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Adherence to Biochemical Monitoring Recommendations in Patients Starting with Renin Angiotensin System Inhibitors

A Retrospective Cohort Study in the Netherlands

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Abstract

Background: Renin angiotensin system inhibitors (RASIs) are frequently involved in serious adverse events. These events principally occur in high-risk patients and often arise within the first days after treatment initiation; therefore, guidelines recommend biochemical monitoring within 3 weeks after the start of therapy with RASIs.

Objective: The purpose of this study was to examine the level of biochemical monitoring directly after treatment initiation with RASIs in patients with different risk profiles and to study the attitudes of the physicians involved towards biochemical monitoring.

Methods: We carried out a retrospective analysis of 202 patients who started RASI therapy in 2006 in Groesbeek, the Netherlands. We determined the rate of serum creatinine and potassium monitoring within 3 weeks after the start of therapy. In addition, we studied the intentions and attitudes towards biochemical monitoring during RASI therapy among 68 general practitioners and medical specialists by way of a brief questionnaire.

Results: Serum creatinine and potassium monitoring after treatment initiation was performed in 34% and 28% of patients, respectively. Of all the patients, 29% had two or more additional risk factors for renal function deterioration. In these high-risk patients, creatinine was significantly less often monitored compared with low-risk patients (22% vs 39%). In contrast

to these findings, the prescribing physicians claimed to check serum creatinine within 2 weeks after treatment initiation in 85% of their patients. Most of the prescribing physicians (88%) rated this monitoring as (very) important.
Conclusions: We demonstrated that, despite positive intentions of physicians, the biochemical monitoring recommendation in patients treated with RASIs is poorly met. In addition, serum creatinine monitoring was significantly less often performed in high-risk patients compared with low-risk patients.

Background

For several years, the prescription of renin angiotensin system inhibitors (RASIs), a collective name for angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers, has been on the increase.[1,2] Nowadays, over 10% of the Dutch population use RASIs,[1] which unambiguously decrease morbidity and mortality in patients with hypertension, heart failure and renal disease.[3-8] However, RASIs may cause serious adverse effects, of which hypotension, hyperkalaemia and renal function decline are leading problems. RASIs are in the top ten list of drugs involved in potentially avoidable hospital admissions related to medications.[9-14] Biochemical monitoring in patients treated with RASIs is widely recommended as a strategy to prevent or minimize adverse effects; however, inappropriate monitoring is one of the main contributors of avoidable adverse drug events.[15,16] It has been demonstrated that patients treated with RASI therapy can safely benefit from spironolactone treatment when used in conjunction with appropriate biochemical monitoring.[17]

In the 1990s, it was demonstrated that general practitioners (GPs) from the UK performed serum creatinine monitoring in only 29% of their patients within 3 months after starting treatment with ACEIs.[18] These results were attributed to the lack of clear guidelines regarding biochemical monitoring.

Since then, guidelines have reached a firm position in healthcare. Today, guidelines, advisory groups and product labels recommend monitoring serum creatinine, sometimes combined with potassium. Most of these guidelines recommend monitoring before onset of therapy and within 1–3 weeks after onset.[19-32] In addition, some guidelines also recommend monitoring after dosage increase,[23,24,26,27,30-32] and periodically as routine monitoring.[19-21,24,26,27,29,30,32-35]

Although adverse effects can occur during any phase of RASI therapy, they mostly develop within the first few days of therapy or during intercurrent illness and change in co-medication.[36,37] No study has investigated the level of monitoring directly after starting therapy with RASIs.[18,38,39] The primary aim of our study was to assess the level of biochemical monitoring within this relevant timeframe. Furthermore, we examined the level of monitoring in high- and low-risk patients, and the difference in monitoring between GPs and medical specialists. Finally, we studied the intentions and attitudes of the prescribers towards biochemical monitoring.

Methods

Setting

We designed our study within the population of Groesbeek, the Netherlands. Groesbeek is a village with approximately 19 000 inhabitants, close to the city of Nijmegen. Its cohesive population with a relatively large number of elderly, and consequently high occurrence of co-morbidity, makes it a relevant setting to address our research questions.

Study Population

We included all patients who started RASI therapy in 2006. This cohort was followed up from 12 months before RASI therapy initiation until 18 months after starting therapy. Data were collected from the community pharmacy, the nine GPs in Groesbeek and from the two nearby

hospitals where residents from Groesbeek are almost exclusively referred to (Radboud University Nijmegen Medical Centre [RUNMC] and Canisius-Wilhelmina Hospital [CWZ], Nijmegen).

The ethics committees of both hospitals decided that our study did not require formal evaluation according to the national law on medical research. All patients of the community pharmacy had been informed that their medical records could be used for research on quality control.

Data Collection

We reviewed medical records from the GPs, the community pharmacy and hospitals to record information on individual patient characteristics, RASI therapy and adverse effects. The patient data we gathered were demographic characteristics, co-morbidity (heart failure, hypertension, diabetes mellitus, chronic kidney disease (creatinine clearance ≤60 mL/minute calculated with the Modification of Diet in Renal Disease formula), cognitive disorders and co-medication (potassium supplements, diuretics, NSAIDs, digoxin and β-blockers). With regard to RASI therapy, we registered the type of physician prescribing and date of starting therapy with RASI, indication, type and dosage of RASI, and measurements of serum creatinine and potassium at different stages during therapy. The adverse effects that we recorded were hospitalization during follow-up and development of potentially clinically relevant biochemical abnormalities. This was defined as a rise of more than 25% of the initial serum creatinine value or hyperkalaemia (serum potassium level >5.4 mmol/L).[14,28,36,40,41]

At the start of data collection, all physicians involved, i.e. the nine GPs in Groesbeek and the 24 cardiologists and 35 internists from the RUNMC and CWZ, received a 6-item anonymous questionnaire (see Supplemental Digital Content 1, http://links.adisonline.com/DSZ/A49) through the mail and e-mail, which covered physicians' attitude and intentions towards biochemical monitoring. After 4 weeks, we followed up the physicians by sending a reminder questionnaire. A large majority of the physicians involved were unaware of our study purpose. The questionnaire consisted of five questions on a continuous scale and one question on a verbal rating scale.

Analyses

We determined the level of serum creatinine and potassium monitoring at different timepoints before and after starting therapy with RASIs. As our main outcome was the level of biochemical monitoring within 3 weeks after starting therapy with RASIs, we explored the influence of clinical and patient characteristics on the level of monitoring within this timeframe.

First, we used univariate analysis to examine the influence of sex, co-morbidity, co-medication and type of prescribing physician on adherence to biochemical monitoring within 3 weeks of starting therapy with RASIs. We used Pearson's chi-squared or Fisher exact test to determine the statistical strength of the association. Variables found to be associated with a p-value lower than 0.05 were considered statistically significant. Those variables with the strongest association, both on statistical strength and point estimate, were used in the multivariate analysis.

Second, we applied the multivariate analysis to determine the impact of these variables on the level of biochemical monitoring.

Using univariate analysis, we further explored the level of biochemical monitoring within 3 weeks of starting therapy with RASIs in patients at high-risk for biochemical disturbances. We categorized patients as high-risk if two or more additional risk factors for biochemical disturbances were present. Risk factors for renal function deterioration were heart failure, chronic kidney disease, age above 70 years and concomitant use of NSAIDs, loop diuretics or thiazide diuretics.[14,41,42] Risk factors for hyperkalaemia were heart failure, chronic kidney disease, diabetes, age above 70 years, concomitant use of NSAIDs, potassium-sparing diuretics and β-blockers, and a baseline potassium level above 4.5 mmol/L before starting RASI therapy.[14,40,43-46]

We analysed the data of our questionnaire among physicians by descriptive statistics. To depict questions on a continuous scale we used the median value. We also used proportions to

describe the ordinal scale variable. All analyses were performed with the SPSS statistical software version 16.0 (SPSS Inc., Chicago, IL, USA).

Results

Cohort

In 2006, 202 patients started RASI therapy (table I). The mean age of the study population was 63 years (range 20–90 years) and among this population, 56% were female and 3% lived in a nursing home. RASI therapy was initiated because of one or more of the following indications: hypertension (85%), heart failure (10%), myocardial infarction (18%) and albuminuria (17%). In 59%, hypertension was the only indication. RASI therapy was started by a GP in 56% of the patients and by a medical specialist in the remaining population.

Table I. Baseline characteristics of patients

Characteristic	Value [n (%)]
Total no. of patients	202
Sex	
male	88 (44)
female	114 (56)
Age [y]	63 (20–90)[a]
Medical history	
hypertension	172 (85)
heart failure	20 (10)
diabetes mellitus	63 (31)
creatinine clearance <60 mL/min	28 (14)
cognitive disorders	6 (3)
Co-medication	
loop diuretics	32 (16)
thiazide diuretics	101 (50)
potassium-sparing diuretics	19 (9)
β-blockers	143 (71)
digoxin	9 (5)
NSAIDs	41 (20)
potassium supplements	1 (0.5)
Prescribing physician	
general practitioner	113 (56)
medical specialist	89 (44)
cardiologist	67 (33)
internist	20 (10)
other	2 (1)
First prescribed RASI	
ACEI	165 (82)
angiotensin receptor blocker	37 (18)
Nursing home inhabitant	5 (3)

a Mean (range).

ACEI = angiotensin converting enzyme inhibitor; **RASI** = renin angiotensin system inhibitor.

Serum Creatinine and Potassium Monitoring

In 34% of patients (95% CI 28, 41) the serum creatinine level was measured within 3 weeks after onset of treatment and the potassium level was checked in 28% of the patients (95% CI 22, 34). As expected, the level of potassium monitoring was strongly associated with the level of creatinine monitoring since both tests are often requested simultaneously. In addition, univariate analysis showed that myocardial infarction as an indication for RASI therapy, medical specialist as the treating physician, concomitant use of β-blockers and male sex were most strongly associated with the level of biochemical monitoring (table II).

Multivariate analysis, performed with these four variables, showed that medical specialists monitored the serum creatinine (odds ratio [OR] 2.7; 95% CI 1.3, 5.7) and potassium levels (OR 6.7; 95% CI 2.8, 15.7) more often compared with GPs (table III). Furthermore, monitoring was more frequently performed in patients with myocardial infarction as an indication for RASI therapy (OR for creatinine monitoring 3.4; 95% CI 1.3, 8.5; OR for potassium monitoring 3.2; 95% CI 1.2, 7.9) and the level of serum creatinine monitoring was higher in male patients (OR 2.1; 95% CI 1.1, 4.0).

Table IV shows the level of biochemical monitoring in different timeframes during RASI therapy. In most patients (79%; 95% CI 73.4, 84.6), baseline creatinine monitoring within 1 year before treatment initiation was performed. Yearly monitoring during follow-up was performed in a similar number of patients (75%; 95% CI 68.5, 81.5). The level of biochemical monitoring performed by cardiologists and internists during the different timeframes of RASI therapy was similar.

Table II. Univariate analyses of determinants of biochemical monitoring within 3 weeks after starting renin angiotensin system inhibitor (RASI) therapy

Variable	Serum creatinine monitoring <3 wk		Serum potassium monitoring <3 wk	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Male sex	2.4 (1.3, 4.4)	0.00	2.5 (1.3, 4.7)	0.00
Age (y)				
60+	1.0 (0.6, 1.9)	0.92	1.1 (0.6, 2.0)	0.85
70+	0.6 (0.3, 1.1)	0.12	0.6 (0.3, 1.2)	0.15
80+	1.4	0.55[a]	1.9	0.33[a]
Co-morbidity				
diabetes mellitus	0.8 (0.5, 1.6)	0.63	0.8 (0.4, 1.6)	0.55
creatinine clearance <60 mL/min	1.3 (0.6, 2.9)	0.54	1.2 (0.5, 2.9)	0.62
cognitive disorders	2.7	0.67[a]	2.0	1.00[a]
Indication for RASI therapy				
heart failure	0.8 (0.3, 2.2)	0.68	1.1 (0.4, 3.0)	0.85
hypertension	0.3 (0.2, 0.7)	0.01	0.3 (0.1, 0.6)	0.00
myocardial infarction	7.4 (3.3, 16.7)	0.00	9.5 (4.2, 21.3)	0.00
albuminuria	1.2 (0.6, 2.5)	0.68	1.2 (0.5, 2.7)	0.64
Co-medication				
loop diuretics	1.1 (0.4, 3.0)	0.92	1.4	0.57[a]
thiazide diuretics	0.7 (0.4, 1.3)	0.27	0.4 (0.2, 0.8)	0.01
potassium-sparing diuretics	2.0	0.41[a]	1.3	0.68[a]
β-blockers	2.6 (1.4, 5.0)	0.00	2.4 (1.2, 4.7)	0.01
digoxin	1.0	1.00[a]	1.3	0.71[a]
NSAIDs	0.5 (0.1, 1.7)	0.23	0.6	0.56[a]
Prescribing physician				
medical specialist	5.1 (2.7, 9.6)	0.00	11.5 (5.3, 24.9)	0.00
cardiologist	3.2 (1.8, 6.0)	0.00	5.0 (2.6, 9.7)	0.00
internist	2.6 (1.0, 6.7)	0.04	3.6 (1.4, 9.3)	0.01
Nursing home inhabitant	3.0	0.34[a]	4.0	0.14[a]

a In small group numbers, the levels of monitoring were compared using the Fisher exact test instead of the Pearson's chi-squared test; therefore, we could not present 95% CIs for these characteristics.

OR = odds ratio.

High-Risk Patients

Of all patients, 29% (95% CI 23, 35) were defined as high-risk for renal function decline. Both the GPs and medical specialists treated an equal number of high-risk patients, i.e. 31% and 27%, respectively (OR 0.8; 95% CI 0.4, 1.5). The level of creatinine monitoring was significantly lower (22% vs 39%) in high-risk patients compared with low-risk patients (OR 0.4; 95% CI 0.2, 0.9) [figure 1]. Although medical specialists monitored serum creatinine more often (54%) than GPs (19%) [OR 5.1; 95% CI 2.7, 9.6], both groups of physicians monitored significantly less frequently in high-risk patients.

Fifty-three percent of patients were defined as at high-risk for hyperkalaemia. The level of potassium monitoring in this group was similar to that of low-risk patients (27% and 29%; OR 1.1; 95% CI 0.6, 2.0).

Biochemical Disturbances

In patients who were either monitored for serum creatinine (57 [28%]) or potassium (44 [22%]) within 1 year before and 3 months after starting therapy, we assessed the increase in serum creatinine or potassium level. The mean increase in serum creatinine level was 2.6% (2.3 mmol/L) and

Table III. Independent determinants of biochemical monitoring within 3 weeks after starting renin angiotensin system inhibitor (RASI) therapy (multivariate analyses)

Variable	Serum creatinine monitoring <3 wk [OR (95% CI)]	Serum potassium monitoring <3 wk [OR (95% CI)]
Male sex	2.1 (1.1, 4.0)	2.0 (0.9, 4.2)
Myocardial infarction as indication for RASI	3.4 (1.3, 8.5)	3.2 (1.3, 7.9)
Concomitant use of β-blockers	1.8 (0.9, 3.6)	1.3 (0.6, 2.9)
Medical specialist as RASI prescriber	2.7 (1.3, 5.7)	6.7 (2.8, 15.7)

OR = odds ratio.

the mean increase in serum potassium level was 0.1 mmol/L. Potentially clinically relevant biochemical abnormalities during follow-up were found in 22 patients (11%), defined as a rise of more than 25% of their initial serum creatinine (n = 18) and/or serum potassium level above 5.4 mmol/L (n = 5). In the 18 patients with a potentially clinically relevant renal function decline, the mean increase in serum creatinine was 40 mmol/L (range 15–138 mmol/L). The average proportional increase in serum creatinine was 51% (range 28–164%). In the five patients developing hyperkalaemia, the mean potassium level was 5.6 mmol/L (range 5.5–5.8 mmol/L). In four patients (18%), the medication or dosage was adjusted (RASIs, β-blockers, NSAIDs and/or diuretics). Two patients who developed a renal function decline were hospitalized with heart failure. We have no information whether the renal function decline was a cause or effect of the heart failure. In addition, haemolysis might have occurred during the collection of blood, resulting in false positive hyperkalaemia. No patients died during follow-up.

Patients with a high-risk for renal dysfunction encountered a renal function decline significantly more often than patients with a lower risk for renal dysfunction (61% vs 26%; OR 4.4; 95% CI 1.6, 12.1). Patients at high-risk for hyperkalaemia showed a non-significant trend towards a higher prevalence of hyperkalaemia (80% vs 52%; OR 3.7; 95% CI 0.4, 33.2).

Questionnaire

Seventy-six percent of the physicians involved completed the questionnaire about their opinions regarding serum creatinine monitoring during RASI therapy. Sixteen percent of the responders were GPs, 55% were internists and 29% were cardiologists. The physicians claimed to check serum creatinine in 85% (median) of their patients within 2 weeks of starting therapy with RASIs (table V). Eight-eight percent of physicians rated this monitoring as (very) important.

Discussion

Although biochemical disturbances during RASI therapy often arise within the first days after treatment initiation, monitoring was only performed in about one-third of the patients, despite clear guideline recommendations. No study has, to date, investigated the level of biochemical monitoring within this relevant timeframe. Compared

Table IV. Biochemical monitoring in different timeframes before and during renin angiotensin system inhibitor (RASI) therapy

Period of biochemical monitoring during RASI therapy	Patients with serum creatinine monitoring [n (%)]			Patients with serum potassium monitoring [n (%)]		
	GP (n = 113)	specialist (n = 89)	total (n = 202)	GP (n = 113)	specialist (n = 89)	total (n = 202)
Before start of therapy						
<3 mo	56 (50)	66 (74)	122 (60)	52 (46)	62 (70)	114 (56)
<12 mo	84 (74)	75 (84)	159 (79)	73 (65)	69 (78)	142 (70)
After start of therapy						
<3 wk	21 (19)	48 (54)	69 (34)	10 (9)	47 (53)	57 (28)
<3 mo	48 (42)	60 (67)	108 (53)	34 (30)	59 (66)	93 (46)
Yearly (n = 169)						
6–18 mo after start of therapy	69 (74)	58 (76)	127 (75)	64 (69)	54 (61)	118 (70)

GP = general practitioner.

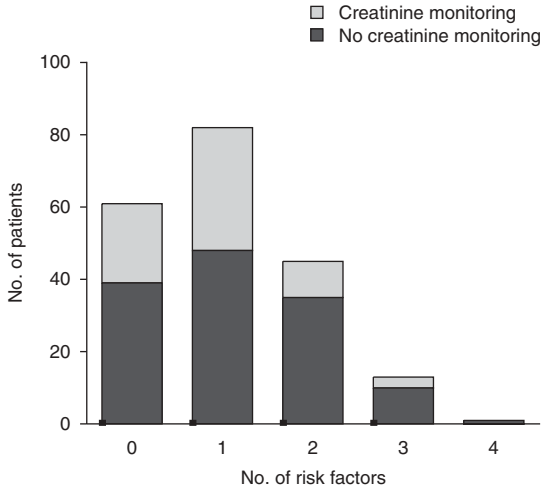

Fig. 1. Prevalence of serum creatinine monitoring within 3 weeks after start of therapy with renin angiotensin system inhibitors in patients with none to four risk factors (age 70+ years, heart failure, chronic kidney disease and concomitant use of NSAIDs, loop diuretics or thiazide diuretics) for renal function decline.

with previous reports, we found similar levels of biochemical monitoring by GPs in the months before and after starting therapy with RASIs.[18,38]

Severe adverse events principally occur in patients with additional risk factors;[40,45,47] however, this knowledge contrasts with our findings, showing a significantly lower level of serum creatinine monitoring in high-risk patients. Medical specialists generally monitored biochemical disturbances more frequently than GPs. Neither GPs nor medical specialists monitored more often in high-risk patients. The better biochemical monitoring by specialists can therefore not be explained by their patients' risk profiles. We hypothesize that logistic reasons and working habits may have determined the level of biochemical monitoring instead of the medical urgency. This idea is supported by our finding that biochemical monitoring was more frequently performed in patients when the indication for RASIs was myocardial infarction. This seems plausible as these patients are usually hospitalized, which facilitates monitoring.

The results of our study show that guidelines on biochemical monitoring were not followed properly by physicians. Given the fact that guidelines are not followed, two perspectives arise: guidelines are too stringent with an impractical nature, or physicians fail to follow sensible guideline recommendations. It is unknown whether the benefits of the recommended biochemical monitoring outweigh the efforts and costs. Our study was not conducted to examine the accuracy of these guideline recommendations. The current monitoring recommendations are possibly too stringent; however, as long as no more evidence is available, we are of the opinion that adherence to current guidelines is the best practice.

In our study, biochemical disturbances mainly occurred in high-risk patients. Although these abnormalities did not seem to have clinical implications, we have no reason for weakening monitoring recommendations as our study was not large enough to reliably examine these clinical consequences. Previous knowledge has unambig-

Table V. Responses to questions regarding serum creatinine monitoring by physicians who prescribed renin angiotensin system inhibitors (RASIs)[a]

Question	GP (n = 8)	Specialist (n = 44)	Total (n = 52)
In what % of patients do you check serum creatinine level <2 wk after start with RASIs?	68 (0–88)	90 (29–100)	85 (24–100)
How important do you rate this monitoring? (%)			
A = very important	38	36	36
B = important	50	52	52
C = moderately important	0	7	6
D = not important	12	5	6
In what % of your patients with RASIs do you check serum creatinine level?			
<12 months before start	78 (5–98)	100 (100–100)	100 (90–100)
within 6–18 months after start	98 (38–100)	100 (50–100)	100 (50–100)

a Values are expressed as median (IQR) unless specified otherwise.

GP = general practitioner; **IQR** = interquartile range.

uously demonstrated that RASIs are frequently involved in potentially avoidable hospital admissions.[9-14]

In recent years, indications for RASIs have broadened and the volume of prescriptions of RASIs has increased markedly;[1,48] however, many physicians feel reluctant to use RASIs or their recommended dosages because of possible adverse effects, especially in high-risk patients.[49] Yet the greatest long-term benefit is observed in patients with the highest risk of developing biochemical disturbances.[36,37,40] This emphasizes the fact that high-risk patients should not be denied optimal treatment, but should be closely monitored.

This is the first study examining biochemical monitoring within the 3 weeks directly after starting therapy with RASIs, as recommended by current guidelines. Monitoring within this timeframe is most relevant as biochemical disturbances usually arise within the first few days after treatment initiation. As RASIs are in the top ten list of drugs involved in serious adverse events, our findings stress the urgency to improve monitoring, especially in high-risk patients. By timely monitoring, serious adverse events can be discovered in time. This study can be used as a basis for quality improvement initiatives. More efforts should be made to investigate barriers in biochemical monitoring in order to introduce effective interventions, such as individualized feedback through the computerized physician order entry system or alerts in the pharmacy before dispensing RASIs in patients without adequate serum creatinine and potassium values. The pharmacists could advise their patients to have a blood test, with an admonition to contact their physician if they have not as yet received instructions to do so.

Limitations

Our study may have several limitations. First, we did not investigate the reasons for low guideline adherence. We do not know whether patients failed to take the test or physicians did not order the test. Patient-related factors such as aversion to blood tests, may have contributed to our findings. However, we anticipate that non-adherence of physicians to the guidelines is the most important factor. We demonstrated that lack of agreement to the guidelines by physicians is not an important barrier in guideline adherence as physicians generally graded biochemical monitoring as (very) important in our questionnaire; however, they substantially overestimated their level of biochemical monitoring. Over-estimating of self-performance by physicians is a familiar phenomenon.[50] Physicians often conflate intentions with their actual behaviour. In this study, we did not investigate the role of other barriers in guideline adherence by physicians such as lack of familiarity with the guidelines and time constraints.[51]

Second, we performed our study within one region and with a relatively small number of patients. However, this context is comparable with previous studies[18] and we do not believe that our observations concerning safety are limited to our study region. A major strength of our study is its population-based design involving patients with different risk profiles, in several settings, with various prescribing physicians investigating monitoring directly after treatment initiation.

Finally, we did not validate our questionnaire; however, we do not expect the results to be different even if it had been validated, since its purpose was to provide us with a general idea about physicians' opinions towards monitoring.

Conclusions

We demonstrated that, despite positive intentions of physicians, the recommended biochemical monitoring in patients starting RASI therapy is poorly performed. Physicians substantially overestimated their level of biochemical monitoring. In addition, serum creatinine monitoring was significantly less often performed in high-risk patients. Since RASI-related adverse effects can result in hospitalization, our findings stress the urgency to investigate and overcome barriers in monitoring.

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This study is recorded according to the STROBE (Strengthening The Reporting of OBservational studies in Epidemiology) statement.

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