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Full Length Article

Risk of cancer after an acute coronary syndrome according to the type of P2Y12 inhibitor

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A R T I C L E I N F O

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A B S T R A C T

Introduction: There are conflicting clinical and laboratory data about the effect of dual antiplatelet therapy (DAPT) on cancer incidence, including analysis suggesting an increased cancer risk. This study aims to analyze if there are differences in the incidence of cancer according to the type of P2Y12 inhibitor prescribed (clopidogrel, prasugrel, or ticagrelor), among a population of acute coronary syndrome (ACS) survivors treated with DAPT.
Material and methods: A retrospective study was conducted among 4229 consecutive ACS patients discharged from a tertiary hospital with DAPT from 2010 to 2016. Cox regression, propensity score, and survival-time inverse probability analysis were done.
Results: A total of 311 were diagnosed of cancer during a median follow-up of 46.2 months. The cumulative incidence function (CIF) of cancer (per 100 patients/year) was 2.2 for clopidogrel, 1.6 for prasugrel, and 0.3 for ticagrelor. After multivariate analysis, we have found that ticagrelor resulted associated with lower cancer risk than clopidogrel (sHR 0.20: 95% CI 0.05–0.84; p = 0.028), without differences between prasugrel and clopidogrel. After propensity score matching, ticagrelor was also associated with lower incidence of cancer than clopidogrel/prasugrel (sHR 0.22; 95% CI 0.05–0.90; p = 0.036), regardless of DAPT duration.
Conclusion: DAPT with ticagrelor could be associated with lower follow-up cancer incidence than DAPT with clopidogrel or prasugrel after an ACS.

Several studies have found an association between aspirin treatment and a reduction in the incidence of newly diagnosed cancer [1,2]. The pathophysiological explanation of these findings is based on the antiplatelet, anti-inflammatory, and proapoptotic effects of aspirin [3]. All these studies, together with the role of platelets in the natural history of cancer [4], suggest that other antiplatelet drugs might have a similar effect, which could be enhanced by combining several antiplatelet drugs. However, contrary to expectations, there are conflicting clinical and laboratory data about the effect of combined aspirin with a P2Y12 inhibitor on cancer incidence [5–7], including analyses suggesting an increased cancer risk [8–10]. To date, it has not yet been possible to demonstrate if the association of dual antiplatelet therapy (DAPT) with cancer risk observed in several studies [10–12] was causal -indirect promotion of tumor growth, easier metastatic dissemination due to instability of platelet-tumor cell aggregates or/and inability to keep cancer cells locally in situ are considered [11] or casual -higher diagnosis rate in DAPT patients due to an increase in bleeding events [12]. Currently, there are three available pharmacological options for DAPT prescription: aspirin plus clopidogrel, aspirin plus ticagrelor, and aspirin plus prasugrel. Direct comparisons from clinical trials of DAPT with clopidogrel versus prasugrel showed no difference between both in the risk of cancer [13], whereas DAPT with ticagrelor in comparison with clopidogrel showed a lower -but not significant- rate of cancer incidence [14]. Considering that DAPT is mandatory after an ACS, it would be interesting to know if there are differences in the cancer risk between therapy with ticagrelor, prasugrel and clopidogrel, when they are associated with aspirin. With this study from real-life patients, we aimed to do a comparative analysis of the cancer risk after an ACS according to the type of DAPT (aspirin plus clopidogrel, prasugrel, or ticagrelor).

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1. Methods

1.1. Study design and population

The data analyzed in this study were obtained from a retrospective clinical registry including all patients consecutively discharged from the Cardiology Department of a tertiary hospital from 2010, January 1, to December 31, 2016, with the primary and definitive diagnosis of ACS (n = 6068). Diagnosis of ACS was based on clinical guidelines [15,16]. Patients were classified as having ST-elevation myocardial infarction (STEMI) or non-ST elevation ACS (NSTE-ACS), including in the last group non-ST elevation MI [NSTEMI] and unstable angina. For the purpose of the present study, focusing in study differences between the P2Y12 inhibitors in patients treated with DAPT after an ACS, we excluded patient treated with single antiplatelet therapy or triple therapy (n = 946). Moreover, since our aim was to study the association of DAPT with de novo cancer, we excluded patients who presented prior history of cancer (n = 581). Patients without data of follow up (n = 313) were also excluded. There were not significant differences in baseline characteristics between those patients with and without follow-up data (Supplementary data). Therefore, the final cohort of the present study consisted of 4229 patients (see flow diagram of study population in Supplementary data). The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the local ethics committee.

1.2. Follow-up and outcomes

The primary endpoint was new diagnosis of cancer. The ascertainment of cancer status and death during follow-up was carried out between November and December of 2017 by trained physicians. Adjudication of cancer events was performed by personnel unaware of the endpoints of interest for this analysis. The electronic medical record, and all the medical attendances and hospital records, were reviewed for each patient. Follow-up "de novo" cancer was defined as non-benign neoplasm diagnosed after hospital discharge, being the diagnosis based on pathologic data and clinical information. The first priority to confirm the diagnosis of cancer was a definitive pathologic diagnosis from a pathology report. If there was no definitive pathologic diagnosis available, then the non-benign neoplasm diagnosis was established by the best pathologic data available, clinical information (such as anatomic distribution of the neoplasm from imaging reports), and the consensus opinion of the physicians that adjudicated the events. For verified non-benign neoplasm events, the dates of initial detection and histological diagnosis and the anatomic/tissue location of the malignant neoplasm were determined. Cancer types were classified by anatomic and system primary involvement. For each patient in the study, we have also collected information about bleeding events and vital status. Data on vital status, and information about bleeding, were obtained from hospital and/or administrative (vital statistics records, hospital discharge data, and emergency department data) data records, by contacting the patients or their relatives by phone, and/or by contacting the primary care physicians for additional information, when necessary. Bleeding events were classified according to BARC (Bleeding Academic Research Consortium) criteria [17]. Due to the retrospective nature of our study and the difficulty for the accurate identification of all BARC type 1 bleeding, this type of bleeding was not included in the present study. Therefore, only the BARC 2 to 5 bleeding events were analyzed.

1.3. Statistical analyses

The statistical analysis was performed with SPSS 25.0 (IBM Corporation, Armonk/New York, United States), R version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria), and Stata MP64 version 15 (StataCorp, College Station, Texas). Baseline characteristics according to type of DAPT and cancer status were described by using number and percentage -for categorical data-, and mean ± standard difference -for continuous data-. Differences in characteristics were assessed by using chi-square tests, 2-sample Student *t*-tests and one-way analysis of variance (ANOVA test). For the baseline variables of the study, we had < 1% missing data. No method was used to impute missing values or adjust the model for the presence of missing data. A competing risk model was used to estimate the cumulative incidence function (CIF) of new cancer, accounting for death as a competing episode. All variables associated with post-discharge new cancer basing on clinical plausibility or p-value < 0.05 in the univariate analyses were included in a multivariate model. Therefore, the multivariate models were adjusted for the following covariates: age, sex, smoking, hypertension, dislipemia, peripheral artery disease, HIV infection, anemia, MDRD-4 < 60 ml/min/1.73 m2, multivessel coronary artery disease, complete revascularization, beta-blocker therapy, DAPT duration and type of DAPT. Because we cannot assume proportional hazards for all the covariates, we fit a competing risks flexible parametric regression analysis (Royston-Parmar model) using the stpm2cr command of STATA, that allow us to estimate the cancer-specific hazard for each type of DAPT in a competing risks situation. The adjusted hazards were expressed as subhazard ratios (sHR) with their corresponding 95% confidence intervals (95% CI). Because of important differences in key baseline characteristics between the three P2Y12 inhibitors, we have complemented our study with a propensity score (PS) analysis. Propensity scores were estimated using a non-parsimonious multivariate logistic regression model, being DAPT with ticagrelor (versus DAPT with clopidogrel or prasugrel) the dependent variable, and those characteristics that were different between patients treated and no-treated with DAPT with ticagrelor as covariates (see Supplementary data). The area under the curve for the PS model was 0.80, which indicated a good discrimination for the model. The competing risks flexible parametric regression analysis was repeated adjusting by PS − to balance the covariate distribution between the treatment and control observations − and by those covariates associated with follow-up new cancer in the univariate analyses − to further mitigate from residual confounding in the survival modeling−. Moreover, we performed a subsequent PS matching to assemble a cohort in which all the measured covariates would be well balanced across the comparator group. The 1:1 nearest-neighbor matching without replacement, and with a caliper width of 0.1 of the standard deviation of all PSs was used. The standardized difference measure was used to test how well the controls match the cases (see Supplementary data). In the PS-matched population, the cancer risk was evaluated using a competing-risks regression analyses. Statistical significance of differences in cancer rates was assessed with the Gray test. In addition to this, survival-time inverse probability weighting (IPW) regression adjustment was also used to evaluate the association between DAPT with ticagrelor and cancer, in comparison with DAPT with clopidogrel or prasugrel. All values were considered statistically significant when the p-value was lower than 0.05.

2. Results

2.1. Cancer incidence

From the 4229 patients, a total of 311 were diagnosed of cancer for first time during a median time of follow-up of 46.2 months (25th to 75th percentile: 20.1 to 68.0 months). Among patients who developed cancer, the median time from ACS discharge to cancer diagnosis was 28.1 months (25th to 75th percentile: 12.9 to 44.3 months). Incidence density rates for cancer diagnosis (per 100 persons-year) was 2.1 (95% CI 1.8–2.3) (Fig. 1A). Types of cancer were classified according to system involvement (Fig. 1B). The most common types of cancer were genital (n = 62; 19.9%), digestive (n = 57; 18.3%), urinary (n = 56; 18.0%), and respiratory (N = 49; 15.8%). Table 1 shows the baseline

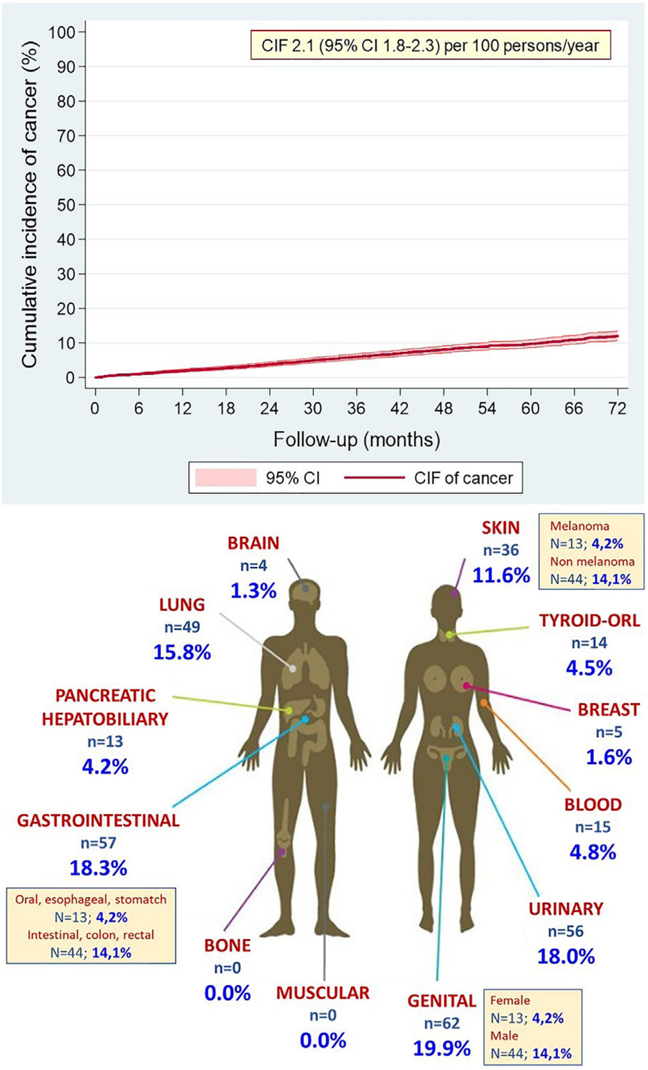

Fig. 1. Incidence density rates for the detection of new cancer during follow-up (1A) and location according to system involvement.

characteristics, laboratory, echocardiographic and angiographic data, together with medical therapy, stratified by cancer status during the follow-up.

2.2. DAPT-related differences in new cancer diagnosis

DAPT with clopidogrel was prescribed in 3530 patients (83.2%) for an average of 14.1 ± 13.4 months, with prasugrel in 252 patients (6.0%) for 12.9 ± 8.8 months, and with ticagrelor in 459 patients (10.8%) for 11.6 ± 4.8 months. Differences in baseline characteristics between different types of DAPT were summarized in Table 2. During follow-up, cancer was diagnosed in 296 with clopidogrel (8.4%; CIF 2.2 per 100 patients/year, 95% CI 1.9–2.4), 13 with prasugrel (5.2%; CIF 1.6 per 100 patients/year, 95% CI 0.9–2.7), and 2 with ticagrelor (0.4%; CIF 0.3 per 100 patients/year, 95% CI 0.1–1.4).

In 2067 patients (48.7%), DAPT duration was > 1 year. There was not difference in the cumulative incidence of cancer among patients treated with DAPT ≤1 year vs > 1 year (2.1 vs 2.0 per 100 patients/year, respectively; p = 0.840). For patients treated with DAPT ≤1 year, ticagrelor was significantly associated with incidence of cancer in comparison with clopidogrel (p = 0.042) and prasugrel (0.046). For those treated with DAPT > 1 year, the group of patients treated with ticagrelor have lower incidence of cancer, but differences were not statistically significant (p = 0.162 in comparison with clopidogrel; p = 0.649 in comparison with prasugrel) (Fig. 2).

Table 1
Baseline characteristics by cancer status.

Variable	Cancer (n = 311)	No cancer (n = 3930)	P-value
Age, years	69.1 ± 11.0	63.9 ± 13.4	< 0.001
Female sex, %	16.1	23.2	0.004
Body mass index, kg/m^2	28.0 ± 4.6	28.3 ± 4.4	0.303
Active smoking, %	38.9	36.3	0.380
Hypertension, %	69.8	61.3	0.003
Diabetes, %	25.1	23.8	0.608
Dislipemia, %	72.7	66.5	0.025
Peripheral artery disease, %	16.1	8.4	< 0.001
Prior heart failure, %	2.6	2.5	0.932
Chronic obstructive pulmonary disease, %	9.3	8.9	0.815
HIV infection, %	1.0	0.5	0.330
ACS type, %			0.434
UA	8.9	9.6	
NSTEMI	44.3	47.3	
STEMI	46.9	43.1	
Killip class ≥2, %	11.9	13.0	0.576
Atrial fibrillation, %	8.0	8.4	0.814
LVEF ≤40%	14.8	14.4	0.841
Anemia, %	17.7	14.0	0.078
MDRD-4 < 60 ml/min/1.73 m2, %	26.7	21.4	0.030
Multivessel coronary artery disease, %	58.2	49.4	0.003
PCI, %	86.8	88.6	0.336
Drug eluting stent, %	75.2	78.0	0.253
CABG, %	1.3	1.3	0.927
Complete revascularization, %	83.6	77.1	0.008
P2Y12 inhibitor, %			< 0.001
Clopidogrel	95.2	82.3	
Prasugrel	4.2	6.1	
Ticagrelor	0.6	11.6	
DAPT duration, months	15.0 ± 14.6	13.7 ± 12.4	0.108
Beta-blocker, %	77.2	82.0	0.036
ACEI/ARB, %	71.4	66.9	0.107
Spironolactone, %	8.7	6.9	0.243
Statin, %	95.5	95.4	0.949

ACEI/ARB: Angiotensin Converting Enzyme Inhibitors/Angiotensin Receptor Blockers; ACS: Acute Coronary Syndrome; CABG: Coronary Artery Bypass Graft; DAPT: Dual Antiplatelet Therapy; HIV: Human Immunodeficiency Virus; LVEF: Left Ventricular Ejection Fraction; MDRD-4: Modification of Diet in Renal Disease (MDRD) equation version 4; NSTEMI: Non ST-segment Elevation Myocardial Infarction; PCI: Percutaneous Coronary Intervention; STEMI: ST-segment Elevation Myocardial Infarction; UA: Unstable Angina.

2.3. Type DAPT, bleeding and cancer

During the follow up, 1263 patients presented BARC type ≥2 bleeding. From 311 patients with new follow-up cancer, 169 (54.3%) had BARC type ≥2 bleeding: 129 (41.5%) were prior to cancer diagnosis, and 40 (12.9%) were after cancer diagnosis (Fig. 3). The cumulative incidence of cancer (per 100 persons/year) was higher in patients with prior follow-up bleeding [2.6 (95% CI 2.2–3.1) vs 1.8 (95% CI 1.6–2.1); p = 0.002]. Similarly, the cumulative incidence of bleeding (per 100 persons/year) was higher in patient with follow-up new cancer [17.4 (95% CI 15.0–20.3) vs 9.3 (95% CI 8.7–9.8); p < 0.001]. However, the differences that we found for cancer risk in relation with type of DAPT were not observed for bleeding risk, without differences in the cumulative incidence of BARC type ≥2 bleeding between DAPT with clopidogrel, ticagrelor, and prasugrel (Fig. 3).

2.4. Multivariate analysis for cancer risk according to type of DAPT

After adjustment for those variables associated with cancer in the univariate analysis (age, sex, hypertension, dislipemia, peripheral artery disease, anemia, MDRD-4 < 60 ml/min/1.73 m2, multivessel coronary artery disease, complete revascularization, and beta-blocker

Table 2
Characteristics of patients by type of P2Y12 platelet inhibitor used.

Variable	Clopidogrel (n = 3530)	Prasugrel (n = 252)	Ticagrelor (n = 459)	P-value
Age, years	65.4 ± 13.5	59.4 ± 10.3	58.2 ± 10.5	< 0.001
Female sex, %	23.7	17.9	17.2	0.001
Body mass index, kg/m^2	28.2 ± 4.3	28.8 ± 4.3	28.1 ± 4.7	0.088
Active smoking, %	36.5	45.2	52.1	< 0.001
Hypertension, %	64.3	54.4	48.1	< 0.001
Diabetes, %	23.0	52.0	15.5	< 0.001
Dislipemia, %	66.3	72.2	68.8	0.100
Peripheral artery disease, %	10.0	5.2	3.7	< 0.001
Prior heart failure, %	2.8	1.2	0.7	0.007
Chronic obstructive pulmonary disease, %	9.5	8.7	4.8	0.004
HIV infection, %	0.6	0.4	0.4	0.853
ACS type, %				< 0.001
UA	9.5	5.6	6.3	
NSTEMI	46.7	29.0	35.9	
STEMI	43.8	65.5	57.7	
Killip class ≥2, %	13.8	11.5	7.0	< 0.001
Atrial fibrillation, %	9.5	4.4	2.2	< 0.001
LVEF ≤40%	14.4	17.9	12.2	0.119
Anemia, %	15.6	11.9	5.7	< 0.001
MDRD-4 < 60 ml/min/1.73 m2, %	24.0	18.3	6.8	< 0.001
Multivessel coronary artery disease, %	51.4	53.6	37.7	< 0.001
PCI, %	87.4	95.6	92.8	< 0.001
Drug eluting stent, %	76.1	86.5	86.5	< 0.001
CABG, %	1.6	0.4	0.2	0.026
Complete revascularization, %	79.4	71.8	67.1	< 0.001
DAPT duration, months	14.1 ± 13.4	12.9 ± 8.8	11.6 ± 4.8	< 0.001
Beta-blocker, %	80.7	91.3	83.7	< 0.001
ACEI/ARB, %	67.6	65.1	65.6	0.511
Spironolactone, %	7.1	8.7	5.9	0.360
Statin, %	95.0	97.2	97.6	0.016

ACEI/ARB: Angiotensin Converting Enzyme Inhibitors/Angiotensin Receptor Blockers; ACS: Acute Coronary Syndrome; CABG: Coronary Artery Bypass Graft; DAPT: Dual Antiplatelet Therapy; HIV: Human Immunodeficiency Virus; LVEF: Left Ventricular Ejection Fraction; MDRD-4: Modification of Diet in Renal Disease (MDRD) equation version 4; NSTEMI: Non ST-segment Elevation Myocardial Infarction; PCI: Percutaneous Coronary Intervention; STEMI: ST-segment Elevation Myocardial Infarction; UA: Unstable Angina.

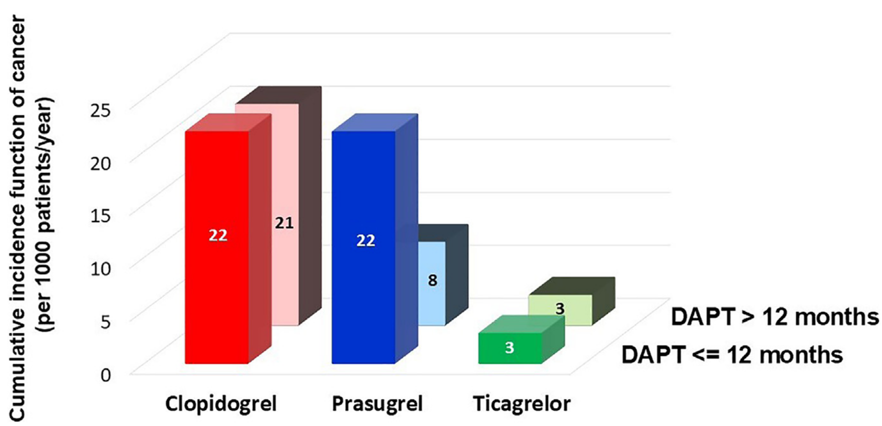

Fig. 2. Cumulative incidence function (per 1000 patients/year) according to the type and duration of dual antiplatelet therapy (DAPT).

therapy), and for other variables with known biological plausibility (smoking, HIV infection, DAPT duration), we have found that ticagrelor resulted associated with lower follow-up cancer risk than clopidogrel (sHR 0.20: 95% IC 0.05–0.84; p = 0.028), without differences between prasugrel and clopidogrel (Table 3). Fig. 4 shows the adjusted cumulative incidence function of cancer for the three P2Y12 inhibitors, with lower rates of cancer among patients with DAPT with ticagrelor. These results were maintained even after excluding cancers detected in the first 1 year after DAPT (see Supplementary data).

2.5. Propensity score analysis for ticagrelor vs clopidogrel/prasugrel

After including the PS to receive ticagrelor in the same previously described multivariate analysis, DAPT with ticagrelor resulted associated with lower follow-up cancer risk (sHR for ticagrelor vs clopidogrel/prasugrel 0.22, 95% CI 0.05–0.91; p = 0.035). Even after adjusting for the IPW, ticagrelor continued to be associated with lower cancer risk (sHR 0.22, 95% CI 0.05–0.87; p = 0.031). Using a PS matching, we obtained two similar groups of 455 patients: one with DAPT with ticagrelor, another one with DAPT with clopidogrel/prasugrel. In this matched population, DAPT with ticagrelor was also associated with lower incidence of new cancer in comparison with DAPT with clopidogrel/prasugrel (sHR 0.22; 95% CI 0.05–0.90; p = 0.036) [Supplementary data].

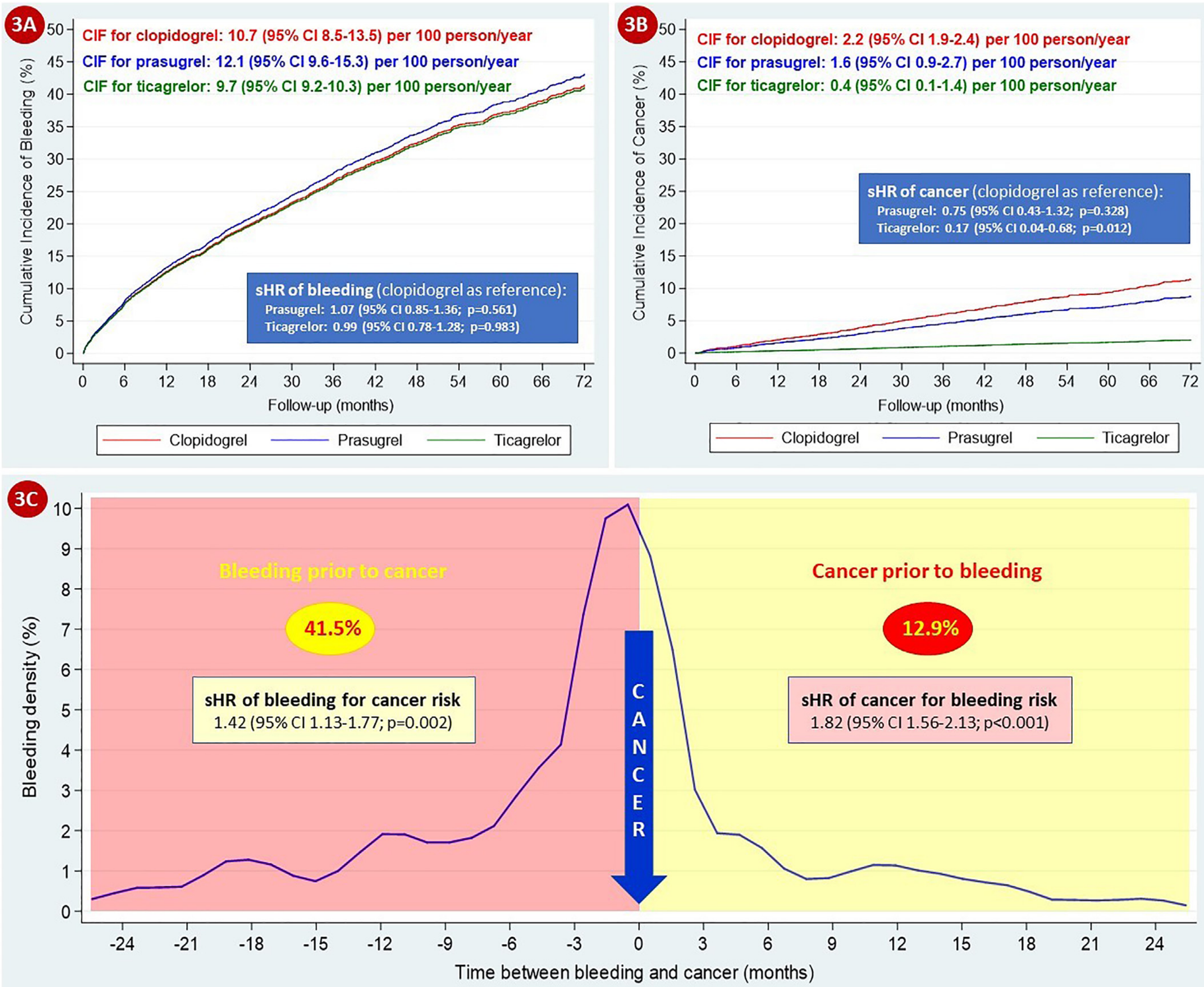

Fig. 3. Relationship between cancer, bleeding and type of dual antiplatelet therapy (DAPT). 3A) Cumulative incidence function (CIF) for bleeding according to type of DAPT. 3B) CIF for cancer according to type of DAPT. 3C) Temporal relation between follow-up bleeding and cancer.

Table 3
Competing risk multivariate analysis for new follow-up cancer using a flexible parametric survival model.

Variable	sHR	95% CI	P-value
Age (per decade)	1.55	1.39–1.73	< 0.001
Female sex	0.55	0.41–0.77	< 0.001
Active smoking	1.45	1.11–1.89	0.007
Hypertension	0.91	0.70–1.19	0.495
Dislipemia	1.29	1.01–1.68	0.047
Peripheral artery disease	1.67	1.22–2.29	0.001
HIV infection	2.11	0.61–7.26	0.235
Anemia	1.17	0.87–1.59	0.296
MDRD-4 < 60 ml/min/1.73 m2	1.08	0.83–1.42	0.546
Multivessel coronary artery disease	1.12	0.89–1.42	0.329
Complete revascularization	1.07	0.79–1.47	0.651
Beta-blocker	0.85	0.66–1.11	0.247
P2Y12 inhibitor (clopidogrel as reference)			
Prasugrel	0.89	0.51–1.56	0.696
Ticagrelor	0.20	0.05–0.84	0.028
DAPT duration	0.99	0.99–1.01	0.172

DAPT: Dual Antiplatelet Therapy; HIV: Human Immunodeficiency Virus; MDRD-4: Modification of Diet in Renal Disease (MDRD) equation version 4.

3. Discussion

Basing on our knowledge, this is the first study to provide a direct comparison about the cancer risk between the different P2Y12 inhibitors in "real world" patients treated with DAPT after an ACS. Our report goes a step further by showing that ticagrelor could be associated with lower follow-up cancer incidence than DAPT with clopidogrel or prasugrel after an ACS.

Several findings deserve special attention. First, the cumulative incidence function of cancer was low, 2.1 per 100 people per year. This was consistent with the annual cancer rate previously reported in prior studies, which ranges between 1.5 and 3% [7,10,13]. Second, the most frequent locations were the urinary (18%), lung (15.8%) and colorectal (14.1%), and prostate in males (14.1%). With the exception of urinary cancer -that showed a higher rate in our study in comparison with prior studies-, the rates of lung and colorectal cancer were similar to those previously described in the TRILOGY-ACS trial [13] (14.4% lung, 12.5% colorectal, 12.7% prostate), and in the recent study of Leader et al. [7] (13.7% colorectal, 7.4% lung). Third, there was a strong interrelation between cancer and bleeding, which was concordant with prior reports [18,19]. In our study, the peak of bleeding rate coincided with the date of cancer diagnosis, which suggested that many cancers

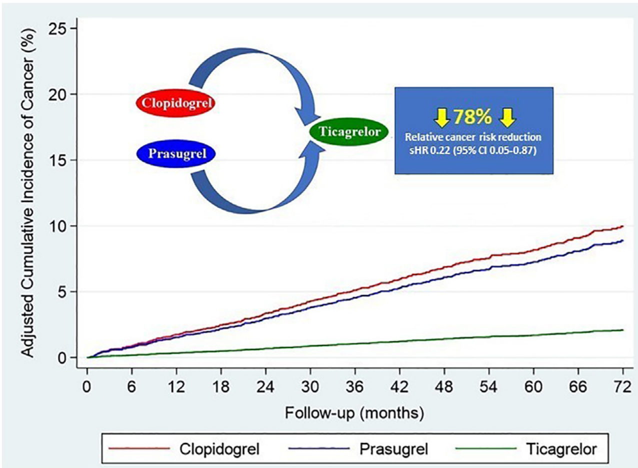

Fig. 4. Cumulative incidence function for new cancer and risk by type of dual antiplatelet therapy.

were diagnosed in relation to a bleeding episode. In an unadjusted way, we have seen that people with a bleeding event have up to 42% more risk of being diagnosed of cancer than those who have not bled. Moreover, after the diagnosis of cancer, there is a higher risk of bleeding (in an unadjusted way, 82% more risk of bleeding than those without cancer).

In relation with DAPT therapy and de novo cancer risk, we have not observed differences regarding to DAPT duration. In spite of the alarm that had been generated with the results of the DAPT study [9], subsequent studies had presented results similar to ours [7,18,20], without finding higher rates of cancer when DAPT extended beyond the first year. More interesting, we have reported a significant difference between DAPT with ticagrelor and DAPT with prasugrel or clopidogrel. In the PLATO, DAPT with ticagrelor in comparison with DAPT with clopidogrel was associated with less new diagnosis cancer incidence, however, the difference was not relevant [14]. And in the substudy of TRILOGY-ACS have confirmed that there are not differences in cancer diagnosis after ACS between clopidogrel and prasugrel [13]. In our study, there was a significant difference in the incidence of cancer between patients treated with clopidogrel and prasugrel (CIF 2.2 and 2.1 per 100 person/year, respectively) vs ticagrelor (CIF 0.3 per 100 person/year), and this lower CIF of cancer with ticagrelor was independently of DAPT duration. After adjusting by confounding variables, we reported a relative risk difference of 78% in cancer rate at 72 months in favour of ticagrelor.

The findings of our study regarding type of DAPT and cancer risk are biologically plausible in view of a handful of recent studies that have proved a relation between adenosine and cancer [21] (Fig. 5). Unlike the clopidogrel and prasugrel, ticagrelor is not a thienopyridine, but rather belongs to a new class of P2Y12 receptor inhibitors known as cyclopentyl-triazolo-pyrimides, with certain characteristics that make it unique. This drug is a very selective antagonist for the P2Y12 receptor on platelets and binds reversibly and directly to this receptor without any need for bioactivation [22]. Several studies consistently showed that ticagrelor inhibits the cellular uptake of adenosine, in addition to antagonizing the P2Y12 receptor [23]. This additional effect of ticagrelor beyond P2Y12R antagonism was in part as a consequence of ticagrelor inhibiting the equilibrative nucleoside transporter 1 (ENT1) on platelets, leading to accumulation of extracellular adenosine and activation of G-coupled adenosine receptors [24]. Adenosine exerts its biological effects by interacting with 4 G-protein–coupled receptors: A1R and A3R are coupled to Gi, the inhibitory G protein, which inhibits adenylyl cyclase and thus decreases intracellular cAMP, whereas A2AR and A2BR are coupled to the stimulatory G protein, Gs, which stimulates adenylyl cyclase, increasing intracellular cAMP [25]. The A1 and A3 receptors have high affinity for adenosine, whereas the A2A receptors has a lower affinity (the A2BR a much lower affinity) [22]. Basing on this, low concentrations of adenosine, which activate A1R and A3R, promote neutrophil chemotaxis and phagocytosis, whereas high concentrations of adenosine, which activate A2R, inhibit neutrophil trafficking, granule release, and the production of reactive oxygen species and inflammatory mediators [26]. The rise in extracellular adenosine observed in patients treated with ticagrelor leads to an increase in intracellular levels of cAMP, that activate specific intracellular proteins, such as protein kinase A and protein kinase G, which phosphorylate proteins that regulate different physiological processes, e.g. transcription factors and ion channels, resulting in diverse biological effects [25]. Higher levels of cAMP, either by stimulating its formation or by preventing its degradation, inhibit pro-inflammatory cytokines, e.g. TNF-α and IL-1β, together with a significant number of factors that stimulate cancer cell proliferation and survival, including transforming growth factor b1 and platelet-derived growth factor, which are involved in the promotion of epithelial-mesenchymal transition (EMT), migration and metastasis formation [27]. So the increase in extracellular adenosine levels secondary to the inhibition by ticagrelor of the cellular uptake of adenosine leads to a downregulation of relevant transcription factors involved in the EMT process [28]. Several studies have proved that ticagrelor specifically inhibited tumor cell platelet interactions and decreased tumor cell adhesion by acting primarily on platelets [29], underscoring a potential clinical use of this agent in cancer therapy in the future. In rodent models of ovarian cancer, ticagrelor -given by daily gavage- reduced the growth of primary tumors [30]. Moreover, ticagrelor treatment was also associated with a marked reduction in tumor cell-platelet aggregates in the lungs [5]. This could explain, at least in part, the lower cancer rate that we observed with ticagrelor in comparison with prasugrel/clopidogrel after ACS in patients treated with DAPT.

4. Limitations

This is a retrospective nonrandomized study, and the observational nature of the analysis entails the obvious limitations. In this way, some risk factors for cancer, such as diet, occupation, and family history, were not registered in this cohort, and residual confounding is probable. Therefore, it remains a possibility that these and other unknown factors may have mediated the impressive decrease in cancer incidence seen with combined antiplatelet therapy with clopidogrel/prasugrel, rather than a true drug effect. Nevertheless, most major risk factors were registered and accounted for in multivariate analysis, and propensity scoring and instrumental variable analysis adjusted for confounding by indication. Moreover, our study was not designed to assess the short-term effect of DAPT on cancer incidence. In this sense, patients were not included in a cancer screening program prior to the start of the DAPT. In addition to this, the risk of missing cancer diagnoses during follow-up is a real possibility given the retrospective nature of the design. Finally, although findings were statistically significant, the small sample size and number of events are a potential limitation, and confirmation with a larger cohort may be warranted.

5. Conclusions

In patients treated with DAPT after ACS, ticagrelor seems to be associated with lower incidence of de novo cancer during follow-up in comparison with prasugrel and clopidogrel, irrespective of DAPT duration. Further studies are needed to confirm our results. The current findings call for a better understanding of shared risk factors and underlying mechanisms.

Declaration of interest

None.

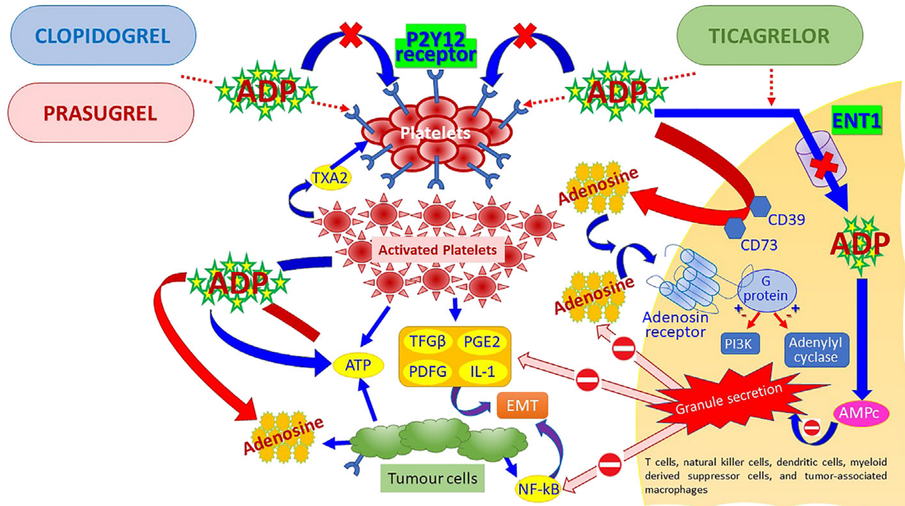

Fig. 5. Effects of antagonism of P2Y12 receptors and of inhibition of equilibrative nucleoside transporter 1 (ENT1) on the development of cancers.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2018.12.014.

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