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ORIGINAL ARTICLE

Cardiovascular toxicity induced by TKIs in patients with chronic myeloid leukaemia: Are women and men different?

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Abstract

Aims Knowledge of the effects of sex in cardio-oncology is limited, particularly in patients treated with tyrosine kinase inhibitors (TKIs) for chronic myeloid leukaemia (CML). This study aims to evaluate the influence of gender differences on the incidence of cardiovascular toxicity in patients with CML.

Methods The study population consisted of 148 patients (45% women, mean age: 58 ± 14.2 years) diagnosed with CML treated with TKIs. The HFA-ICOS score estimated cardiovascular risk. The HFA-ICOS score revealed that 12% of men and 6% of women were categorized as very high risk while 45% of men and 50% of women fell into the high-risk group. Myocardial ischaemia, peripheral artery disease, venous thromboembolism, pulmonary hypertension and new-onset arterial hypertension during treatment with TKIs were recorded.

Results The incidence of global events between men and women was comparable (35% vs 32%, $P = 0.68$). There were 33% who experienced a cardiovascular event during TKI therapy, with a significant sex difference in arterial thrombosis incidence ($P = 0.02$) and venous thrombosis incidence ($P = 0.02$). Patients treated with ponatinib had a 41% event rate, followed by nilotinib (32%) and imatinib (32%). The HFA-ICOS score demonstrated greater predictive efficacy for events in the female group [area under the curve (AUC) = 0.797] compared with the male group (AUC = 0.537). Very high [hazard ratio (HR) 3.07; confidence interval (CI) 1.11, 8.47 $P = 0.03$] and high (HR 3.29; CI 1.17, 9.26 $P = 0.02$) HFA-ICOS scores were associated with increased event risk, particularly in women. Diabetes was women's strongest predictor of events (HR 5.40; CI 1.37, 21.3 $P = 0.01$).

Conclusions Our study showed a similar frequency of cardiovascular events between men and women. Accurate cardiovascular risk stratification with HFA-ICOS score in cancer patients is crucial. Diabetes and the HFA-ICOS score were significant predictors of events in the female groups. A sex approach in clinical practice could be pursued to improve the appropriateness of care.

Keywords cardio-oncology; cardiovascular toxicity; chronic myeloid leukaemia; BCR-ABL; gender differences; sex differences; tyrosine kinase inhibitors

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Introduction

The field of cardio-oncology is dynamic, with new and effective cancer therapies approved every year. Management of the cardio-oncology patient is complex, and preventive strategies and surveillance protocols have been proposed during anticancer treatment.[1] Gender differences in prevalence, clinical course, therapeutic approach and prognosis have been observed regarding several cardiovascular diseases.[2,3] The effect of cigarette smoking, diabetes, hypertension and obesity in causing heart failure appears to be greater in women,[4] and a sex-based approach could promote personalization of care and patients' quality of life.

The knowledge of the effects of sex in cardio-oncology is limited, particularly the impact of sex on cardiotoxicities.[5,6] Sex likely influences not only the biological basis of cancer susceptibility but also the response to oncological and cardiovascular therapies.[7,8] Male cancer patients treated with anthracyclines have a greater risk of cardiovascular events, and these differences could be explained by family history and cardiovascular risk factors.[9] Regarding immunotherapy, women are more likely to experience cardiovascular events than male patients.[10,11] There is no universal answer regarding the relationship between sex and the incidence of cardiovascular toxicity in patients with chronic myeloid leukaemia (CML).

CML has a worldwide annual incidence rate of 0.87 people per 100 000, increasing with age up to 1.52 in patients older than 70.[12] This form of leukaemia predominantly affects adults and is rarely found in children. There is a slight predominance in men, and the median age of diagnosis is 56 years.[12] According to the American Cancer Society's 2024 estimates for CML in the United States, approximately 9280 individuals will be diagnosed with CML (5330 males and 3950 females).[13] Roughly 1280 deaths are expected due to CML (750 men and 530 women).[13] Tyrosine kinase inhibitors (TKIs) are the first-line therapy for most patients with CML and have demonstrated positive and persistent results in this patient population. They are small molecules that occupy the ATP-binding site of the receptor tyrosine kinase, inhibiting abnormally elevated kinase activity and uncontrolled cell growth.[14] TKIs used in CML are specifically BCR-ABL inhibitors, which target the abnormal BCR-ABL protein that causes the disease. The first-generation BCR-ABL TKI, imatinib, was the initial breakthrough in CML treatment, followed by second-generation inhibitors such as dasatinib, nilotinib and bosutinib, and the third-generation TKI, ponatinib, which was developed to target resistant mutations.[15]

The widespread diffusion of this new therapeutic option in recent years, especially nilotinib and ponatinib, has highlighted cardiovascular side effects like atherosclerosis, arterial hypertension and arterial thrombotic events.[16–19] Post-menopausal women appear to be more sensitive to cardiovascular toxicity than men.[20] Male sex was confirmed to be a significant risk factor in patients with Hodgkin's lymphoma treated with chemotherapy and pre-existing heart disease, and male sex was associated with poor survival in patients treated with imatinib.[21,22]

To date, the HFA-ICOS score is a handy tool for cardiovascular toxicity risk stratification for most families of antineoplastic drugs.[23] This score has proven valid for more personalized cardiovascular risk stratification in CML patients and is more sensitive than the SCORE tables.[24] Our study aimed to evaluate the influence of sex on the incidence of cardiovascular toxicity from TKIs.

Methods

An observational retrospective study was conducted, enrolling consecutive patients with CML treated with TKIs and followed up at our cardio-oncology clinic. Patient enrolment began in December 2021. The inclusion criteria were age $>$ 18 years and age $<$ 75 years, CML with the indication for treatment with TKis (imatinib, nilotinib, dasatinib, ponatinib, bosutinib and asciminib) for at least 1 year and left ventricle ejection fraction $>$ 50%. Patients with recent revascularization $<$ 30 days, presence of severe concomitant diseases such as cerebrovascular diseases with sequelae and severe renal dysfunction defined as the presence of reduced glomerular filtration rate $<$ 30 mL/min/1.73 m^2 severe liver dysfunction defined by the presence of liver cirrhosis or Child–Pugh Class C, and history of collagenopathy, moderate valvular defects, complex cardiac arrhythmias and adverse prognosis with life expectancy $<$ 1 year were excluded. At baseline, patients performed a cardiological evaluation including collection of clinical history and cardiovascular risk factors, assessment of the risk profile of cardiovascular toxicity using the HFA-ICOS risk in accordance with the latest ESC guidelines,[1] physical examination and measurement of blood pressure, electrocardiogram with QTc evaluation and venous sampling with evaluation of cardiac biomarkers, creatinine and complete lipid profile.[12] The HFA-ICOS score divided the population based on the risk of cardiovascular toxicity into low, medium, high or very high risk as established in the model. Patients without risk factors are considered 'low risk'. Patients with one or more risk factors are classified according to the highest risk factor present.

The following cardiovascular adverse events were retrospectively recorded during TKI treatment in patients who had undergone at least 1 year of therapy: myocardial ischaemia and peripheral artery disease (PAD), venous thromboembolism (VTE), pulmonary hypertension (PH) and new-onset arterial hypertension. Median patient follow-up was 956 days (2.6 years).

The patients were divided into two groups based on sex. Parametric quantitative variables were reported as mean

and standard deviation (*SD*), and non-parametric variables were reported as median and interquartile range (IQR). The differences between the analysed groups were studied using the two-tailed Student's *t*-test on independent samples or the Mann–Whitney *U* test as appropriate. Categorical variables were reported as percentages, and the difference between these was assessed using χ^2 tests. Univariable and cause-specific multivariable Cox models were estimated, and variables were selected for outcome using clinically relevant variables without significant missing values (i.e., <5%) to univariable analyses (i.e., those with a *P* value ≤ 0.1) in a full-model approach. A *P* value < 0.05 was considered statistically significant. Statistical analysis was performed using RStudio software (version 2024.09.0+375 RStudio).

Results

The study population consisted of 148 patients (45% women *n* = 66, mean age: 58 ± 14.2 years) diagnosed with CML being treated with TKIs. 49% of the population (*n* = 72) was receiving nilotinib. As regards baseline cardiovascular risk factors, 17% (*n* = 25) had diabetes mellitus, 60% (*n* = 87) had arterial hypertension, 38% (*n* = 56) were obese and 26% (*n* = 38) were smokers. None of the women were being treated or had previously received therapy with oestrogens or oral contraceptives. *Table* 1 summarizes the clinical data, information on the antineoplastic treatment they received and the cardiovascular toxicity risk score assessment using the HFA-ICOS score at baseline. Twelve per cent (*n* = 10) of men and 6% of women (*n* = 4) were in the very high-risk HFA-ICOS group. Forty-five per cent (*n* = 37) of men and 50% of women (*n* = 33) were in the high-risk HFA-ICOS group. In terms of events, 33% of the population experienced an event during TKI therapy (*Table* 2). There were no statistically significant differences in the incidence of global events between men and women (35% vs. 32%, *P* = 0.68). The incidence of arterial thrombosis during therapy was significantly higher in the male group than in the female patient group (23% vs. 9%, *P* = 0.02). The incidence of venous thrombosis during therapy was significantly higher in the female group than in the male patient group (6% vs. 0%, *P* = 0.02). There were no statistically significant differences in arterial and pulmonary hypertension incidence during treatment (*Table* 2). Overall, adverse events were significantly more frequent in the very high- and high-risk groups (90%) than in the low- and moderate-risk groups (10%) with $P < 0.0001$ (*Figure* 1). Patients with high [hazard ratio (HR) 3.29; confidence interval (CI) 1.17, 9.26 with *P* = 0.02] and very high (HR 3.07; CI 1.11, 8.47 with *P* = 0.03) HFA-ICOS risk scores increased the risk of events. Especially in the female group, the risk increases significantly (female high-risk group: HR 2.79; CI 1.01, 7.53 with *P* = 0.04; female very high-risk group: HR 2.16; CI 0.84, 5.53 with *P* = 0.11). *Figure* 2 describes the TKIs prescribed to patients with a cardiovascular event at follow-up, stratified by sex. In the overall population, 41% of patients treated with ponatinib developed a cardiovascular event. Following this, in order of incidence, 32% of patients treated with nilotinib and imatinib developed a cardiovascular event. Twenty-six per

Table 1 General characteristics of the study population and in the male and female groups.

	Overall population *n* = 148	Male group *n* = 82	Female group *n* = 66
Age (years)	58 (20)	58 (20)	58 (20)
BSA (m^2)	1.86 (0.23)	1.93 (0.21)	1.79 (0.16)
Diabetes % (*n*)	17% (25)	11% (9)	24% (16)
Hypertension % (*n*)	60% (87)	61% (50)	56% (37)
Obesity % (*n*)	38% (56)	34% (28)	42% (28)
Dyslipidaemia % (*n*)	48% (71)	46% (38)	50% (33)
Family history of CVD % (*n*)	14% (20)	18% (15)	7.5% (5)
Smoking history % (*n*)	26% (38)	22% (18)	30% (20)
Previous chemotherapy % (*n*)	3% (2)	0	4.5% (3)
Previous radiotherapy % (*n*)	1% (1)	1% (1)	0
Previous antithrombotic therapy % (*n*)	10% (14)	10% (8)	9% (6)
Nilotinib % (*n*)	49% (72)	44% (36)	54% (36)
Ponatinib % (*n*)	11.3% (17)	8.5% (7)	15% (10)
Dasatinib % (*n*)	13% (19)	19.5% (16)	4.5% (3)
Imatinib % (*n*)	25% (37)	26% (21)	24% (16)
Bosutinib % (*n*)	1.5% (2)	1% (1)	1% (1)
Asciminib % (*n*)	0.7% (1)	1% (1)	0
HFA-ICOS low risk % (*n*)	19% (28)	19% (16)	18% (12)
HFA-ICOS moderate risk % (*n*)	24% (36)	23% (19)	26% (17)
HFA-ICOS high risk % (*n*)	47% (70)	45% (37)	50% (33)
HFA-ICOS very high risk % (*n*)	9% (14)	12% (10)	6% (4)

Note: Values are reported as median (IQR) and percentage % (and number *n*).
Abbreviations: BSA, body surface area; CVD, cardiovascular disease; HFA, Heart Failure Association; ICOS, International Cardio-Oncology Society.

Table 2 Events recorded in our population divided by gender.

Sex	Arterial thrombosis	New onset of arterial hypertension	VTE	PH	Global events
Female (n = 66)	9% (6)	12% (8)	6% (4)	7.5% (5)	35% (23)
Male (n = 82)	23% (19)	7.3% (6)	0% (—)	1.2% (1)	32% (26)
Overall population (n = 148)	17% (25)	9.5% (14)	3% (4)	4% (6)	33% (49)
P value (χ^2 test)	0.02	0.32	0.02	0.05	0.68

Abbreviations: PH, pulmonary hypertension; VTE, venous thromboembolism.

Figure 1 Description and distribution of events in the study population according to HFA-ICOS risk score. HFA, Heart Failure Association; ICOS, International Cardio-Oncology Society.

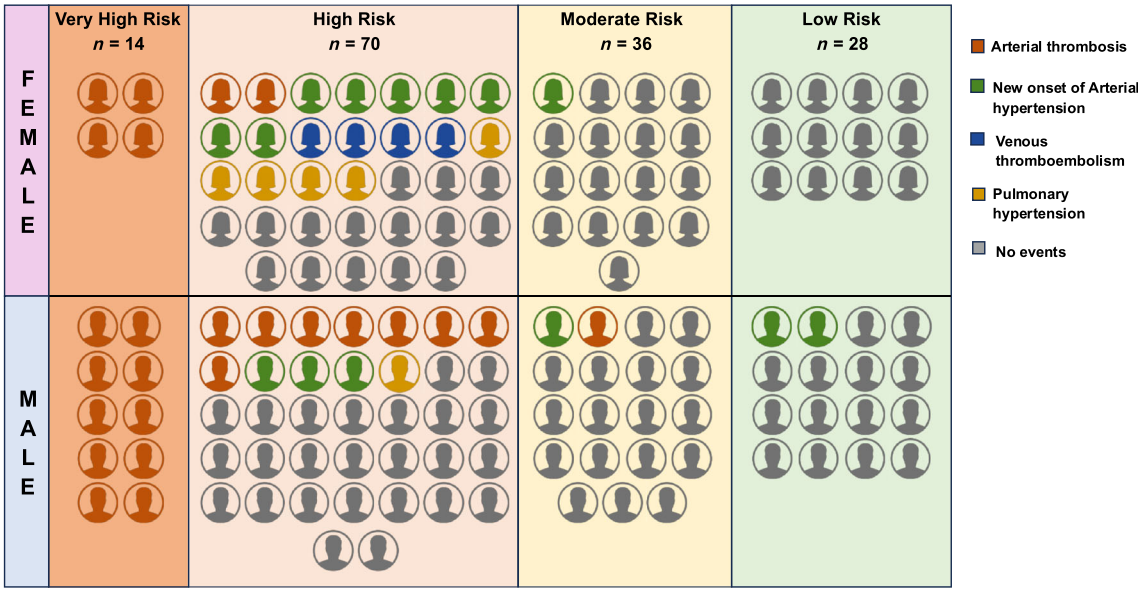
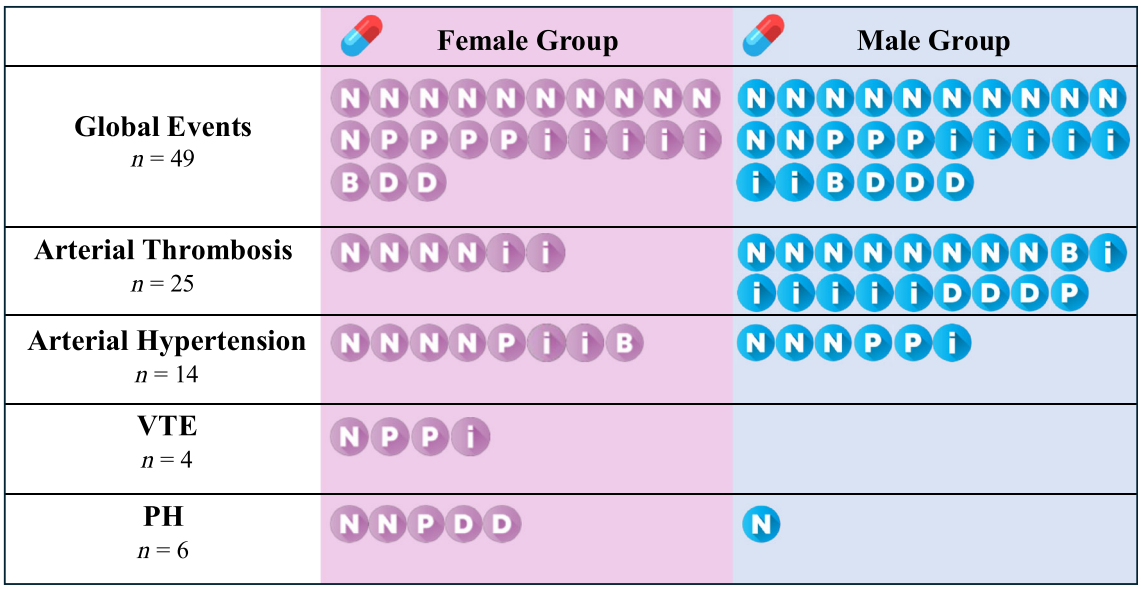


Figure 2 Description of TKIs used in the sex-evaluated event group. B, bosutinib; D, dasatinib; I, imatinib; N, nilotinib; P, ponatinib; PH, pulmonary hypertension; VTE, venous thromboembolism.



cent of patients receiving dasatinib experienced arterial thrombosis and pulmonary hypertension. Both patients (100%) receiving bosutinib therapy had an event. At multivariable analysis, previous chemotherapy (P = 0.01) and diabetes mellitus (P = 0.02) during follow-up were independently associated with events (*Table* 3). Regarding the HFA-ICOS score, we performed a receiver operating characteristic analysis to evaluate the performance of this score in the groups of women and men. The differences in area under the curve (AUC) may suggest that the HFA-ICOS score is more effective in predicting events in the female subgroup (AUC = 0.797) than in the general population (AUC = 0.647) and men (AUC = 0.537) (*Figure* 3).

Women

The group of women who had arterial thrombosis during TKI treatment (six patients) were all at high and very high risk according to the HFA-ICOS score, with an average age of 60 years. All of them suffered from arterial hypertension and hypercholesterolemia, with an average total cholesterol value of 176 mg/dL. Five (83%) patients had diabetes. Three (50%) of the patients were smokers and obese, and none had a family history of cardiovascular disease.

Fifty per cent of female patients who had a VTE event during treatment with TKI therapy were hypertensive, diabetic and suffered from hypercholesterolemia. None were obese or had a family history of cardiovascular disease or thrombophilia.

Men

In the male group, patients with arterial thrombosis during TKI treatment (n = 19) had a mean age of 58 years. Ten of these 19 were at very high risk according to the HFA-ICOS classification, 8 were at high risk and 1 was at moderate risk. Seventy-four per cent (n = 14) of the male patients who had arterial thrombosis suffered from arterial hypertension and 68% (n = 13) from hypercholesterolemia with an average total cholesterol value of 183 mg/dL. Six patients (31%) were smokers and obese. Only one patient (5%) had diabetes. Five patients (26%) had a family history of cardiovascular disease. Only two had a pre-therapy cardiovascular event. Unlike women, univariate and multivariate analyses showed no cardiovascular risk factors related to the event (*Table* 3).

Discussion

There is a gap in evidence regarding the difference in the incidence of cardiovascular toxicity in male or female patients diagnosed with CML being treated with TKIs. Our study showed no differences in the incidence of global events between males and females; however, the men group was more affected by arterial thrombotic events such as coronary artery disease while the women group more frequently experienced venous thromboembolic events. This aligns with data from the literature regarding the general population, showing that arterial thrombotic events are more frequent in males and venous diseases are more frequent in women.[25,26] It is known that anti-BCR-ABL TKIs can cause vascular toxicity, which could be detected early by measuring arterial stiffness, as shown in patients undergoing treatment with anthracyclines.[27]

Cardiovascular risk factors such as arterial hypertension and diabetes were present in almost the entire population with events. Diabetes and HFA-ICOS risk score were the significant predictors of events in the female groups. Although females showed a lower number of events, in line with the literature, our study demonstrated that more attention would be needed in the management of female patients who have had previous chemotherapy diabetes and with a high or very high HFA-ICOS risk score. This subgroup of patients was found to be more associated with the incidence of events.

Our study highlights the importance of the risk stratification tool proposed by HFA-ICOS. This score helps predict cancer patients treated with very high and high-risk BCR-ABL TKIs who are more likely to have a cardiotoxic event, especially in the women group. The HFA-ICOS score is significant when evaluating the female group, as it significantly increases the risk of events in high- and very high-risk patients.

The female sex has shown a lower probability of mortality in some studies of patients with chronic lymphocytic leukaemia. However, other studies in the literature performed in different patient settings confirm that female sex, age and body surface area were highly predictive of severe cardiovascular toxicity in advanced renal cancer patients treated with sunitinib.[28]

Moreover, in patients with CML in the chronic phase receiving imatinib, male sex, increasing age and previous non-TKI treatment were associated with poor survival.[29] This type of chemotherapy in patients with CML can worsen atherosclerotic processes and determine arterial thrombosis, as seen in our population. Applying sex-related management could help in the early prediction of cardiovascular events by using more tailored surveillance programmes in cancer patients and also, if needed, second-level diagnostic tools and by early introducing specific cardioprotective drugs.[30]

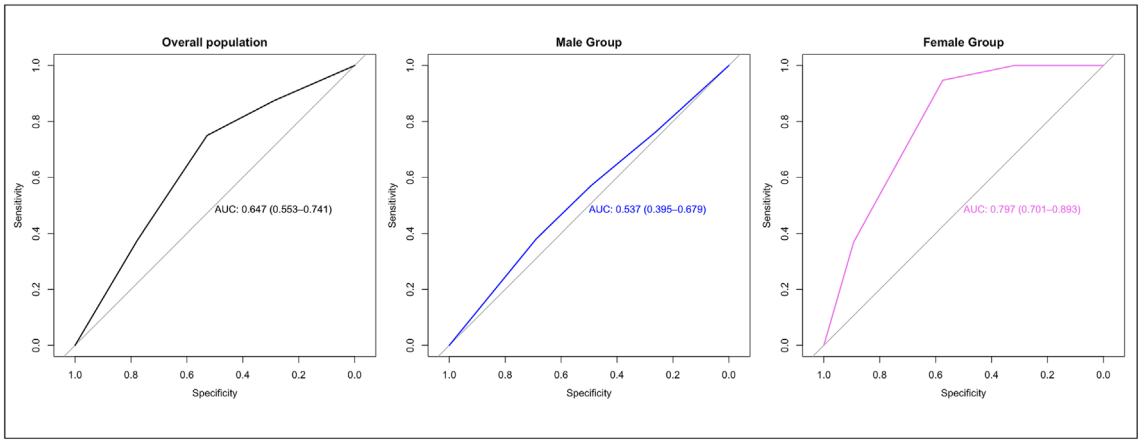
It also could have relevant therapeutic implications, as antiplatelet therapy is the first-line strategy to prevent arterial thrombotic events. At the same time, anticoagulation plays a significant role in preventing VTE. In our study, ponatinib was found to be the TKI most related to a cardio-

Table 3 Univariate and multivariate analysis on global events.

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Global events	Overall population $n = 148$					
Age	1	0.97, 1.02	0.84			
Sex	1.24	0.66, 2.31	**0.50**	1.03	0.52, 2.06	NS
Previous chemotherapy	4.06	1.24, 13.3	**0.02**	4.81	1.33, 17.4	**0.01**
Arterial hypertension	1.80	0.93, 3.50	**0.08**	1.17	0.54, 2.52	0.70
Diabetes mellitus	2.39	1.23, 4.65	**0.01**	2.35	1.10, 5.01	**0.02**
Obesity (BMI > 30)	1.28	0.66, 2.46	0.47			
Dyslipidaemia	1.46	0.77, 2.76	0.25			
Smoke	1.12	0.54, 2.31	0.76			
Family history of cardiovascular disease	1.30	0.55, 3.12	0.55			
	Female group $n = 66$					
Age	1.01	0.98, 1.04	0.55			
Previous chemotherapy	3.87	1.09, 13.7	**0.03**	11.2	2.10, 59.8	**0.005**
Arterial hypertension	9.97	2.23, 44.6	**0.003**	3.40	0.56, 20.9	0.20
Diabetes mellitus	6.38	2.32, 17.5	**<0.001**	5.40	1.37, 21.3	**0.01**
Obesity (BMI > 30)	2.68	0.92, 7.85	0.07			
Dyslipidaemia	8.64	1.93, 38.7	**0.005**	1.40	0.22, 9.06	0.70
Smoke	1.20	0.44, 3.25	0.72			
Family history of cardiovascular disease	0.64	0.08, 4.82	0.66			
	Male group $n = 82$					
Age	1	0.95, 1.02	0.36			
Arterial hypertension	1	0.29, 1.65	0.40			
Diabetes mellitus	1.05	0.15, 2.83	0.56			
Obesity (BMI > 30)	1	0.36, 1.96	0.52			
Dyslipidaemia	1.09	0.24, 1.47	0.26			
Smoke	1.07	0.35, 3.23	0.91			
Family history of cardiovascular disease	1.81	0.66, 4.97	0.25			

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio.

Figure 3 The receiver operating characteristic curves illustrate the performance of the HFA-ICOS score in predicting cardiovascular toxicity for the general population, male and female groups. AUC, area under the curve; HFA, Heart Failure Association; ICOS, International Cardio-Oncology Society.



vascular event and, subsequently, in order of incidence, nilotinib. Previous studies stressed the importance of prophylaxis with aspirin in patients treated with ponatinib, showing a lower incidence of cardiovascular toxicity with this therapy.[31,32] According to our data, preventive treatment with aspirin could also be considered in patients treated with nilotinib, especially in patients with very high and high HFA-ICOS scores. Our data confirm that dasatinib is a safe drug for systemic arterial thrombotic events, even if it is correlated with pulmonary hypertension. For this reason, the ESC cardio-oncology guidelines underline the importance of performing an echocardiogram at baseline (class I) independently of baseline risk compared with other TKIs (class IIa).[1]

Study limitations

The main limitation of our study is that it reflects the experience of a single centre with a small sample size, which made it difficult to match the two groups for risk factors, and therefore, they are slightly more represented in the female group. Another limitation is defined by the study's design, which is retrospective and observational.

Conclusions

Our study did not show a different frequency in the occurrence of cardiotoxic events between males and females; however, it showed sex differences regarding the type of events that occur. Mainly, males experienced more frequent arterial thrombotic events, while women had venous thrombotic events. Our study highlights the importance of accurate CV risk stratification at baseline in cancer patients. Diabetes and HFA-ICOS risk score were the significant predictors of events in the female groups. A sex-based approach could also have a relevant role in applying tailored and effective preventive strategies in clinical practice.

Conflict of interest statement

The authors declare no conflict of interest.

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Data availability statement

All data is available upon request.

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