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ORIGINAL ARTICLE



The role of selective imidazoline receptor agonists in modern hypertension management: an international real-world survey (STRAIGHT)

Markus P. Schlaich^{a,b,c} , Wael Almahmeed^d, Samir Arnaout^e, Dorairaj Prabhakaran^{f,g}, Julia Zhernakova^h, Nadezhda Zvartauⁱ and Aletta E. Schutte^{j,k} 

^aDobney Hypertension Centre, School of Medicine – Royal Perth Hospital Unit/Medical Research Foundation, University of Western Australia, Perth, Australia; ^bDepartments of Cardiology and Nephrology, Royal Perth Hospital, Perth, Australia; ^cNeurovascular Hypertension and Kidney Disease Laboratory, Baker Heart and Diabetes Institute, Melbourne, Australia; ^dHeart and Vascular Institute, Cleveland Clinic Abu Dhabi, Abu Dhabi, United Arab Emirates; ^eDivision of Cardiology, Department of Internal Medicine, American University of Beirut-Medical Center, Lebanon; ^fChronic Disease, Centre for Control of Chronic Conditions (CCCC), New Delhi, India; ^gEpidemiology, Public Health Foundation of India (PHFI), New Delhi, India; ^hNational Medical Research Center of Cardiology, Moscow, Russia; ⁱAlmazov National Medical Research Centre, Saint-Petersburg, Russia; ^jHypertension in Africa Research Team, MRC Unit for Hypertension and Cardiovascular Disease, North-West University, Potchefstroom, South Africa; ^kSchool of Population Health, The George Institute for Global Health, University of New South Wales, Sydney, Australia

ABSTRACT

Background: Multiple pharmacologic strategies are currently available to lower blood pressure (BP). Renin-angiotensin system (RAS)-inhibitors, calcium channel blockers and diuretics are widely recommended as first line therapies. Sympathetic activation is an important contributor to BP elevation but remains unopposed or is even increased by some of these drug classes. Selective imidazoline receptor agonists (SIRAs) reduce increased central sympathetic outflow and are considered as add-on therapy in most guidelines. We conducted an international survey to evaluate contemporary hypertension management strategies in countries with high prescription rates of SIRAs to better understand the rationale and practical indications for their use in a real-world setting.

Methods: Physicians from seven countries (India, Jordan, Lebanon, Russia, Saudi Arabia, South Africa, United Arab Emirates) were asked to complete a web-based questionnaire and comment on clinical case scenarios to provide information on their current practice regarding antihypertension strategies, underlying rationale for their choices, and adherence to relevant guidelines.

Results: 281 physicians completed the questionnaire including mainly cardiologists (35%) and general practitioners (32%). 96% reported using European (60%) or local (56%) guidelines in their daily practices. The majority of responding physicians (83%) had knowledge of SIRAs and 70% prescribed SIRAs regularly typically as a third line antihypertensive strategy (63%). The preferred combination partners for SIRAs were RAS-inhibitors (72%).

Conclusions: Contemporary hypertension management varies between countries and therapeutic approaches in a real-world setting are not always in line with recommendations from available guidelines. In the countries selected for this survey prescription of SIRAs was common and appeared to be guided predominantly by considerations relating to the underlying pathophysiologic mechanism of sympathetic inhibition.

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Selective imidazoline receptor agonists; antihypertensive medication; real-life; sympathetic nervous system; hypertension management; metabolic effects; obesity

Introduction


Raised blood pressure is the leading cause of death globally, resulting in more than 10.4 million deaths each year¹. Hypertension is often linked to other comorbidities including obesity^{2,3}, metabolic syndrome^{4,5}, chronic kidney disease⁶, and diabetes mellitus⁷.

The etiology of hypertension is multifactorial and involves genetic, behavioral and environmental factors which interact through complex pathophysiological processes⁸. Several studies highlighted a crucial role of the sympathetic nervous system (SNS) activation as a major contributor to the

development and sustenance of hypertension^{9–12}. Indeed, by acting on key organs such as the heart and kidneys through adrenergic neurotransmitters, the SNS is able to respond to alterations in blood pressure by adjustment of cardiac output, vasoconstriction of peripheral vessels, and interaction with other relevant systems such as the RAS. Overactivation of the SNS has been identified as a key contributor to hypertension initiation and development^{10,11,13}.

Many therapeutic strategies are currently at the physician's disposal to lower blood pressure, such as RAS inhibitors, calcium channel inhibitors, diuretics, beta- and alpha-blockers,

CONTACT Markus P. Schlaich  markus.schlaich@uwa.edu.au  Dobney Hypertension Centre, School of Medicine – Royal Perth Hospital Unit, The University of Western Australia, Level 3, MRF Building, Rear 50 Murray St, Perth, 6000 WA, Australia

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and others¹². Nevertheless, as effective as these drugs are, blood pressure control rates remain low worldwide and are below 50% in most countries. Beaney et al. demonstrated in the “May Measurement Month” campaign in 2018 that of all the people screened, 34% had hypertension and 59.5% of them were aware of their condition. 55.3% were under treatment, and 60% of these people had their blood pressure controlled. Overall, of all the hypertensive people screened, only 33.2% had their blood pressure controlled.¹⁴

The second generation of centrally acting antihypertensive agents, called selective imidazoline receptor agonists (SIRAs), which are highly selective for the imidazoline I₁ receptor while having a low affinity for alpha 2-adrenergic receptors, are also available^{15,16}. Several studies have demonstrated these specific binding properties, with moxonidine showing 10–700-fold greater affinity for I1 receptors compared with alpha 2-adrenergic receptors in the rostral ventrolateral medulla, depending on the study.^{15–19}

SIRAs control blood pressure effectively with significantly less adverse effects such as sedation, dry mouth or mental depression that are usually associated with other centrally-acting antihypertensives^{20–23}. Despite this known action on the sympathetic nervous system which remains unopposed with most other drug classes, and its effect on lowering blood pressure, there is currently very few comprehensive clinical trials with hard outcomes parameters available comparing its effectiveness with standard treatments²⁴. In these studies, SIRAs efficacy were not statistically different compared to ACE inhibitor²⁵, beta-blockers²⁶, CCB²⁷ or HCTZ²⁸ on lowering blood pressure. Unfortunately, no large-scale outcome studies with SIRAs have been conducted in hypertensive cohorts, which may in part explain that the drug class is usually not considered a first line choice.

SIRAs are commonly prescribed when blood pressure is not normalized by prescription of the three major drug classes. Several studies indicated that SIRAs may be particularly effective in certain patient groups characterised by increased sympathetic tone including obese patients with the metabolic syndrome^{2,29,30}, or for postmenopausal women^{31,32}. This is likely due to SIRAs having additional beneficial actions on metabolic homeostasis. Indeed, several studies demonstrated that SIRAs were associated with metabolic benefits such as lowering body weight of obese patients²² as well as triglycerides, improving insulin resistance^{21,23,33} impaired glucose tolerance^{34,35}, and hyperlipidaemia^{21,23,36}, thereby resulting in a reduced overall cardiovascular risk. However, the class of SIRAs does not receive much attention in international hypertension management guidelines^{37,38}. As current guidelines are evidence-based and preferentially recommend drug classes for which hard endpoint trials are available, to this day, no comparative large scale trial using SIRAs had been conducted with hard endpoints, thereby potentially limiting their prescription despite proven BP lowering efficacy and apparent additional metabolic benefits.

Against this background we wondered how physicians in countries with relatively high prescription rates for SIRAs use this drug class in their real-world settings. The aim of the

international STRAIGHT (**S**elective imidazoline receptor agonists **T**reatment **R**ecommendation and **A**ction **I**n **G**lobal management of **H**yper**T**ension) survey was therefore to evaluate hypertension management strategies in countries with high prescription rates of SIRAs and to better understand the rationale and indications for their use in a real-world setting. The ultimate goal was to identify gaps in guideline-based contemporary hypertension management and thereby inform on potential future studies required to substantiate current use of SIRAs by robust scientific evidence.

Methods

A Steering Committee (SC) was constituted to lead the project, with at least one representative from each of the countries involved.

Based on relevant literature reviews and clinical expertise of all the SC members, a questionnaire was developed to allow assessment of prescription habits specific to SIRAs. The first section obtained information on physician profile and general information; general hypertension management; knowledge on SIRAs; current treated population and motivation for using SIRAs. In the second section multiple-choice questions relating to five selected clinical case scenarios were detailed to provide information regarding current practice of hypertension treatment. The questionnaire was available in English and Russian to ensure appropriate comprehension of the questions raised. Countries considered to have a high prescription rate for SIRAs were those which had the highest sales volume according to Abbott’s internal files.

We invited 5074 physicians by e-mail only, after obtaining written consent, spread across seven countries including India, Jordan, Kingdom of Saudi Arabia, Lebanon, Russia, South Africa and United Arab Emirates to participate by completing an online survey. Contacted physicians were mainly cardiologists, general practitioners, endocrinologists and nephrologists.

The survey consisted of a 10-min, self-administered questionnaire, completed between 18 January 2019 and 1 July 2019.

Questions were divided in multiple-choice responses and unique choice. The results were anonymous and analyzed in aggregate only. Results were expressed as percent of total respondents for each question.

Results are reported descriptively.

Full questionnaire and results of the clinical cases are available in [Supplementary material](#).

Results

Physician profile

Of the 5074 physicians who were contacted by email, 281 completed the questionnaire resulting in a response rate of 5.5%. The majority (52%) of respondents were male, mostly cardiologists (35%) and general practitioners (32%). Most of them (73%) had been treating hypertension for more than

10 years. 38%, 25% and 18% of responding physicians reported that they saw between 30–50 hypertensive patients, 10–30 hypertensive patients, and 50–80 hypertensive patients in an average week, respectively. This suggests that participating physicians were quite experienced and managed hypertension very frequently (Figure 1).

Guideline use and general approach

Among the 281 responding physicians, 96% reported they were using guidelines in their daily practice for the management of hypertensive patients. They reported mainly use European (ESC/ESH 2018) and national guidelines, respectively (60% and 56%). 44% of responding physicians declared to use American guidelines (ACC/AHA 2017; ASH/ISH 2013) (Figure 2).

Before initiating any antihypertensive treatment, respondents reported to routinely assess the general cardiovascular risk (96%), diabetes status (96%), kidney function (96%) and hypertension-mediated organ damage (94%), followed by obesity (90%) and sleep apnea (62%).

Knowledge and prescription of SIRAs'

To avoid bias in the answers regarding SIRAs, the following definition of the therapeutic class was given to physicians filling the questionnaire: "Selective Imidazoline Receptor Agonists (SIRAs) are centrally acting antihypertensive agents exhibiting only low affinity to central α_2 -adrenoceptors as compared to I1-imidazoline receptors. They reduce peripheral sympathetic activity."

Among the 281 responding physicians, 234 (83%) had already heard about the term "Selective Imidazoline Receptor Agonists" (92% of GPs and 79% of all other specialties), and 198 (70%) had previously prescribed SIRAs. SIRAs were mainly prescribed by physicians with more than 15 years of experience (50%) and mostly by GPs rather than other specialties (85% vs 64%) (Figure 3).

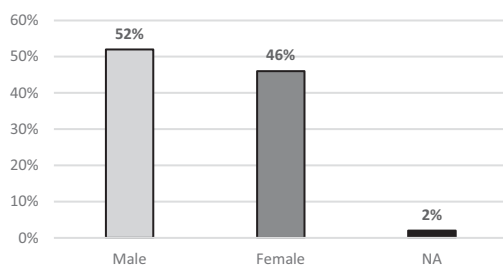
The main reasons for prescribing SIRAs were for their general efficacy (80%), their efficacy in patients with resistant hypertension (78%), their additional metabolic effects (66%) and for their effects on sympathetic nervous system hyperactivity (63%). Besides, SIRAs were mainly prescribed as 3rd line anti-hypertensive therapy (63%). 29% of physicians prescribing SIRAs as a 3rd line therapy also prescribed in 4th line, and 24% prescribed SIRAs as 2nd and 3rd line therapy. Only 11% of the responding physicians prescribed SIRAs as first line therapy.

The leading reasons for prescribing SIRAs as 1st line include efficacy and safety profile, whereas effects on resistant hypertension and effects on SNS hyperactivity are cited mostly for prescription in 4th and 5th line of treatment. Additional metabolic effects were cited as one on the main reasons for prescription in all lines of treatment.

Among the 198 physicians prescribing SIRAs, the preferred antihypertensive agents to combine with SIRAs were RAS-inhibitors (ACE inhibitors and ARBs) (72%). There were no major concerns from prescribing physicians to combine SIRAs with any of the following agents: beta-blockers (47%), non-dihydropyridine-CCB (45%), diuretics (44%) or dihydropyridine-CCB (38%).

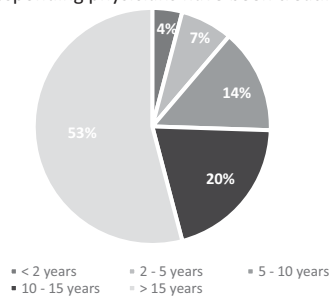
Among the 27% of responding physicians not prescribing SIRAs, the main reasons were that SIRAs are not specifically

(A) Gender of responding physicians



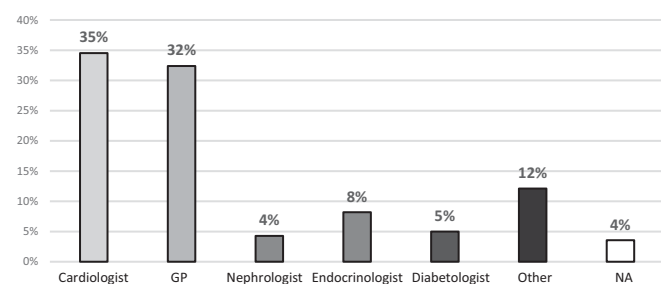
N= 281, Only tick one box

(C) How long responding physicians have been treating hypertension



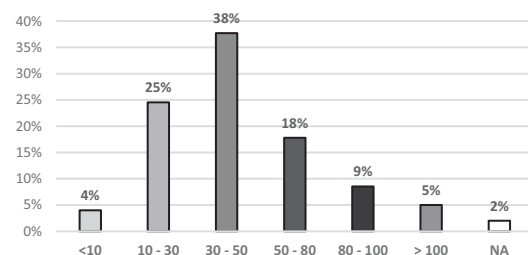
N= 281, Only tick one box

(B) Medical speciality of responding physicians



N= 281

(D) Number of hypertensive patients treated by responding physicians in an average week



N= 281, only tick one box

Figure 1. Responding physicians' profile. (A) Gender of responding physicians; (B) Medical speciality of responding physicians; (C) How long responding physicians have been treating hypertension; (D) Number of hypertensive patients treated by responding physicians in an average week.

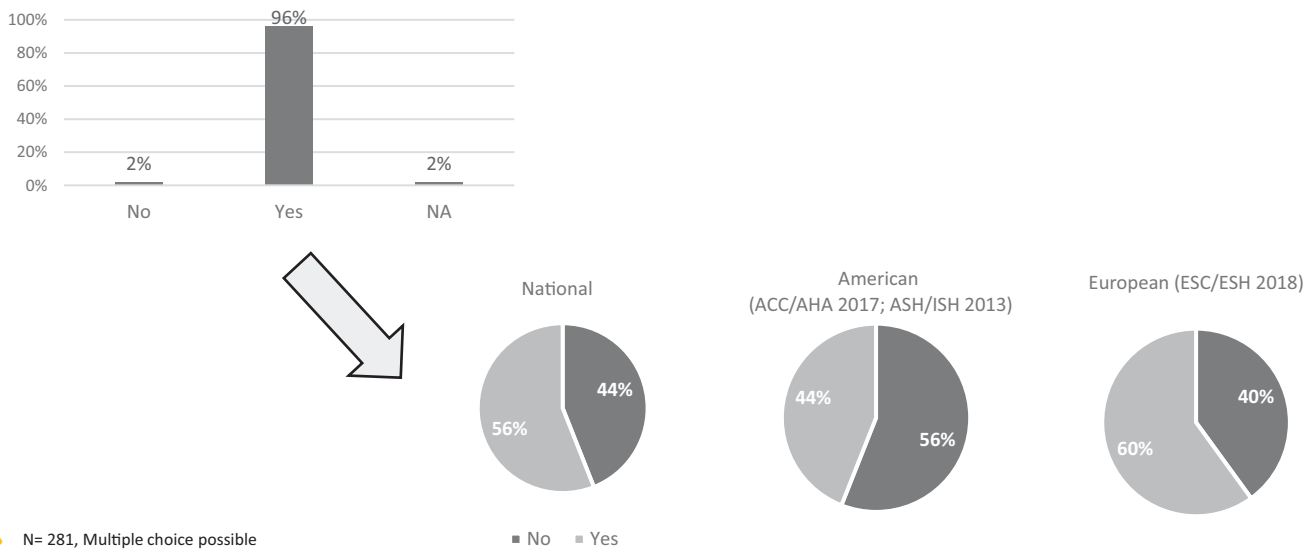


Figure 2. Use of guidelines in physicians' general daily practice.

recommended in current guidelines (58%) and perceived unavailability of SIRAs in the concerned countries (56%), the latter highlighting a knowledge gap regarding the availability of SIRAs in some countries.

According to the 281 responding physicians, patients' profiles for whom prescription of SIRAs may be most beneficial included patients with diabetes, metabolic syndrome or impaired glucose metabolism (70%), obesity (65%), age between 40 and 65 years (63%), and hypertensive emergencies (59%).

Discussion

The STRAIGHT study aimed to evaluate in real-world settings the management of hypertension in several countries in which prescription of SIRAs is relatively common in order to obtain information on the state of knowledge of SIRAs, main indications for their use, and patient populations mainly treated with SIRAs. We hoped to identify gaps in guideline-based contemporary hypertension management and thereby inform on potential future studies required to substantiate current use of SIRAs by robust scientific evidence. Only 5.5% of physicians who were contacted completed the questionnaire. This low rate of response is common in this kind of online research^{39–43}, as physicians were contacted by e-mail only, with no incentive provided, which might have introduced a bias as some countries included in the study may not have been familiar with this kind of survey and this type of communication. A monthly newsletter providing updates on the medical research and reminding physicians to participate was also sent out during the opening of the database (see [Supplementary materials](#)).

The physicians included in this study were mostly cardiologists or general practitioners with more than 15 years of professional experience indicating that responding physicians had substantial experience in the management of hypertension and high exposure to affected patients, thereby reducing potential impact of inadequate responses due to lack of

experience. Furthermore, the participating healthcare providers would have been exposed to several iterations of relevant hypertension guidelines over the years and the reported reliance on national or international guidelines in clinical management of hypertension was high and suggestive of a well-educated group of physicians. Selection bias may have played a role here in that only those physicians quite familiar with hypertension guidelines and its treatment may have opted to participate and results may therefore not necessarily be representative of physicians in respective countries.

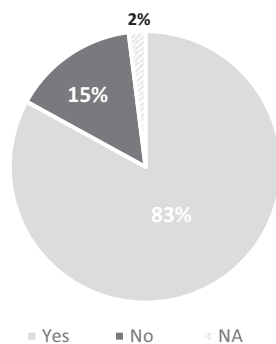
SIRAs as a therapeutic drug class was well known by the responding physicians and the majority of participating physicians (70%) had previously prescribed SIRAs. Of note, the STRAIGHT survey was intentionally carried out in countries with high rates of prescription of SIRAs, which may have introduced a bias as it was clearly mentioned that the administrated questionnaire was predominantly about SIRAs. Thus, health care professionals who already had knowledge of this therapeutic class might have responded preferentially.

In the surveyed countries, physicians were clearly aware of the factors they should assess prior to initiating antihypertensive therapy (general cardiovascular risk, diabetes, obesity, kidney function and HT-mediated organ damage), as recommended by latest international guidelines^{37,38}.

Sleep apnea appeared as a somewhat neglected factor, although it is diagnosed in at least 1/3rd of hypertensive patients and is considered as a risk factor increasing the risk of cardiovascular events (such as stroke, heart failure or premature death), calculated by the Systemic COronary Risk Evaluation (SCORE) system⁴⁴. Furthermore, sleep apnea is strongly associated with sympathetic activation leading to hypertension development^{45,46}. It is also a known risk factor for secondary hypertension and resistant-hypertension^{37,38,44}.

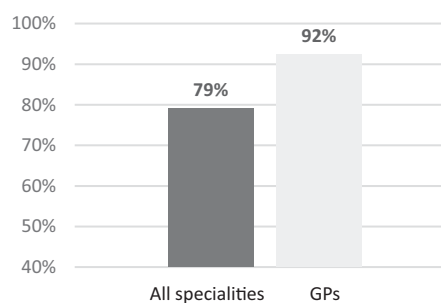
Besides, 48% of responding physicians chose "other" as a category regarding additional factors to assess. Given that the options provided were not exhaustive it was the view of the Steering Committee that "other" would likely have

(A) % of HCPs having already heard about SIRAs



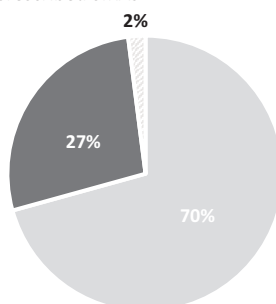
N= 281, Only tick one box

(B) % of HCPs having already heard about SIRAs, GPs vs all specialties



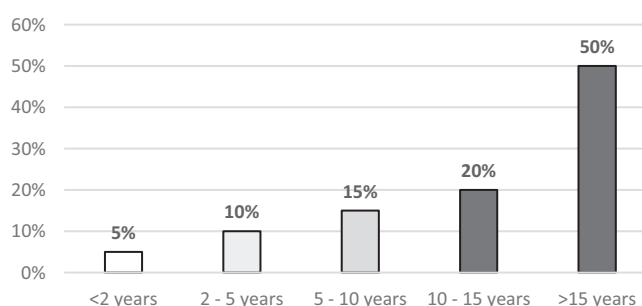
N= 91 GPs and n=190 for other specialties

(C) % of HCPs having already prescribed SIRAs



N= 198, Only tick one box

(D) % of SIRAs prescription according to HCPs' practice experience



N= 198

Figure 3. Physicians' behavior regarding SIRAs. (A) Percentage of responding physicians having already heard about SIRAs; (B) Percentage of physicians having already heard about SIRAs with a split according to the medical specialty (GPs vs all); (C) Percentage of responding physicians having already prescribed SIRAs; (D) Percentage of responding physicians having already prescribed SIRAs with a split according to the medical specialty (GPs vs all).

included conditions such as atrial fibrillation, previous stroke, peripheral artery diseases (PAD), and others, which health care professionals may be assessing before initiation of anti-hypertensive therapy.

Cost-effectiveness and safety profile were rarely mentioned as a specific reason for prescribing SIRAs. This most likely reflects the absence of any concerns of prescribing physicians with cost effectiveness and safety in regard to SIRAs, but alternatively could be interpreted as SIRAs not being considered to perform well in these categories. Indeed, SIRAs not infrequently are being confused with first generation centrally acting antihypertensive agents such as clonidine, guanfacine and alpha-methyl-dioxyphenylalanine (dopa), all of which have a much higher affinity for α_2 -adrenoreceptors and therefore cause associated side effects such as drowsiness, tiredness and sedation much more commonly than SIRAs^{47,48}.

The fact that SIRAs are not prominent in most current hypertension guidelines and the perceived non-availability of them in the concerned countries were the reasons most cited for not prescribing SIRAs.

This highlights two major issues: (i) further education seems required to ensure that treating physicians are indeed aware of the therapeutic options available to them in their respective countries and (ii) that the knowledge of current guidelines while reportedly widely used may be restricted to the main messages conveyed and not to more detailed aspects of hypertension management. Indeed, current

European guidelines recommend the use of five major classes of antihypertensives agents (angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers and diuretics). Other anti-hypertensive drug classes are no longer recommended for the routine treatment of hypertension, mainly due to the absence of hard outcome trials or poorer tolerability relative to the newer major drug classes²⁰.

The fact that even though SIRAs are not clearly specified in guidelines and often summarized and combined with other older and less well tolerated centrally acting agents yet are being commonly prescribed not only as 4th or 5th line treatment highlights a mismatch between clinical practice and guidelines recommended treatment. Based on this survey the clinical experience with SIRAs seems quite positive, but the lack of well conducted studies prevents this drug class from being recommended in times of evidence-based medicine. Relevant and appropriately designed studies are therefore required to substantiate what seems to be common clinical practice in the surveyed countries and provide robust scientific evidence for inclusion in guideline-based recommendations.

Regarding the availability of SIRAs, this point might reflect a confusion about SIRAs as a therapeutic class and the commercial name of the products as SIRAs are available in all the countries included in the STRAIGHT survey. This could also be due to a non-availability of SIRAs in the concerned hospitals or clinics.

According to this survey and contrary to current guidelines, SIRAs are frequently prescribed as 3rd line therapy, predominantly for their efficacy (general or on resistant hypertension) and for their additional metabolic effects. Indeed, SIRAs are well known for their beneficial effects on various metabolic parameters such as impaired glucose intolerance, insulin resistance or dyslipidemia^{22,23,34,49}. SIRAs are mostly prescribed in combination, and preferred combination partners were RAS blockers (ACEi or ARBs). One of the leading reasons for this might be the cost-effectiveness of ACEi and ARBs in the concerned countries, as well as their favorable side effects profile.

Combination of Calcium channel blockers with SIRAs may also represent a useful combination given that some CCBs may raise sympathetic activity which could be counteracted by SIRAs while exploiting the beneficial metabolic effects of both drug classes⁵⁰. In the context of current treatment recommendations for early combination therapy²⁰, it is perhaps important to note that SIRAs can safely be combined with all of the five major classes of antihypertensive agents without any major contraindications.

According to responding physicians, patients with diabetes, metabolic syndrome, impaired glucose metabolism and obesity are likely to specifically benefit from SIRAs, which they relate to their well described beneficial effects of SIRAs on metabolic parameters^{21,22,34,50}.

Perhaps surprisingly, prescribing SIRAs for hypertensive emergencies was a common indication particularly from Russian respondents (38% of Russian respondents on this item, versus 19% for Saudi Arabia and 2% for the rest of the world). While there are no international studies in this field using SIRAs, a publication in Russian supports the utility in the setting of hypertensive emergencies. In contrast, cardiac arrhythmias as an indication were ranked last (22%) although it has been shown that the autonomic nervous system is involved in the pathogenesis of cardiac arrhythmias^{21,51,52} and a reduction in the sympathetic overdrive using SIRAs has been shown in a randomized controlled clinical trial to reduce the re-occurrence of atrial fibrillation with SIRAs compared to placebo⁵³.

The clinical cases provided in this survey allowed to better understand SIRA prescription in daily practices in several countries with high prescription rates to determine how responding physicians would have treated a specific patient. In most of the situations, SIRAs were considered a useful therapeutic option.

Conclusion

Our findings indicate that SIRAs were well known and frequently prescribed by experienced health care providers in a range of clinical scenarios. Future studies are needed to explore the validity of the basis of the current practical use of SIRAs to enrich the evidence for guideline development and identification of hypertensive patient cohorts likely to specifically benefit from SIRAs treatment.

Sympathetic activation likely represents a neglected priority that should be addressed to improve BP control rates and thereby CV outcomes for the large cohort of patients with hypertension.

Transparency

Declaration of funding

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Declaration of financial/other relationships

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Author contributions

All authors designed the medical research, analyzed the results and reviewed and approved the final draft of the paper. All authors agree to be accountable for all aspects of the work.

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ORCID

Markus P. Schlaich  <http://orcid.org/0000-0002-1765-0195>
Aletta E. Schutte  <http://orcid.org/0000-0001-9217-4937>

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