

ORIGINAL RESEARCH

## Major adverse cardiovascular events associated with VEGF-targeted anticancer tyrosine kinase inhibitors: a real-life study and proposed algorithm for proactive management

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**Background:** Vascular endothelial growth factor receptor (VEGFR)-targeted tyrosine kinase inhibitors (TKIs) are widely used in cancer treatment and burdened by cardiovascular toxicity. The majority of data come from clinical trials, thus in selected populations. The aim of our study is to evaluate the cardiotoxicity profile of VEGFR-targeted TKIs and the impact of cardiovascular risk factors in a real-life population.

**Patients and methods:** In this cohort, population-based study, patients treated with VEGFR-targeted TKIs, bevacizumab and trastuzumab between 2009 and 2014 were analyzed. A multi-source strategy for data retrieval through hospital, pharmaceutical and administrative databases of the Lombardy region, Italy, has been adopted. The primary endpoint was to determine the incidence and type of major adverse cardiovascular events (MACEs) along with their temporal trend. The secondary endpoint was to define the impact of cardiovascular risk factors in the occurrence of MACEs.

**Results:** A total of 829 patients were treated with VEGFR-targeted TKIs. Eighty-one MACEs occurred in the first year of follow-up [crude cumulative incidence (CCI): 9.79%] mainly consisting of arterial thrombotic events (ATEs, 31 events, CCI: 3.99%), followed by rhythm disorders (22 events, CCI: 2.66%), pulmonary embolisms and heart failures (13 events each, CCI: 1.57%). While the incidence of most MACEs showed a plateau after 6 months, ATEs kept increasing along the year of follow-up. Hypertension and dyslipidemia were associated with an increase in risk of ATEs [relative risk difference (RRD) +209.8% and +156.2%, respectively], while the presence of previous MACEs correlated with a higher risk of all MACEs in multivariate analysis (RRD 151.1%, 95% confidence interval 53.6% to 310.3%,  $P < 0.001$ ).

**Conclusions:** MACEs occur in a clinically significant proportion of patients treated with VEGFR-targeted TKIs, with ATEs being predominant, mainly associated with hypertension and dyslipidemia. A clinical algorithm for effective proactive management of these patients is warranted.

**Key words:** VEGFR-targeted TKIs, major adverse cardiovascular events, cardiotoxicity, cardio-oncology

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### INTRODUCTION

The inhibition of angiogenesis is an important component of many anticancer therapies and the main pharmacological target is the vascular endothelial growth factor (VEGF) pathway.<sup>1</sup> The first agent developed to target VEGF is bevacizumab,<sup>2</sup> a monoclonal antibody used in association with chemotherapy for the treatment of many solid tumors (colorectal cancer, renal cell carcinoma, ovarian cancer, cervical cancer and glioblastoma). Besides bevacizumab, other approaches have shown to be effective in the

inhibition of angiogenesis: soluble VEGF decoy receptors, anti-VEGF receptor (VEGFR) antibodies and small-molecule tyrosine kinase inhibitors (TKIs). Differently from monoclonal antibodies, which are able to bind VEGF with high affinity, TKIs have mainly promiscuous activity,<sup>3-6</sup> and due to the high sequence similarity in the ATP binding pocket, their inhibition is directed also against other non-angiogenic tyrosine kinase receptors such as platelet-derived growth factor receptor, fibroblast growth factor receptor, rearranged during transfection, c-KIT and others, often inducing off-target toxicities.<sup>7</sup>

Since VEGF is strictly involved in the vascular homeostasis, cardiotoxicity is a class effect of these drugs. To date, cardiovascular toxicity of bevacizumab has been extensively studied in clinical trials and in the context of general oncology practice in expanded access trials,<sup>8,9</sup> whereas incidence of these side-effects during treatment with anti-VEGF multi-target TKIs has yet to be comprehensively established. Several meta-analyses of randomized clinical trials involving sunitinib, sorafenib and pazopanib have shown an increased relative risk for hypertension, arterial thrombotic events (ATEs) and decline in left ventricular ejection fraction (LVEF) with respect to controls.<sup>10-18</sup> Of note, an increased risk of venous thrombotic events (VTEs) with VEGF TKIs has not been reported, possibly because of underreporting due to the association of malignancies *per se* with VTEs<sup>12,13,19</sup> (Supplementary Table S1, available at <https://doi.org/10.1016/j.esmoop.2021.100338>). However, all these data could underestimate the real burden of VEGFR-targeted TKI-induced cardiovascular toxicity because they are based on clinical trials largely excluding patients with history of cardiovascular events or displaying concomitant risk factors.

Given these limitations, and based on the need of understanding the real impact of cardiovascular adverse effects of anti-VEGF TKIs on cancer treatment for establishing optimal proactive management, we decided to investigate the incidence of the cardiovascular toxicity, in terms of occurrence of major adverse cardiovascular events (MACEs), of pazopanib, sorafenib and sunitinib in a real-life population. To this aim, we adopted a comprehensive multi-source approach by interrogating and cross-referencing several different sources of data available in the Lombardy region in Italy (population 10.04 million) for data retrieval and contextualization in terms of cardiovascular risk. Two cohorts of patients treated with bevacizumab and trastuzumab, for which the profile of cardiotoxicity is well established, have been chosen in parallel to assess the reliability of our research method.

## PATIENTS AND METHODS

### *Data sources and methodology of data retrieval and cross-referencing*

Through administrative databases of Lombardy region, Italy, for drug dispensation by hospital pharmacies and registries of outpatient services for administering anticancer treatment, we have identified patients resident in Lombardy

receiving at least one cycle of bevacizumab (for colon cancer), pazopanib, sunitinib, sorafenib (for renal cancer) or trastuzumab (for breast cancer), from 2009 to 2014 and who have been on treatment or on follow-up for at least 1 year, or have died due to cancer within 1 year.

Subsequently, by cross-referencing these data with hospital discharge cards (HDCs), through administrative medical codes of the International Classification of Diseases (ICD-9), we have identified patients who have been hospitalized after start of this treatment for MACEs defined as: myocardial infarction, pulmonary embolism (PE) and pathology of the right heart, conduction disorders and arrhythmias, heart failure (HF) and cerebrovascular events. The diagnoses and procedures/interventions contained in the administrative databases were coded with the ICD-9-Clinical Modification system revision 2007 (in the United States), used in Lombardy since 2010. The diagnoses and surgical procedures contained in the HDC file determine the allocation of each hospitalization case to a specific diagnosis-related group (DRG) by an algorithm called 'grouper'. DRGs represent an aggregation tool for hospital admissions strongly conditioned by hospital funding rules and procedures carried out during hospitalization (see also [Supplementary Methods 1](#) System of code classification of diseases, available at <https://doi.org/10.1016/j.esmoop.2021.100338>).

Finally, we assessed the concomitant cardiovascular risk factors by collecting for each patient demographic data and comorbidities according to: (i) secondary diagnoses of the HDC and (ii) outpatient pharmaceutical prescriptions on the basis of the Anatomical Therapeutic Chemical (ATC) classification. Moreover, we have evaluated complexity of patients by calculating the Charlson Comorbidity Index (ChCI)<sup>20</sup> and prescriptions for known cardiac risk factors such as hypertension, diabetes and dyslipidemia.

This multi-source approach is outlined in [Figure 1](#) and [Supplementary Figure S1](#), available at <https://doi.org/10.1016/j.esmoop.2021.100338>.

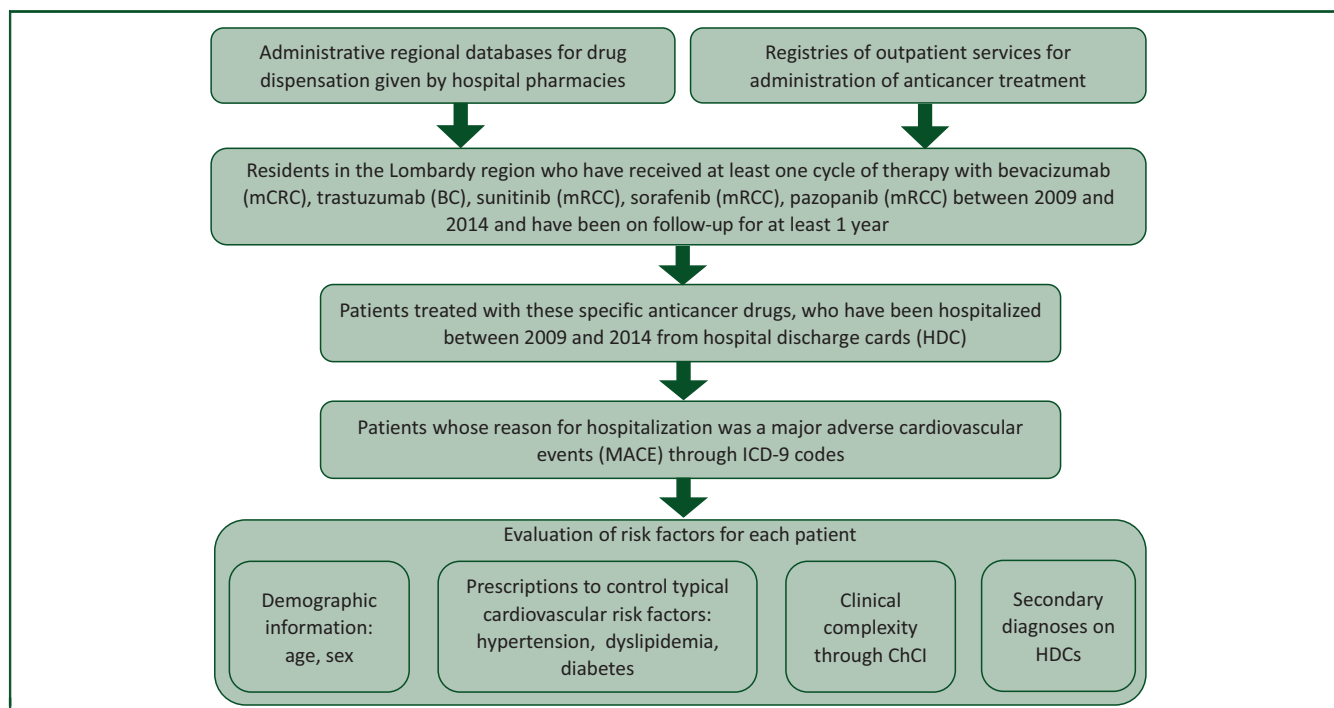
### *Definition of major adverse cardiovascular events (MACEs), prognostic factors and comorbidity indicators*

Starting from these diagnoses, we considered four categories of MACEs: thrombotic events (both cardiac and vascular peripheral arteries), PE, HF, rhythm disorder.

We considered as cardiovascular risk factors: age, sex, hypertension, diabetes, dyslipidemia and a history of a previous cardiovascular events (before the start of anti-cancer treatment). Diagnosis of hypertension, diabetes and dyslipidemia was derived from HDC or the registration of antihypertensive drugs, statins and anti-diabetic drugs in outpatient pharmaceutical prescriptions according to ATC classification system. The ChCI,<sup>20</sup> which is used in risk methodologies adjustment for outcome assessment, was adopted for evaluating the impact of comorbidities.

### *Statistical methods*

For each drug, demographic and clinical characteristics of the sample were summarized using descriptive



**Figure 1. Data sources for defining study population and elements for cardiovascular risk contextualization.**

BC, breast cancer; ChCI, Charlson Comorbidity Index; ICD-9, International Classification of Diseases; MACEs, major adverse cardiovascular events; mCRC, metastatic colorectal cancer; mRCC, metastatic renal cell carcinoma.

statistics. Overall survival curve was estimated using the Kaplan–Meier method. Punctual estimates with 95% confidence intervals (CIs) were provided at 1 to 5 years.

Cumulative incidence curve of MACE was estimated accounting for the presence of competing risks [crude cumulative incidence (CCI)].<sup>21</sup> This approach was used since not all patients had a registration of a MACE during the follow-up, but some of them died without previously experiencing a MACE (death acting as a competing risk avoiding subsequent observation of MACE). Competing risk setting was also considered to compute the CCI of different types of MACE (thrombotic events, PE, HF and dysrhythmias). For each endpoint, CCI is the estimates of the probability that the specific MACE event is observed as the first event within a follow-up time  $t$ , in the presence of all other events acting as competing risks.<sup>21</sup>

The measure that was considered clinically useful to estimate the impact of the prognostic factors on MACE was the relative risk difference (RRD). Since cardiovascular risk factors in the analysis were all reported as categorical, the putative best prognostic category was used as reference one; thus, RRD is the relative increase of CCI of MACE at a given time for patients having a specific modality of the putative prognostic factor, with respect to patients having reference modality.

To estimate the RRD for each putative prognostic factor, a pseudo-value regression model on CCI was fitted.<sup>22</sup> For each covariate, RRD was estimated at each time point, together with 95% CI.

Finally, a multivariable regression model was fitted including all the putative prognostic factors (sex, age,

hypertension, dyslipidemia, diabetes, previous MACE before starting the drug treatment) and providing adjusted estimate of RRD, CIs and  $P$  values (see also [Supplementary Methods 2](https://doi.org/10.1016/j.esmoop.2021.100338), available at <https://doi.org/10.1016/j.esmoop.2021.100338>).

## RESULTS

### *Demographics and patients' characteristics*

From the record linkage of the aforementioned sources of data, 221 354 residents in Lombardy underwent at least one cycle of anticancer therapy between 2009 and 2014. We have considered and analyzed: 829 patients treated with the VEGFR-targeted TKIs pazopanib, sunitinib and sorafenib for metastatic renal cell carcinoma; 2601 patients with bevacizumab for metastatic colorectal cancer; and 4317 patients with trastuzumab for breast cancer.

Patients receiving TKIs were predominantly male (73.4%), >65 years old (53.8%) and 69.9% of them took antihypertensive drugs. 26.9% took statins and 15.56% were in therapy with anti-diabetic drugs. Almost all patients had had a hospitalization before the study period (99.0%), whereas only 15.9% had had a previous MACE. Sixty-two percent of patients had a score >1 by ChCI ([Table 1](#), panel A).

### *Incidence of MACEs*

In the overall population, patients on treatment with TKIs displayed a high incidence of MACEs within 1 year (81 events, CCI: 9.79%): 33 thrombotic events (CCI: 3.99%), 22

**Table 1. Patients' characteristics (panel A) and cumulative incidence of death without MACE, MACEs and of each single MACE, in the overall population, at 1 year of follow-up (panel B)**

	Pazopanib/sunitinib/sorafenib, n (%) (n = 829)	Bevacizumab, n (%) (n = 2601)	Trastuzumab, n (%) (n = 4317)
<b>Panel A</b>			
Male sex	609 (73.5)	1558 (59.9)	24 (0.6)
Age >65 years	446 (53.8)	1331 (51.2)	1165 (28.2)
Hypertension	580 (70.0)	1323 (50.9)	1599 (38.7)
Dyslipidemia	223 (26.9)	455 (17.5)	576 (13.9)
Diabetes	129 (15.6)	336 (12.)	276 (6.7)
Previous MACE	132 (15.9)	179 (6.9)	132 (3.2)
Charlson Comorbidity Index >1	514 (62)	1986 (76.4)	1779 (43)
<b>Panel B</b>			
Death without MACE	239 (28.9)	662 (25.5)	129 (3.1)
MACE	81 (9.8)	176 (6.8)	107 (2.6)
Thrombotic events	33 (4)	70 (2.7)	21 (0.5)
Pulmonary embolism	13 (1.6)	46 (1.8)	11 (0.3)
Heart failure	13 (1.6)	13 (0.5)	50 (1.2)
Rhythm disorder	22 (2.7)	47 (1.8)	25 (0.6)

MACE, major adverse cardiovascular events.

rhythm disorders (CCI: 2.66%), 13 PEs (CCI: 1.57%) and 13 HFs (CCI: 1.57%). A total of 239 patients died without having had a MACE (CCI: 28.9%) (Table 1, panel B). On bevacizumab, the incidence of MACEs at 1 year was 6.77% (176 events), with predominance of thrombotic events (70 events, CCI: 2.69%). In the cohort of patients treated with trastuzumab, the incidence of MACEs at 1 year was 2.59% (107 events) and the majority of patients displayed HF (50 events, CCI: 1.21%).

The cumulative incidence of MACEs while on treatment with TKIs increased linearly, from 4.34% at 3 months and reaching 9.79% after 1 year; the same trend was noticed for bevacizumab (from 2.38% to 6.77%). Interestingly, in the TKI cohort, the incidence of PE, HF and rhythm disorders reached a plateau after 6 months, whereas the cumulative incidence of thrombotic events kept increasing all along the first year of treatment (Figure 2). Moreover, for the first 6 months of treatment, the incidence of rhythm disorders was higher than that of thrombotic events (2.53% versus 1.69%), with a change after 9 months, when thrombotic events took over. These trends were not observed with bevacizumab and trastuzumab, where the cumulative incidence of all MACEs kept increasing during the time of treatment.

### The impact of cardiovascular risk factors on MACEs

The impact of each risk factor (sex, age, hypertension, dyslipidemia, diabetes, ChCI, previous occurrence of MACEs) on the occurrence of MACE was estimated by RRD (Table 2, see also Supplementary Tables S2-S7, available at <https://doi.org/10.1016/j.esmoop.2021.100338>).

While male sex, diabetes and a ChCI >1 did not associate with a higher risk of MACEs, age >65 years was a significant risk factor for rhythm disorders for TKIs (RRD +444.5%). Among other prognostic factors, hypertension and dyslipidemia both correlate with a higher risk of thrombotic events (RRD +178% and +156.2%, respectively), while hypertension and having had previous MACEs are associated

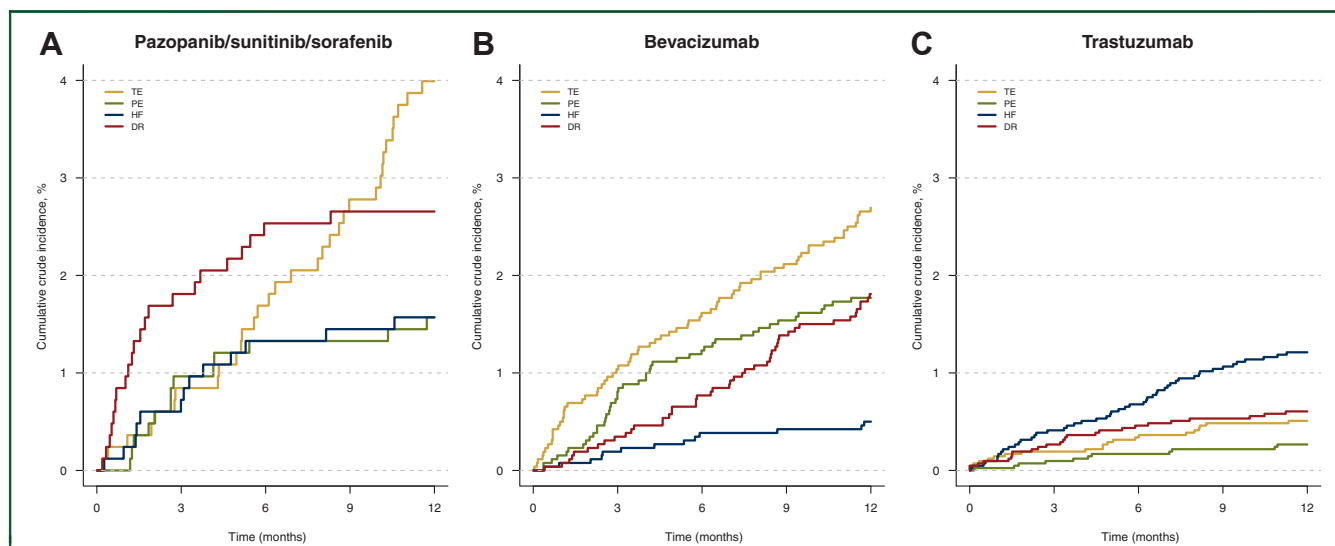
with an increased risk of all MACEs (RRD +101% and +165%, respectively).

The prognostic effect of all these risk factors was then analyzed in a multivariate survival model. Due to the limited events, we estimated the RRD as a composite endpoint, taking together all different types of MACEs (ATEs, arrhythmias, HF, PE). The only significant risk factor related to the treatment with TKIs was having had a previous MACE (RRD 151.1%); in the case of bevacizumab, dyslipidemia and having had a previous MACE were significant risk factors (RRD 67.3% and 92.6%, respectively) and for trastuzumab, hypertension and having had a previous MACE (RRD 194.6% and 619.5%, respectively) (Supplementary Table S8, available at <https://doi.org/10.1016/j.esmoop.2021.100338>).

### DISCUSSION

The aim of this study was to analyze the occurrence of MACEs during treatment with the TKIs pazopanib, sorafenib and sunitinib in a real-life population including patients with a history of previous cardiovascular events and concomitant risk factors who are often excluded from clinical trials. To our knowledge, this is the first study adopting a comprehensive methodology through a multi-source strategy for data retrieval and a multi-dimensional approach for this risk estimation and allows to derive some conclusions that can help in establishing a proactive cardio-oncology management. Two cohorts of patients treated with bevacizumab and trastuzumab, for which the profile of cardiotoxicity is well established, have been chosen in parallel to assess the reliability of our research method.

Firstly, the incidence of MACEs with TKIs at 1 year of follow-up was 9.8% and mainly consisting of ATEs (31 events, CCI 3.99%), followed by rhythm disorders (22 events, CCI 2.66%), PEs and HFs (13 events each, CCI: 1.57%). This incidence rate is higher than reported in literature (incidence of each single MACE <1%),<sup>21-24</sup> likely because of the presence of impactful comorbidities and cardiovascular risk factors in a real-life setting: about



**Figure 2. Dynamic trend of incidence of MACEs in the study cohort.**

(A) Dynamic trend of incidence of MACEs in the cohort of patients treated with pazopanib/sunitinib/sorafenib. (B) Dynamic trend of incidence of MACEs in the cohort of patients treated with bevacizumab. (C) Dynamic trend of incidence of MACEs in the cohort of patients treated with trastuzumab. DR, rhythm disorder; HF, heart failure; MACEs, major adverse cardiovascular events; PE, pulmonary embolism; TE, thrombotic events.

three-quarters of patients in our cohort (73.5%) were males older than 65 years of age, displaying a history of previous MACEs (15.9%) and a history of hypertension (67.0%), dyslipidemia (26.9%) or diabetes (15.6%). Several meta-analyses of randomized clinical trials with sunitinib, sorafenib and pazopanib have shown an increased incidence and risk ratio/odds ratio (RR/OR) for some MACEs,<sup>10-16,18,19,25</sup> but the enrolled patients in those clinical trials were younger than those in the general community and without pre-existing cardiovascular comorbidities. Similar to our study, in a report by Hamnvik et al.,<sup>26</sup> a population of 1120 patients treated with sorafenib, sunitinib or pazopanib was considered; 65% of the patients had a baseline hypertension and 54.4% were older than 60 years of age. These two factors, together with a body mass index  $\geq 25$  kg/m<sup>2</sup>, identified patients at risk for significant anti-VEGF therapy-induced blood pressure elevation.

The main MACEs observed in our study were ATEs (3.99% while on TKIs), consistent with data from the meta-analysis

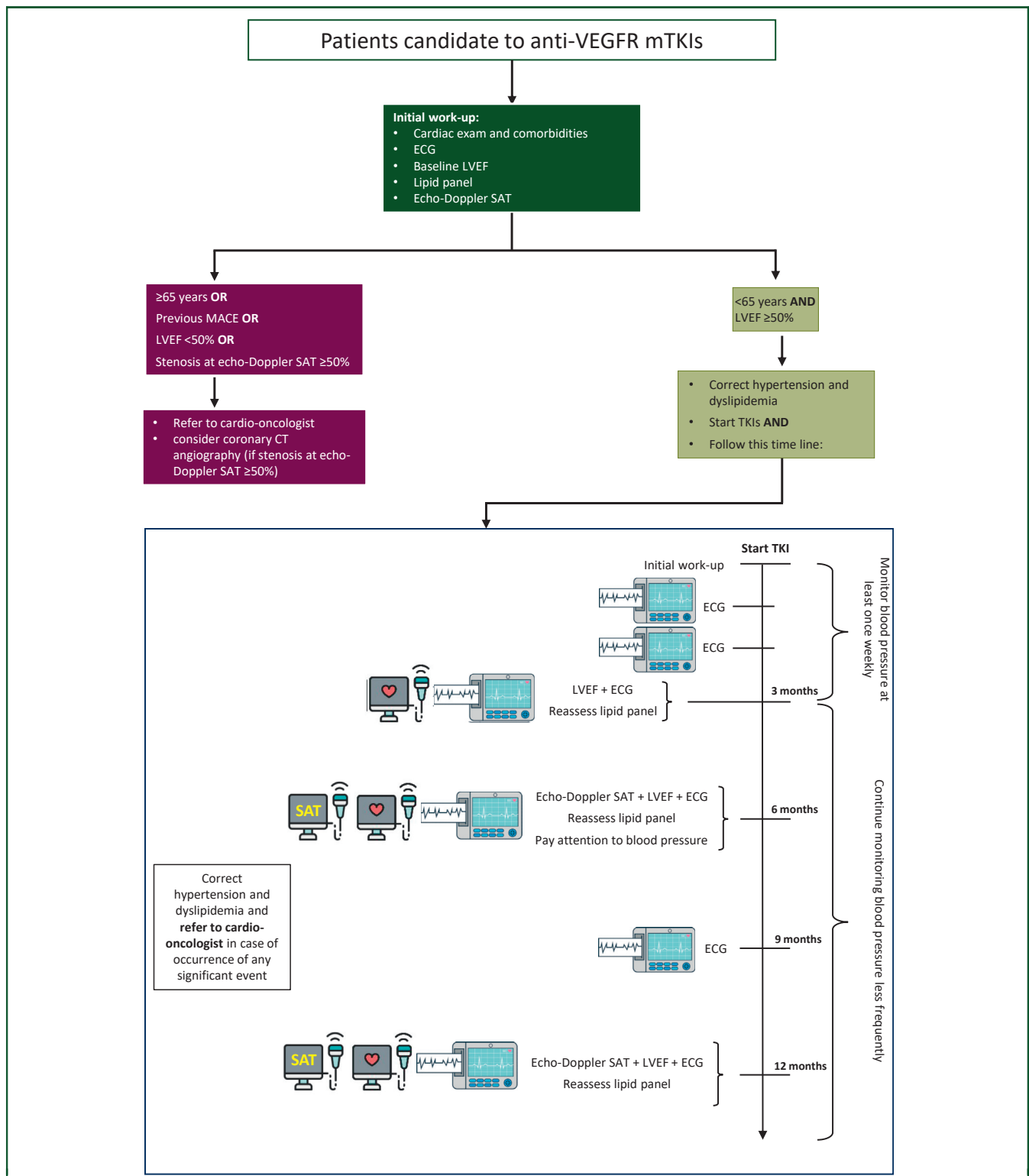
by Choueiri et al.<sup>10</sup> and by Abdel-Qadir et al.,<sup>19</sup> where an increased incidence and RR/OR for ATEs were recorded (RR 3.03 and OR 1.52, respectively). In contrast, we report lower incidence of congestive HF (1.57%) as compared with the meta-analyses by Abdel-Qadir et al.,<sup>19</sup> Qi et al.,<sup>25</sup> Ghattalia et al.<sup>14</sup> and Richards et al.<sup>15</sup> in which this MACE was more often reported while on treatment with TKIs.

Secondly, differently from these previous studies, in our population, we retrieved longitudinal data of time of occurrence of MACEs associated with TKIs, allowing to draw a dynamic picture and possibly identify appropriate time-points for proactive management. Under this regard, for the first 6 months of treatment, the incidence of rhythm disorders was higher than that of thrombotic events, with a change in trend after 9 months, when thrombotic events took over in terms of frequency. According to the definition of MACE, arrhythmic events that occurred in our study were those that led to hospitalization, and therefore the incidence of possible asymptomatic QTc increase was not

	Pazopanib/sunitinib/sorafenib	Bevacizumab	Trastuzumab
Male sex		✓ (Thrombosis)	
Age >65 years	✓ (Arrhythmia)	✓	✓ (Arrhythmia, HF)
Hypertension	✓ (Thrombosis, HF)	✓ (Thrombosis, arrhythmia)	✓ (Thrombosis, arrhythmia, pulmonary embolism)
Dyslipidemia	✓ (Thrombosis)	✓ (Thrombosis)	✓ (Thrombosis)
Diabetes		✓ (Arrhythmia)	✓ (Thrombosis)
ChCI >1		✓ (Arrhythmia)	
Previous MACE	✓	✓	✓

In parentheses the MACE with the highest relative risk difference recorded. ChCI, Charlson Comorbidity Index; HF, heart failure; MACE, major adverse cardiovascular events.





**Figure 3. Proposed algorithm for monitoring and preventing the risk of MACEs during TKI therapy.** ECG, electrocardiogram; GLS, global longitudinal strain; LVEF, left ventricular ejection fraction; MACEs, major adverse cardiovascular events; TKIs, tyrosine kinase inhibitors; SAT, supra-aortic trunk.

reported. For 90%, the event recorded was rhythm disorders (atrial fibrillation) and in 5% the appearance of atrio-ventricular block. We might explain the high incidence of atrial fibrillation in the first 6 months of treatment, and especially in the first month, as a consequence of the acute

hemodynamic effects caused by the start of anti-VEGFR treatment, e.g. the rise in blood pressure and diastolic dysfunction of the left ventricle. Following, in the second trimester, it could be possibly related to an initial remodeling of the atrial chambers. Differently, other anti-VEGF

drugs such as bevacizumab usually results in a more delayed rise in blood pressure and therefore might have less impact as for this type of MACE. It should be considered also that atrial dysfunction is the major resultant of cardiac remodeling in many types of heart diseases, thus a high incidence of arrhythmia in our real-world population was expected. All these findings suggest the need of a close monitoring of arrhythmias, HF and PE during the first months of treatment through an echocardiography at baseline and every 3 months for the first 6 months (as suggested in the European Society for Medical Oncology recommendations 2020 for the monitoring of HF while on treatment with cardiotoxic agents) or, where possible, through the assessment of global longitudinal strain, which has been shown to be more predictive for the development of cardiotoxicity than changes in LVEF.<sup>27,28</sup> In contrast, the rate of thrombotic events kept steadily rising, likely because of an increasing endothelial damage, suggesting a different monitoring in this context in terms of diagnostic tests and the potential need of prescription of an adequate therapy to prevent thrombotic adverse effects that, based on timing of onset, should be carried out for the whole duration of treatment, also considering the bleeding risk.

Finally, among pre-existing risk factors, in the TKI population having had a previous MACE, age over 65 years, hypertension and dyslipidemia were related to a higher risk of MACEs within 1 year, whereas diabetes was less impactful. In particular, age >65 years is a risk factor for arrhythmias (RRD 444.5%); hypertension is a risk factor for thrombosis (RRD 209.8%) and HF (RRD 414.6%); dyslipidemia is a risk factor for thrombosis (RRD 156.2%); to have had a previous MACE is a risk factor for all MACEs both at univariate and multivariate analysis. One limitation of the multivariate analysis was that, due to the limited events, we estimated the RRD for MACEs as a composite endpoint, taking together all different types of MACEs (ATEs, arrhythmias, HF, PE).

Based on these results, we propose an algorithm for monitoring and preventing the risk of MACEs during TKI therapy (Figure 3). Since hypertension, dyslipidemia and a history of previous MACE are the main risk factors for thrombotic events, we think it would be advisable to carefully evaluate the cardiovascular history and comorbidities of patients candidate to TKIs, recommending a regular monitoring of blood pressure and introducing anti-hypertensive drugs<sup>29-32</sup> as soon as there is a registration of increased blood pressure. It appears also important to correct a baseline dyslipidemia through statins and reassess a lipid panel at 3, 6 and 12 months.<sup>33</sup> We suggest a more comprehensive screening at baseline including echo-Doppler of the supra-aortic trunk (SAT) allowing estimation of atherosclerotic burden, as known risk factor for thromboembolic events that have been shown to steadily increase over time during treatment. In case of stenosis  $\geq 50\%$ , a cardio-oncologist evaluation and, in case of exclusion of other contraindications, a coronary computed tomography angiography are recommended. Further, all

patients treated should undergo an echo-Doppler of the SAT at 6 months and then every 6 months. Finally, based on the rising incidence of arrhythmia (the most frequent observed MACEs) during the first 3 months and reaching a plateau thereafter, we suggest electrocardiogram to be repeated every 3-4 weeks for the first 3 months.

This study has some limitations. Firstly, data are retrospective, although the methodology adopted, based on retrieval through administrative sources from a whole country region, allowed comprehensive and unbiased selection of MACEs blindly cross-matched as for the association with TKI treatment, overall making the analysis more reliable. Secondly, we carried out a competitive risk analysis where we assessed the rate of death for all-cause cardiovascular events and MACEs. Our rate of MACEs could be masked by the high incidence of deaths that is expected for metastatic tumors. Although this limitation is valuable for all the drugs analyzed, it should be noted that trastuzumab patients are the only one showing a low rate of death without MACE and MACE at all, and, at least for the first 6 months of treatment, a higher rate of MACE than death. These data have to be underlined because the masking effect previously stated could be more prevalent in the population treated with bevacizumab and TKIs, bringing to an underestimation of the rate of adverse cardiovascular effect. Also, the trend of MACEs could have been higher than assessed considering that: (i) data were limited to Lombardy region, Italy, and (ii) we assessed MACEs based on hospital admissions in this area, thus potentially missing cardiovascular events that occurred and were diagnosed in other parts of the country or, also importantly, did not require hospitalization, appeared during hospitalization for other reasons or occurred with fatal event outside the hospital. It should be noted also that data were based on different administrative sources, and therefore nonhomogeneous, with no verification of the clinical, laboratory tests or radiological findings supporting the reported diagnosis. Another limitation is the missing information on TKI treatment adherence or smoking habits (a well-established cardiovascular risk factor) in our cohort but this was due to the methodology adopted of retrospectively having retrieved data through administrative medical codes and pharmaceutical prescriptions from a whole region of the country rather than having followed up a clinically annotated cohort.

## Conclusions

In conclusion, this multi-source, multi-dimensional analysis of MACEs occurring in cancer patients indicates that treatment with anti-VEGFR TKIs in the real-life setting is burdened with a potentially higher risk of MACEs than reported in literature, mainly thrombotic events, indicating the need for a tailored cardiological follow-up of these patients focused on preventive measures with an appropriate timing of monitoring.

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**DISCLOSURE**

The authors have declared no conflicts of interest.

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