Epidemiology and clinical characteristics of chronic venous disease in Romania

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Abstract. Chronic venous disorder (CVD) is a complex disease, that affects millions of people worldwide, and due to the fact that in its early stages is often overlooked by healthcare providers and ignored by the patient, the assessment of incidence and prevalence of CVD is difficult to be made. The aim of this project was to assess the CVD prevalence, risk factors and clinical characteristics in the adult population in Romania. A cross-sectional survey was carried out in Romania from June 2015 to July 2015, including 185 general practitioners (GPs). Data regarding patient characteristics, risk factors, family medical history, CVD signs and symptoms, C-classification, and pharmacological management of CVD were collected. The study included 7,210 patients, predominantly female (71.0%), with the mean age of 58.2 years. Within the study population, 2,271 (31.5%) patients had already the CVD diagnosis established prior to the study visit, while for 2,664 (36.9%) patients, CVD was diagnosed during the visit, while for the rest of the patients, 2,275 (31.6%), CVD diagnosis was not established prior or during the study visit. Age, female, sex and previous pregnancies were major risk factors for developing CVD. The newly diagnosed CVD rate was 36.9% and the directly calculated CVD prevalence in June-July 2015 was 68.4%, while the indirectly calculated CVD prevalence was 80.7%. CVD is a very common disease, with a prevalence of CVD within the study population in June-July 2015 of 68.4%. The newly diagnosed CVD cases represent 36.9% of patients included in this study, nevertheless both parameters could be underestimated, as long as a significant percentage of patients presenting symptoms, but no CVD signs, were not considered by GPs as CVD cases.

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Introduction

Chronic venous disease (CVD) is a common but complex disease and data regarding its prevalence are still underestimated, as long as CVD early signs and symptoms are overlooked by both health-care professionals and patients, nevertheless the CVD is negatively impacting on the patient's quality of life and has a high impact on health-care budgets. The most common CVD manifestations are telangiectasias, reticular or varicose veins, accompanied or not by pain, swelling sensation, leg edema, skin modifications or ulcerations. The exact prevalence of CVD is difficult to be estimated and available results are widely varying from 2 to 56% in male population and from 1 to 60% in female population. These huge differences appear mainly due to the fact that different studies included variable population in terms of age, race, measuring methods and method used to diagnose disease, relaying only on self-reported symptoms or standardized physical examination (1). At the initiative of the International Union of Phlebology, a large-scale international survey named Vein Consult Program (VCP) was carried out in 20 countries. The Vein Consult Program concluded that the worldwide presence of CVD was 83.6% and the study underlined the importance of adequate screening for CVD and training of both general practitioners (GPs) and specialist physicians (2). The main goal of CVD treatment is reducing the symptoms (heaviness, leg pains, oedema and swelling) as well as preventing complications. Along with advice regarding lifestyle changes (e.g., weight loss, practice a sport, wear appropriate heels), patients need medication. The primary options of treatment are micronized purified flavonoid fraction (MPFF) and pentoxifylline, combined, if necessary, with compression (3).

Materials and methods

The study had a multicentre, cross-sectional, observational design and took place in Romania, based on a transversal method. In this study were included adult patients recruited by 185 GPs as investigators, selected in compliance with national regulations, in a randomly manner from Romania's health care system. The recruitment took place in June-July 2015 and each

investigator was allowed to include 40 consecutive patients, with the minimum age at inclusion of 18 years. Patients attending for emergency visits were excluded. The total number of patients included was 7,210. After obtaining the patient signed informed consent regarding study participation, the following information was collected: Demographic data, CVD presence and frequency of disease's signs and symptoms, medical history and associated risk factors, the clinical, aetiological, anatomical and pathophysiological (CEAP) clinical stages, and therapeutic management practice.

The observational study was approved by the National Agency for Medicines and Medical Devices (NAMMD) and received positive opinion from the National Bioethics Committee for Medicine and Medical Devices (NBCMMD), number 17 SNI/17 June 2015.

Statistical analysis. Statistical analysis was performed with SPSS version 15 (SPSS Inc., Chicago, IL, USA) and included the following: Descriptive analysis, Chi-square test and ANOVA with post hoc Tukey's test.

The scales variables were reported with mean and standard deviation, and summarize categorical variables using frequencies and percentages. P-value <0.05 was considered to indicate a statistically significant difference.

Results

In total, 7,210 patients were included in the survey, mostly female (71.01%), with a mean age of 58.2±14.5 years. The male population was significantly older than female (P<0.001), while mean body mass index (BMI) value for the total group in the overweight category (27.3±5.005 kg/m^2) with no significant sex differences. When the distribution of total study population was analyzed regarding CVD diagnosis the following data were obtained: 2,271 (31.5%) patients had already the CVD diagnosis established prior to the study visit, for 2,664 (36.9%) patients, CVD was diagnosed during the study visit, while for the rest of the patients, 2,275 (31.6%), CVD diagnosis was not established prior or during the study visit. Nevertheless, when data were analyzed regarding signs and symptoms reported either spontaneously by the patient, or as a consequence of physician questions and clinical examination, it was noted a that only 1,394 patients (19.3%) did not report any symptoms or signs suggestive for CVD, while 672 patients (9.3%) presented just symptoms, but no CVD sign, fact that is placing them into CEAP C0s category. Data for the total study population were analyzed regarding CEAP class and the following results were obtained: C0s (9.3%), C1 (21.4%), C2 (15.1%), C3 (21%), C4a (10.4%), C4b (1.1%), C5 (1.6%) and C6 (0.8%) (Table I).

Data regarding CVD diagnosis and classification were analyzed and it was observed that for 6 patients (representing 0.08% from the study population) the CVD diagnosis was established, despite of the fact that patients did not present any CVD sign or symptoms. C0s stage was not considered by GP as CVD for 569 patients (7.89% of the study population and 84.7% of the C0s population), while for another 318 patients (4.41% of the study population and 6.18% of the C1-C6 population) presenting both CVD signs and symptoms specific for C1-C6 stages, the CVD diagnosis was not established by GPs.

Patient's CVD symptoms reported data proved a significant sex difference in spontaneous reporting in favor of female population, difference which was partially maintained when data regarding CVD symptomatology were obtained after GPs questions. In addition, a difference was observed between patient spontaneous reporting compared to reporting after GPs questions (28.7 vs. 71.3%) (Table II). For the total group of patients included in the survey, the most common spontaneously reported complains were regarding 'sensation of heavy legs' (53.44%), followed by 'sensation of swelling' (41.62%) and 'pain' (38.96%). The percentage of CVD symptoms reported in response to the questions set by the physician increased as follows: 'sensation of heavy legs' (61.30%), followed by 'sensation of swelling' (43.68%) and 'pain' (47.16%) (Table II).

Patients (50.85%) addressing GPs due to consultation regarding another disease. GPs methodology regarding CVD diagnostic was analyzed and it was noted that only 55.7% of GPs are asking directly questions regarding CVD complains, while only 62.7% are examining all patients. The CVD prevalence directly calculated by GP answers was 68.4%, while the rate of new cases diagnosed with CVD during GPs office visit was 36.9% (Table III).

When data were cross-checked regarding CVD symptoms reported after GP questions and associated CVD signs, we indirectly calculated the 'real' CVD prevalence as 80.7%. Most of the difference between the direct and indirect prevalence calculation comes from the C0s class CVD patients, which were not considered as CVD patients in most of the cases. We identified through indirect calculation a C0s prevalence of 9.3%.

We performed analysis comparing C0s and C1-C6 patients, which proved that patients included in the C1-C6 group were significantly older, with higher BMI, compared to C0s patients (P<0.001). Significant differences were found when patient's answers were analyzed in regards to spontaneous CVD complains or CVD symptoms reported in response to the questions set by the physician. There was a clear predominance of CVD complains within the C1-C6 group (P<0.001), nevertheless even in C0s stage the following patients' spontaneously reported symptoms were registered at high rates: 'Pain' (38.7%), 'sensation of heavy legs' (41.5%) (Table IV).

There were significant differences between groups regarding the time when CVD symptoms were most intense: after standing a long time (p<0.001) and during the night (p=0.024), as well as in regards to the frequency of CVD symptoms appearance, occasionally (p<0.001), regularly, respectively all the time (p=0.004) (Table IV). The average number of symptoms is significantly higher in C1-C6 group (P<0.001) (Table IV). Interestingly, within the C0s group, after physician questions, the average number of symptoms decreased compared to the spontaneous reporting (1.34±0.72 vs. 1.52±0.83). The significant differences regarding risk factors were observed for family CVD history, smoker status, previous pregnancy (P<0.001), and sitting <5 h/day as well (Table IV).

We compared the therapeutic management practice between C0s and C1-C6 patients and a significant difference was noted between the groups in regards to addressing GPs office for CVD reason as well as receiving recommendation towards a specialist physician (Table V). All patients diagnosed with CVD (prior or during the visit) received lifestyle

Table I. Patient characteristics and reporting of CVD symptoms.

Total group - descriptive data	Female	Male	Total	P-value
Age (years)				
N	5,108	2,088	7,196[a]	<0.001
Mean ± SD	57.6±14.735	59.5±14.077	58.2±14.572	
BMI				
N	5,120	2,090	7,210	0.682
Mean ± SD	27.3±5.107	27.4±4.746	27.3±5.005	
Age (years)	No. of patients[a]	Percent (%)		
<45	1,344	18.7		
45-54	1,095	15.2		
55-64	2,209	30.7		
65-74	1,581	22.0		
≥75	967	13.4		
Total	7,196	100.0		
CEAP classification	No. of patients	Percent (%)		
No. of CVD	1,394	19.3		
C0s	672	9.3		
C1	1,543	21.4		
C2	1,091	15.1		
C3	1,512	21.0		
C4a	752	10.4		
C4b	76	1.1		
C5	113	1.6		
C6	57	0.8		

[a]Data for 14 patients not shown. CVD, chronic venous disorder; BMI, body mass index; CEAP, clinical, aetiological, anatomical and pathophysiological.

advice and the most common prescription of venoactive drug was MPFF (74.6% of treated patients) with a treatment duration of ≥12 weeks (93.5% of treated patients). It is important to mention that only 103 out of 672 C0s patients were in fact diagnosed with CVD and as a consequence only those received treatment. We analyzed the entire CVD group regarding GPs recommendations for a specialist consultation and 42% of CVD patients received such recommendation, most of them being referred to a vascular surgeon (41.7%).

Discussion

The study took place in 2015 and the newly diagnosed CVD rate was 36.9% and the reported CVD prevalence in June-July 2015 was 68.4%. These figures do not include all possible CVD patients and, therefore, when we indirectly calculated the CVD prevalence by including patients with concomitant symptoms, and no signs (C0s) and the once not diagnosed with CVD, instead presenting both signs and symptoms we reached a prevalence rate of 80.7%. Indeed, this value of the prevalence rate might be overestimated, due to the fact that some of the symptoms such as night cramps, sensation of heavy legs or restless legs could be caused also by other diseases than CVD and often, it is not possible to make a differential diagnosis, between CVD C0s stage and other diseases, especially in a GP office, were it is usually not possible to perform additional examinations such as duplex-ultrasound, nevertheless it is important to mention that apart of those patients, there were relatively high percentage of patients reporting specific CVD symptoms and some presenting even CVD signs, but GPs considered that CVD suspicion could not be formulated for those patients. Those data are suggestive for the fact that patients are ignoring CVD-related symptoms, while physicians are overlooking them, making early CVD diagnosis and implementation of adequate therapeutic management not to be applied in early disease stages. A similar conclusion regarding adequate screening and additional training for physicians was reached by the Vein Consult Program (2). The percentage of C1-C6 CVD patients was 71.4%, which is higher than in most of the results from other countries, and this might be explained due to the fact that the mean age of patients included in this survey was higher than the one registered for other countries (2,4-7). In Romania, according to Sponsor's internal unpublished data, in the studies SEPIA (2004), VEIN CONSULT (2009) and Vein PREVENT (2010), the CVD diagnosis rates increased in

Table II. CVD symptoms and signs.

Symptoms/signs reporting method	Total group (n=7,210)	% of patients	Female (%)	Male (%)
Direct reporting	2,066	28.7	74.1	25.9
After physician's questions	5,144	71.3	69.8	30.2

Patient spontaneous reporting of health issues	Total group (n=7,210)	Percent (%)
Pain	2,809	38.96
Sensation of heavy legs	3,853	53.44
Sensation of swelling	3,001	41.62
Cramps	2,280	31.62
Sensation of burning	1,443	20.01
Telangiectasias	2,112	29.29
Reticular veins	1,148	15.92
Varicose veins	1,920	26.63
Swollen legs	966	13.40
Skin alterations	566	7.85
Leg ulcer	105	1.46
None	1,581	21.93

Symptoms detected during medical consultation after GPs specific questions	Total group (n=7,210)	Percent (%)
Pain	3,400	47.16
Sensation of heavy legs	4,420	61.30
Sensation of swelling	3,149	43.68
Cramps	2,279	31.61
Sensation of burning	1,740	24.13
None	1,394	19.33

Patient spontaneous reporting of health issues	Female (n=5,120) (%)	Male (n=2,090) (%)	P-value
Pain	40.3	35.6	<0.001
Sensation of heavy legs	58.1	42.0	<0.001
Sensation of swelling	46.3	30.2	<0.001
Cramps	32.7	28.9	<0.001
Sensation of burning	21.0	17.7	<0.001
Telangiectasias	34.1	17.6	<0.001
Reticular veins	18.0	10.7	<0.001
Varicose veins	28.2	22.7	<0.001
Swollen legs	14.5	10.7	<0.001
Skin alterations	7.6	8.6	0.150
Leg ulcer	1.2	2.1	0.003
No problem	18.1	31.2	<0.001

Patient reporting symptoms after physician addressing specific questions	Female (n=5120) (%)	Male (n=2090) (%)	P-value
Pain	47.8	45.6	0.090
Sensation of heavy legs	64.9	52.4	<0.001
Sensation of swelling	47.5	34.2	<0.001
Cramps	31.9	31.0	0.481
Sensation of burning	24.3	23.6	0.529

Table III. Reason attending GPs office and GPs methodology in establishing CVD diagnosis.

Reason of doctor visit	No. of patients	Percent (%)
Medical consult for CVD	589	8.17
Medical consult for other disease	3,666	50.85
Periodic check-up	2,160	29.96
Administrative reason	343	4.76
Other reason	452	6.27
Total	7,210	100.00
GPs methodology to establish CVD diagnosis	**No. of patients**	**Percent (%)**
Ask directly all patients about CVD	4,016	55.7
Ask directly all patients during summer time about CVD	340	4.7
Ask directly some of the patients about CVD	1,682	23.3
Ask directly about CVD when I have enough time	648	9.0
Ask all patients about predisposing jobs	2,391	33.2
Ask all patients about predisposing jobs during summer time	103	1.4
Ask some of the patients about predisposing jobs	833	11.6
Ask about predisposing jobs only when I have time	242	3.4
Examine all patients	4,523	62.7
Examine all patients only during summer time	222	3.1
Examine some of the patients	1,288	17.9
Examine only when I have time	389	5.4
Ask directly and examine only when the patient complains	681	9.4
GPs establishing CVD diagnosis for the patients included in the study	**No. of patients**	**Percent (%)**
No	2,275	31.6
Yes	4,935	68.4
Total	7,210	100.0
GPs establishing CVD diagnosis for the patients included in the study	**No. of patients**	**Percent (%)**
CVD diagnosed prior study visit	2,271	31.5
CVD diagnosed during study visit (new cases)	2,664	36.9
CVD diagnosis was not established	2,275	31.6
Total	7,210	100.0

CVD, chronic venous disorder; GPs, general practitioners.

recent years: +32% (2004), +45% (2009) and 66% (2010). This increase is probably due to trainings and the raised awareness. On the other hand, the number of patients who addressed the physicians in order to ask questions about the CVD is very low and almost unchanged: 9% (2004); 10% (2009) and 9% (2010) and 8.7% in this survey. It is important to continue to support the GPs to evaluate constantly the presence of CVD symptoms and to educate the adult population to address their physician.

This survey measured the prevalence of CVD in a population visiting a GPs office in Romania. Despite randomly choosing sites all over Romania and including consecutive patients addressing the GPs office, the population included in the survey does not exactly represent the average population of Romania. The mean age (58.2 years) of the study population is higher than the median age registered for Romania population (41.1 years) (8). The female predominance (71.0%) is also higher. These differences have influenced the reported prevalence of CVD for Romanian population. In addition, we need to keep in mind that for this observational study the CVD was classified by using only the C (clinical) part of CEAP and classification was done by GPs, which are not routinely using the CEAP classification. This fact could link to a moderate reproducibility of data, as already described in the literature (9). Another important aspect regarding prevalence is the involvement of correct diagnosis of the C0s stage of CVD. Despite the fact that the C0s profile is a globally recognized, data regarding its prevalence are limited. C0s patients are defined as those presenting with one or more CVD-related symptoms, without presenting any clinical signs of the disease during a physical examination. Some indirect calculations of C0s prevalence

Table IV. Comparison of clinical characteristics of C0s vs. the C1-C6 CVD patients.

Characteristics	C0s (n=672)	C1-C6 (n=5,144)	P-value
Age	56.7±15.0	60.2±13.4	<0.001
BMI	26.4±4.1	27.9±5.2	<0.001
Female (% of patients)	62	76	<0.001
Patient spontaneous reporting of health issues	C0s (n=672) (%)	C1-C6 (n=5,144) (%)	P-value
Pain	38.7	49.6	<0.001
Sensation of heavy legs	41.5	69.5	<0.001
Sensation of swelling	25.0	55.1	<0.001
Cramps	28.7	40.6	<0.001
Sensation of burning	18.2	25.7	<0.001
Telangiectasias	0.7	41.0	<0.001
Reticular veins	0.3	22.3	<0.001
Varicose veins	0.3	37.3	<0.001
Swollen legs	0.6	18.7	<0.001
Skin modifications	0.6	10.9	<0.001
Leg ulcer	0.0	2.0	<0.001
No problem	0.0	3.6	<0.001
CVD symptoms reported when questioned by physician	C0s (n=672) (%)	C1-C6 (n=5,144) (%)	P-value
Pain	39.0	55.3	<0.001
Sensation of heavy legs	36.9	73.7	<0.001
Sensation of swelling	19.0	56.6	<0.001
Cramps	22.5	35.3	<0.001
Sensation of burning	16.7	25.7	<0.001
Average number of reported CVD symptoms	C0s (n=672) (%)	C1-C6 (n=5,144) (%)	P-value
Spontaneously reported by patient	1,52±0,83	2,40±1,36	<0.001
Reported by patient when questioned by physician	1,34±0,72	2,47±1,25	<0.001
Time when CVD symptoms are most intense	C0s (n=103) (%)	C1-C6 (n=4,826) (%)	P-value
In the morning	1.9	4.1	0.271
After standing a long time	54.4	69.7	<0.001
In the evening	64.1	65.6	0.747
During the night	14.6	24.2	0.024
Frequency of CVD symptoms	C0s (n=103) (%)	C1-C6 (n=4,826) (%)	P-value
Rarely	11.7	8.2	0.209
Occasionally	54.4	34.1	<0.001
Regularly	30.1	44.4	0.004
All the time	2.9	12.4	0.004
Risk factors	C0s (n=672) (%)	C1-C6 (n=5,144) (%)	P-value
Positive CVD family history	6.0	46.3	<0.001
Positive CVD family history - relative 1st degree (1 parent)[a]	85.0	74.5	0.130

Table IV. Continued.

Positive CVD family history - relative 1st degree (2 parents)[a]		12.5	17.5	0.406
Positive CVD family history - relative 2nd degree[a]		15.0	17.2	0.710
Positive CVD family history - relative 3rd degree[a]		2.5	2.9	0.871
Smoker		4.8	19.0	<0.001
Standing <5 h/day		35.0	44.1	0.064
Standing 5-10 h/day		50.5	45.6	0.327
Standing >10 h/day		14.6	10.3	0.158
Sitting <5 h/day		39.8	50.2	0.037
Sitting 5-10 h/day		46.6	40.4	0.208
Sitting >10 h/day		13.6	9.3	0.144
For women only	C0s (%)		C1-C6 (%)	P-value
Previous pregnancy	52.8		67.8	<0.001

[a]Answers available only for 2,424 patients. CVD, chronic venous disorder; BMI, body mass index.

Table V. Comparison of the therapeutic management in C0s vs. the C1-C6 CVD patients.

Medical consultations	C0s (n=672) (%)	C1-C6 (n=5,144) (%)	P-value
Addressing for CVD consultation	0.4	8.72	<0.001
Recommendation for a specialist consultation	0.5	39.8	<0.001
	CVD diagnosis for this patient		
CVD classification[a]	No	Yes	Total
C0s	569	103	672
C1-C6	318	4,826	5,144
Patient diagnosed with CVD referred to a specialist.	N	(%)	
Yes	2,075	42.0	
No	2,860	58.0	
Preferences for specialist recommendation	N	(%)	
Internal medicine	249	12.0	
Vascular surgery	865	41.7	
Dermatology	413	19.9	
Cardiology	270	13.0	
General surgery	37	1.8	
Imagistics	212	10.2	
Other	29	1.4	

[a]Based on registered CVD symptoms and clinical examination. CVD, chronic venous disorder.

was made for certain studies as follows: VEINES study (3.8%), Brazilian survey (3.9%), Polish study (13-23%), the San Diego Vein Study (15%) and was directly detected through the Vein Consult Program to be ~20% of the population (10), while a meta-analysis estimated the prevalence as ~20% (11). In the present study we identified through indirect calculation a C0s prevalence of 9.3%. There were significant differences between C0s and C1-C6 CVD patients. As expected, C0s patients were younger, with lower BMI, with less CVD-related symptoms, and overall less treated compared to C1-C6 CVD stages.

An important aspect that needs further investigation, will be the relative low percentage of patients referred to venous specialist (42.0%). Among referrals most of those were towards vascular surgeons (41.7%), regardless of the fact that corre-

sponding CEAP class for those patients would not be indicative for surgery. Only 19.9% of referred patients were directed towards dermatologists. One explanation for this type of referral behavior might be the availability of different venous specialists in certain geographic areas, or GPs intrinsic psychological variables, where GPs who consider disease as serious or are less tolerant regarding unknown details about the proper disease management have a higher referral rate. A similar pattern regarding variations in GPs referral was noted also by other studies, nevertheless a large proportion of it cannot be explained easily (12). All patients diagnosed with CVD (prior or during the visit) received lifestyle advice and within this group of patients the most common prescription of venoactive drug was MPFF (74.6% of treated patients) with a treatment duration of ≥12 weeks (93.5% of treated patients). It is important to mention that only 103 out of 672 C0s patients were in fact diagnosed with CVD and as a consequence only those received treatment.

Whether pharmacological therapy can heal CVD remains unclear, nevertheless there is evidence suggesting a possible effect on leg-ulcer healing (13). Prophylactic use of venoactive drugs might be possible given the anti-inflammatory mechanisms of venoactive drugs, which could suggest that retardation of CVD progression is possible, nevertheless more research is needed in this direction. Available literature data prove that the use of venoactive drugs is safe and economic (14,15). In other literature it is suggested that the use of textile biomaterials in patients with high risks in developing CVD, might be an efficient method of preventing the occurrence of CVD (16). Also, for CVD patients with co-morbidites, mainly diabetes, it is crucial to implement promptly all possible therapeutic methods, if possible by preventing the occurrence of the CVD ulcers, which could become extremely difficult to treat (17). For those patients, the diabetic neuropathy, additional to CVD is negatively impacting the patient's quality of life and those conditions are associated with important health care costs (18).

All healthcare providers should focus on increasing patient treatment adherence, where GPs, venous specialists as well as pharmacists have to deliver correct and complete information that will enable patients to follow correctly the prescribed treatment (19).

In conclusion, CVD is a very common disease, with a prevalence of CVD in Romania within the study population in June-July 2015 of 68.4%. The newly diagnosed CVD cases represent 36.9% of patients included in this study, nevertheless both parameters could be underestimated, as long as a significant percentage of patients presenting symptoms, but no CVD signs were not considered by GPs as CVD cases. Additional training for GPs regarding recognition of CVD in early stages is critical, together with initiation of CVD therapeutic management and referral to venous specialist, mainly in advance disease stages.

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Availability of data and materials

The datasets generated and/or analyzed during the present study are not publicly available due to the fact that they belong to Servier, as Sponsor of the study, but are available from the corresponding author on reasonable request, and with prior permission of Servier.

Authors' contributions

TF and SB, DEB contributed to the design of study, acquisition of data and review of the manuscript. IAM contributed to the conception, writing and reviewing of the manuscript. OV contributed to the design, analysis and interpretation of the patient data, writing and reviewing the manuscript. All authors read and approved the final version of manuscript.

Ethics approval and consent to participate

The observational study was approved by the National Bioethics Committee for Medicines and Medical Devices (NBCMMD) with approval no. 17 SNI dated 17 June 2015, and signed written informed consent was obtained from all the patients.

Patient consent for publication

Not applicable.

Competing interests

IAM is an employee of Servier. OV received honoraria for the interpretation of data. The other authors declare that they have no competing interests.

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