

ORIGINAL RESEARCH

Major Adverse Cardiovascular Events in Patients With Renal Cell Carcinoma Treated With Targeted Therapies



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ABSTRACT

BACKGROUND The risk for major adverse cardiovascular events (MACE) with targeted therapies for patients with advanced renal cell carcinoma (RCC) in real-world practice remains unclear.

OBJECTIVES The aim of this study was to compare the risk for MACE associated with targeted cancer therapies with that associated with cytokine treatment in patients with advanced RCC.

METHODS Using Taiwan's National Health Insurance Research Database, a retrospective nationwide cohort study was conducted involving patients with advanced RCC who had received targeted therapy (sunitinib, sorafenib, pazopanib, everolimus, or temsirolimus) or cytokine therapy (interleukin-2 or interferon gamma) from 2007 to 2018. Cox proportional hazards models were used to estimate the risk for MACE (a composite of myocardial infarction, ischemic stroke, heart failure, and cardiovascular death) in the cohort using the propensity score method of stabilized inverse probability of treatment weighting.

RESULTS In this cohort of 2,785 patients with advanced RCC, 2,257 (81%) and 528 (19%) had received targeted and cytokine therapy, respectively. After stabilized inverse probability of treatment weighting, the incidence rates of MACE were 6.65 and 3.36 per 100 person-years in the targeted and cytokine therapy groups, respectively (HR: 1.80; 95% CI: 1.19-2.74). Baseline history of heart failure (HR: 3.88; 95% CI: 2.25-6.71), atrial fibrillation (HR: 3.60; 95% CI: 2.16-5.99), venous thromboembolism (HR: 2.50; 95% CI: 1.27-4.92), ischemic stroke (HR: 1.88; 95% CI: 1.14-3.11), and age \geq 65 years (HR: 1.81; 95% CI: 1.27-2.58) were independent risk factors for targeted therapy-associated MACE.

CONCLUSIONS Among patients with advanced RCC, the risk for MACE associated with targeted cancer therapy is higher than that associated with cytokine therapy. (J Am Coll Cardiol CardioOnc 2022;4:223-234) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

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**ABBREVIATIONS
AND ACRONYMS****CV** = cardiovascular**GBM** = generalized boosted model**MACE** = major adverse cardiovascular event(s)**mTOR** = mechanistic target of rapamycin**NHIRD** = National Health Insurance Research Database**RCC** = renal cell carcinoma**sIPTW** = stabilized inverse probability of treatment weighting**TKI** = tyrosine kinase inhibitor**VEGF** = vascular endothelial growth factor**VEGFR** = vascular endothelial growth factor receptor

Renal cell carcinoma (RCC) accounts for approximately 2% of cancer diagnoses and deaths worldwide, and this percentage is projected to increase.¹ Targeted cancer therapies, including tyrosine kinase inhibitors (TKIs) with anti-vascular endothelial growth factor (VEGF) activity and mechanistic target of rapamycin (mTOR) inhibitors are first-line treatments for advanced or metastatic RCC. Although they are highly effective in improving survival, treatment-related adverse events are an important consideration when prescribing these drugs. VEGF receptor (VEGFR) TKIs have been linked to hypertension,^{2,3} arterial thromboembolic events,⁴⁻⁶ and heart failure.⁷ The relative risk for adverse cardiovascular (CV) effects with these VEGFR TKIs has been shown to range between 1.38 and 22.7, with the strongest associations with hyper-

tension. By contrast, reports of CV events associated with the use of mTOR inhibitors in patients with advanced RCC are less common. One observational study that evaluated targeted therapy-associated CV toxicity in 159 patients with advanced RCC revealed that patients who received mTOR inhibitors frequently experienced adverse CV events.⁸ With the increasing use of these drugs among patients with advanced RCC, further characterization of targeted therapy-associated major adverse CV events (MACE) and identification of high-risk groups is necessary. In light of this, we used the Taiwan National Health Insurance Research Database (NHIRD) to conduct a nationwide cohort study to estimate the incidence of MACE and identify high-risk groups among patients with advanced RCC treated with targeted therapies, namely, VEGFR TKIs and mTOR inhibitors.

METHODS

DATA SOURCE. The Taiwan Cancer Registry is a national database maintained by the Ministry of Health and Welfare that has prospectively collected newly diagnosed cancer cases from hospitals with 50 or more beds since 1979. The quality of the cancer registry is longitudinally monitored by a review board, with a verified diagnosis rate of 97.6% through histologic or cytologic examinations.⁹ Patient

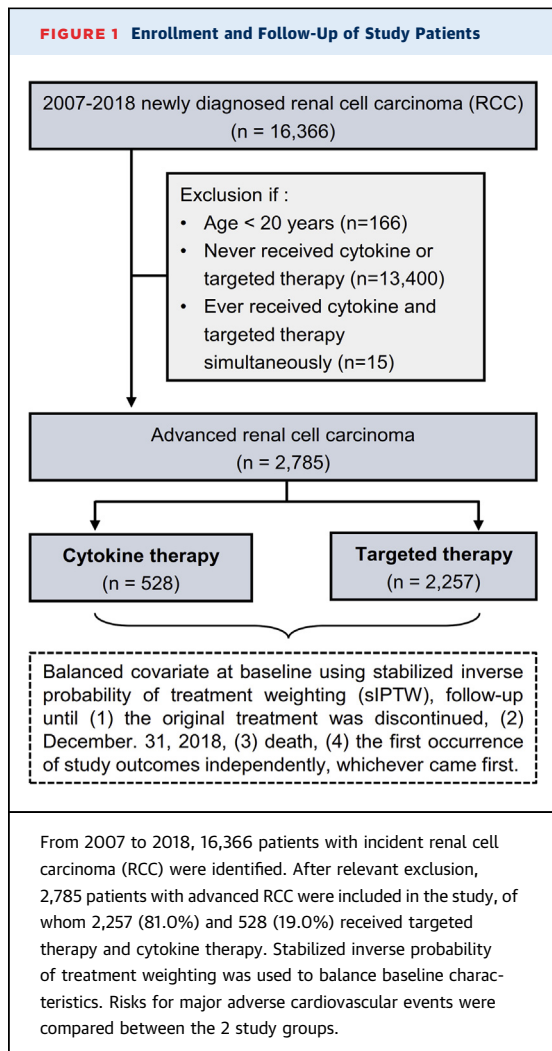
demographics and tumor characteristics, including tumor staging, histology, and grade, are recorded in the database. Taiwan's NHIRD and National Death Registry were previously described.¹⁰ By linking the Taiwan Cancer Registry, NHIRD, and National Death Registry using patients' encrypted IDs, we were able to obtain longitudinal data on patients with newly diagnosed cancer from their initial diagnosis to their primary treatment and subsequent treatment course until any outcomes of interest or death. The Institutional Review Board of Chang Gung Medical Foundation reviewed our research protocol and determined that it was exempt from review (201901029B1).

STUDY POPULATION AND TREATMENT GROUPS. We identified patients with newly diagnosed RCC (International Classification of Diseases-9th Revision code 189, International Classification of Diseases-10th Revision code C64) from the Taiwan Cancer Registry between January 1, 2007, and December 31, 2018. We excluded patients who had never received cytokine or targeted therapy or who had ever received cytokine and targeted therapy simultaneously. A flow-chart of patient inclusion and exclusion is presented in [Figure 1](#). Patients who had received interleukin-2 or interferon gamma were classified as the cytokine group, whereas those who had received targeted drugs, including sunitinib, sorafenib, pazopanib, temsirolimus, and everolimus, were in the targeted drug group. The Anatomical Therapeutic Chemical codes for these drugs are listed in [Supplemental Table 1](#).

STUDY DESIGN, OUTCOMES, AND COVARIATES. We used a retrospective nationwide cohort design. The date of initial prescription of cytokines or targeted drugs was assigned as the index date. Patients were followed from the index date until they discontinued cytokines or targeted drugs, the first occurrence of any of the study outcomes, death, or the end of follow-up (ie, December 31, 2018). The study outcomes comprised myocardial infarction, ischemic stroke, heart failure, and CV death. All study outcomes were required to be principal discharge diagnoses to avoid misclassification ([Supplemental Table 2](#)). The same patient may have had more than 1 study outcome; hence, the composite of MACE is based on the study outcome that first occurred during the study duration. The accuracy of diagnosis codes of these CV outcomes has been validated in previous

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

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NHIRD studies, with high positive predictive values.^{11,12} We considered numerous comorbidities related to MACE, namely, coronary artery disease, diabetes, hypertension, hyperlipidemia, chronic kidney disease, alcoholism, venous thromboembolism, peripheral arterial disease, atrial fibrillation, chronic obstructive pulmonary disease, liver cirrhosis, and osteoporosis. The comorbidities were obtained using International Classification of Diseases-Ninth Revision and International Classification of Diseases-Tenth Revision codes (Supplemental Table 2). Various medications related to CV diseases, including aspirin, P2Y₁₂ inhibitors, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta-blockers, statins, metformin, dipeptidyl peptidase 4 inhibitors, and sodium-glucose cotransporter protein-2 inhibitors, were also considered in this study (Supplemental Table 1).

STATISTICAL ANALYSIS. We used the propensity score method of stabilized inverse probability of

treatment weighting (sIPTW) to ensure a similar distribution of baseline characteristics between the two treatment groups.¹³ The main advantage of sIPTW is that it allows researchers to estimate the average treatment effect for the population with a designated type I error while maintaining the original sample size.¹⁴ We used the generalized boosted model (GBM) to obtain the propensity scores for sIPTW. GBM estimation involves an iterative process with multiple regression trees to capture complex and nonlinear relationships between the study groups and pretreatment covariates without overfitting the data.¹⁵ All the covariates listed in Table 1 were included in the GBM. We trimmed the propensity score data with no or minimal overlap between the 2 study groups to minimize residual confounding.¹⁶ We used the absolute standardized mean difference to examine the balance of baseline characteristics between the groups.¹⁷ An absolute standardized mean difference ≤ 0.1 indicated a nonsignificant clinical difference in baseline characteristics between the groups.¹⁸

The incidence rates of the study outcomes were the total number of study outcomes during the follow-up period divided by the sum of the patients' follow-up times in person-years. The cumulative incidence was plotted using the method of Fine and Gray, accounting for the competing risk for noncardiac death. Both the Cox proportional hazards model and the Fine and Gray subdistribution hazard model were used to compare the risk for the study outcomes among the cancer therapy groups.¹⁹ Only the cancer therapy grouping was included in the Cox model or Fine and Gray model, because the 2 groups were well balanced in baseline characteristics after sIPTW.²⁰ The Kolmogorov-type supremum test of Schoenfeld residuals was used to evaluate for the proportional hazards assumption in the Cox model and Fine and Gray model.²¹ All P values of the Kolmogorov-type supremum test were >0.05 , indicating no violation of proportional hazards. The HRs of the study outcomes in the targeted therapy group relative to the cytokine group and their respective CIs were calculated according to the Cox model. Given the high cancer mortality rate of patients with advanced RCC, we used a cause-specific hazard model to account for the competing risk for noncardiac death to estimate the subdistribution HRs.²² Subgroup analyses using forest plots were performed to determine whether the risks of the targeted therapy group relative to the cytokine group were maintained under different conditions.²³ We performed sIPTW for each subgroup analysis to ensure a balance between the groups' baseline characteristics.

TABLE 1 Baseline Demographics and Clinical Characteristics								
	Before siPTW^a				After siPTW^a			
	Total (N = 2,785)	Cytokine Therapy (n = 528)	Targeted Therapy (n = 2,257)	ASMD^b	Total (N = 2,713)	Cytokine Therapy (n = 471)	Targeted Therapy (n = 2,242)	ASMD^b
Sex				0.032				0.011
Female	733 (26.32)	145 (27.46)	588 (26.05)		712 (26.23)	122 (25.84)	590 (26.32)	
Male	2,052 (73.68)	383 (72.54)	1,669 (73.95)		2,001 (73.77)	349 (74.16)	1,652 (73.68)	
Age at index date, y								
Median (IQR)	63 (17)	59 (18)	64 (18)		63 (17)	61 (19)	63 (18)	
20-64	1,530 (54.94)	340 (64.39)	1,190 (52.72)	0.228	1,501 (55.33)	275 (58.40)	1,226 (54.69)	0.074
65-74	704 (25.28)	113 (21.40)	591 (26.19)		681 (25.11)	113 (23.96)	568 (25.36)	
75-84	444 (15.94)	63 (11.93)	381 (16.88)		431 (15.88)	71 (15.10)	360 (16.05)	
≥85	107 (3.84)	12 (2.27)	95 (4.21)		100 (3.67)	12 (2.54)	88 (3.91)	
Urbanization				0.101				0.026
Urban area	806 (28.94)	152 (28.79)	654 (28.98)		779 (28.71)	132 (27.97)	647 (28.86)	
Suburban area	826 (29.66)	169 (32.01)	657 (29.11)		808 (29.77)	146 (30.97)	662 (29.52)	
Rural area	1,058 (37.99)	185 (35.04)	873 (38.68)		1,037 (38.22)	179 (37.94)	858 (38.28)	
Not specified	95 (3.41)	22 (4.17)	73 (3.23)		89 (3.30)	14 (3.11)	75 (3.34)	
Monthly income, NTD				0.128				<0.001
Dependent	939 (33.72)	160 (30.30)	779 (34.51)		918 (33.84)	162 (34.34)	756 (33.74)	
<15,000	617 (22.15)	110 (20.83)	507 (22.46)		604 (22.26)	104 (22.11)	500 (22.29)	
15,000-24,999	712 (25.57)	154 (29.17)	558 (24.72)		685 (25.25)	119 (25.19)	566 (25.26)	
≥25,000	517 (18.56)	104 (19.70)	413 (18.30)		506 (18.65)	86 (18.36)	420 (18.71)	
EC ^c				0.154				0.056
1	208 (7.47)	36 (6.82)	172 (7.62)		201 (7.39)	33 (6.86)	168 (7.51)	
2	839 (30.13)	138 (26.14)	701 (31.06)		820 (30.24)	138 (29.36)	682 (30.43)	
3	991 (35.58)	218 (41.29)	773 (34.25)		956 (35.25)	167 (35.50)	789 (35.19)	
4	747 (26.82)	136 (25.76)	611 (27.07)		736 (27.12)	133 (28.28)	603 (26.87)	
Charlson comorbidity score								
Median (IQR)	3 (3)	3 (4)	3 (3)		3 (3)	3 (3)	3 (3)	
0	230 (8.26)	44 (8.33)	186 (8.24)	0.151	229 (8.43)	35 (7.44)	194 (8.64)	0.089
1 or 2	897 (32.21)	198 (37.50)	699 (30.97)		884 (32.58)	165 (34.96)	719 (32.08)	
≥3	1,658 (59.53)	286 (54.17)	1,372 (60.79)		1,600 (58.99)	271 (57.60)	1,329 (59.29)	
Combined nephrectomy	1,394 (50.05)	252 (47.73)	1,142 (50.60)	0.057	1,361 (50.17)	231 (49.07)	1,130 (50.40)	0.027
Myocardial infarction	63 (2.26)	7 (1.33)	56 (2.48)	0.085	59 (2.16)	8 (1.64)	51 (2.27)	0.047
Ischemic stroke	147 (5.28)	24 (4.55)	123 (5.45)	0.042	142 (5.25)	24 (5.13)	118 (5.27)	0.007
Heart failure	64 (2.30)	7 (1.33)	57 (2.53)	0.087	60 (2.19)	7 (1.40)	53 (2.36)	0.072
Coronary artery disease	228 (8.19)	30 (5.68)	198 (8.77)	0.120	215 (7.92)	32 (6.74)	183 (8.17)	0.056
Diabetes mellitus	1,028 (36.91)	172 (32.58)	856 (37.93)	0.112	988 (36.40)	165 (35.08)	822 (36.68)	0.034
Hypertension	1,897 (68.11)	328 (62.12)	1,569 (69.52)	0.156	1,842 (67.88)	312 (66.15)	1,530 (68.25)	0.046
Hyperlipidemia	1,316 (47.25)	208 (39.39)	1,108 (49.09)	0.196	1,277 (47.07)	213 (45.11)	1,064 (47.48)	0.049
Chronic kidney disease	606 (21.76)	85 (16.10)	521 (23.08)	0.177	582 (21.44)	90 (19.05)	492 (21.95)	0.074
Alcoholism	21 (0.75)	2 (0.38)	19 (0.84)	0.060	21 (0.77)	3 (0.72)	17 (0.77)	0.006
Venous thromboembolism	85 (3.05)	10 (1.89)	75 (3.32)	0.090	81 (2.98)	11 (4.11)	70 (3.13)	0.057
Peripheral arterial disease	14 (0.50)	1 (0.19)	13 (0.58)	0.063	13 (0.48)	1 (0.35)	12 (0.54)	0.058
Atrial fibrillation	57 (2.05)	7 (1.33)	50 (2.22)	0.068	53 (1.97)	7 (1.38)	47 (2.09)	0.056
Osteoporosis	45 (1.62)	10 (1.89)	35 (1.55)	0.026	46 (1.71)	11 (2.38)	35 (1.57)	0.061
COPD	67 (2.41)	12 (2.27)	55 (2.44)	0.011	65 (2.41)	13 (2.68)	53 (2.36)	0.021
Liver cirrhosis	74 (2.66)	17 (3.22)	57 (2.53)	0.042	71 (2.62)	14 (2.94)	57 (2.55)	0.025
Coronary intervention ^d	137 (4.92)	17 (3.22)	120 (5.32)	0.104	129 (4.77)	19 (4.10)	110 (4.91)	0.040

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We performed a univariable analysis by using the Cox model to identify the risk factors significantly associated with MACE among the targeted therapy group. A Cox multivariable regression model with the significant covariates in univariable analysis was conducted to obtain the adjusted HRs.

To compare the incidence of MACE among the patients receiving different targeted therapies, we used a Cox model to obtain the HRs for the 4 types of targeted therapy using sunitinib as a reference group. The significance level was set at $P < 0.05$.

TABLE 1 Continued

	Before sIPTW ^a				After sIPTW ^a			
	Total (N = 2,785)	Cytokine Therapy (n = 528)	Targeted Therapy (n = 2,257)	ASMD ^b	Total (N = 2,713)	Cytokine Therapy (n = 471)	Targeted Therapy (n = 2,242)	ASMD ^b
Drug prescribed within 30 d of index date								
Aspirin	358 (12.85)	61 (11.55)	297 (13.16)	0.049	348 (12.84)	63 (13.35)	285 (12.73)	0.019
P2Y ₁₂ inhibitor ^c	115 (4.13)	13 (2.46)	102 (4.52)	0.112	111 (4.09)	16 (3.47)	94 (4.21)	0.040
ACE inhibitors or ARBs	768 (27.58)	122 (23.11)	646 (28.62)	0.126	744 (27.41)	125 (26.43)	619 (27.62)	0.028
Beta-blockers	674 (24.20)	122 (23.11)	552 (24.46)	0.032	648 (23.89)	108 (22.87)	540 (24.11)	0.030
Calcium channel blockers	603 (21.65)	155 (29.36)	448 (19.85)	0.222	581 (21.42)	105 (22.25)	476 (21.24)	0.025
Diuretic agents	787 (28.26)	137 (25.95)	650 (28.80)	0.064	762 (28.10)	126 (26.67)	637 (28.40)	0.040
Statins	329 (11.81)	34 (6.44)	295 (13.07)	0.225	310 (11.44)	43 (9.15)	267 (11.92)	0.093
Insulin	359 (12.89)	50 (9.47)	309 (13.69)	0.132	344 (12.67)	52 (10.97)	292 (13.03)	0.065
Metformin	285 (10.23)	54 (10.23)	231 (10.23)	<0.001	269 (9.92)	46 (9.77)	223 (9.95)	0.006
Sulfonylurea	322 (11.56)	62 (11.74)	260 (11.52)	0.007	299 (11.03)	48 (10.16)	251 (11.22)	0.035
Thiazolidinedione	37 (1.33)	12 (2.27)	25 (1.11)	0.090	31 (1.15)	5 (1.09)	26 (1.16)	0.007
DPP-4 inhibitors	209 (7.50)	12 (2.27)	197 (8.73)	0.286	198 (7.32)	27 (5.64)	172 (7.67)	0.084
SGLT-2 inhibitors	10 (0.36)	0 (0.00)	10 (0.44)	0.094	9 (0.32)	0 (0.00)	9 (0.39)	0.089

Values are n (%) unless otherwise indicated. ^aAll covariates listed were used to calculate the propensity score. ^bAn ASMD of ≤ 0.1 indicates a nonsignificant difference. ^cEC 1: civil servants and full-time or regularly paid personnel in governmental agencies and public schools; EC 2: employees of privately owned enterprises or institutions; EC 3 self-employed, other employees or paid personnel, and members of the farmers' or fishers' association; EC 4: members of low-income families, military service members, and veterans. ^dPercutaneous coronary intervention or coronary bypass surgery. ^eClopidogrel or ticagrelor.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ASMD = absolute standardized mean difference; COPD = chronic obstructive pulmonary disease; DPP-4 = dipeptidyl peptidase 4; EC = enrollee category; NTD = new Taiwan dollars; sIPTW = stabilized inverse probability of treatment weighting; SGLT-2 = sodium glucose cotransporter protein-2.

To conduct a more focused analysis on the cardiotoxicity of VEGFR TKIs, we performed a sensitivity analysis excluding mTOR inhibitors. sIPTW was also conducted on this new cohort. In addition, Cox proportional hazards models were used to obtain the HRs for MACE between the cytokine and targeted therapy groups. We used R version 3.6.3 (R Foundation for Statistical Computing) for GBM, and the rest of the statistical analyses were conducted using SAS version 9.4 (SAS Institute).

RESULTS

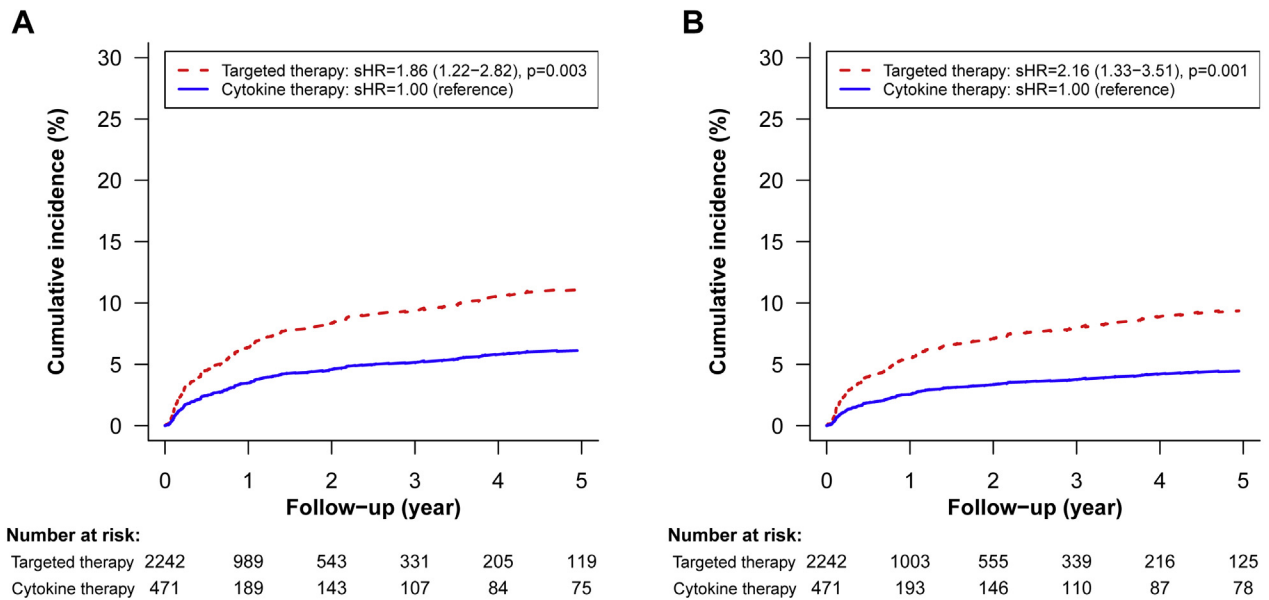
COHORT CHARACTERISTICS. From 2007 to 2018, 16,366 patients with incident RCC were identified

(Figure 1). A total of 13,400 patients were excluded because they had not received cytokine or targeted therapy. We also excluded patients <20 years of age (n = 166) and patients who had received both cytokine and targeted therapy simultaneously (n = 15). Ultimately, 2,785 patients with incident RCC were included in the study, of whom 2,257 (81.0%) and 528 (19.0%) received targeted and cytokine therapy, respectively. Most patients (73%) were men, and the median age at index date was 63 years (IQR: 17 years). The patients in the cytokine group were generally younger at their respective index dates than were those in the targeted therapy group. Only small differences in other baseline characteristics were identified between the groups before sIPTW; after sIPTW,

TABLE 2 Clinical Outcomes After Stabilized Inverse Probability of Treatment Weighting

	Incidence (95% CI) per 100 Person-Years		Cox Analysis With Cytokine as Reference		Competing Risk Analysis With Cytokine as Reference	
	Cytokine Therapy (n = 471)	Targeted Therapy (n = 2,242)	HR (95% CI)	P Value	sHR (95% CI)	P Value
MACE	3.36 (2.04-4.68)	6.65 (5.74-7.56)	1.80 (1.19-2.74)	0.005	1.86 (1.22-2.82)	0.003
Myocardial infarction	0.30 (0.04-0.91)	0.41 (0.18-0.63)	1.31 (0.31-5.48)	0.71	1.28 (0.31-5.31)	0.73
Ischemic stroke	0.36 (0.07-1.02)	0.77 (0.46-1.07)	2.05 (0.58-7.26)	0.26	1.98 (0.56-7.02)	0.29
Heart failure	0.53 (0.14-1.27)	0.82 (0.50-1.14)	1.33 (0.46-3.82)	0.59	1.42 (0.49-4.08)	0.51
CV death	2.41 (1.30-3.52)	5.55 (4.72-6.37)	2.10 (1.29-3.41)	0.002	2.16 (1.33-3.51)	0.001
All-cause mortality	43.02 (38.33-47.71)	49.12 (46.67-51.58)	1.00 (0.89-1.13)	0.97	—	—

A Cox proportional hazards model censored at death was used to estimate a cause-specific hazard, while subdistribution HRs were estimated using the method of Fine and Gray. CV = cardiovascular; MACE = major adverse cardiovascular events; sHR = subdistribution hazard ratio.

FIGURE 2 Fine and Gray Cumulative Incidence Rates of MACE and CV Death

After adjustment for competing risk events (noncardiovascular deaths), the risks for **(A)** major adverse cardiovascular events (MACE) and **(B)** cardiovascular (CV) death were consistently higher in the targeted therapy group than in the cytokine therapy group. sHR = subdistribution hazard ratio.

no statistically significant differences in demographics, comorbidities, or medications at baseline were identified between the groups. The patient characteristics are presented in [Table 1](#). The sample sizes of the groups were slightly smaller after sIPTW than before sIPTW. The histologic information of RCC is shown in [Supplemental Table 3](#).

TEMPORAL TRENDS AND TREATMENT DURATION OF CYTOKINE AND TARGETED THERAPY. The rates of cytokine and targeted therapy use in different periods are shown in [Supplemental Figure 1](#). After 2009, the rate of cytokine use decreased gradually, whereas that of targeted therapy increased progressively. The treatment durations of cytokine and targeted therapy are summarized in [Supplemental Table 4](#). The majority of patients received either cytokine therapy or targeted drug for <6 months.

INCIDENCE AND RISKS FOR CV EVENTS. The incidence of MACE was significantly higher in the targeted therapy group than in the cytokine therapy group (HR: 1.8; 95% CI: 1.19-2.74, $P = 0.005$) ([Table 2](#)). The incidence rates of myocardial infarction, ischemic stroke, and heart failure were consistently higher in the targeted therapy group than in the cytokine therapy group, but these were not statistically significant. The incidence of CV death was significantly higher in the targeted therapy group than in the cytokine therapy group (HR: 2.1; 95% CI: 1.29-3.41, $P = 0.002$) ([Table 2](#)). However, the all-cause mortality rate was similar between the groups ($P = 0.97$). After adjusting for competing risks (non-CV deaths), MACE and CV death risks were consistently higher in the targeted therapy group than in

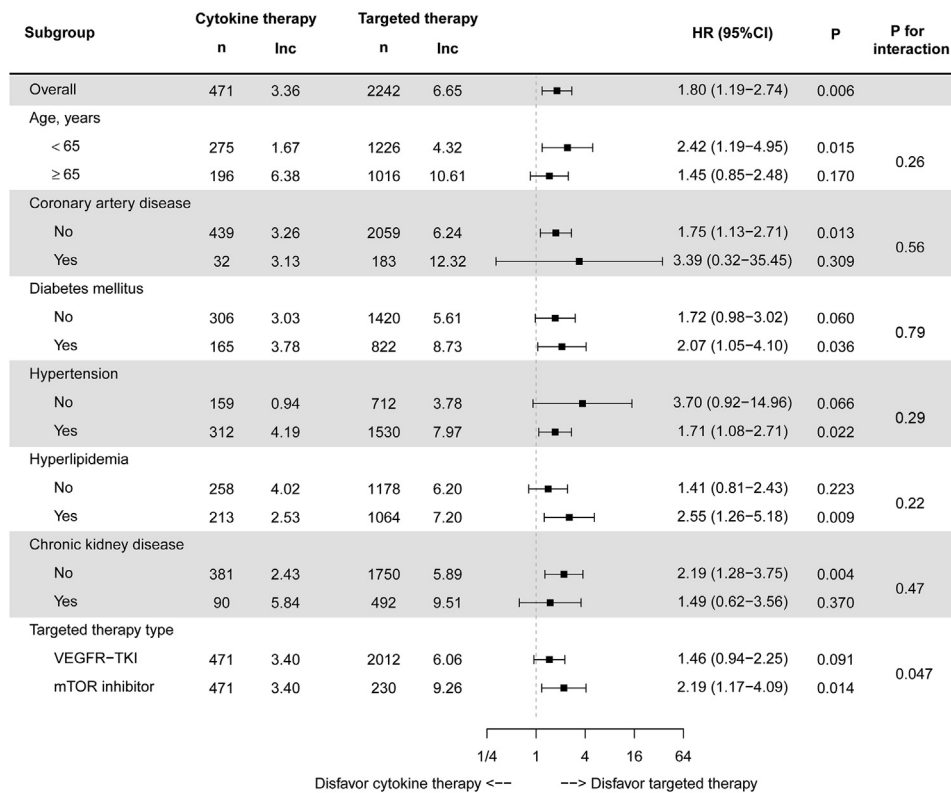
TABLE 3 Follow-Up Time, Time to Event, and Overall Survival

	Cytokine Therapy (n = 528)	Targeted Therapy (n = 2,257)	Total (n = 2,785)	P Value
Follow-up time, mo ^a				
Median (IQR)	7.16 (30.49)	10.12 (19.61)	9.76 (21.29)	0.15
Time to events, mo ^b				
Median (IQR)				
MACE	7.03 (29.09)	9.95 (19.19)	9.53 (20.67)	0.001
Myocardial infarction	7.16 (29.54)	10.09 (19.61)	9.69 (21.22)	0.48
Ischemic stroke	7.06 (29.14)	10.05 (19.35)	9.63 (20.90)	0.18
Heart failure	7.06 (30.49)	9.99 (19.12)	9.59 (20.99)	0.23
CV death	7.16 (30.49)	10.12 (19.61)	9.76 (21.29)	0.001
Overall survival, mo ^c				
Median (IQR)	8.08 (2.80)	13.08 (3.35)	12.42 (3.03)	0.87

^aThe duration of follow-up is from the index date (start of treatment for cytokines or targeted therapy) till death or December 31, 2018 (i.e., the end of follow-up). The Wilcoxon rank sum test was used to compare the follow-up time between the 2 study groups. ^bThe duration of time to event is from the index till discontinued cytokines or targeted drugs, the first occurrence of the study event, death, or the end of follow-up, whichever came first. ^cThe duration of overall survival is from the index date to death or the end of follow-up, whichever came first. The log-rank test was used to compare the time to event and overall survival between the 2 study groups.

Abbreviations as in [Table 2](#).

FIGURE 3 Risk for MACE by Subgroup



Patients receiving targeted therapy had a higher risk for MACE than did those receiving cytokine therapy regardless of age or conventional CV risk factors (coronary artery disease, diabetes, hypertension, hyperlipidemia, and chronic kidney disease). When dividing the targeted cancer therapy group into the vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitor (TKI) and mechanistic target of rapamycin (mTOR) inhibitor subgroups, the VEGFR TKI and mTOR inhibitor subgroups had an individually higher risk for MACE than did the cytokine therapy group, and the interaction effect of higher CV risk was more apparent in the mTOR inhibitor subgroup (interaction $P = 0.047$). Inc = incidence rate (per 100 person-years); other abbreviations as in [Figure 2](#).

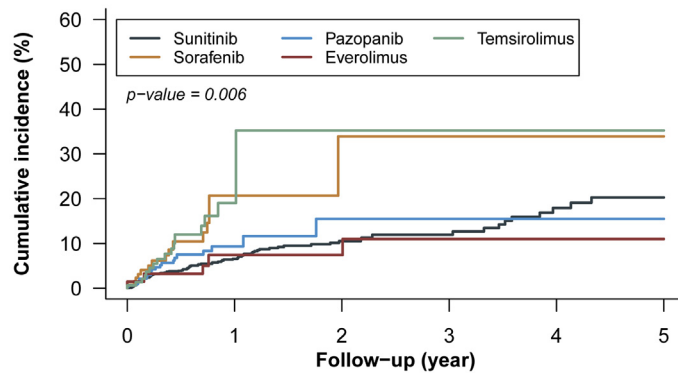
the cytokine therapy group ([Figure 2](#)). The median time to MACE in the targeted and cytokine therapy was 9.9 and 7.0 months, respectively. The median overall survival was 13.0 months in the targeted group and 8.0 months in the cytokine group ([Table 3](#)).

MACE SUBGROUP ANALYSIS. In subgroup analysis, patients receiving targeted therapy had a higher risk for MACE than those receiving cytokine therapy regardless of age or conventional CV risk factors (coronary artery disease, diabetes, hypertension, hyperlipidemia, and chronic kidney disease) ([Figure 3](#)). The targeted cancer therapy group was also categorized according to the VEGFR TKI and mTOR inhibitor subgroups, and siPTW was used to balance the baseline characteristics of the 3 subgroups. The VEGFR TKI and mTOR inhibitor subgroups had a higher risk for MACE than did the cytokine therapy group, and the interaction effect of higher CV risk was

more apparent in the mTOR inhibitor subgroup (interaction $P = 0.047$).

MACE AMONG DIFFERENT TARGETED THERAPIES. We identified significant differences in MACE risk among patients treated with different VEGFR TKIs and mTOR inhibitors ([Figure 4](#)). The incidence of MACE was higher among patients receiving temsrolimus or sorafenib than among those receiving sunitinib therapy ([Table 4](#)).

MULTIVARIABLE ANALYSIS OF RISK FACTORS FOR MACE AMONG PATIENTS RECEIVING TARGETED THERAPIES. Demographics and common comorbidities were evaluated as predictors of MACE in patients receiving targeted therapy in the original cohort ($n = 2,257$). The multivariable analysis revealed that age (≥ 65 vs < 65 years; HR: 1.81; 95% CI: 1.27–2.58), ischemic stroke (HR: 1.88; 95% CI: 1.14–3.11), venous thromboembolism (HR: 2.50; 95% CI: 1.27–4.92), atrial

FIGURE 4 Fine and Gray Cumulative Incidence Rates of MACE for Each Targeted Therapy Type

Number at risk:						
Sunitinib	1584	548	267	143	89	48
Sorafenib	134	31	13	9	6	5
Pazopanib	307	95	36	15	9	3
Everolimus	72	49	39	29	25	15
Temeirolimus	160	29	14	5	3	3

There were significant differences in MACE risk among patients treated with different VEGFR TKIs and mTOR inhibitors. The incidence of MACE was higher among patients receiving temsirolimus or sorafenib than among those receiving sunitinib therapy. Abbreviations as in [Figures 2 and 3](#).

fibrillation (HR: 3.60; 95% CI: 2.16-5.99), and history of heart failure (HR: 3.88; 95% CI: 2.25-6.71) were independently associated with an elevated risk for MACE among patients receiving targeted therapy ([Table 5](#)).

SENSITIVITY ANALYSIS OF VEGFR TKI. After excluding 232 users of mTOR inhibitors, there were 2,025 patients receiving VEGFR TKI ([Supplemental Table 5](#)). We performed sIPTW on this new cohort. There were 476 patients in the cytokine group and 2,009 patients in the VEGFR TKI group ([Supplemental Table 5](#)). The results showed that the VEGFR TKI group had a significantly higher incidence of MACE (HR: 1.78; 95% CI: 1.17-2.71; $P = 0.007$) and CV death (HR: 2.02; 95% CI: 1.25-3.28; $P = 0.004$) than the

cytokine therapy ([Supplemental Table 6](#)). There was no significant difference in the all-cause mortality rate between the groups ($P = 0.88$). The risks for MACE and CV death were consistently higher in the VEGFR TKI therapy group than in the cytokine therapy group after adjustment for competing risk events (noncardiac deaths) ([Supplemental Table 6, Supplemental Figure 2](#)).

DISCUSSION

This nationwide population-based cohort study characterized and compared CV outcomes associated with targeted therapies (VEGFR TKIs and mTOR inhibitors) with those associated with cytokine therapy in patients with advanced RCC. The risk for MACE (namely myocardial infarction, ischemic stroke, heart failure, or CV death) with targeted therapies with VEGFR TKIs (ie, sunitinib, sorafenib, or pazopanib) or mTOR inhibitors (ie, everolimus or temsirolimus) was higher than that associated with cytokine therapy during a follow-up period of up to 5 years ([Central Illustration](#)). There was a numerically higher incidence of myocardial infarction, ischemic stroke, and heart failure in the targeted therapy group compared with the cytokine therapy group, although this was not statistically significant. However, there was a significantly higher rate of CV death in the targeted therapy group compared with the cytokine therapy group. No significant difference in all-cause mortality was observed between the groups. The value of this comprehensive longitudinal follow-up cohort study using a large representative sample is in the elucidation of CV risks with targeted cancer therapy used commonly to treat advanced RCC.

In our study, the rate of CV death was significantly higher in the targeted therapy group than in the cytokine therapy group. In the targeted therapy group, patients who received VEGFR TKI accounted for nearly 90% of the population; the higher CV risk of the targeted group was driven primarily by the VEGFR TKI-treated patients. This finding is consistent with a population-based cohort study involving patients older than 65 years with advanced RCC, with a numerically higher, but not statistically significant, risk for CV death (HR: 1.56; 95% CI: 0.71-3.40).⁶ In the present study, the rates of myocardial infarction and ischemic stroke were also numerically higher in the targeted therapy group than in the cytokine therapy group (0.41 vs 0.30 and 0.77 vs 0.36 per 100 person-years, respectively), consistent with a meta-analysis of clinical trials that reported a higher risk for arterial thromboembolic events among patients treated

TABLE 4 Incidence of Major Adverse Cardiovascular Events by Targeted Therapy Type

	Incidence (95% CI) per 100 Person-Years	Univariable HR (95% CI)	P Value
Sunitinib (n = 1,584)	5.72 (4.59-6.86)	Reference	—
Sorafenib (n = 134)	12.26 (5.74-18.77)	1.94 (1.11-3.39)	0.021
Pazopanib (n = 307)	7.38 (4.12-10.65)	1.20 (0.75-1.92)	0.45
Everolimus (n = 72)	2.68 (0.87-5.89)	0.57 (0.23-1.40)	0.21
Temeirolimus (n = 160)	13.73 (6.81-20.66)	2.11 (1.24-3.59)	0.006

with sorafenib and sunitinib (relative risk: 3.03; 95% CI: 1.25-7.37) compared with control patients.⁴

Some mechanisms underlying the increased risk for MACE associated with VEGFR TKIs have been proposed. First, VEGF signaling inhibitors have been associated with hypertension.²⁴ VEGF decreases the production of endothelin-1, a potent vasoconstrictor, and induces the production of 2 vasodilators, prostacyclin, and nitric oxide. VEGF signaling inhibitors may cause an imbalance between vasodilation and vasoconstriction, thereby altering glomerular function and contributing to hypertension, which is a well-known risk factor for CV death.^{25,26} Second, multireceptor TKIs, including VEGFR and platelet-derived growth factor receptor inhibitors, could destabilize the coronary microvascular endothelial network and reduce coronary flow reserve, leading to an increased risk for thrombosis and arterial ischemic events, including myocardial infarction and ischemic stroke.^{27,28}

Of note, the baseline characteristics of CV disease in the patients in our study were different from those in randomized clinical trials comparing targeted therapy and cytokine therapy in RCC.^{29,30} In contrast to randomized trials that typically exclude patients with pre-existing CV disease, heart failure, and stroke, our study was conducted in a broad population in real-world practice that did not exclude patients with pre-existing CV disease. Furthermore, risk factors such as hypertension, diabetes, and hyperlipidemia were present in 68.1%, 36.9%, and 47.2% of the patients in our study. In a high-CV risk population, the substantially higher risk for MACE in the targeted therapy group than the cytokine therapy group may explain why we did not detect an overall mortality difference between groups. Further prospective studies are warranted to confirm these results.

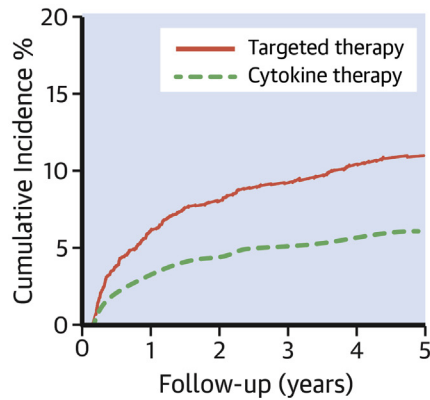
The increased risk for MACE associated with targeted cancer therapies was more apparent among the patients treated with mTOR inhibitors than among those treated with VEGFR TKIs (*P* for interaction = 0.047). Despite growing evidence of the CV toxicity of VEGFR TKI in patients with advanced RCC, reports of adverse CV events associated with mTOR inhibition in patients with advanced RCC are scarce. In a phase III trial, the incidence of adverse metabolic effects (namely, hypertriglyceridemia, hypercholesterolemia, and hyperglycemia) was higher among patients with metastatic RCC who had received everolimus than among those who had received a placebo (71% vs 30%, 71% vs 32%, and 50%

TABLE 5 Cox Proportional Hazards Regression Analysis of Potential Baseline Risk Factors for Targeted Therapy–Associated Major Adverse Cardiovascular Events (N = 2,257)

	Univariable HR (95% CI)	P Value	Multivariable HR (95% CI)	P Value
Atrial fibrillation	6.64 (4.11-10.73)	<0.001	3.60 (2.16-5.99)	<0.001
Heart failure	5.97 (3.56-10.03)	<0.001	3.88 (2.25-6.71)	<0.001
Ischemic stroke	3.02 (1.87-4.89)	<0.001	1.88 (1.14-3.11)	0.014
Myocardial infarction	2.60 (1.37-4.93)	0.003	1.56 (0.75-3.25)	0.23
Hypertension	2.64 (1.68-4.14)	<0.001	1.64 (1.00-2.68)	0.052
Age ≥65 y	2.47 (1.77-3.43)	<0.001	1.81 (1.27-2.58)	0.001
Coronary intervention	2.47 (1.49-4.08)	<0.001	1.28 (0.71-2.31)	0.41
Venous thromboembolism	2.20 (1.12-4.32)	0.021	2.50 (1.27-4.92)	0.008
Charlson comorbidity score ≥3	1.86 (1.30-2.67)	<0.001	0.98 (0.64-1.49)	0.91
Chronic kidney disease	1.71 (1.23-2.38)	0.001	1.23 (0.85-1.77)	0.27
Male	1.42 (0.95-2.12)	0.091		
Diabetes mellitus	1.31 (0.95-1.79)	0.096		
Hyperlipidemia	1.18 (0.86-1.61)	0.306		
Peripheral arterial disease	1.17 (0.16-8.36)	0.876		

vs 23%, respectively).³¹ Similar abnormal metabolic findings were also reported in a clinical trial of temsirolimus in the treatment of advanced RCC.³² The key role of PI3K/AKT/mTOR signaling in glucose and lipid metabolism may explain why targeting this pathway in cancer treatment may cause a range of metabolic derangements.²⁵ One observational study evaluating the CV toxicity induced by targeted therapies in 159 patients with advanced RCC revealed that those who had received mTOR inhibitors frequently developed adverse CV conditions; 17% (4 of 24) developed grade 1 heart failure after everolimus therapy, and 24% (4 of 17) developed grade 3 hypertension after temsirolimus therapy.⁸ The present study contributes to this body of research by detailing the long-term CV safety profile of mTOR inhibitors in treating patients with advanced RCC.

This study identified 5 risk factors—age (≥65 years), ischemic stroke, venous thromboembolism, history of heart failure, and atrial fibrillation—strongly associated with MACE in patients with advanced RCC receiving targeted treatment cancer therapies. Because VEGF signaling inhibition contributes to hypertension, pre-existing or coexisting risk factors for hypertension may also be risk factors for MACE with targeted therapy. For instance, elevated blood pressure with increased afterload induced by targeted therapy could impair myocardial perfusion and microcirculation, which could manifest as a deterioration in cardiac function in a patient with pre-existing heart failure, thereby increasing the patient’s risk for additional CV events. Older age, a history of ischemic stroke, and atrial fibrillation are

CENTRAL ILLUSTRATION Increased Risk for Major Adverse Cardiovascular Events Associated With Targeted Therapies for Advanced Renal Cell Carcinoma

	Incidence (95% CI) (100 person-years)	Subdistribution HR (95% CI)
Targeted therapy (N=2,242)	6.65 (5.74-7.56)	1.86 (1.22-2.82)
Cytokine therapy (N=471)	3.36 (2.04-4.68)	Reference

Risk factors for targeted therapy-associated MACE	HR (95% CI)
Heart failure	3.88 (2.25-6.71)
Atrial fibrillation	3.60 (2.16-5.99)
Venous thromboembolism	2.50 (1.27-4.92)
Ischemic stroke	1.88 (1.14-3.11)
Age ≥ 65 years	1.81 (1.27-2.58)

In patients with advanced renal cell carcinoma, the use of targeted cancer therapy, including vascular endothelial growth factor receptor tyrosine kinase inhibitor and mechanistic target of rapamycin inhibitors, had a higher risk of MACE (MI, stroke, HF, and cardiovascular death).

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The incidence of major adverse cardiovascular events (MACE) was higher in the targeted therapy group than in the cytokine therapy group. In patients with advanced renal cell carcinoma, prior heart failure, atrial fibrillation, venous thromboembolism, ischemic stroke, and age ≥ 65 years were risk factors for MACE. MACE served as a composite endpoint of myocardial infarction (MI), ischemic stroke, heart failure (HF), and cardiovascular death.

well-known risk factors for CV events. The use of VEGF inhibitors may predispose patients with these risk factors to a further increased risk for thrombosis and CV events. Identifying these risk factors can help clinicians identify high-risk patients earlier with the goal of improving outcomes in patients with advanced RCC treated with targeted therapies.

Interestingly, the risk for MACE was significantly higher among patients treated with sorafenib (HR: 1.94; 95% CI: 1.14-3.39) and temsirolimus (HR: 2.11; 95% CI: 1.24-3.59) than among those treated with sunitinib. A previous meta-analysis of clinical trials reported that the risk for arterial thromboembolic events was numerically higher among patients treated with sorafenib (rate ratio: 3.10; 95% CI:

1.22-7.85) than among those treated with sunitinib (rate ratio: 2.39; 95% CI: 0.12-49.41), although the difference was statistically nonsignificant (P for difference = 0.89).⁴ Similarly, in another study involving patients 65 years or older with advanced RCC, the adjusted HRs for acute myocardial infarction, stroke, and CV death were higher for patients treated with sorafenib than for those treated with sunitinib (2.40 vs 1.06, 5.30 vs 2.28, and 1.88 vs 1.31, respectively).⁶ The incidence of CV toxicity may differ among patients treated with different TKIs,²⁷ although the mechanisms underlying the different rates of adverse CV events among patients treated with different targeted therapies remain unclear. The incidence of cardiac and vascular toxicity may be

correlated with the number and type of kinases inhibited.²⁷ Additional studies are warranted to investigate these results.

STUDY LIMITATIONS. First, because of the retrospective nature, there is a risk for residual confounding. Patients with baseline CV risk factors may be more likely to be monitored for CV toxicity than those without baseline risk factors. We thus used propensity scores and inverse probability of treatment weighting to balance the groups' baseline characteristics and ensure similar distribution of baseline CV characteristics between groups to mitigate potential biases between the targeted therapy and cytokine therapy groups. Although the sample sizes of the groups after sIPTW were slightly smaller than those before sIPTW (99.3% and 89.2% for the targeted and cytokine therapy groups, respectively), we expect the effects on our main findings to be minimal because the results of GBM are less affected by the trimming rate.³³

Second, because of the relatively small sample size in the targeted therapy subgroup (only 72 patients treated with everolimus), we could not adjust for covariates in our models evaluating risk for MACE.

Third, there may be an inherent overall survival difference between cytokine and targeted therapy groups. We thus used a competing-risks approach. Fourth, the NHIRD database lacks data on factors such as body mass index and smoking.

Fifth, the study outcomes were required to be principal discharge diagnoses. Thus, we did not evaluate those outcomes that did not require hospitalization, resulting in a potential detection bias. Sixth, the treatment duration of targeted therapy was longer than the cytokine group, which might have influenced the clinical outcomes.

Seventh, we included both VEGFR TKIs and mTOR inhibitors in the targeted therapy group, although the mechanisms of toxicity are likely to be different between VEGFR TKIs and mTOR inhibitors.

Finally, the information on prescribed drugs for cancer therapy may not reflect actual use; therefore, we were unable to account for the impact of noncompliance or treatment modifications, which may have occurred.

CONCLUSIONS

This cohort study showed that patients with advanced RCC treated with targeted cancer therapies

exhibit a significantly higher risk for MACE, especially CV death, compared with those treated with cytokine therapy. Among the patients treated with targeted therapies, we identified 5 independent risk factors—age ≥ 65 years, ischemic stroke, venous thromboembolism, atrial fibrillation, and heart failure—associated with an increased risk for MACE in patients with advanced RCC. These findings may inform the evaluation of CV risk when considering targeted cancer therapies for patients with advanced RCC in real-world clinical practice.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with advanced RCC, targeted cancer therapies, including VEGFR TKIs and mTOR inhibitors, are associated with a higher risk for MACE, namely, myocardial infarction, ischemic stroke, heart failure, and CV death. Factors independently associated with a higher risk for targeted therapy-associated MACE were age ≥ 65 years, ischemic stroke, venous thromboembolism, atrial fibrillation, and a history of heart failure.

TRANSLATIONAL OUTLOOK: Detailed evaluation of targeted therapy-related adverse events is important in informing the treatment of advanced RCC. Identifying high-risk patients and addressing cardiotoxicity early is crucial when treating patients with targeted therapies.

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KEY WORDS cardiovascular toxicity, renal cell carcinoma, targeted cancer therapy

APPENDIX For supplemental tables and figures, please see the online version of this paper.

