

The new HFA/ICOS risk assessment tool to identify patients with chronic myeloid leukaemia at high risk of cardiotoxicity

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Abstract

Aims Tyrosine kinase inhibitors (TKIs) used to treat chronic myeloid leukaemia (CML) can cause cardiovascular adverse events. So far, the Systematic Coronary Risk Evaluation (SCORE) charts of the European Society of Cardiology (ESC) have been used to identify cancer patients at increased cardiovascular risk. The primary aim of our study was to evaluate the usefulness of the new cardiovascular risk assessment model proposed by the Cardio-Oncology Study Group of the Heart Failure Association (HFA) of the ESC in collaboration with the International Cardio-Oncology Society (ICOS) to stratify the cardiovascular risk in CML patients, compared with SCORE risk charts. The secondary aim was to establish the incidence of adverse arterial events (AEs) in patients with CML treated with TKIs and the influence of preventive treatment with aspirin.

Methods and results A retrospective single-centre observational study was carried out on 58 patients (32 men and 26 women; mean age \pm SD: 59 \pm 15 years) with CML treated with TKIs for a median period of 43 \pm 31 months. Cardiological evaluation was performed and cardiovascular risk was estimated with SCORE risk charts and with the new risk assessment tool proposed by HFA/ICOS. AEs were recorded. According to SCORE charts and the new HFA/ICOS risk stratification tool, respectively, 46% (Group A1) and 60% (Group A2) of patients were at high–very high risk, and 54% (Group B1) and 40% (Group B2) at low–moderate risk. AEs were significantly more frequent in Group A1 than Group B1 (P value $<$ 0.01) when considered overall; they were significantly more frequent in Group A2 than Group B2 either overall or considered individually. HFA/ICOS risk stratification tool was significantly more sensitive than SCORE (P $<$ 0.01) in identifying patients at higher risk of cardiovascular toxicity. In addition, we did not find AEs in patients pretreated with aspirin.

Conclusions The new HFA/ICOS risk stratification model allows a more tailored cardiovascular risk stratification in patients with CML and it is more sensitive than SCORE charts.

Keywords Cardio-oncology; Cardiovascular prevention; Chronic myeloid leukaemia; Nilotinib; Ponatinib; Cardiovascular toxicity

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Introduction

BCR-ABL tyrosine kinase inhibitors (TKIs) are used to treat chronic myeloid leukaemia (CML), and they have dramatically improved the prognosis of patients. However, they can cause various cardiovascular adverse events (CAEs).¹ Particularly, nilotinib (a second-generation TKI) and ponatinib (a third-generation TKI) can cause accelerated atherosclerosis

and arterial thrombotic events (myocardial ischaemia, stroke, and peripheral artery disease).^{2,3} Nilotinib can also cause hyperglycaemia and QTc prolongation, while ponatinib can cause new-onset arterial hypertension. Dasatinib can determine pulmonary arterial hypertension and QTc prolongation.^{4–7}

Cardiovascular (CV) risk factors could increase the risk to develop CV events during anticancer treatment. Therefore,

the European Society of Cardiology (ESC) guidelines on CV prevention propose optimization of CV risk profile in cancer patients.⁸

To date, the usefulness of the Systematic Coronary Risk Evaluation (SCORE) of the ESC to identify patients with increased risk of occurrence of arterial occlusive events (AOEs) during ponatinib treatment has been suggested.⁹ SCORE estimates the 10 year risk of fatal CV events and it is based on sex, age, smoking, systolic blood pressure, and total cholesterol level. Caocci *et al.* demonstrated that patients treated with nilotinib and ponatinib belonging to the high and very high SCORE risk group have increased incidence of AOEs.^{10,11}

Recently, the Cardio-Oncology Study Group of the Heart Failure Association (HFA) of the ESC in collaboration with the International Cardio-Oncology Society (ICOS) proposed a baseline CV risk stratification proforma that can be used specifically to stratify CV risk in cancer patients before starting potentially cardiotoxic cancer therapies.¹²

Thus, the primary aim of the study was to evaluate the usefulness of the new CV risk assessment model proposed by HFA/ICOS to stratify the CV risk in patients with CML, compared with SCORE risk charts. The secondary aim was to establish the incidence of adverse arterial events (AEs) in patients with CML treated with BCR-ABL TKIs and the influence of preventive treatment with aspirin.

Methods

A real-life retrospective observational, single-centre study was carried out on patients affected by CML treated with TKIs from 2016 to 2021 for a median period of 43 ± 31 months. Patients were followed at the Haematology Unit of the University Hospital Paolo Giaccone in Palermo (Italy), and the cardiological evaluation was performed at the cardio-oncology lab of the Cardiology Unit of the same hospital.

Inclusion criteria were:

1. age ≥ 18 years; and
2. TKIs (imatinib, nilotinib, dasatinib, and ponatinib) treatment for at least 1 year.

Exclusion criteria were:

1. previous or ongoing solid tumours;
2. recent myocardial infarction or coronary revascularization (<1 month); and
3. presence of severe concomitant diseases such as cerebrovascular diseases with sequelae, severe renal dysfunction defined as the presence of reduced glomerular filtration rate < 30 mL/min/1.73 m² assessed using CKD-EPI equation, severe liver dysfunction defined by the presence of liver cirrhosis or Child–Pugh Class C, and history of collagenopathy.

A total of 54 patients underwent cardiological clinical and instrumental assessment including blood chemistry tests, ankle-arm index (ABI index) measurement, blood pressure measurement, an electrocardiogram with QTc interval measurement, carotid ultrasound, and colour Doppler echocardiogram. Due to SARS-CoV-2 pandemic, in four patients, the occurrence of CAEs during haematology treatment and CV risk were evaluated remotely by telephone interview and, therefore, instrumental examinations were not performed.

Baseline CV risk was retrospectively estimated using SCORE risk charts^{8–13} and the HFA/ICOS CV risk assessment tool.¹²

The HFA/ICOS tool includes a specific CV risk stratification proforma for multitarget TKIs (second-generation and third-generation BCR-ABL TKIs) used in patients with CML. The following variables are taken into account in this model:

- 1 previous CV diseases (arterial vascular diseases, arterial thrombosis with TKIs, heart failure, BCR-ABL TKI-mediated left ventricular dysfunction, pulmonary arterial hypertension, baseline left ventricular ejection fraction < 50%, abnormal ABI index, venous thromboembolism, arrhythmias, and QTc prolongation);
- 2 demographic and other CV risk factors (CV disease 10 year risk score > 20%, age, arterial hypertension, diabetes, hyperlipidaemia, chronic kidney disease, and family history of thrombophilia); and
- 3 life style and other factors (obesity, current smoker, or significant smoking).

Each risk factor mentioned above assume a score (low, medium 1 or medium 2, high, or very high risk) as established in the model.¹²

Patients with no risk factors are considered at 'low risk'. Patients with one or more risk factors are categorized according to the highest risk factor present: patients with one or more very high risk factors—their risk level is 'very high'. Patients with one or more high risk factors—their risk level is 'high'. Medium risk factors are given a point weighting as medium 1 or medium 2: patients with one medium 1 risk factor only are 'low risk'. Patients with a single medium 2 risk factor or more than one medium 1 risk factor with points totalling 2–4 are 'medium risk'. Patients with several medium risk factors with points totalling 5 or more points are 'high risk'.¹²

The SCORE risk charts are used in apparently healthy people: low-risk patients had calculated SCORE < 1%, moderate-risk patients had SCORE ≥ 1 and <5%, high-risk patients had SCORE ≥ 5% and <10%, and very-high-risk patients had SCORE ≥ 10%.⁸ In accordance with previous and current ESC guidelines on CV prevention, patients with established CV diseases (previous myocardial infarction, coronary revascularization, and other arterial revascularization procedures) are considered at very high risk.^{8–14}

The following CAEs occurring during TKIs treatment were considered: new-onset myocardial ischaemia [acute coronary

syndrome (ACS) and chronic coronary syndrome (CCS)], peripheral arterial diseases (PAD), cerebrovascular disease, new-onset carotid atherosclerosis or progression of pre-existing disease, QTc interval prolongation, supraventricular and ventricular arrhythmias, heart failure, pulmonary hypertension, and new-onset arterial hypertension.

In addition in the data analysis, we considered separately CAEs as all adverse CV events described above and AEs as myocardial ischaemia, PAD, and new-onset or progression carotid diseases.

Acute coronary syndrome and CCS were defined in agreement with current ESC guidelines. ACS included unstable angina and myocardial infarction with or without ST segment elevation.^{15,16} CCS included patients with coronary artery diseases and 'stable' anginal symptoms and/or dyspnoea; patients with new onset of heart failure or left ventricular dysfunction due to coronary artery diseases; and asymptomatic patients in whom coronary artery diseases were detected during cardiological visit.

Progression of pre-existing atherosclerosis disease was considered such as the appearance of carotid plaque in patients with previous intimal medial thickening or at least 50% increase in pre-existing plaque. In addition, pre-clinical atherosclerosis was defined as asymptomatic carotid plaques (thickness > 1.5 cm) or increased intimal medial thickness (>0.9 mm).¹⁷

Patients were divided into four groups according to baseline CV risk:

A1 group: high and very high CV risk according to SCORE charts of the ESC guidelines on CV prevention;

A2 group: high and very high CV risk according to the HFA/ICOS risk assessment tool;

B1 group: low–moderate risk according to SCORE charts and ESC guidelines on CV prevention; and

B2 group: low–moderate risk according to the HFA/ICOS risk assessment tool.

Echocardiographic evaluation (TTE) was carried out using a GE Vivid E95 ultrasound system prime echocardiography machine and a 4Vc-D (1.4–5.2 MHz) linear transducer. An assessment of the cardiac chamber dimensions and an evaluation of the systolic and diastolic ventricular function were carried out according to the ASE/EACVI recommendations.^{18,19} Myocardial deformation indices of left ventricle (global longitudinal strain) were measured in all patients using GE software (*Echopac V.202*, GE), with STE method (*Speckle Tracking Echocardiography*). Normal reference values were considered: $-21.5 \pm 2\%$, with lower limit of normal of -18% .¹⁸

A carotid ultrasound scan was performed with the same machine, with a 7.5–10 MHz linear probe.

Quantitative variables were reported as mean and standard deviation (SD); the differences between the analysed groups were studied with the two-tailed Student *t*-test for in-

dependent samples. A *P* value < 0.05 was considered statistically significant. Qualitative variables were reported as a percentage. The analyses were performed using *MedCalc*® software.

Results

A total of 58 CML patients were retrospectively identified (32 men and 26 women; mean age \pm SD: 59 ± 15 years). The prevalence of CV risk factors in the whole population and other patients' characteristics are shown in *Table 1*. The majority of the patients (33 patients, 57%) were treated with nilotinib and/or ponatinib after other drugs failure, 11 patients (19%) were treated with dasatinib, and 14 patients (24%) were treated with imatinib. Eighteen patients (31%) were treated with aspirin in primary prevention. The median time of exposure to anti BCR-ABL TKIs was 43 ± 31 months.

The cumulative incidence rate of AEs was 36%. AEs included only arterial events (myocardial ischaemia, PAD, and new-onset or progression carotid diseases). AEs were considered separately and overall, and they occurred in 21 patients. Seven patients (12% of the whole population) developed myocardial ischaemia (two ACS and five CCS), six (10%) PAD, and eight (13%) new-onset or progression of

Table 1 Patients' characteristics

	Population
Patients, <i>n</i> (%)	58 (100%)
Age (years)	59 ± 15
Men/women, <i>n</i> (%)	32 (55%)/26 (45%)
BSA (m ²)	1.8 ± 0.3
CV risk factors	
Arterial hypertension (n. pt/%)	30 (52%)
Dyslipidaemia (n. pt/%)	27 (46%)
BMI ≥ 25 (n. pt/%)	21 (36%)
Diabetes (n. pt/%)	9 (15%)
Smoking (n. pt/%)	15 (26%)
Family history of cardiovascular diseases (n. pt/%)	7 (12%)
Pre-clinical atherosclerosis (asymptomatic carotid plaques or increased intima media thickness) (n. pt/%)	18 (31%)
Previous cardiovascular events (acute or chronic coronary syndromes) (n. pt/%)	5 (38%)
Nilotinib and/or ponatinib (n. pt/%)	33 (57%)
Dasatinib (n. pt/%)	11 (19%)
Imatinib (n. pt/%)	14 (24%)
Treatment with aspirin (n. pt/%)	18 (31%)
Angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker (n. pt/%)	25 (43%)
Beta-blockers (n. pt/%)	10 (17%)
Calcium channel blocker (n. pt/%)	5 (8%)
Mineralocorticoid receptor antagonist or other diuretic (n. pt/%)	5 (8%)
Statin (n. pt/%)	27 (46%)

BMI, body mass index; BSA, body surface area; CV, cardiovascular.

pre-existing carotid atherosclerosis. None of the patients had a stroke. All the patients that experienced AEs were treated with nilotinib over at least 4 years and with multiple lines of therapy. Moreover, none of the patients treated with nilotinib who developed AEs was treated with aspirin in primary prevention. None of the patients treated with ponatinib showed AEs; however, they all received aspirin in primary prevention and were on low-dose ponatinib over 12–24 months. No patient treated with nilotinib developed a significant QTc prolongation. Two patients (3% of the whole population) treated with nilotinib developed new-onset atrial fibrillation and had to be treated with oral anticoagulation. Nine patients (15%) showed new-onset arterial hypertension (five with nilotinib, three with imatinib, and one with ponatinib). Seven patients (12%) treated with dasatinib developed pleural effusion, and two (3%) showed reversible pulmonary hypertension that regressed after treatment discontinuation.

Eight per cent of the population (of whom only 1% was treated with imatinib) presented hyperamylasaemia, cytopenia, and severe anaemia. None of the patients treated with imatinib developed severe CV complications.

Thus, among CML patients, AEs were more frequent in patients treated with nilotinib.

According to the SCORE charts evaluation, 27 patients (46%) were at high and very high risk (Group A1) and 31 patients (54%) at low and moderate risk (Group B1). According to HFA/ICOS risk stratification tool, 35 patients (60%) were at high and very high risk (Group A2) and 23 patients (40%) at low and medium risk (Group B2).

Considering CV stratification according to the SCORE charts, AEs were overall significantly more frequent in Group A1 ($P < 0.01$) than Group B1. However, when considered individually, the incidence of myocardial ischaemia ($P = 0.15$) and PAD ($P = 0.26$) in Group A1 and Group B1 statistical significance was not reached. Progression of carotid atherosclerosis was significantly higher in A1 group compared with B1 group (P value < 0.01). Using HFA/ICOS risk stratification tool, AEs were significantly more frequent in Group A2 than

Group B2, either overall ($P < 0.01$) or considering individually myocardial ischaemia and PAD ($P = 0.01$ and $P = 0.03$, respectively) or progression of carotid atherosclerosis (P value = 0.01) (Table 2).

In addition, based on these values, sensibility (S_E) and specificity (S_P) of SCORE and HFA/ICOS risk stratification tool in identifying patients showing overall and individual AEs were analysed. The HFA/ICOS risk assessment model was significantly more sensitive than SCORE ($P < 0.01$) (Table 3).

Discussion

Our study showed that the new risk stratification tool proposed by HFA/ICOS allows a tailored CV risk stratification to develop adverse events in cancer patients treated with BCR-ABL TKIs. In fact, the peculiarities of the new HFA/ICOS risk assessment tool are that it is specifically designed for cancer patients and it includes not only the evaluation of CV risk factors and the presence of previous CV diseases (arterial vascular disease, left ventricular dysfunction, pulmonary arterial hypertension, or myocardial infarction) but it also provides specific charts according to the antineoplastic scheduled treatment.¹²

To the best of our knowledge, this study is the first one to have applied the new HFA/ICOS model in the real-life baseline risk stratification of CML patients treated with BCR-ABL TKIs. At present, only SCORE charts have been used in this setting of patients. For instance, Caocci *et al.* showed that the SCORE risk charts predict AOs in CML patients treated with ponatinib.¹⁰

The new HFA/ICOS risk tool has been so far evaluated in real life in patients with breast cancer to predict the occurrence of left ventricular dysfunction by Tini *et al.*²⁰

Our study confirms that SCORE risk charts are predictive of arterial events in patients treated with nilotinib and/or ponatinib, and it demonstrates that the HFA/ICOS tool is more sensitive compared with SCORE risk charts to predict

Table 2 Arterial occlusive events in patients at high–very high cardiovascular risk and low–moderate cardiovascular risk

	Myocardial ischaemia	Peripheral artery disease	Progression of carotid atherosclerosis	Overall arterial thrombotic events/progression of carotid atherosclerosis
Very high–high SCORE (A1, $n = 27$)	18%	15%	26%	59%
Moderate–low SCORE (B1, $n = 31$)	6%	6%	1%	13%
P value	0.15	0.26	<0.01	<0.01
Very high–high HFA/ICOS risk assessment (A2, $n = 35$)	22%	17%	21%	60%
Medium–low HFA/ICOS risk assessment (B2, $n = 23$)	0%	0%	0%	0%
P value	0.01	0.03	0.01	<0.01

HFA, Heart Failure Association; ICOS, International Cardio-Oncology Society; SCORE, Systematic Coronary Risk Evaluation.

Table 3 Sensibility and specificity of SCORE chart and new assessment risk tool proposed by HFA/ICOS

	Myocardial ischaemia		Peripheral artery disease		Overall arterial thrombotic events and progression of carotid atherosclerosis	
	S _E	S _P	S _E	S _P	S _E	S _P
SCORE	71%	57%	67%	56%	80%	71%
HFA/ICOS risk assessment	100%	46%	100%	44%	100%	62%
P value	<0.01	0.24	<0.01	0.20	<0.01	0.31

HFA, Heart Failure Association; ICOS, International Cardio-Oncology Society; SCORE, Systematic Coronary Risk Evaluation.

arterial events in patients with CML treated with BCR-ABL TKIs.

Another interesting finding of our study was that all the patients with AEs were under treatment with nilotinib, for at least 4 years, and had received multiple lines of therapy. AEs during treatment with nilotinib occurred equally with 400 or 600 mg dose. None of these patients received preventive treatment with aspirin.

We could deduce that the preventive use of aspirin, the use of low doses, and the shorter duration of therapy might explain the low incidence of AEs in patients treated with ponatinib compared with patients treated with nilotinib. Previous studies stressed the importance of prophylaxis with aspirin in patients treated with ponatinib.^{21,22} Especially, a study showed a lower incidence of AEs in patients treated with aspirin, during ponatinib treatment.¹⁰ According to our data, the preventive treatment with aspirin should also be considered in patients treated with nilotinib, especially in patients with high and very high CV risk.

Our data confirm that dasatinib is a safe drug in relation to arterial thrombotic events, even though it is correlated with pulmonary hypertension and pleural effusion.

The main limitation of our study is the small sample size that reflects the experience of a single centre. The second

limitation is the retrospective features of the study; however, it has the advantage to depict a slice of real life.

In conclusion, our study shows that the new risk assessment model proposed by HFA/ICOS is useful and more sensitive than the SCORE risk charts in this specific setting to identify patients at increased risk of CV toxicities. Once again, it highlights the importance of an accurate baseline CV risk assessment, CV risk factors correction, and also preventive treatment with aspirin aid to reduce AEs in patients treated with ponatinib and nilotinib. Our results are preliminary and larger multicentric prospective studies are needed to confirm them.

Conflict of interest

None relating to this work declared.

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