

Prevalence of cardiovascular risk factors, target organ damage, and subclinical and symptomatic cardiovascular disease in a national population of patients with chronic myeloid leukemia

Prevalencia de los factores de riesgo cardiovascular, lesión de órgano diana y enfermedad cardiovascular subclínica y sintomática en una cohorte nacional de pacientes con leucemia mieloide crónica

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Abstract

Introduction: Treatment of chronic myeloid leukemia (CML) with tyrosine kinase inhibitors (TKIs) has improved the life expectancy of these patients. However, TKIs have been related to an increase in cardiovascular events. These occur especially in patients who already had cardiovascular risk factors (CVRF). **Material and methods:** An observational cross-sectional study of patients with CML under treatment with TKI was conducted. The prevalence of CVRF, target organ damage and subclinical and symptomatic atherosclerotic cardiovascular disease (ASCVD) was studied. **Results:** 73 patients were included. 63.01% were male. The median age was 56 years (IQR 45 – 67,50). 47.95% had high blood pressure, 17.33% diabetes mellitus, 40.79% dyslipidemia, 50.68% overweight, 26.03 obesity and 21.92% were smokers. 19.20% presented microalbuminuria, 8.20% left ventricular hypertrophy and 19.18% chronic kidney disease. 32.90% had high values of hsCRP and 26% high values of pulse wave velocity. 11.07% had ASCVD. Patients treated with nilotinib had a higher prevalence of dyslipidemia, smoking, peripheral arterial disease, and ASCVD. **Conclusions:** The prevalence of CVRF was higher than that described in the general Spanish population. Patients treated with nilotinib had a higher prevalence of uncontrolled hypertension, dyslipidemia, smoking, peripheral arterial disease, and established atherosclerotic cardiovascular disease than patients treated with imatinib and dasatinib.

Keywords: Chronic myeloid leukemia. Tyrosine kinase inhibitors. Cardiovascular disease.

Resumen

Introducción: Los inhibidores de la tirosina cinasa (ITC) han mejorado el pronóstico de la leucemia mieloide crónica (LMC). Sin embargo, los ITC se han relacionado con un incremento en los eventos cardiovasculares que se producen fundamentalmente en pacientes que ya presentaban factores de riesgo cardiovascular (FRCV). **Material y métodos:** Estudio observacional, descriptivo y transversal de pacientes con LMC en tratamiento con ITC. Se estudió la prevalencia de FRCV, lesión de órgano diana y enfermedad cardiovascular aterosclerótica (ECVA) subclínica y sintomática. **Resultados:** Se reclutaron 73 pacientes. El 63,01% eran varones con una mediana de edad de 56 años (intervalo intercuartílico [IQR]: 45-67,50). El

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47,95% presentó hipertensión arterial (HTA), el 17,33% diabetes mellitus, el 40,79% dislipidemia, el 50,68% sobrepeso, el 26,03% obesidad y el 21,92% eran fumadores. El 19,20% presentaron microalbuminuria, el 8,20% hipertrofia ventricular izquierda y el 19,18% enfermedad renal crónica. El 32,90% tuvieron valores elevados de proteína C reactiva ultrasensible y el 26% valores de velocidad onda de pulso elevados. Un 11,07% tuvieron ECVA. Los pacientes tratados con nilotinib tuvieron mayor prevalencia de dislipidemia, tabaquismo, enfermedad arterial periférica y ECVA. **Conclusiones:** La prevalencia de FRCV es mayor a la descrita en población general española. Los pacientes tratados con nilotinib presentaron mayor prevalencia de HTA no controlada, dislipidemia, tabaquismo, enfermedad arterial periférica y ECVA establecida que los pacientes tratados con imatinib y dasatinib.

Palabras clave: Leucemia mieloide crónica. Inhibidores de la tirosina cinasa. Enfermedad cardiovascular.

Introduction

Chronic myeloid leukemia (CML) was turned upside down after the appearance of tyrosine kinase inhibitors (TKI) targeting the BCR-ABL1 protein back in 2001.¹⁻³ Currently, the prognosis of these patients is similar to that of the overall population of the same age and sex.⁴

The higher life expectancy described followed by a higher rate of cardiovascular disease (CVD) is the sum of two factors: the previous presence of cardiovascular risk factors (CVRF) and side effects associated with the administration of TKI.⁵⁻⁷ This is due to the fact that these drugs do not trigger the selective inhibition of tyrosine kinase targeting BCR-ABL1, but also act on other tyrosine kinases that participate in cardiovascular physiology. These include the vascular endothelial growth factor receptor 1 to 3, TIE-2, alpha and beta receptor derived from platelet growth, and the fibroblast growth factor receptor 1 to 4, among others.^{8,9}

Similarly, each TKI produces specific cardiovascular effects. Imatinib,¹⁰ and bosutinib¹¹ have a neutral cardiovascular profile. Dasatinib¹² has been associated with pleural and pericardial effusion, and pulmonary hypertension. Nilotinib promotes the development of dyslipidemia and atherosclerotic cardiovascular disease (ASCVD) especially peripheral arterial disease (PAD).¹³ There is a higher rate of arterial hypertension (AHT), ASCVD, and thromboembolic disease in patients treated with ponatinib.¹⁴

Most cardiovascular events occur in patients who already had CVRF. It is for that reason that cardiovascular examination before starting treatment with TKI is necessary to reduce the chances of developing cardiovascular events.¹³ However, the diagnosis of CVRF is often insufficient since the preclinical states of CVD can be omitted. We should understand that there is a continuum from the presence of CVRF until the development of CVD and that it can be diagnosed preclinically to prevent the development of complications. Atherosclerosis

is a pathological and progressive inflammatory process that occurs throughout years and is promoted by different CVRF. In the early stages it can go unnoticed (subclinical ASCVD). However, in the long term, it causes most cases of ischemic heart disease, ischemic stroke, and arteriopathy, both aortic and peripheral.¹⁵⁻¹⁷ Target organ damage (TOD) is defined as structural or functional changes in terminal arteries or organs (heart, blood vessels, brain, eyes, and kidney) due to CVRF like hypertension or diabetes mellitus. It is a marker for preclinical or asymptomatic CVD and indicative of a higher risk for developing CVD. Some types of TOD—especially in their early stages—are reversible.¹⁸

TOD and subclinical ASCVD are widely known concepts used in the general population in the diagnosis and control of CVD. They can help us assess the actual risk of developing endovascular complications and can modify the CVRF. However, until now, they have not been used systematically in patients with neoplastic diseases. Cardio-onco-hematology, a relatively new medical specialty, has been focused on damage to the heart by chemotherapy agents, immunomodulating agents, and new targeted therapies. However, to this date, no special attention has been paid to organ damage due to CVRF and these therapies.¹⁹ In Spain, the incidence rate of CVRF, TOD, and subclinical and asymptomatic ASCVD in populations with CML is still unknown. As far as we know, this is the first study ever published that analyses this incidence rate in a cohort of Spanish patients with CML treated with TKI.

Material and methods

Observational, descriptive, cross-sectional study of patients diagnosed with CML on active treatment with TKI at Hospital Virgen de las Nieves, Granada, Spain. Data were collected between May 2018 and May 2019. Out of the 74 patients diagnosed with CML, 73 participated in the study. The prescription of TKI by the hematologist prior to the consultation assessment of

CVRF was done following the routine clinical practice based on the following criteria: in elderly patients or patients with short life expectancies, pluripathologic or highly polymedicated patients, the first-line therapy option regarding TKI was imatinib. In young patients or with big desires of interrupting treatment in the future, the first-line option was a second-generation TKI. Choosing between a second-generation TKI and a first-line TKI was based on the patient's comorbidities. Nilotinib was avoided in patients with established CV events or multiple CVRF. Dasatinib was avoided in patients with a past medical history of pleural effusion or overt fluid retention. To this date, the use of bosutinib in Spain as a first-line therapy to treat CML had not been approved.

Information on the prevalence of traditional CVRF and CVD before starting treatment with TKI was provided after reviewing the patients' past medical history while data on the CVRF and CVD when the study was curated and analyzed directly by the lead investigator during the patient's examination.

The diagnosis of subclinical ASCVD was based on the measurement of baseline values of ultrasensitive C-reactive protein (US-CRP) (pathological values $> 5 \mu\text{g/L}$) and pulse wave velocity (PWV) above the corresponding values according to age and sex (in the indirect measurement of PWV the Mobil-OGraph validated system was used). TOD was defined like this: left ventricular hypertrophy (LVH) according to Sokolow-Lyon and Cornell electrocardiographic criteria (sum of the voltage of R-wave in V5-V6 leads + S-wave in V1 lead $> 35 \text{ mm}$) or the Cornell voltage criterion (sum of R-wave in aVL lead + S-wave in V3 lead $> 20 \text{ mm}$ in women or $> 28 \text{ mm}$ in men); kidney damage defined as microalbuminuria (2 fresh urine measurements with an albumin/creatinine ratio between 30 mg/g and 300 mg/g) or glomerular filtration rate measured using the CKD-EPI formula (Chronic Kidney Disease Epidemiology Collaboration) with values between 45 and $60 \text{ mL/min/1.73 m}^2$. Arterial pressure was measured at the office following the recommendations established in the latest version of the clinical practice guidelines on the management of AHT²⁰ using the Omron M3 IT-HEM7131U-E device.²¹ Also, through ambulatory blood pressure monitoring (ABPM) using the SpaceLabs 90207 oscillometric system (SpaceLabs Inc, United States),²² that was also used to diagnosed masked AHT, white-coat AHT, and for the follow-up of arterial pressure.

This study was approved by the Ethics Committee of the Province of Granada, Spain (code 5c07f325e14f4a852ee4d0047025daf9baaa41c7).

Results

The patients' mean age was 56 years (interquartile range [IQR], 45-67,50). A total of 63.01% of the patients were men. A total of 39 patients were treated with a daily dose of first-line therapy with imatinib 400 mg, 24 with nilotinib 300 mg twice/day, and 10 with a daily dose of dasatinib 100 mg. A total of 16 patients crossed over to second-line therapy (9 patients to nilotinib 300 mg twice/day or 400 mg twice/day, and 7 patients to dasatinib), and 1 patient to third-line therapy with dasatinib. Treatment went on a median of 60 months (IQR, 32-116.50) with longer courses for patients treated with imatinib (median, 94 months; IQR, 32-94) compared to nilotinib (median, 47 months; IQR, 18-62,50), and dasatinib (median, 33.50 months; IQR, 19.50-49.00). The prevalence of CVRF before treatment with TKI and during the assessment is shown on [table 1](#).

When patients were assessed, 47.90% of them were found to be hypertensive with mean systolic arterial pressure values of $137.44 \text{ mmHg} \pm 19.92 \text{ mmHg}$ and mean diastolic arterial pressure values of $81.15 \text{ mmHg} \pm 10.09 \text{ mmHg}$. All except for 1 patient underwent 24-h ABPM. Only 28.60% of hypertensive patients remained under proper arterial pressure monitoring according to ABPM. The statistically significant factors associated with uncontrolled arterial pressure were age, overweight, PWV, established CVD, and high/very high cardiovascular risk. No correlation between treatment with TKI and AHT was reported, although a statistically significant correlation was seen with nilotinib.

The prevalence of TOD, subclinical ASCVD, and symptomatic ASCVD is shown on [table 2](#). All ASCVD events occurred after treatment with TKI started. The prevalence of subclinical ASCVD biomarkers and TOD in the cardiovascular risk groups according to the SCORE scale was studied.²³ Although the prevalence of subclinical ASCVD biomarkers and TOD was higher in the group with higher cardiovascular risk (CR) no statistically significant differences were seen between the groups. Almost 50% of the patients with low CR had subclinical ASCVD and TOD. The distribution of TOD and subclinical ASCVD based on the patients' CR is shown on [table 3](#).

To study the cardiovascular effects of TKI, only patients treated with TKI monotherapy across their past medical oncology history were selected. Afterwards, they were divided into 2 groups: patients treated with imatinib and dasatinib and patients treated with nilotinib only. The latter group had a higher prevalence of

Table 1. Prevalence of cardiovascular risk factors in a population with chronic myeloid leukemia (CML) treated with tyrosine kinase inhibitors (TKI). Data on the prevalence of cardiovascular risk factors (CVRF) after diagnosis of CML and during study assessment were collected. When CML was diagnosed, no data on pathological alcohol use, overweight, and obesity was collected. A statistical comparison between the 2 groups of treatment was conducted (imatinib+dasatinib vs nilotinib)

CVRF	After CML diagnosis				While treated with TKI			
	Overall pop. CML	Imatinib + dasatinib	Nilotinib	P	Overall pop. CML	Imatinib + dasatinib	Nilotinib	P
	73 (%)	35 (%)	22 (%)		73 (%)	35 (%)	22 (%)	
Hypertension	20 (27.40)	4 (11.4)	2 (9.1)	1	35 (47.95)	13 (37.10)	13 (59.10)	0.105
Diabetes mellitus	10 (13.70)	3 (8.6)	1 (4.5)	1	13 (17.33)	4 (11.40)	5 (22.70)	0.286
Dyslipidemia	16 (21.90)	5 (14.3)	3 (13.6)	1	40 (40.79)	12 (13.40)	15 (68.20)	0.013
Active smoker	16 (21.90)	7 (20.0)	12 (54.5)	0.010	16 (21.92)	4 (11.40)	10 (45.50)	0.004
Alcohol use	-	-	-	-	11 (15.07)	4 (11.40)	5 (22.70)	0.286
Overweight	-	-	-	-	37 (50.68)	17.80 (46.80)	12 (54.50)	0.661
Obesity	-	-	-	-	19 (26.03)	9 (25.70)	5 (22.70)	0.799

Pop, population.

dyslipidemia, smoking, PAD, and ASCVD. No statistically significant differences were seen regarding the presence of TOD or subclinical ASCVD. However, there was a higher rate of uncontrolled AHT according to the ABPM (Tables 4-6).

Discussion

With the arrival of different generation of TKI, the prognosis of CML has changed dramatically from a lethal disease within a few months after diagnosis to a chronic condition with a similar life expectancy compared to that of the general population.⁴ The increased survival rate has been followed by a higher rate of ASCVD due to the presence of CVRF and the cardiometabolic toxic effects of TKI.^{5,6} The latter can be explained by the fact that the inhibition of tyrosine kinase targeting the BCR-ABL1 protein is not selective, which means that it can act on other kinases including some that participate on vascular biology.

Before selecting the most appropriate TKI the patients' hematologic and cardiometabolic profile should be known. The chances of developing side effects would drop consequently. It is widely known that most cardiovascular events occur in patients who already have CVRF and/or high/very high cardiovascular risk. The long-term analysis of the ENESTnd clinical trial (Evaluating nilotinib efficacy and safety in clinical trials-newly diagnosed patients) revealed that estimating CR using the

Framingham Risk Score predicted the development of CVD during treatment with nilotinib.^{24,25} However, the routine assessment of these patients—focused on the presence of CVRF—can be, in most cases, insufficient and underestimate the true risk of ASCVD.

In the general population, low and intermediate risk patients according to the Framingham Risk Score or the SCORE scale especially benefit from the assessment of subclinical ASCVD and TOD since it can re-categorize these patients' CR to avoid underestimating the true risk of developing CVD at the end.²⁶ We believe that in patients with CML treated with TKI plus cardiac damage, subclinical ASCVD and TOD should be thoroughly assessed including central and peripheral arterial and renal assessments. In our own experience, every patient's blood should be tested including a complete blood count followed by a urine test with albuminuria, an electrocardiogram, a thoracic x-ray, the ankle-brachial index, and an estimate of cardiovascular risk. Other tests like the PWV and the echocardiogram can be very useful to achieve more accurate diagnoses of subclinical atherosclerosis and ventricular hypertrophy in certain situations.

We can compare our findings on the prevalence of CVRF, subclinical CVD, TOD, and ASCVD with the results from landmark studies conducted among the Spanish general population, as well as with other studies on patients with CML and similar characteristics regarding age, sex, and duration of treatment.²⁷⁻²⁹ To

Table 2. Prevalence of target organ damage, risk biomarkers of atherosclerosis, and cardiovascular disease in a population treated with tyrosine kinase inhibitors (TKI). The overall number of patients and percentage was collected

Item	Subjects (%)
Microalbuminuria (30 mg/g to 300 mg/g)	14 (19.20)
LVH	6 (8.20)
Chronic kidney disease (CKD-EPI to estimate GFR<60 mL/min)	14 (19.18)
Pathological CRP (> 5 mg/L)	24 (32.90)
Pathological PWV	19 (26.00)
Ischemic stroke	3 (4.10)
Ischemic heart disease	3 (4.10)
Peripheral arterial disease	6 (8.22)
Atherosclerotic cardiovascular disease	11 (11.07)

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CRP, C-reactive protein; GFR, glomerular filtration rate; LVH, left ventricular hypertrophy; PWV, pulse wave velocity.

Table 3. Prevalence of target organ damage and/or subclinical atherosclerotic cardiovascular disease distributed by cardiovascular risk factor (RCV) (SCORE)

	Low CVR=29 (50.9%)	Moderate CVR=11 (19.3)	High/very high CVR=17 (29.8)	P
ASCVD/ TOD no	15 (51.7)	5 (45.5)	5 (29.4)	0.336
ASCVD/ TOD yes	14 (48.3)	6 (54.5)	12 (70.6)	

ASCVD, atherosclerotic cardiovascular disease; TOD, target organ damage.

compare the effect of treatment with TKI on the cardiovascular health of our population, only patients treated with 1 TKI during their past medical oncology history were selected. Afterwards, patients were categorized into 2 groups: patients on imatinib and dasatinib, and patients on nilotinib. The former, with a more neutral cardiovascular profile; the latter with the highest rate of cardiovascular side effects reported.

In our study, the prevalence of AHT (47.95%), diabetes mellitus (17.33%), and overweight (50.68%) was above average nationwide (42.60%, 13.80%, and 39.30%, respectively).³⁰⁻³² Regarding the remaining traditional CVRF, the prevalence of dyslipidemia is lower compared to that described in the Spanish general

Table 4. Distribution of cardiovascular risk factors based on each group of treatment. The measurement of arterial blood pressure was performed through 24-hour ambulatory blood pressure monitoring (ABPM)

	Imatinib + dasatinib 35 (%)	Nilotinib 22 (%)	P
Sex (male)	24 (68.60)	13 (59.10)	0.465
Age, median (IQR)	60 (46.00-76.00)	56.50 (45.00-65.25)	0.451
Arterial hypertension	13 (37.10)	13 (59.10)	0.105
Uncontrolled AHT	7 (20.00%)	10 (45.50%)	0.041*
Diabetes mellitus	4 (11.40)	5 (22.70)	0.286
Dyslipidemia	12 (34.30)	15 (68.20)	0.013*
Overweight	17 (48.60)	12 (54.50)	0.661
Obesity	9 (25.70)	5 (22.70)	0.799
Smoking	4 (11.40)	10 (45.50)	0.004*
Alcohol	4 (11.40)	5 (22.70)	0.286

*Statistically significant results.

AHT, arterial hypertension; IQR, interquartile range.

Table 5. Distribution of target organ damage and atherosclerotic risk biomarkers based on each group of treatment

	Imatinib + dasatinib 35 (%)	Nilotinib 22 (%)	P
Pathological CRP	9 (25.70)	8 (36.40)	0.392
Microalbuminuria	8 (22.90)	3 (13.60)	0.502
CKD (CKD-EPI to estimate GFR<60 mL/min)	6 (17.01)	3 (13.60)	1
LVH	3 (8.60)	2 (9.10)	1
Pathological ABI	7 (20.00)	6 (27.30)	0.524
Pathological PWV	9 (25.70)	7 (31.80)	0.618

ABI, ankle-brachial index; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CRP, C-reactive protein; GFR, glomerular filtration rate; LVH, left ventricular hypertrophy; PWV, pulse wave velocity.

population (40.79% in our cohort compared to the 50.68% described in the ENRICA clinical trial) while the prevalences of obesity (26% in our population, 22.90% in the national study on di@betes), and smoking (21.92% in our population, and 23% according to the latest report on smoking from the Spanish Statistical

Table 6. Distribution of cardiovascular disease based on each group of treatment

	Imatinib + dasatinib 35 (%)	Nilotinib 22 (%)	P
Ischemic heart disease	1 (2.90)	2 (9.10)	0.553
Stroke	0 (0)	3 (13.60)	0.053
PAD	0 (0)	4 (18.20)	0.019*
Established ASCVD	1 (2.90)	7 (31.80)	0.004*
CR			0.131
Low	21 (60.00)	8 (36.40)	
Moderate	4 (11.40)	7 (31.80)	
High/very high	10 (28.60)	7 (31.80)	

*Statistically significant results.

ASCVD, atherosclerotic cardiovascular disease; CR, cardiovascular risk; PAD, peripheral arterial disease.

Office) are similar in both populations.^{31,33} Regarding other populations with CML like the one described by Coutinho²⁷—with similar age and percentage of male patients—the prevalence of dyslipidemia (40.79%), and smoking (21.92%) was higher in our case with similar results of AHT and diabetes.

When both groups of treatment were compared (imatinib + dasatinib vs nilotinib), patients treated with nilotinib had a higher prevalence of dyslipidemia and smoking compared to those from the imatinib and dasatinib group ($P = .013$ and $P = .004$, respectively). No statistically significant differences were seen in the rate of CVRF prior to starting treatment with TKI between the 2 groups of treatment (imatinib + dasatinib vs nilotinib).

In addition to the known effect tobacco has on lipids, we know that up to 50% of patients treated with nilotinib develop dyslipidemia.²⁹ However, the mechanism is still unknown. It has been speculated that nilotinib could, in some cases, elevate the levels of cholesterol associated with low density lipoproteins (LDL-c) due to an increased concentration of proprotein convertase subtilisin/kexin type 9 (PCSK9), which is mediated by the inhibition of mTORC1. These changes happen early at the beginning of treatment—within the first 12 months—and are kept during treatment.³⁴⁻³⁶

Regarding TOD, 8.20% of our patients had LVH while 19.20% had microalbuminuria. A total of 26% of these patients had elevated PWV levels while 32.90% had elevated US-CRP levels. There is no data on other populations with CML in whom these values were measured. However, we believe that they expose these patients' atherosclerotic inflammatory state. The

US-CRP levels were high in all the subgroups analyzed of patients with CML. In our study we found that almost 50% of the patients with low CR had subclinical ASCVD and TOD. These results make us rethink the hypothesis on whether the search for subclinical ASCVD and TOD should be included in the routine assessment of patients with CML treated with TKI. Also, whether treatment should be intensified in this group of patients (eg, hygienic-dietary measures, stricter LDL-c levels, etc.).

A total of 11.07% of our population had established ASCVD: 4.10% had ischemic heart disease and ischemic stroke while 8.22% had PAD. Patients treated with nilotinib had more chances of presenting with PAD and established ASCVD compared to those treated with imatinib and dasatinib, which confirms what we already knew on the capacity of nilotinib to trigger ASCVD and, especially, PAD. In Spain, the multicenter observational SIMETAP clinical trial³⁷ of over 6000 patients determined that 9.20% of these patients had ASCVD (4.80%, 3.80%, and 2.30% had coronary artery disease, CVD, and PAD, respectively). Regarding the study conducted by Coutinho²⁷, our incidence rate is lower because his study described 18.70% of the patients with CVD at the beginning of the study and 33% 5 years into treatment with TKI. Although this study does not delve into the type of TKI used in the patients, we believe that the high rate of CVD reported is due to the fact that the study included ASCVD (ischemic heart disease, stroke, and PAD, but also any location and degree of atherosclerosis), as well as non-atherosclerotic CVD (heart failure mainly). Other studies like the one conducted by Breccia²⁸ reported an incidence rate of ASCVD close to 8.5%. At this point, the previous selection of TKI is again significant depending on each patient's cardiovascular profile since it reduces the future chances of developing ASCVD.

Although in our study the initial selection of treatment with TKI was based on each patient's past medical history—both hematological and cardiovascular—to minimize the chances of mid- and long-term adverse events no statistically significant differences were found regarding the prevalence of CVRF in the different groups of treatment, except for the prevalence of smoking.

We are aware of our study limitations. It was an observational uncontrolled study and, since it dealt with an uncommon disease, the size of our sample was small. Also, the diagnosis of CVRF and ASCVD by a non-specialist physician in the management of CVD may have been underestimated, which could show in the rate of CVRF reported prior to starting treatment with TKI.

Conclusion

The rate of AHT, diabetes, overweight, and ASCVD in our population was above average nationwide. In the group of patients treated with nilotinib, the prevalence of PAD and ASCVD was higher compared to that of patients treated with imatinib and dasatinib.

Although the study design is only hypothesis-generating, our results added to the knowledge we have on the overall population are a reminder that the detection of subclinical CVD and TOD can help us improve the selection process of a segment of the population on which we should be stricter in the control of CVRF since these individuals have a higher risk of ASCVD. For that reason, it somehow seems important to include in the assessment protocols that patients about to start TKI or who are already on TKI should be tested to rule out the presence of subclinical ASCVD and TOD to prevent any disease progression into CVD. The therapeutic strategies that should be followed in this population would include healthy eating habits (low level of saturated fats, and a diet rich in fiber, fruit, and vegetables, among other), prescription of physical workout, quitting toxic habits, stricter levels of cholesterol or glycemia, etc.

The results of our study encourage us to keep on working on this unexplored line since it has been demonstrated that a strict control of CVRF improves the prognosis of patients with CML treated with TKI.

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Conflicts of interest

None reported.

Ethical disclosures

Protection of human subjects and animals in research. The authors declare that no experiments were performed on humans or animals for this study.

Patients' data protection. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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