus par le médecin et ceux à partir desquels ils proposaient une action spécifique. Enfin, la dernière partie concernait la gestion des dyskaliémies à proprement parler, afin d'évaluer le comportement du médecin face à la découverte d'une hypo ou hyperkaliémie chez un patient insuffisant cardiaque, insuffisant rénal, puis spécifiquement si le patient était sous IEC/ Antagoniste des récepteurs de l'angiotensine II (ARA2) ou ARM.

Les résultats montrent une grande hétérogénéité des réponses apportées par les praticiens, tant à propos des définitions que des prises en charge. Les seuils de prise en charge sont malgré tout cohérents avec les recommandations à l'exception de quelques extrêmes. En effet, le taux moyen d'intervention était à 5,32 ± 0,34 mmol/l (4,5–6,5) pour l'hyperkaliémie et 3,23 ± 0,34 mmol/l (2,0–6,5) pour l'hypokaliémie. La concentration moyenne de potassium pour laquelle le patient était adressé aux urgences par le médecin était de 6,14 ± 0,55 (4,5–10) pour l'hyperkaliémie et 2,69 ± 0,42 (1–4) mmol/l pour l'hypokaliémie.
Les recommandations préconisent en première ligne la prise en charge diététique en cas de dyskaliémie (19, 23, 94-96). Or, cette prise en charge diététique n'était évoquée que par 4,6 % des médecins interrogés. Cette proportion est plus élevée dans d'autres études, comme par exemple une étude menée en Europe chez des néphrologues et des cardiologues -dont des praticiens français (97), mais dans cette étude, les questions à ce sujet étaient explicites

(réponse fermée à choix multiples) alors que nous avions choisi de laisser le médecin généraliste s'exprimer librement et sans proposition préétablie sur le sujet. Quand on les interrogeait spécifiquement au sujet d'un patient sous bloqueur du SRAA ; l'approche prédominante de traitement de l'hyperkaliémie par les généralistes interrogés (40 %) était la baisse de la posologie ou l'arrêt définitif des traitements bloqueurs du SRAA, privant ainsi le patient d'un médicament reconnu efficace sur la réduction du risque cardio-vasculaire et rénal et du risque de décès.

L'enquête montre également que les médecins généralistes français semblent rarement se référer à leurs confrères spécialistes cardiologues ou néphrologues pour la prise en charge des hyper et hypokaliémies. Toutefois, l'accès à ces deux spécialistes reste complexe en France du fait de la démographie médicale. Les recommandations existantes dans les deux spécialités révèlent également des disparités.

Il n'existe pas à l'heure actuelle de recommandations spécifiques pour la prise en charge de la dyskaliémie en médecine générale. L'hétérogénéité observée dans notre étude et ce manque de recours aux spécialistes soulignent la nécessité de développer des algorithmes visant à normaliser les pratiques de gestion ambulatoire et peut-être éviter les comportements potentiellement néfastes pour le patient tels que l'inertie (par exemple : pas de contrôle de la kaliémie, pas de changement de traitement ou arrêt définitif d'un médicament utile).

Cette enquête est à notre connaissance la première étude décrivant de manière détaillée les pratiques des médecins généralistes -français en l'occurrence- face à la découverte d'une dyskaliémie.

Il existe un besoin majeur de recommandations spécifiques destinées à la prise en charge des dyskaliémies en soins primaires. Ces recommandations devront être établies par des cardiologues, néphrologues, endocrinologues et thérapeutes en collaboration avec des médecins généralistes et des urgentistes.

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ORIGINAL RESEARCH ARTICLE

Hyperkalaemia and hypokalaemia outpatient management: a survey of 500 French general practitioners

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Abstract

Aims How general practitioners (GPs) manage dyskalaemia is currently unknown. This study aimed at describing GP practices regarding hypokalaemia or hyperkalaemia diagnosis and management in their outpatients.

Methods and results A telephone survey was conducted among French GPs with a 20-item questionnaire (16 closed-ended questions and 12 open-ended questions) regarding their usual management of hypokalaemia or hyperkalaemia patients, both broadly and more specifically in patients with heart failure and/or chronic kidney disease and/or in patients treated with angiotensin-converting enzyme/angiotensin receptor blockers or mineralocorticoid receptor antagonists. We aimed to interview 500 GPs spread geographically throughout France. This descriptive survey results are presented as mean ± standard deviation (if normally distributed or as median and inter-quartile range if the distribution was skewed). Categorical variables are expressed as frequencies and proportions (%). A total of 500 GPs participated in the study. Dyskalaemia thresholds (for diagnosis and intervention) and management patterns were highly heterogeneous. The mean ± SD (range) potassium level leading to 'intervene' was 5.32 ± 0.34 mmol/L (4.5–6.5) for hyperkalaemia and 3.23 ± 0.34 mmol/L (2.0–6.5) for hypokalaemia. Potassium levels leading to refer the patient to the emergency department (ED) were 6.14 ± 0.55 (4.5–10) and 2.69 ± 0.42 mmol/L (1–4), respectively. Potassium binders (51–65%) or potassium supplements (67–74%) were frequently used to manage hyperkalaemia or hypokalaemia. GPs uncommonly referred their dyskalaemic patients to cardiologists or nephrologists (or to the emergency department, if the latter was deemed necessary owing to the severity of the dyskalaemia). We identified an association between the close vicinity of GP office from an ED and 'referring a heart failure patient' (19.2% with ED vs. 8.6% without ED) and referring a heart failure and chronic kidney disease patient on mineralocorticoid receptor antagonist (16.7% with ED vs. 9.3% without ED). Although the majority (67%) of GPs had an electrocardiogram on hand, it was rarely used (14%) in dyskalaemic patients. Subgroup analyses considering gender, age of the participating GPs, and high-income/low-income regions did not identify specific patterns regarding the multidimensional aspect of dyskalaemia management.

Conclusions Owing to the considerable heterogeneity of French GP practices toward dyskalaemia diagnosis and management approaches, there is a likely need to standardize (potentially enabled by therapeutic algorithms) practices.

Keywords General practitioners; Hyperkalaemia; Hypokalaemia; Heart failure; Chronic kidney disease/ mineralocorticoid receptor antagonist

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Introduction

Hypokalaemia and hyperkalaemia are frequent electrolyte disorders consistently found to be associated with increased mortality across various patient populations. Observational data indeed report a U-shaped association between serum potassium levels and mortality, with both hypokalaemia and hyperkalaemia being associated with worse outcomes.

Dyskalaemia is particularly common among patients with cardiovascular diseases [heart failure (HF),[1] arterial hypertension, and coronary artery disease[2]], notably in association with older age and co-morbidities such as chronic kidney disease (CKD) and diabetes, and is related to renin–angiotensin–aldosterone system inhibitors (RAASis), in particular mineralocorticoid receptor antagonists (MRAs) (hyperkalaemia) and non-potassium-sparing diuretic use (hypokalaemia).[3]

The lowest risk of all-cause mortality across studies is observed for blood potassium levels from 4 to 4.5 mEq.[4] There is, however, no actual international consensual agreement regarding a cut-off value for defining hyperkalaemia or hypokalaemia. Potassium thresholds indeed differ between the various guidelines.[5–8] Hyperkalaemia is, however, frequently defined by serum levels ≥ 5 or 5.5 mmol/L,[9,10] while the European Resuscitation Council defines hyperkalaemia as a plasma level > 5.5 mmol/L.[7,8] Hypokalaemia is generally defined by a serum level ≤ 3.5 or even 4 mmol/L.[10] In case of severe hyperkalaemia > 6 or 6.5 or hypokalaemia < 3 mmol/L, initiation of emergency care is recommended.[7,8,10]

While the management of acute or emergent dyskalaemia is reasonably well established,[9] the optimal management of moderate hyperkalaemia or hypokalaemia or with progressive onset is conversely currently undetermined in outpatients frequently managed by general practitioners (GPs).

In light of the latter, this study aimed to describe French GP practices with regard to dyskalaemia management in their outpatients, with special emphasis on HF and/or CKD patients, two frequently associated conditions.

Methods

Study design and patient population

A telephone survey, the Management of HyperKALaemia and Hypokalaemia by General Practitioners Study ('KAL GP' Study), was conducted among French GPs. To obtain a nationally representative sample, the study aimed to interview 500 GPs spread geographically throughout France. We performed a random draw in the directories of each French department. In order to obtain the targeted sample size, a constant proportion of GPs, representative of the number of GPs in each region, was calculated. Medical Associations, the Council of the Order of Physicians, Regional Unions in Healthcare, physician groups on social networks, and previously interviewed GPs were asked to disseminate a proposal to participate in the Kal GP Survey. A total of 618 calls were made in order to obtain the expected 500 responses. The 118 doctors who did not respond did not express a refusal but simply did not answer the message left (most often at the secretariat).

All participants were GPs who had general practice as their main activity, excluding physicians practicing exclusively 'alternative medicine', such as osteopathy, acupuncture, and homoeopathy; these physicians represent a small proportion of French doctors.

The telephone survey was conducted by a single physician (L. A. V.) by questionnaire. There were no missing data.

This questionnaire was previously validated after testing on a GP sample (composed of 10 GP residents and GPs from the University's Department of General Medicine) after expert review.[11] Verifications were made to ensure that all questions were understood. Any comment they may have regarding the understanding of the questionnaire was sought. There were no negative comments, and the answers were precise enough to enable interpretation. We did not repeat the questionnaire in order to assess the consistency in the answers because we were looking for spontaneous data.

The first portion of the questionnaire consisted of demographic and clinical practice information of the participating GPs: gender, age, geographical situation, and care management (eight closed-ended questions). The second portion consisted of the physician's current knowledge relative to hyperkalaemia and hypokalaemia definitions and intervention with regard to dyskalaemia (four closed-ended questions for both hyperkalaemia and hypokalaemia). The third portion concerned the management of hyperkalaemia and hypokalaemia (six open-ended questions each) specifically in the setting of either CKD or HF history, aimed at assessing the physician's behaviour with regard to angiotensin-converting enzyme inhibitors (ACEis), angiotensin receptor blockers (ARBs), or MRAs using two clinical cases (Data S1).

Open-ended questions were used in order not to influence the responses. The responses were then classified based on verbatim responses, which were subsequently grouped together when expressing the same response. Thus, 'ion exchange resin', sodium polystyrene sulfonate (SPS; Kayexalate©), and 'hyperkalaemia drug' were deemed as expressing the same response because there are currently no other available hyperkalaemia treatment in France other than SPS or calcium polystyrene sulfonate (Sorbisterit®). Similarly, when the GPs proposed 'hospitalization', 'emergency hospitalization', calling the 'emergency medical service', or calling an 'ambulance', these responses were also considered to express the same objective of referring the patient to an 'emergency department' (ED).

Ethical committee approval is not required for this type of professional survey in France, and collected data were anonymized.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD) if normally distributed or as median and

inter-quartile range if the distribution was skewed. Categorical variables are expressed as frequencies and proportions (%).

Analyses were performed using SAS® R9.4 (SAS Institute, Cary, NC, USA).

Results

Characteristics of participating general practitioners

Five hundred GPs participated in this survey, the characteristics of whom are summarized in *Table 1*. Median age was 34 years (extremes 26–69), and the majority of responders (63%) were women. There were 10/101 French administrative 'regions' for which we were unable to find physicians available to participate in the survey. GPs estimated that access to a cardiologist was easier than access to a nephrologist. Although the majority (67%) of GPs had an electrocardiogram (ECG) device, it was rarely used (13.6%) in dyskalaemic patients.

Potassium definitions and management

Thresholds to define hyperkalaemia/hypokalaemia, as well as for intervention, are presented in *Table 2*. A wide range of answers were observed for both items. The mean ± SD (range) potassium level leading to 'intervene' (as depicted in the succeeding section) was 5.32 ± 0.34 mmol/L (4.5–6.5) for hyperkalaemia and 3.23 ± 0.34 mmol/L (2.0–6.5) for hypokalaemia. The mean ± SD potassium level for referring the patient to the ED was 6.14 ± 0.55 (4.5–10) and 2.69 ± 0.42 (1–4) mmol/L, respectively.

Hyperkalaemia management in chronic kidney disease and/or heart failure patients

Ruling out pseudo-hyperkalaemia with a second blood sample was sought in approximately half of the cases (56%).

Dietary potassium restriction recommendations were scarcely recommended (4.6%). GPs reported that they seldom reduced or discontinued 'drugs prone to induce hyperkalaemia' for CKD (14%) or HF (25%) patients but frequently prescribed a potassium-binding resin (65% or 51%, respectively). Adding a loop diuretic was uncommonly implemented (1.4% and 9.8%, respectively, for CKD and HF). GPs sought the advice of a cardiologist (for a HF patient) or nephrologist (for a CKD patient) in, respectively, 27% and 36% of cases. GPs rarely referred the HF (12.8%) or CKD (6%) patients to an ED(*Table 3*).

When GPs were specifically asked regarding their behaviour when confronted with hyperkalaemia in patients treated with an ACEi/ARB (without any detail regarding medical history) and in patients with HF and CKD treated with an MRA (*Figure 1*), discontinuing the drug was the option most often chosen (~40%), whereas down-titration was seldom proposed (~10–15%). Maintaining the same doses was not uncommon (~10–20%), along with the prescription of a potassium binder (~20–30%), while loop diuretic prescription was relatively sparse (8–15%). Seeking a specialist's advice was quite common, and more frequent for a cardiologist (30–40% depending on the drug) than a nephrologist (10–25% depending on the drug). The declared approach was only very moderately modified by the clinical setting (HF and/or CKD).

Once normalization was achieved, the most common practice (~20%) was the permanent discontinuation of ACEi/ARB or MRA. In contrast, ~10% of GPs reported maintaining a low dose of ACEi/ARB or MRA following normalization, while a similar proportion reported restoring the initial dose (*Figure 2*).

Hypokalaemia management in chronic kidney disease or in heart failure patients

Approximately 50% of the GPs reported seeking the aetiology of hypokalaemia in patients with either CKD or HF (*Table* 3). Discontinuation or down-titration of potassium-modifying drugs was commonly reported (~30%), and potassium supplements were frequently reported to be prescribed (~70%). MRA use was scarcely reported (<5%), while none of the

Table 1 Characteristics of participating general practitioners

Characteristic	*n*	Mean ± SD/*n* (%)	Min–max	Median (Q1–Q3)
Male gender	500	186 (37.2%)		
Age (years)	500	39.9 ± 11.7	26.0–69.0	34.0 (31.0–49.5)
Is there an emergency department in the city you are currently living in?	500	198 (39.6%)		
Is there a laboratory in the city you are living in?	500	310 (62.0%)		
Do you have an easy access to a cardiologist?	500	429 (85.8%)		
Do you have easy access to a nephrologist?	500	237 (47.4%)		
Do you have an ECG device?	500	334 (66.8%)		
If you have an ECG device, do you use it in case of hypokalaemia or hyperkalaemia?	500	68 (13.6%)		

Table 2 Definition of potassium levels and thresholds for intervention (n = 500)—closed-ended questions

	Hyperkalaemia			Hypokalaemia		
	Mean ± SD	Min–Max	Median (Q1–Q3)	Mean ± SD	Min–Max	Median (Q1–Q3)
Definition level	5.12 ± 0.33	4.0–6.1	5.0 (5.0–5.5)	3.38 ± 0.29	2.0–5.5	3.5 (3.3–3.5)
Intervention level	5.32 ± 0.34	4.5–6.5	5.4 (5.0–5.5)	3.23 ± 0.34	2.0–6.5	3.2 (3.0–3.5)
'ECG' level	5.65 ± 0.38	4.5–7.0	5.5 (5.5–6.0)	3.02 ± 0.31	1.5–3.5	3.0 (2.9–3.2)
'ED' level	6.14 ± 0.55	4.5–10.0	6.0 (6.0–6.5)	2.69 ± 0.42	1.0–4.0	2.8 (2.5–3.0)

Table 3 Main results for clinical hypokalaemia or hyperkalaemia management approaches (n = 500); open-ended questions regarding chronic kidney disease or heart failure patients (in the absence of details regarding current medication)

Potassium management	Hyperkalaemia		Hypokalaemia	
Second blood test for confirmation ***	282 (56.4%)			
Dietary measures******	23 (4.6%)		15 (3.0%)	
Clinical examination******	208 (41.6%)		132 (26.4%)	
	CKD patients*	HF patients**	CKD patients*	HF patients**
Biological monitoring as the only intervention	36 (7.2%)	36 (7.2%)	25 (5.0%)	21 (4.2%)
Aetiology search	142 (28.4%)	193 (38.6%)	232 (46.4%)	238 (47.6%)
Potassium-modifying drug reduction or discontinuation	71 (14.2%)	126 (25.2%)	140 (28.0%)	156 (31.2%)
Add or increase SPS	325 (65.0%)	255 (51.0%)	Add or increase K + supplement 334 (66.8%)	368 (73.6%)
Add or increase loop diuretic	7 (1.4%)	49 (9.8%)	Add or increase MRAs 7 (1.4%)	20 (4.0%)
Seek advice from a cardiologist	8 (1.6%)	135 (27.0%)	14 (2.8%)	103 (20.6%)
Seek advice from a nephrologist	181 (36.2%)	22 (4.4%)	142 (28.4%)	18 (3.6%)
Referral to ED or hospitalization	30 (6.0%)	64 (12.8%)	23 (4.6%)	30 (6.0%)

CKD, chronic kidney disease; ED, emergency department; HF, heart failure; MRAs, mineralocorticoid receptor antagonists; SPS, sodium polystyrene sulfonate.
Legend: Corresponding questions:
*Question 2.1. In the presence of hyperkalaemia/hypokalaemia at levels defined from (Question 1.2 to Question 1.4) in a patient with CKD, what is your approach?
**Question 2.2. And if this patient has HF, what is your approach?
***Data extracted from open-ended Questions 2.1 and 2.2 considered together.

participants reported prescribing other potassium-modulating agents such as ACEi/ARB use. In these patients, GPs were more prone to refer CKD patients to a nephrologist (~30%) than HF patients to a cardiologist (<10%).

Finally, descriptive exploratory subgroup analyses

Considering gender, age (younger or older than 40 years) of the participating GPs, and high-income/low-income regions did not identify specific patterns regarding the multidimensional aspect of dyskalaemia management (data not shown). If any, we identified an association between the close vicinity of GP office from an ED and 'referring an HF patient' (19.2% with ED vs. 8.6% without ED) and 'referring an HF and CKD patient on MRA' (16.7% with ED vs. 9.3% without ED).

Discussion

This study is, to our knowledge, the first survey depicting declared GP practices regarding dyskalaemia, and it provides a number of noteworthy findings. The management of potassium disturbances appears to be very heterogeneous with regard to both dyskalaemia thresholds (for diagnosis and intervention) and management patterns. The latter most likely mirror the variety of available therapeutic options. Of note, in all likelihood, country-specific feature was the widespread use of potassium binders to manage hyperkalaemia (with a parallel widespread use of potassium supplementation to treat hypokalaemia). Another major finding is that GPs uncommonly referred their dyskalaemic patients to cardiologists and nephrologists (or the ED, if the latter was deemed necessary owing to the severity of the dyskalaemia) and that their management of potassium disorders was only very moderately modified by the presence or absence of HF and/or CKD (*Figure* 1). Of note, the patterns we observed generally did not differ between women and men and between younger and older GPs.

Reported thresholds for defining hyperkalaemia and hypokalaemia in this primary care setting were found to be consistent with those typically recommended in various guidelines.[5–8] A clear stepwise approach (i.e. the stronger the severity of the dyskalaemia, the higher the likelihood to perform an ECG and to refer the patient to the ED) was identified.

Figure 1 Initial GP behaviour (n = 500) in the presence of hyperkalaemia (level according to each physician) in patients treated with ACEi/ARBs (in the absence of details regarding medical history) or in patients with HF and/or CKD treated with MRA. *Refer to open-ended Question 2.5: In the presence of hyperkalaemia at a threshold defined in Question 1.2 to Question 1.4, what is your approach in a patient under renin–angiotensin system inhibitor (ACEi/ARB) treatment? (several answers were possible). **Refer to open-ended Question 2.3: In a patient with HF and CKD, under aldosterone antagonist (MRA) (Aldactone© spironolactone; or Inspra©, eplerenone) treatment, what is your approach in the presence of hyperkalaemia at a threshold defined in (Question 1.2 to Question 1.4)? (several answers were possible). Legend: HF, heart failure; CKD, chronic kidney disease; ACEi, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; ED or hospitalization, emergency department or hospitalization; GP, general practitioner; MRA, mineralocorticoid receptor antagonist.

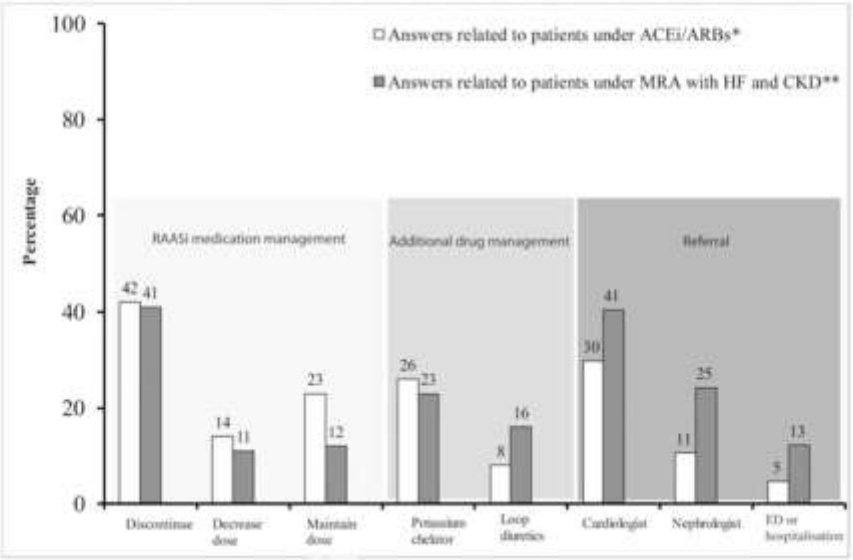
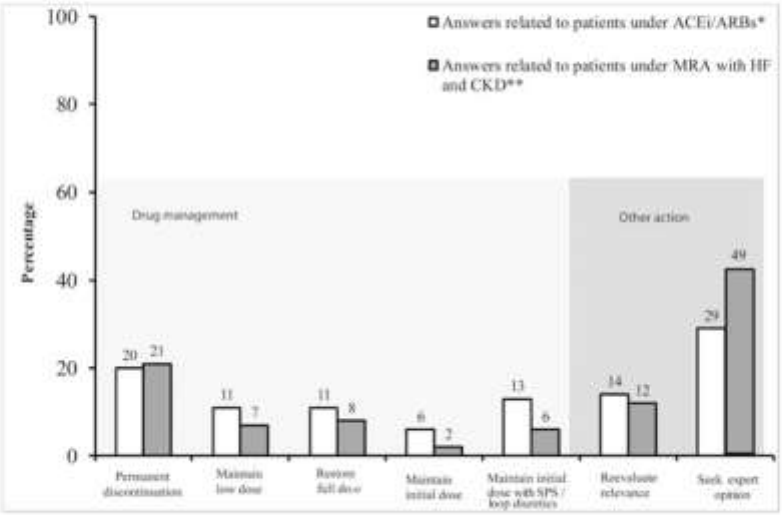


Figure 2 GP approach (n = 500) after normalization of hyperkalaemia in patients under ACEi/ARBs (in the absence of details regarding medical history) and patients under MRA and history of HF and CKD. *Refer to open-ended question 2.6: After resolution of hyperkalaemia, what is your approach toward these drugs (ACEi/ARBs)? (several answers were possible). **Refer to open-ended question 2.4: After resolution of hyperkalaemia, what is your approach toward these drugs (Aldactone©, spironolactone; or Inspra©, eplerenone)? (several answers were possible). Legend: HF, heart failure; CKD, chronic kidney disease; ACEi, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; SPS, sodium polystyrene sulfonate; GP, general practitioner; MRA, mineralocorticoid receptor antagonist.



Few practitioners perform an ECG in case of dyskalaemia even though they own the device. ECG is nevertheless recommended when confronted with dyskalaemia in the emergency setting.[6,7] Importantly, ECG was repeatedly shown to be an insensitive indicator of the severity of hyperkalaemia because cardiac manifestations can be non-specific or even absent at potassium levels that are associated with an increased mortality risk.[9,12,13] Despite the latter, recent attempts to detect hyperkalaemia with only two-lead ECG have been developed[14] and may ultimately lead to practice changes.

The management of potassium disorders is highly heterogeneous, which most likely coincides with the variety of available treatment approaches. It should be noted that the treatment approach for patients with hyperkalaemia is currently undergoing change with the recent availability in the USA and European Union of new-generation potassium binders,[4] which, as of yet, are not reimbursed in France. Until recently, the recommendations were to (i) restrict the dietary potassium intake; (ii) avoid potassium supplements and drugs affecting renal function; and (iii) initiate a non-potassium-sparing diuretic or increase the dose if already receiving a diuretic[15] (which, however, may lead to excessive fluid depletion and a worsening in renal function, along with an overstimulation of the RAAS).[16] The latter is unfortunate, owing to the major role of RAASi including MRAs in the cardiorenal continuum, as emphasized subsequently.

In the present survey, physicians very rarely raised in a spontaneous manner the notion of dietary measures (4.6% in hyperkalaemia and 3% in hypokalaemia). It should nevertheless be emphasized that the sustainability of such dietary restrictions (for hyperkalaemia) on the long term is questionable and may eventually deprive patients of 'healthy' foods, that is, a Dietary Approaches to Stop Hypertension diet. We recently[17] reported a retrospective chart review depicting recurrent hyperkalaemia management practices in five European countries (including France) by interviewing 500 physicians (including 50 cardiologists and 50 nephrologists per country). In this latter study, ~91% of nephrologists and 85% of cardiologists (consistent results were observed in France) declared having prescribed a low-potassium diet. Of note, the above physicians were interviewed regarding their management of recurrent hyperkalaemia using a closed-ended questionnaire, whereas open-label questions were asked to our GPs in the current study.

A predominant approach for treating hyperkalaemia reported in the present study consisted of the discontinuation or down-titration of RAASi, whereas, of note, their up-titration was by contrast never proposed in the setting of hypokalaemia. ACEi, ARBs, and MRAs may inherently expose them to an increased risk of hyperkalaemia, particularly when administered in combination,[18] while RAASi is among the drugs that confer the most significant survival benefit in patients with cardiovascular and renal diseases. Indeed, major clinical trials in HF have demonstrated a reduction in both cardiovascular and overall mortality with RAASi treatment leading to a Class I indication in major European and US guidelines.[19] Compliance to these guidelines[20] and the prescription of guideline-recommended target doses has moreover been found to be associated with better outcomes in observational studies.[21] Current international CKD guidelines recommend using RAASi in order to achieve nephroprotection, because they enable preserving kidney function and delay the progression to dialysis in CKD.[4,22] Recent guidelines further propose algorithms for therapeutic dose adjustment in case of hyperkalaemia.[23] Notwithstanding the latter, observational studies have nonetheless shown suboptimal MRA use, dose titration, and poor clinical follow-up.[22,24–27] In a recent observational study including all Stockholm citizens initiating MRA therapy, the development of hyperkalaemia within a year was associated with a four-fold significantly higher risk in overall mortality. Following the occurrence of hyperkalaemia, 47% discontinued MRA, whereas only 10% reduced the prescribed dose. Strikingly, when MRA was discontinued, most patients (76%) were not reintroduced to MRA therapy during the subsequent year.[24] Depriving patients of RAASi, highly recommended treatments based on a very high level of evidence, may ultimately lead to worse outcomes in the cardiorenal continuum.[17]

In the present study, SPS prescription and potassium supplementation for hyperkalaemia and hypokalaemia treatments, respectively, were highly prevalent. Of note, with regard to hyperkalaemia, GPs did not cite bicarbonates (used in 10% of cases by French nephrologists and cardiologists) and barely prescribed loop diuretics (compared to ~48% prescription rate in France among nephrologists and cardiologists according to our previous study).[17] Thiazide diuretics were just not quoted by the GP participants.

The high prescription rate of SPS reported herein is specific to France, corroborating previous studies,[28,29] including our latest study (~45%),[17] whereas SPS is much less prescribed in other countries,[17] with concerns regarding its safety being repeatedly raised.[30] Patients with HF and/or CKD or with cardiovascular co-morbidity are complex patients to manage and most often warrant a multidisciplinary approach. While access to a cardiologist was reported herein as relatively easy (85.8%), access to a nephrologist reportedly remained more difficult (47.4%). Access to a cardiologist's or nephrologist's advice is largely dependent on current French medical demographics. There is a shortage of these two specialists in France, which delays access to consultation, but also makes direct access by telephone difficult. This may contribute to the poor cooperation between the GPs and these specialists. Of note, we did not identify regional differences in the dyskalaemia management pattern, while the closed vicinity of GPs' office and ED was found to be associated with more referrals.

Ultimately, GPs rarely referred to a cardiologist or nephrologist in a situation of hyperkalaemia or hypokalaemia. These

two specialists may also carry different messages and different practices as previously described,[17] which may lead to some confusion on the part of GPs and ultimately deprive their HF or CKD patients of life-saving drugs (in case of a permanent discontinuation of RAASi). Acknowledging that there are no specific recommendations for the management of dyskalaemia in general practice, while there are cardiology and nephrology guidelines, with some inconsistencies, our main hypothesis is indeed that GPs might be somehow confused by different treatment options suggested by cardiologists versus nephrologists. We propose that including GPs in future guideline development may increase their applicability.

In our view, the heterogeneity observed in the present study strongly highlights the need to develop algorithms aimed at standardizing outpatient management practices and possibly avoid inaccurate behaviour, such as therapeutic inertia (e.g. no potassium recheck, no drug changes or RAASi dose maintenance in the setting of hyperkalaemia, and lack of mitigation strategy). A major strength of this survey is the in-depth analysis of open-ended questionnaires, which allowed accurately retrieving the heterogeneity of potassium disorder management.

The present study has several limitations. First, our study likely presents a selection bias: the population is not representative of the overall GP population in France given that the average age of the participating GPs was noticeably younger (39.9 vs. 50.6 years[31]); indeed, the GPs who accepted the phone interview responded initially mostly via the Internet and had been contacted through social networks. In the same manner, the proportion of men and women also differed from the overall population of French GPs (62.8% vs. 48.2%[31]). Secondly, there may be a possible imbalance between rural and urban areas, because the professional location of the GPs was not collected in most instances. Thirdly, the collected data were declarative and not corroborated by patient record review. Our original approach confronted the doctor with everyday situations and was deemed the most suitable to seek relevant insights on the management of dyskalaemia by GPs. Fourthly, thiazides were not spontaneously quoted by the GPs, while asking them specifically—which we did not—might have been informative.

Finally, the external validity could be questioned owing to the widespread use of 'old-generation' potassium binders in France compared with other countries. However, the recent availability of better-tolerated potassium binders may ultimately lead to a widespread use of these compounds in other countries.

Conclusions

Owing to the major heterogeneity of French GP practices toward hypokalaemia and hyperkalaemia diagnosis and management practices in their outpatients, including those with HF and or CKD, there is a likely need to standardize (potentially enabled by therapeutic algorithms) and evaluate standardized practices.

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Conflict of interest

L.A.V., Z.L., and J.M.B. have nothing to declare. P.R. reports personal fees (consulting) from Idorsia and G3P and honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, CVRx, Fresenius, Grunenthal, Novartis, Novo Nordisk, Servier, Stealth Peptides, Ablative Solutions, Corvidia, Relypsa, and Vifor Fresenius Medical Care Renal Pharma; outside the submitted work, P.R. is the cofounder of CardioRenal. N.G. reports personal fees (consulting) for Novartis and Boehringer, outside of the submitted work.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1. Telephone survey.

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Synthèse Article 3

Dyskalemia: a management problem for students

Article « sous presse » (accepté le 13 octobre 2020) à Fundamental and Clinical Pharmacology.

L'objectif principal de cette étude était d'évaluer les connaissances des étudiants en médecine générale concernant les dyskaliémies et leurs compétences concernant leur prise en charge à partir de vignettes cliniques.

Nous avons interrogé l'ensemble des étudiants en médecine générale de la faculté de médecine de Nancy (Université de Lorraine) à l'aide d'un auto-questionnaire (N=357). Il était divisé en deux sections : les premières questions portaient sur la perception de la dyskaliémie et les suivantes étaient des situations cliniques à réponse libre. Nous avons comparé les réponses des étudiants à l'enseignement dispensé au deuxième cycle des études médicales, et aux consensus d'experts pour la prise en charge des dyskaliémies. Deux cent questionnaires ont pu être analysés.

Les seuils de dyskaliémies étaient plutôt en accord avec la littérature. Néanmoins les connaissances pour la prise en charge de la dyskaliémie étaient très variables d'un étudiant à un autre. L'examen clinique était rarement mentionné ainsi que l'adressage aux spécialistes cardiologues ou néphrologues.

Les étudiants semblaient favoriser l'utilisation de résines échangeuses d'ions pour le traitement de l'hyperkaliémie. En cas d'hyperkaliémie dans un contexte d'insuffisance cardiaque et rénale, la prise en charge était majoritairement axée sur le risque rénal. La prise en charge de l'hyperkaliémie différait considérablement des directives européennes (conférences de consensus). Ils avaient tendance à interrompre définitivement les IEC/ARA2 et / ou les ARM sans envisager de les réintroduire par la suite. La prise en charge était toutefois globalement conforme à ce qui est enseigné dans le module "Néphrologie" du programme universitaire au chapitre intitulé "Anomalies de l'équilibre potassique", enseignement théorique ne prenant pas en compte la complexité rencontrée en cas de comorbidités telles que l'association avec l'insuffisance cardiaque, et qui recommande, en cas d'hyperkaliémie modérée, "l'arrêt de médicaments induisant une hyperkaliémie", sans envisager leur réintroduction.

D'autre part, dans le chapitre dédié à la façon de traiter l'insuffisance rénale chronique, la possibilité de l'arrêt "temporaire" de l'IEC ou de l'ARA2 était discutée, sans aucune référence aux ARM qui ne sont pas mentionnés dans le programme.

Le risque associé à l'hypokaliémie était globalement sous-estimé par les étudiants.

Ce travail montre que les étudiants en médecine sont confrontés à des contradictions dans leurs apprentissages car il n'existe au final pas de consensus clair pour la prise en charge de ces patients atteints du syndrome cardio-rénal.

Cette étude est la première, à notre connaissance, qui interroge les connaissances sur les dyskaliémies des étudiants en médecine générale, futurs médecins généralistes. La principale force de cette étude réside dans l'utilisation d'un questionnaire ouvert, qui a permis de ne pas influencer les réponses des étudiants.

Cette étude met en évidence un manque de cohérence entre la formation initiale des futurs médecins généralistes et les recommandations concernant les patients souffrant d'insuffisance cardiaque et rénale. Il en résulte souvent une gestion inadéquate et une réticence à réintroduire des médicaments sujets à induire une hyperkaliémie (IEC / ARA2 et ARM) après un premier épisode d'hyperkaliémie. Il est essentiel que les étudiants en médecine soient très tôt confrontés à ce type de situations complexes de prise en charge du syndrome cardio-rénal, en raison de la prévalence croissante de ce syndrome chez les patients âgés atteints de diabète, d'insuffisance cardiaque et de maladie rénale.

Dyskalemia: a management problem for students

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Words count: 3833

Abstract

Background: Although dyskalemia is common, its management can be problematic for students and general practitioners, especially when it occurs in patients with heart and renal failure. The basic academic knowledge of general medicine students, who have often not yet encountered clinical situations of dyskalemia, remains unclear in this regard.

Objectives: The purpose of this study was to evaluate the knowledge and reflexive practices of general medicine students in regard to dyskalemia.

Methods: A cross-sectional survey, based on a self-questionnaire, of all of the students enrolled in general medicine studies at the Faculty of Medicine at the University of Nancy (France) at the end of their degree. The students were asked questions pertaining to specific clinical situations. The answers were compared to the information provided in the medical curriculum as well as to the relevant European guidelines.

Results: We collected 290 of the questionnaires (participation rate: 81.2%). The hyper- and hypo-kalemia thresholds considered pathological (3.5-5.0 mmol/L) were known by 78% and 67% of the students, respectively. The perception of danger in case of severe hypokalemia was underestimated by 62.7% of them. In most cases, the proposed management of hyperkalemia in heart and renal failure did not comply with the relevant guidelines. The students tended to favor permanent discontinuation of the administration of converting enzyme inhibitors (ACE) and/or mineralocorticoid receptor antagonists (MRA) without considering the need for their reintroduction (51.6%). Sodium polystyrene sulfate was frequently seen as an appropriate first-line treatment for hyperkalemia (45%).

Conclusions: The knowledge and competence of general medicine students appear to be lacking for hyperkalemia in heart and renal failure, and they are long way from full compliance with the relevant European guidelines. Exposure to complex clinical situations as part of the medical curriculum, therefore, seems essential to improve the way dyskalemia is managed in France.

Strengths and limitations of this study

1) The main strength of this study lies with the use of an open-ended questionnaire, which ensured that there were no leading questions and not suggest possible answers to the situations described.
2) The second strength: The questionnaires were filled out in the presence of a friendly and neutral team, without direct intervention but with immediate availability of assistance if required (self-administered questionnaire).
3) The third strength: Methodological bias was minimized by providing resources to organize the task of collecting, analyzing, and processing the information.
4) The first limitation: Sample selection bias cannot be fully ruled out, although we are confident that we were able to ensure adequate representativity of the population of students enrolled in French general medicine studies.
5) The second limitation: we cannot exclude that the respondents were the most motivated students, however we had a high response rate of over 81%.

1. Background

Dyskalemia (hypokalemia and hyperkalemia) are potentially dangerous conditions (1,2). It is mostly encountered in high-risk patients (e.g., with heart failure, renal failure, cardio-renal syndrome, diabetes, hypertension) but also, occasionally and unexpectedly, people without comorbidities (3). Management is not consensual according to the guidelines in place, and the thresholds for hypokalemia and hyperkalemia are not universal (4).

Many studies of patients with heart failure have focused on the association between blockers of the renin-angiotensin-aldosterone system (RAAS) and anti-aldosterone, as all may trigger hyperkalemia and can be a source of problems, particularly for general practitioners (5-8). In contrast, loop diuretics may lead to hypokalemia or dehydration, which can be difficult to manage in the context of renal insufficiency (9).

It is not precisely known how general practitioners deal with dyskalemia, especially as there is not a specific decision tree to guide them in this regard. While the way they go about this is presumably based on their prior experiences and on interactions with other specialists, the basic academic knowledge and skills of general medicine students who have not yet encountered clinical situations of dyskalemia remains largely unknown.

2. Methods

2.1. Objectives

The main objective of this study was to evaluate the knowledge of French general medicine students regarding dyskalemia.

The secondary objective was to evaluate how they manage clinical situations involving dyskalemia.

2.2. Type of study

All of the students (from the first to the third year of study) at the end of their general medical studies in Nancy, France, (N=357) were asked to answer a self-questionnaire, kind of like Durieu et al, regarding the perception of adverse drug reactions (10) during their final exams in June 2017. The questionnaire was in two parts: the first two questions focused on the perception of dyskalemia and the next three questions were clinical situations with open answers, to avoid influencing the answers. The questionnaire was constructed in such a way that the study reflects a general medicine context, where more information is not available at the start usually limited to the only information available in the medical report. The objective was to evaluate the student's "reflex" management without suggesting a list of predefined answers so as not to influence the student. The answer was open-ended.

The questionnaire was first tested with ten students to ensure that it was fully understood in the first round and that the answers were stable in the second round, as well as to ensure the validity of the questionnaire (11).

The results were analyzed by collecting the terms in verbatim form. Thus, "monitoring under scope", "intravenous hydration", and "calcium gluconate" were classified under the term "hospitalization/emergency" as these treatments are not available in the public health care system; "taking vital signs" and "blood pressure measurement" were classified under "assessment/clinical examination". The analysis and classification of the verbatim statements were performed after comparing the independent analyses of two authors (S. L. and B. J.M.) followed by arbitration.

The answers were then compared to the treatment stipulated in the medical curriculum (from the University College of Nephrology Teachers) (12), and then to the treatment recommended by the relevant European guidelines (12,13). The answers were stratified by the years of study.

2.3. Statistical analysis

The analyses were performed using SAS® R9.4 software (SAS Institute, Cary, NC, USA). The bilateral significance level was set at $p < 0.05$.

All of the students' answers, which were generally binary, were proportionally described in the general population according to the year of study. Those regarding the hyperkalemia and hypokalemia thresholds were categorized; their distribution was analyzed according to the year of study.

The proportion of answers that were in keeping with the curriculum and the relevant European recommendations/literature data/expert opinions were based on indicator variables. These were created from the students' answers, as well as the information in the curriculum and the European guidelines.

Each indicator variable was rated "1" if the student's answer was in keeping with the medical curriculum or the guidelines, and "0" if the answer was non-compliant.

The results were compared according to the years of study using Fisher's exact test, and the thresholds of dyskalemia according to the years of study were compared using a Chi^2 test of homogeneity.

3. Results

The percentage of questionnaires returned was 81.2% (n=290/357). Three questionnaires were partially completed and were not included (Figure 1).

3.1. Description of the population

The general medicine students who responded to the questionnaire were evenly distributed among the three years of internship (33.8% in the first year, 35.9% in the second year, and 30.3% in the third year).

3.2. Overall results and by the years of study and compare with the relevant guidelines

3.2.1. Limits of kalemia considered to be pathological

The students considered a mean hyperkalemia of 5.1 mmol/L to be pathological. The minimum hyperkalemia value proposed by one student was 3.5 mmol/L and the maximum value was 6.5 mmol/L. The mean hypokalemia considered to be pathological by the students was 3.4 mmol/L (minimum 2.5 mmol/L and maximum 3.8 mmol/L). (table 1)

		Hyperkalemia threshold				**Hypokalemia threshold**			
Year	n=287	**K< 5 17 (5.9%)**	**K=5 192 (66.9%)**	**5 < K ≤ 5.5 71 (24.7%)**	**K > 5.5 7 (2.4%)**	**K < 3 8 (2.8%)**	**3 ≤ K < 3.5 53 (18.5%)**	**K=3.5 224 (78%)**	**K > 3.5 2 (0.7%)**
1st	n=97	10 (18.2%)	72 (74%)	11 (11.3%)	4 (4.1%)	4 (4.1%)	16 (16.5%)	76 (78.4%)	1 (1%)
2nd	n=103	6 (5.8%)	61 (59.2%)	34 (33%)	2 (1.9%)	3 (2.9%)	17 (16.5%)	82 (79.6%)	1 (1%)
3rd	n=87	1 (1.1%)	59 (67.8%)	26 (29.9%)	1 (1.1%)	1 (1.1%)	20 (23%)	66 (79.5%)	0 (0%)
		p=0.0005				*p=0.85*			

Table 1: Hyperkalemia and hypokalemia threshold (mmol/L) according to the years of study.

There was a statistically significant difference in the hyperkalemia thresholds for the different years of study (p=0.0005). Nearly a quarter of the students rated the threshold for hypokalemia as being strictly below 3.5 mmol/L (21.3%, n=61/287) (Table 1).

The kalemia thresholds considered to be pathological according to the curriculum (11) and the relevant guidelines (13) were the same (hypokalemia = 3.5 mmol/L and hyperkalemia = 5.0 mmol/L). This hypokalemia threshold was indicated by 78% (n=224/287) of the students, while

this hyperkalemia threshold was indicated by 66.9% (n=192/287) of the students, and 59.6% (n=171/287) of the students correctly identified both of these pathological thresholds.

3.2.2. Perception of danger

More than half of the general medicine students thought that severe hyperkalemia was more of a “concern” than severe hypokalemia (60.3% (n=173/287) vs. 26.5% (n=76/287)); for 10.8% (n=31/287) both types of kalemia were a concern, while for 2.4% (n=7/287) severe dyskalemia was not a concern. The students' answers were similar across all internship years (p=0.74).

There was no difference in terms of what the students had been taught regarding the danger associated with hyperkalemia versus hypokalemia. The Expert Consensus of the European Society of Cardiology has stated that hypokalemia maybe even more dangerous than hyperkalemia (14) (only 26.5% (n=76/287) of the students shared this opinion).

3.2.3. Clinical cases and comparison with evidence by medicine

The students were presented with 3 hypothetical clinical situations:

1/ Isolated hypokalemia at 2.6 mmol/L (Figure 2)

Most of the students stated that they would perform an electrocardiogram (ECG) (79.8%, n=229/287) and oral potassium supplementation (70.7%, n=203/287); while 16.7% (n=48/287) would provide intravenous supplementation. Half of them (53.7%, n=154/287) would request another kalemia test and 59.9% (n=172/287) would perform additional biological tests. Only a quarter of the students (28.6%, n=82/287) would undertake oral questioning and a clinical examination of the patient. They were generally not inclined to ask for advice from a specialist (28.6%, n=82/287). The further along the student was with their studies, the less likely they were to perform an electrocardiogram (ECG) in case of isolated hypokalemia (p=0.0001). On the other hand, they would more often request additional biological tests (p=0.004). The students in the second year were the most inclined to supplement with potassium (p=0.029) and they were the least inclined to refer their patients to the emergency department or to a hospital (p=0.025). There was not a statistical difference between the internship year in terms of checking the kalemia a second time (p=0.33) or performing an interview and a clinical examination (p=0.47).

More than 50% of the students provided answers that were in keeping with the medical curriculum and with the data in the literature, except for the items "Interrogation/clinical

examination" (28.6%, n=82/287) and "Diet rich in potassium" (1.4%, n=4/287). The major difference lies in the way the patient would be supplemented with potassium: 70.7% (n=203/287) of the patients would be given an oral supplementation in accordance with the data in the literature (15,16). Indeed, interrogation, clinical examination and further investigations are essential to determine whether the patient should be hospitalized, and if so, the route of administration will be intravenous. If there is good tolerance and no signs of severity, the route of administration will be oral. There is no discrepancy between curriculum and expert opinion.

2/ Isolated hyperkalemia at 5.7mmol/L (Figure 3)

Approximately three-quarters of the students indicated that they would first request another kalemia test (75.3%, n=216/287). An ECG was favored by 59.9% (n=172/287), and slightly less than half would prescribe an ion-exchange resin (44.9%, n=129/287) or additional biological testing (47%, n=135/287). Very few would undertake oral questioning and a clinical examination of the patient (15.7%, n=45/287) or ask for the opinion of a specialist (20.6%, n=59/287). Students in the first year of internship were the most likely to favor performing an ECG ($p < 0.0001$) and to treat the patient with Polystyrene Sulfonate (p=0.0002), while students in the second year were the least likely to recommend an ECG ($p < 0.0001$) and to treat with Polystyrene Sulfonate (p=0.0002). There was not a statistical difference between the year of study with regard to checking the kalemia a second time to rule-out false hyperkalemia (p=0.21) or performing additional biological tests (p=0.098).

In case of true hyperkalemia (excluding false hyperkalemia secondary to hemolysis and/or delayed blood centrifugation), three items were different between the medical curriculum and the expert opinions: the students agreed with the curriculum in terms of performing an ECG (59.9%, n=172/287) but also with the experts' opinions in regard to not performing additional biological examinations (53%, n=152/287) or prescribing Sodium Polystyrene Sulfonate (55.1%, n=158/287), at this level of kalemia.

3/ Hyperkalemia of 6.0 mmol/L in a patient with heart and kidney failure (Figure 4)

The answers of the students regarding the management of this situation were very heterogeneous: half of them would perform an ECG (51.2%, n=147/287, 51.6% of the students would discontinue the MRA and/or ACE inhibitor (n=148/287), while a third would reduce their dose (34.5%, n=99/287). More than a third of the students (39.7%, n=114/287) stated that they would treat this hyperkalemia with an ion-exchange resin. Less than half of the students

(42.5%, n=122/287) indicated that they would ask for specialist advice. The further along the general medicine student was with their studies, the more they favored prescribing an ion-exchange resin (p=0.023), and the more they would perform another check of the kalemia ($p < 0.0001$) to rule-out a false hyperkalemia (due to the sampling process e.g. at home, with delayed centrifugation leading to hemolysis) and additional biological examinations (p=0.024). There was not a statistical difference between the years of study in regard to whether they would perform an ECG (p=0.42) or transfer the patient to the emergency department (p=0.085).

Several items were discordant between the medical curriculum and the guidelines: the students' answers were in keeping with the European guidelines to not undertake additional biological examinations (80.1%, n=230/287). On the other hand, only 3.8% (n=11/287) followed the guidelines for "temporary" discontinuation of MRA and/or ACE, and more than 51.6% (n=148/287) recommended "permanent" discontinuation. Increasing the dosage of Furosemide was considered appropriate by 20.6% (n=59/287).

4. Discussion

To our knowledge, this is the first study to evaluate the competence and the perception of danger of graduating French general medicine students regarding dyskalemia.

- The knowledge regarding the management of dyskalemia was highly variable from one student to the next and according to how close they were to completion of their medical degree.
- The thresholds for dyskalemia were not well known and there was inadequate recognition of the risk associated with hypokalemia.
- French medical students appear to favor the use of ion exchange resins. This is specific to France and probably due to what is taught in the medical curriculum.
- In case of hyperkalemia in the context of heart and renal failure, management was mostly focused on the renal risk, while ignoring the cardiovascular benefit.
- The students tended to be disinclined to examine patients in case of dyskalemia.
- The students tended to see little merit in engaging a specialist when faced with dyskalemia.
- The use of ECG decreased as the studies progressed, probably because the internship in the GP's office has not yet been completed in the seventh-year initial formation.

4.1. Variability of the answers

We were surprised to discover that some students considered extreme and dangerous values to be the pathological thresholds for kalemia: 2.5 mmol/L for hypokalemia and 6.5 mmol/L for hyperkalemia.

The greatest diversity in the answers related to hyperkalemia with heart and renal failure, and was dependent on the level of advancement in the specialty, especially in regard to the prescription of Sodium Polystyrene Sulfonate (28.9% of students in the first year of internship versus 47.1% in the third year) and performing a second kalemia test to rule-out a false hyperkalemia due to the sampling process (19.6% in the first year versus 49.4% in the third year). Four students even stated that they would stop all treatments (1.4%), which is generally thought to be extremely dangerous for the patient.

In case of isolated hypokalemia, management varied also according to the years of study: students in the second year of internship were the most likely to supplement by oral administration and to not refer their patients to the emergency department, unlike the other two years. In addition, there was a difference in the way the potassium would be supplemented: 16.7% would do so intravenously versus 68.3% favoring oral administration.

In the case of isolated hyperkalemia, the approach of the seventh-year medical students was essentially to perform an ECG, to treat with Sodium Polystyrene Sulfonate, and to recheck the kalemia, whereas the approach of the ninth-year medical students was to initially only recheck the kalemia. The thresholds considered pathological are different in each laboratory, and students rely on these standards to manage hyperkalemia.

4.2 Inadequate recognition of the risk related to hypokalemia

The risk associated with hypokalemia is often underestimated by students. Indeed, mortality is significantly increased below a threshold of 4.1 mmol/L in case of hypertension (1) or chronic heart failure (17), and 3.9 mmol/L in case of acute heart failure after myocardial infarction (18). Several studies have also shown that hypokalemia is associated with increased mortality in heart failure (19), and that blood potassium levels below 4.0 mmol/L are associated with an increased risk of all-cause mortality, mortality from cardiovascular disease and progressive heart failure, and an increased rate of all-cause and cardiovascular hospitalizations (9,20). Hypokalemia increases the risk of ventricular arrhythmia and cardiac arrest (2,21); a decrease in blood potassium by 1 mmol/L increases the risk of ventricular arrhythmia by 28% (22). In case of cardiac arrest, kalemia is thought to be significantly lower than in controls, and survivors are often hypokalemic (23-25).

There is a U-shaped relationship between kalemia and all-cause mortality, and levels of potassium that are considered "normal" are also associated with an increased risk of death. In general, the more the potassium level deviates from normal, the higher the mortality (1).

4.3. Widespread use of ion-exchange resins

French general medicine students are taught to use Sodium Polystyrene Sulfonate (SPS), which is an ion-exchange resin. This is in accordance with the practices of French doctors, who use SPS much more frequently than their German, Italian, Spanish, and English colleagues (26). However, there is no evidence regarding the efficacy of SPS in the emergency treatment of hyperkalemia (27, 28). The optimal rate of correction for hyperkalemia is unknown, and the relevance of an immediate decrease of kalemia in patients without cardiac manifestations of hyperkalemia has not been demonstrated (29). Additionally, this drug has not been rigorously evaluated in clinical trials to prove its efficacy and safety in acute or chronic hyperkalemia (30). Since the counter-exchange ion is sodium, extreme caution should be taken in patients with heart failure, as such patients cannot tolerate even a small increase in sodium load (30). It should

be noted that SPS has marketing authorization (MA) in France for medical services rendered that are considered important. This drug was indicated as a first-line treatment for hyperkalemic patients in the French medical curriculum (12) at the time that the questionnaire was distributed (June 2017). This has been modified in the new version of the curriculum released in 2018 by the University College of Nephrology Teachers (version 8), which no longer considers SPS as a necessity but as an option in case of hyperkalemia. Of importance, none of the new-generation potassium binders is reimbursed in France to date, therefore preventing from any related teaching process.

4.4. Management of hyperkalemia in heart and renal failure

The management of hyperkalemia by French general medicine students differs quite considerably from the European guidelines. They tend to discontinue ACE inhibitors and/or MRAs without considering reintroducing them, which can adversely affect patients as the morbi-mortality increases without the use of an optimal dose of these drugs (30-32). Trevisan et al. have shown that after hyperkalemia, 47% of MRA treatments are halted, and they are not reintroduced in 76% of cases (33). Discontinuation of RAAS inhibitor therapy is associated with an increased risk of cardiovascular morbidity and mortality and total mortality (14). The European guidelines in regard to heart failure tolerate a maximum hyperkalemia threshold of 6.0 mmol/L. Above this limit, RAAS inhibitors should be discontinued for a time, but not definitively; between 5.5 and 6.0 mmol/L, there can be brief discontinuation or dose reduction (13,14). Thus, the European guidelines emphasize the need to try to reintroduce RAAS inhibitors as soon as possible, when they have been temporarily halted or the dosage decreased due to hyperkalemia, with close monitoring of kalemia and renal function (13). Increasing the dosage of furosemide, considered as appropriate by 20% of the students, is an acceptable solution in case of hyperkalemia, but it should however be avoided in case of AKI and signs of dehydration.

The management is in accordance with what is taught in the Nephrology module of the medical school curriculum in the chapter entitled "Potassium balance abnormalities" (12). This is theory-based teaching that does not consider the complexity encountered in case of comorbidities such as the association with heart failure, and which recommends, in the case of moderate hyperkalemia, "eviction of hyperkalemic drugs", without their subsequent reintroduction. The risk/benefit ratio of hyperkalemia is not emphasized in teaching, and

general medicine students tend to refer to "*Primum Non Nocere*", which is a concept that has become obsolete.

On the other hand, in the chapter regarding how to treat chronic renal failure, the possibility of "temporary" discontinuation of ACE inhibitors or ARA2 is discussed, without any reference to anti-aldosterone drugs, which are not mentioned in the curriculum. However, this information is too "diluted" to be taken in by the students, especially as it contradicts the information in the chapter "Potassium balance abnormalities".

Medical students are faced with contradictions that are even more prejudicial, as there is no clear consensus regarding the management of these patients with cardio-renal syndrome in general practice. The fear of inducing serious secondary effects (hyperkalemia, deterioration of renal function) has led some doctors to avoid RAAS inhibitors (6), without considering the demonstrated benefit of these molecules on morbi-mortality in the event of heart failure (5, 34,35). Moreover, the use of RAAS inhibitors in France is low compared to Germany, Italy, Spain, and the United Kingdom (26). For this reason, the use of new experimental potassium chelating agents (patiromer or sodium zirconium cyclosilicate (ZS-9)) could be an option in the near future to compensate for this under-prescription (36-40). These drugs have a European MA but are not presently available in France.

4.5. Limited use of interrogation and clinical examination

Surprisingly, we found that the students were very rarely inclined to carry out an interrogation and clinical examination of patients with dyskalemia, even though this is generally considered to be essential during a medical consultation. In case of dyskalemia, it is crucial to identify any dietary issues and clinical elements associated with dyskalemia and to provide advice accordingly. Very few students introduce, and therefore explain to the patient, a potassium-rich diet in case of hypokalemia, whereas it is recommended in association with supplementation (41,42).

4.6. Limited use of specialists

The students indicated that they would rarely request specialist advice and rarely refer their patients to hospitals or emergency departments in case of isolated dyskalemia. They are inclined to manage these situations on their own, especially if they are advanced in their studies. The use of specialists and hospitalization is also low among practicing GPs, ranging from 5.8 to 6.6% according to the study (43-45).

4.7. Use of the ECG

For isolated dyskalemia discovered in general practice, students in the first year of internship more often recommend performing an ECG than those in the following two years of study. This may be a result of the internship with a general practitioner. Indeed, although the availability of the required equipment in doctors' offices varies from 49% to 86% according to the study, the frequency of their use is at least once a week for half of the doctors who have an ECG device available (46,47). Moreover, an ECG is not a very sensitive indicator of the severity of dyskalemia. Cardiac manifestations may be non-specific or absent at potassium concentrations that are associated with a risk of mortality (29). In case of hyperkalemia, an ECG is recommended above 6.0 mmol/L (29), whereas in case of hypokalemia, it is recommended for all patients, irrespective of their potassium level (49).

4.8. Strengths and limitations of the study

The main strength of this study lies with the use of an open-ended questionnaire, which ensured that there were no leading questions.

We limited the potential for bias by clearly explaining the objectives of the study and how the questionnaire was to be filled out before completing it. The questionnaires were filled out in the presence of a friendly and neutral team, without direct intervention but with immediate availability of assistance if required (self-administered questionnaire).

Methodological bias was minimized by providing resources to organize the task of collecting, analyzing, and processing the information. The questions asked were intended to be straightforward, short, neutral, and without ambiguity.

Naturally, sample selection bias cannot be fully ruled out, although we are confident that we were able to ensure adequate representativity of the population of students enrolled in French general medicine studies.

The bias linked to the "experience" of the general medicine students could be assessed by the last question, although this question contained ambiguities. In June 2017, the students who had just started a new stage of internship on May 1st did not necessarily include this in their answer. Indeed, "current or ongoing internships" was not specified. There was, therefore, a loss of information.

The questionnaire is not without its limitations, but overall, we avoided many of the potential biases by excluding any leading questions and by reducing the time needed to complete the

questionnaire. The questions were open-ended so as not to suggest possible answers to the situations described.

In conclusion, the validity of the results clearly needs to take into account the limitations mentioned above, but these do not significantly detract from the coherence and overall meaning of the results.

5. Conclusion

The medical curriculum cannot always take into account the complex situations experienced in clinical practice. Our study points out a lack of coherence between what is taught regarding the management of dyskalemia and the guidelines regarding patients with heart and renal failure. This often results in inadequate management and a reluctance to reintroduce drugs prone to induce hyperkalemia (ACE/ARA2 and MRA) after an initial episode of hyperkalemia. This at least in part explains why France has the lowest level of RAAS inhibitor use in Europe (27), and why these drugs are often used at a suboptimal dosage in heart failure. This is quite the opposite in case of chronic kidney insufficiency, for which France has the highest level of RAAS inhibitor use in Europe (50).

It is essential for medical students to very early on be faced with complex situations in the management of cardio-renal syndrome, due to the increasing prevalence of this syndrome among older patients with diabetes, heart failure, and kidney disease.

Medico-administrative data such as the SNDS (*Système National de Données de Santé*) are collected by the Primary Health Insurance in France, but the tools proposed to SNDS users make their in-depth exploitation difficult. A view based on a generic model of care trajectories could make it possible to identify situations in which the trajectory of care can be improved (e.g., severe hypokalemia, severe hyperkalemia) and thus serve as a basis for more pragmatic teaching, adapted to general practitioners. (51)

Indeed, the recent opening of access to the French nationwide health record database SNDS is a great opportunity to carry out comprehensive health studies at the country level. Happe and Drezen have proposed a toolbox to query and cope with the complexity of care pathways of patients, because access is very difficult for nonexpert data scientists. This toolbox is particularly suitable for understanding timeline representations of individual patient healthcare trajectories in case of heart failure and cardiorenal syndrome. (52)

It would also be appropriate to standardize the guidelines and the curriculum in order to provide pragmatic instruments to help with the management of dyskalemia in patients with heart failure and kidney disease, either as a decision tree or a dedicated computer tool.

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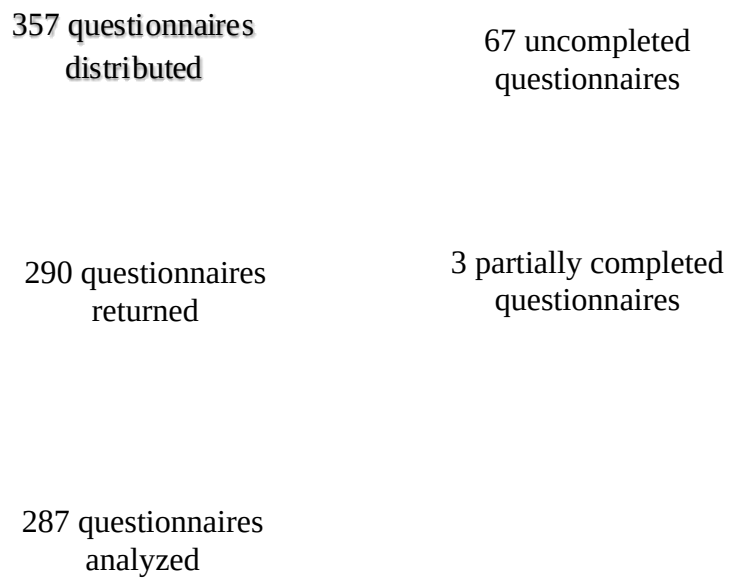

Figure 1: Flowchart of the participants

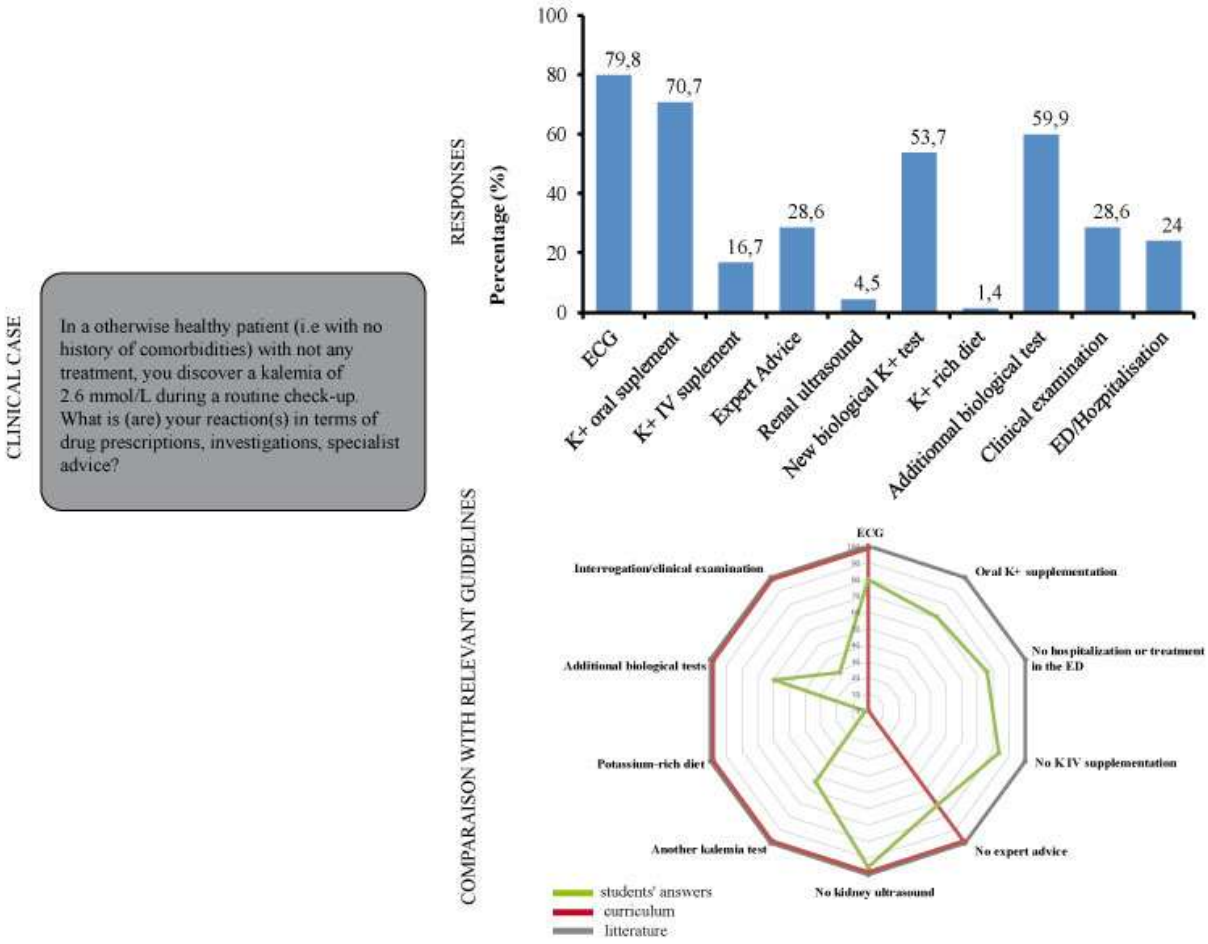

Figure 2: Hypokalemia of 2.6mmol/L in a patient who is not on any treatment: student's responses and comparison with literature and curriculum

The radar chart is represented by student's answers in green, curriculum in red, and expert opinion in grey.

Legend: IV (intravenous), ED (emergency department).

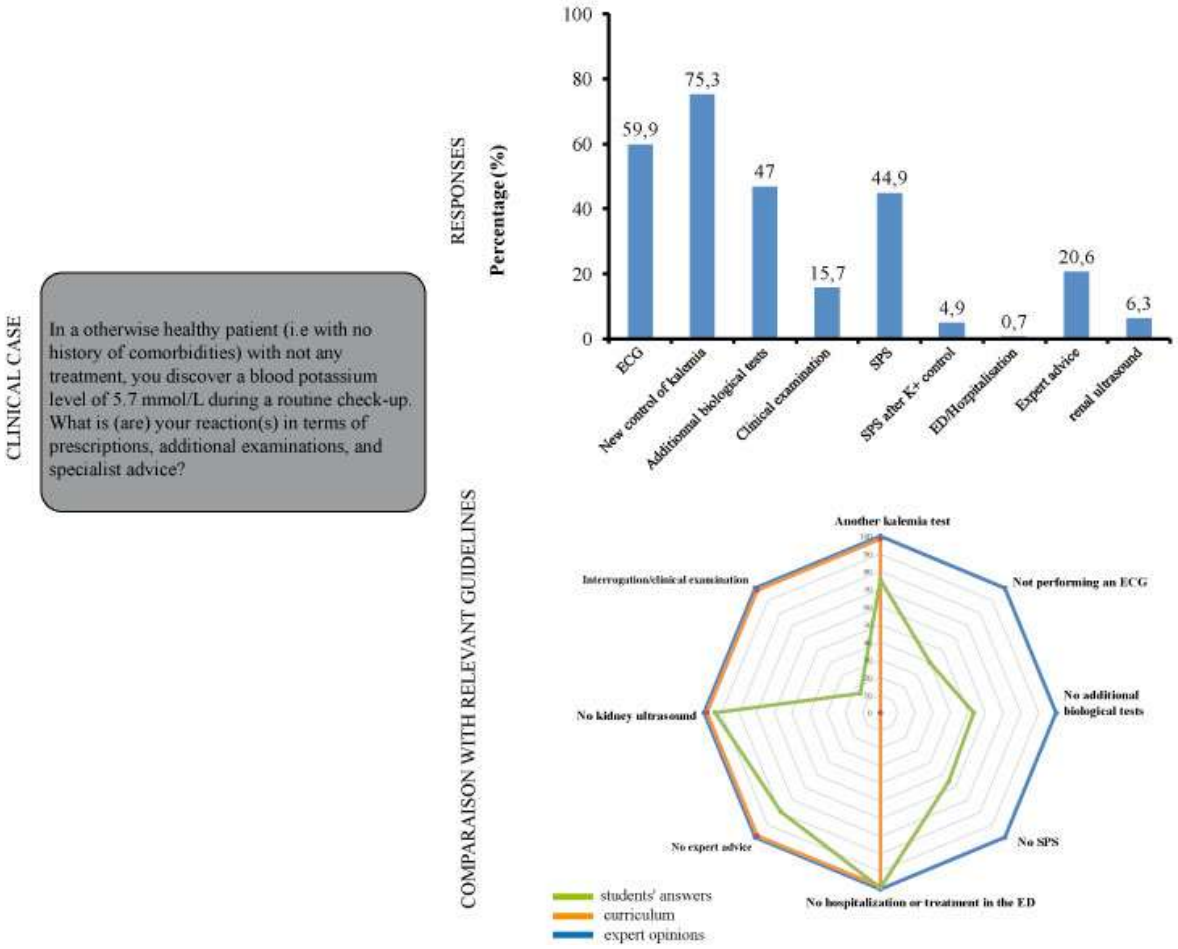

Figure 3: Hyperkalemia of 5.7mmol/L in a patient who is not on any treatment: student's responses and comparison with expert opinions and curriculum

The radar chart is represented by student's answers in green, curriculum in orange, and expert opinion in blue.

Legend: ARM (Angiotensin Receptor Agonist), ACE (Angiotensin-comverting enzyme inhibitors), SPS (Sodium Polystyrene sulfate), ED (emergency department).

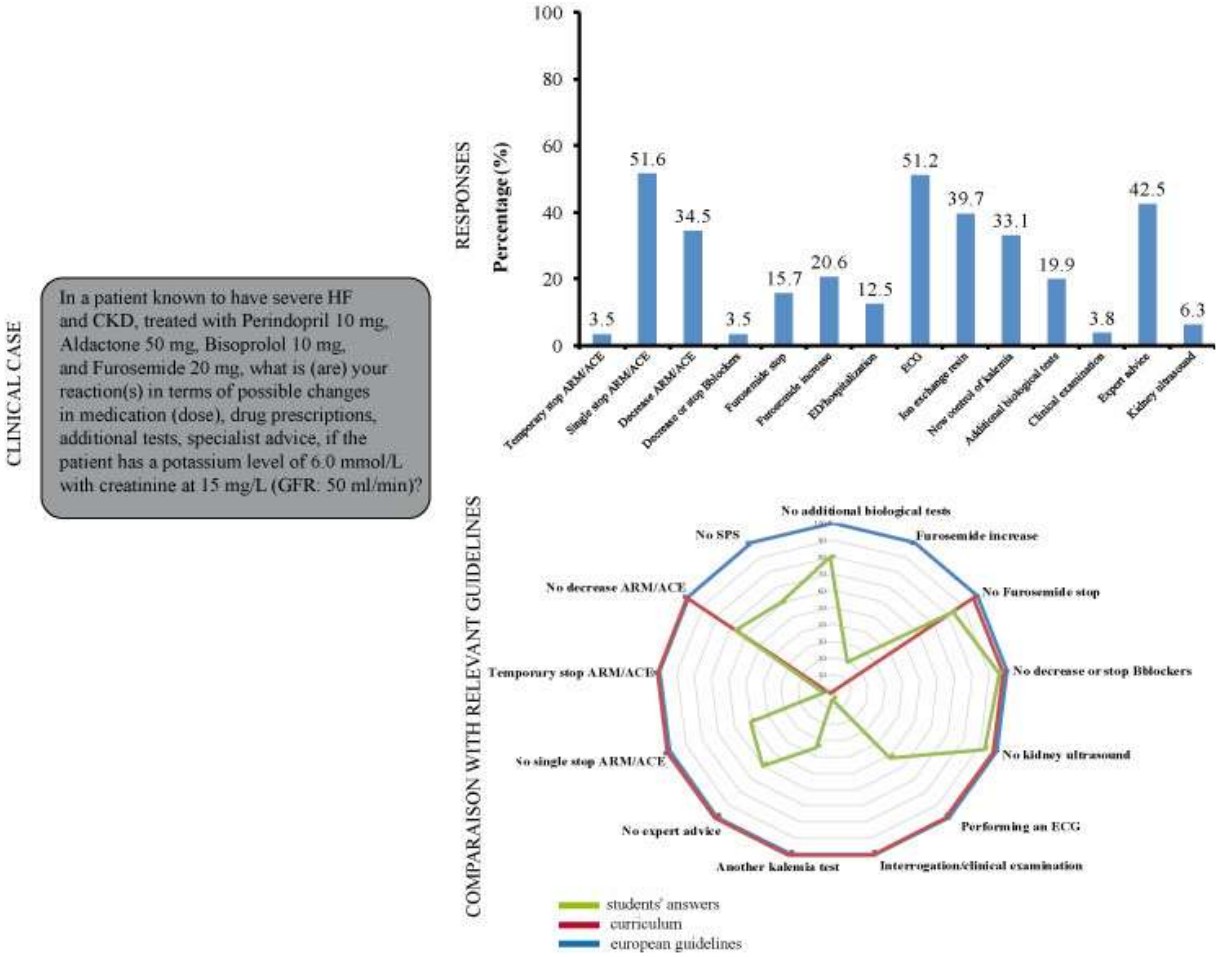

Figure 4: Hyperkalemia of 6.0mmol/L in a patient with heart and kidney failure, student's responses and comparison with European guidelines and curriculum

The radar chart is represented by student's answers in green, curriculum in red, and expert opinion in blue.

Legend: ARM (Angiotensin Receptor Agonist), ACE (Angiotensin-converting enzyme inhibitors), SPS (Sodium Polystyrene sulfate), ED (emergency department), GFR (Glomerular filtration rate), HF (Heart failure), CKD (Chronic kidney disease).