

Lipid-Lowering Therapy Use and Survival Outcomes in Advanced Renal Cell Carcinoma Treated with Toripalimab Plus Axitinib or Sunitinib: A Post Hoc Analysis of the Phase III RENOTORCH Trial

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Abstract

Background: Immune checkpoint inhibitor (ICI)-based combinations are important first-line treatments for advanced renal cell carcinoma (RCC), but factors influencing long-term outcomes remain incompletely understood. Lipid-lowering therapies have been suggested to affect cancer-related immune and metabolic processes, but their clinical relevance in advanced RCC remains unclear. This study aimed to evaluate the association between lipid-lowering therapy use and clinical outcomes in patients with advanced RCC.

Methods: This post hoc analysis was based on data from the phase III RENOTORCH trial, which compared toripalimab plus axitinib with sunitinib as first-line treatment for advanced RCC. Patients were categorized according to recorded oral lipid-lowering therapy use during follow-up. Associations between lipid-lowering therapy and progression-free survival (PFS), overall survival (OS), objective response rate (ORR), and disease control rate (DCR) were evaluated using Cox regression, logistic regression, and inverse probability of treatment weighting (IPTW)-adjusted analyses.

Results: Among 421 randomized patients, 113 (26.8%) received lipid-lowering therapy. In the toripalimab plus axitinib group, lipid-lowering therapy use was associated with improved OS after multivariable adjustment (HR 0.42, 95% CI 0.23–0.77; $P=0.005$) and IPTW adjustment (HR 0.48, 95% CI 0.26–0.88; $P=0.018$). No significant association between lipid-lowering therapy and survival outcomes was observed in the sunitinib group. Lipid-lowering therapy was not significantly associated with ORR or DCR. Exploratory analyses showed no consistent survival difference between statin and non-statin users, and triglyceride-related associations differed between treatment groups.

Conclusions: In this post hoc analysis of the RENOTORCH trial, lipid-lowering therapy use was associated with favorable survival outcomes, particularly OS, among patients receiving toripalimab plus axitinib. These findings provide hypothesis-generating evidence regarding the potential relationship between lipid metabolism and outcomes of immunotherapy-based combination treatment in advanced RCC.

Trial registration: ClinicalTrials.gov identifier: NCT04394975; registered on May 20, 2020.

Highlights

- This study evaluated lipid-lowering therapy use using data from the phase III RENOTORCH trial.
- Lipid-lowering therapy use was associated with improved overall survival in patients receiving toripalimab plus axitinib.
- The observed survival association was not accompanied by improved objective response or disease control rates.
- No consistent survival difference was observed between statin and non-statin lipid-lowering therapies.
- These findings provide hypothesis-generating evidence linking lipid metabolism with immunotherapy-based treatment outcomes.

1. Introduction

Renal cell carcinoma (RCC) is one of the most common malignancies of the urinary system, with clear cell RCC representing the predominant histological subtype. For patients with advanced or metastatic RCC, systemic treatment has evolved from VEGF pathway inhibitors and mTOR inhibitors to immune checkpoint inhibitor (ICI)-based combinations [1–6]. Several phase III trials have demonstrated that ICI-based regimens, including dual immune checkpoint blockade and PD-1/PD-L1 inhibitors combined with VEGF/VEGFR-targeted therapy, improve clinical outcomes compared with sunitinib [7–12]. The RENOTORCH trial also showed that toripalimab plus axitinib provided superior efficacy compared with sunitinib as first-line treatment for advanced RCC [13].

Despite these advances, treatment benefit remains heterogeneous among patients receiving immunotherapy-based combinations. Some patients achieve durable survival benefit, whereas others experience early progression or limited disease control. Therefore, identifying clinical factors associated with immunotherapy efficacy and long-term outcomes remains clinically important [14–16]. In recent years, increasing attention has been paid to concomitant medications, which may influence ICI outcomes by altering the gut microbiome, systemic inflammation, metabolic pathways, or the tumor immune microenvironment [17–20].

Lipid-lowering therapies, particularly statins, have attracted interest because of their potential biological effects beyond lipid regulation. Statins inhibit 3-hydroxy-3-methylglutaryl-coenzyme A reductase and may exert anti-inflammatory, immunomodulatory, anti-angiogenic, and tumor microenvironment-modulating effects [21–26]. Basic studies have also shown that dysregulated cholesterol metabolism can affect CD8 + T-cell exhaustion, antigen presentation, and tumor immune escape, whereas modulation of cholesterol metabolism may enhance antitumor immune responses [27–29]. Clinically, several studies have suggested that statin use may be associated with improved outcomes in patients receiving ICIs; however, findings remain inconsistent across tumor types, treatment settings, and medication exposure definitions [30–34].

In RCC, previous studies have suggested a potential association between statin use and improved survival, but most evidence has come from retrospective or real-world cohorts [35–38]. Whether lipid-lowering therapy influences outcomes in patients receiving modern ICI plus anti-angiogenic therapy remains unclear. Therefore, using data from the phase III RENOTORCH trial, we conducted this post hoc analysis to evaluate the association between recorded oral lipid-lowering therapy use and clinical outcomes, including PFS, OS, ORR, and DCR, in patients with advanced RCC treated with toripalimab plus axitinib or sunitinib.

2. Methods

2.1 Study design and patients

This study was a post hoc analysis of the phase III RENOTORCH trial, a randomized, open-label trial comparing toripalimab plus axitinib with sunitinib as first-line treatment for advanced RCC [13]. The present analysis included all randomized patients with available information on recorded oral lipid-lowering therapy use. Patients were classified according to lipid-lowering therapy use and analyzed overall and separately within the toripalimab plus axitinib and sunitinib treatment groups.

2.2 Exposure and endpoints

Lipid-lowering therapy use was defined as any recorded oral lipid-lowering medication use during the trial follow-up period. Among users, lipid-lowering therapy class was summarized as statin use, non-statin or non-statin-classified lipid-lowering therapy, and combination lipid-lowering therapy. Baseline lipid biomarkers included total cholesterol (TC) and triglycerides (TG).

The main endpoint of this analysis was independent review committee (IRC)-assessed progression-free survival (PFS). Other endpoints included overall survival (OS), investigator-assessed PFS, objective response rate (ORR), and disease control rate (DCR). PFS was defined as the time from randomization to disease progression or death from any cause, and OS as the time from randomization to death from any cause. ORR was defined as the proportion of patients achieving complete or partial response, and DCR as the proportion achieving complete response, partial response, stable disease, or non-CR/non-PD. Tumor response was assessed according to RECIST version 1.1 [39].

2.3 Statistical analysis

Baseline characteristics were summarized according to lipid-lowering therapy use within each treatment group. Continuous variables were presented as median and interquartile range, and categorical variables as frequencies and percentages. Between-group comparisons used the Mann–Whitney U test, chi-square test, or Fisher’s exact test, as appropriate. Standardized mean differences were calculated to assess baseline imbalance.

PFS and OS were estimated using the Kaplan–Meier method and compared using the log-rank test. Cox proportional hazards models were used to estimate hazard ratios and 95% confidence intervals. Univariable analyses were first performed, followed by multivariable Cox models adjusted for lipid-lowering therapy use, treatment arm where applicable, age, sex, BMI, ECOG performance status, interval from diagnosis to randomization, and number of metastatic sites. A sensitivity model excluding BMI and additionally including IMDC risk group was also performed. Post hoc interaction analyses were conducted by adding an interaction term between lipid-lowering therapy use and BMI group, with BMI dichotomized according to the median value. ORR and DCR were evaluated using logistic regression models within each treatment group.

To further account for baseline imbalance, inverse probability of treatment weighting was applied using baseline covariates, followed by weighted Cox regression analyses for IRC-assessed PFS, investigator-assessed PFS, and OS. Additional post hoc analyses explored survival outcomes according to lipid-lowering therapy class and baseline lipid biomarkers. Baseline TG was dichotomized using the clinical cutoff of 1.7 mmol/L among lipid-lowering therapy users and analyzed separately within each treatment arm. All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant. Given the post hoc, hypothesis-generating nature of this analysis, all P values were nominal, with no adjustment for multiple comparisons.

3. Results

3.1 Baseline characteristics according to recorded lipid-lowering therapy use status

A total of 421 patients from the RENOTORCH trial were included in this post hoc analysis. According to the original randomized treatment allocation, 210 patients received toripalimab plus axitinib and 211 patients received sunitinib. Within the toripalimab plus axitinib group, 62 patients received lipid-lowering therapy and 148 did not. Within the sunitinib group, 51 patients received lipid-lowering therapy and 160 did not.

Baseline characteristics were therefore summarized separately within each treatment regimen (Table 1). In the toripalimab plus axitinib cohort, most baseline clinical and disease-related characteristics were generally comparable between patients with and without lipid-lowering therapy. The main imbalances were observed in metabolic comorbidities and lipid-related parameters, particularly diabetes mellitus and baseline triglyceride levels. In the sunitinib cohort, most tumor-related characteristics were also broadly comparable between groups, although patients receiving lipid-lowering therapy tended to have a higher burden of cardiovascular and metabolic comorbidities, including hypertension, coronary artery disease, and elevated baseline triglyceride levels.

Table 1. Baseline characteristics stratified by recorded lipid-lowering therapy use status

Variable	Overall Toripalimab + Axitinib cohort (N=210)	Non-lipid-lowering therapy (n=148)	Lipid-lowering therapy (n=148)
Age, n (%)			
<65	135 (64.3%)	99 (66.9%)	36 (58.1%)
≥65	75 (35.7%)	49 (33.1%)	26 (41.9%)
Sex, n (%)			
Male	162 (77.1%)	114 (77.0%)	48 (77.4%)
Female	48 (22.9%)	34 (23.0%)	14 (22.6%)
BMI, median (IQR)	23.65 (21.73–25.40)	23.53 (21.53–25.26)	23.68 (22.02–25.40)
ECOG performance status, n (%)			
0	109 (51.9%)	77 (52.0%)	32 (51.6%)
1	101 (48.1%)	71 (48.0%)	30 (48.4%)
IMDC risk group, n (%)			
Intermediate risk	40 (19.0%)	32 (21.6%)	8 (12.9%)
Poor risk	170 (81.0%)	116 (78.4%)	54 (87.1%)
KPS, median (IQR)	90 (80–90)	90 (80–90)	90 (80–90)
Time from diagnosis to randomization, months, median (IQR)	1.68 (0.69–10.25)	1.63 (0.62–9.86)	1.84 (0.85–10.25)
Number of metastatic sites, median (IQR)	2 (1–3)	2 (1–3)	2 (1–2)
Diabetes mellitus, n (%)	21 (10.0%)	7 (4.7%)	14 (22.6%)
Hypertension, n (%)	101 (48.1%)	68 (45.9%)	33 (53.2%)
Coronary artery disease, n (%)	8 (3.8%)	6 (4.1%)	2 (3.2%)
Baseline TC, median (IQR), mmol/L	4.48 (3.92–5.15)	4.48 (3.98–5.05)	4.52 (3.84–5.15)
Baseline TG, median (IQR), mmol/L	1.38 (0.99–2.00)	1.33 (0.94–1.90)	1.71 (1.09–2.00)

Variable	Overall Sunitinib cohort (N=211)	Non-lipid-lowering therapy (n=160)	Lipid-lowering therapy (n=51)	P value	SMD
Age, n (%)				0.786	0.043
<65	148 (70.1%)	113 (70.6%)	35 (68.6%)		
≥65	63 (29.9%)	47 (29.4%)	16 (31.4%)		
Sex, n (%)				0.473	0.114
Male	157 (74.4%)	121 (75.6%)	36 (70.6%)		
Female	54 (25.6%)	39 (24.4%)	15 (29.4%)		
BMI, median (IQR)	23.82 (21.68–26.12)	23.66 (21.49–25.93)	24.57 (22.49–26.63)	0.046	0.432
ECOG performance status, n (%)				0.665	0.070
0	109 (51.7%)	84 (52.5%)	25 (49.0%)		
1	102 (48.3%)	76 (47.5%)	26 (51.0%)		
IMDC risk group, n (%)				0.494	0.113
Intermediate risk	40 (19.0%)	32 (20.0%)	8 (15.7%)		
Poor risk	171 (81.0%)	128 (80.0%)	43 (84.3%)		
KPS, median (IQR)	90 (80–90)	90 (80–90)	90 (80–90)	0.716	0.062
Time from diagnosis to randomization, months, median (IQR)	1.61 (0.77–8.53)	1.45 (0.75–8.40)	2.04 (1.05–8.43)	0.207	0.009
Number of metastatic sites, median (IQR)	2 (1–2)	2 (1–2)	2 (1–2)	0.942	0.031
Diabetes mellitus, n (%)	29 (13.7%)	19 (11.9%)	10 (19.6%)	0.163	0.212
Hypertension, n (%)	94 (44.5%)	58 (36.2%)	36 (70.6%)	<0.001	0.688
Coronary artery disease, n (%)	7 (3.3%)	3 (1.9%)	4 (7.8%)	0.038	0.278
Baseline TC, median (IQR), mmol/L	4.53 (3.93–5.30)	4.49 (3.93–5.19)	4.75 (4.02–5.51)	0.183	0.168
Baseline TG, median (IQR), mmol/L	1.43 (1.08–1.92)	1.34 (1.00–1.82)	1.79 (1.38–2.43)	<0.001	0.678

Table note:

Data are presented as n (%) unless otherwise indicated. Continuous variables are presented as median (interquartile range). P values were calculated using the Mann–Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables, as appropriate. Standardized mean differences were calculated to assess baseline differences between patients with and without lipid-lowering therapy. BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IQR, interquartile range; KPS, Karnofsky performance status; SMD, standardized mean difference. TC, total cholesterol; TG, triglycerides

3.2 Survival outcomes and Cox regression analyses according to lipid-lowering therapy use in the toripalimab plus axitinib group

In the toripalimab plus axitinib group, patients receiving lipid-lowering therapy showed numerically improved IRC-assessed progression-free survival compared with those not receiving lipid-lowering therapy. In univariable Cox regression analysis, lipid-lowering therapy was associated with a lower risk of disease progression or death, although the association did not reach statistical significance (HR 0.64, 95% CI 0.39–1.03; $P = 0.067$). This trend remained consistent after multivariable adjustment for age, sex, BMI, ECOG performance status, diagnosis-to-randomization interval, and number of metastatic sites (HR 0.62, 95% CI 0.38–1.03; $P = 0.063$). The corresponding Kaplan-Meier curves are presented in Figure 1, and Cox regression estimates are summarized in Table 2.

For overall survival, lipid-lowering therapy was significantly associated with improved survival in the toripalimab plus axitinib group. In univariable Cox regression analysis, lipid-lowering therapy was associated with a significantly reduced risk of death (HR 0.46, 95% CI 0.26–0.83; $P = 0.010$). This association remained statistically significant in the multivariable Cox model (HR 0.42, 95% CI 0.23–0.77; $P = 0.005$), as shown in Figure 1 and Table 2.

These findings suggest that lipid-lowering therapy was associated with a favorable survival profile in patients receiving toripalimab plus axitinib, with the most pronounced benefit observed for overall survival.

Table 2. Univariable and multivariable Cox regression analysis for IRC-assessed PFS and OS in the toripalimab plus axitinib group

Variable	Univariable HR (95% CI)	P	Multivariable HR (95% CI)	P
IRC-assessed PFS				
Lipid-lowering therapy (yes vs no)	0.64 (0.39–1.03)	0.067	0.62 (0.38–1.03)	0.063
Age (per year)	1.01 (0.99–1.03)	0.544	1.01 (0.99–1.03)	0.318
Sex (female vs male)	0.85 (0.51–1.42)	0.531	0.89 (0.53–1.51)	0.666
BMI (per kg/m ²)	0.94 (0.88–1.01)	0.101	0.95 (0.88–1.02)	0.184
ECOG PS (1 vs 0)	0.94 (0.62–1.43)	0.779	0.97 (0.62–1.52)	0.894
Diagnosis-to-randomization interval (per month)	0.98 (0.97–0.99)	0.007	0.98 (0.97–0.99)	0.008
Number of metastatic sites (per site)	1.11 (0.93–1.31)	0.245	1.11 (0.94–1.32)	0.217
Overall survival				
Lipid-lowering therapy (yes vs no)	0.46 (0.26–0.83)	0.010	0.42 (0.23–0.77)	0.005
Age (per year)	1.02 (0.99–1.05)	0.119	1.03 (1.00–1.06)	0.064
Sex (female vs male)	1.06 (0.61–1.83)	0.833	1.12 (0.64–1.95)	0.689
BMI (per kg/m ²)	0.93 (0.86–1.01)	0.101	0.95 (0.87–1.03)	0.237
ECOG PS (1 vs 0)	1.52 (0.94–2.44)	0.087	1.47 (0.89–2.45)	0.136
Diagnosis-to-randomization interval (per month)	0.99 (0.98–1.00)	0.152	0.99 (0.98–1.00)	0.046
Number of metastatic sites (per site)	1.20 (0.99–1.45)	0.066	1.18 (0.96–1.44)	0.115

Table note:

HRs and 95% CIs were estimated using Cox proportional hazards models within the toripalimab plus axitinib group. For IRC-assessed PFS, 89 events were observed; the multivariable model included 209 patients. For OS, 70 deaths were observed; the multivariable model included 209 patients. The multivariable model included lipid-lowering therapy use, age, sex, BMI, ECOG performance status, diagnosis-to-randomization interval, and number of metastatic sites. HR < 1 indicates a lower risk of progression or death for PFS and a lower risk of death for OS.

3.3 Survival outcomes and Cox regression analyses in the sunitinib group

In the sunitinib group, lipid-lowering therapy was not significantly associated with IRC-assessed progression-free survival. In univariable Cox regression analysis, the HR for IRC-assessed PFS was 0.83 (95% CI 0.54–1.27; P = 0.385). After multivariable adjustment, lipid-lowering therapy remained non-significantly associated with IRC-assessed PFS. The corresponding Kaplan-Meier curves are shown in Figure 2, and Cox regression estimates are summarized in Table 3.

Similarly, no significant association was observed between lipid-lowering therapy and overall survival in the sunitinib group. In univariable Cox regression analysis, the HR for OS was 0.64 (95% CI 0.37–1.11; P = 0.115). After multivariable adjustment, lipid-lowering therapy was not significantly associated with OS (Table 3).

Overall, these results indicate that the favorable association between lipid-lowering therapy and survival outcomes observed in the toripalimab plus axitinib group was not evident among patients receiving sunitinib.

Table 3. Univariable and multivariable Cox regression analysis for IRC-assessed PFS and OS in the sunitinib group

Variable	Univariable HR (95% CI)	P	Multivariable HR (95% CI)	P
IRC-assessed PFS				
Lipid-lowering therapy (yes vs no)	0.83 (0.54–1.27)	0.385	0.85 (0.55–1.32)	0.468
Age (per year)	1.00 (0.97–1.02)	0.723	1.00 (0.98–1.02)	0.771
Sex (female vs male)	1.02 (0.67–1.57)	0.922	1.21 (0.78–1.89)	0.387
BMI (per kg/m ²)	0.96 (0.90–1.01)	0.122	0.96 (0.90–1.01)	0.125
ECOG PS (1 vs 0)	1.07 (0.74–1.55)	0.732	1.17 (0.80–1.73)	0.417
Diagnosis-to-randomization interval (per month)	0.99 (0.98–1.00)	0.032	0.99 (0.98–1.00)	0.018
Number of metastatic sites (per site)	1.06 (0.87–1.28)	0.579	1.06 (0.88–1.29)	0.535
Overall survival				
Lipid-lowering therapy (yes vs no)	0.64 (0.37–1.11)	0.115	0.70 (0.40–1.23)	0.217
Age (per year)	0.99 (0.97–1.02)	0.484	0.99 (0.96–1.01)	0.406
Sex (female vs male)	1.23 (0.75–2.00)	0.418	1.46 (0.88–2.42)	0.147
BMI (per kg/m ²)	0.93 (0.87–1.00)	0.049	0.93 (0.87–1.00)	0.062
ECOG PS (1 vs 0)	1.05 (0.67–1.62)	0.842	1.16 (0.73–1.83)	0.536
Diagnosis-to-randomization interval (per month)	0.99 (0.98–1.00)	0.118	0.99 (0.98–1.00)	0.069
Number of metastatic sites (per site)	1.08 (0.86–1.34)	0.517	1.09 (0.87–1.37)	0.461

Table note:

HRs and 95% CIs were estimated using Cox proportional hazards models within the sunitinib group. For IRC-assessed PFS, 112 events were observed in univariable analyses and 111 events were included in the multivariable model. For OS, 80 deaths were observed in univariable analyses and 79 deaths were included in the multivariable model. The multivariable model included lipid-lowering therapy use, age, sex, BMI, ECOG performance status, diagnosis-to-randomization interval, and number of metastatic sites. HR < 1 indicates a lower risk of progression or death for PFS and a lower risk of death for OS.

3.4 IPTW-adjusted analysis

To further account for potential baseline imbalances between patients with and without lipid-lowering therapy, IPTW-adjusted Cox regression analyses were performed separately within each treatment group, and the results are summarized in Supplementary Table S6.

In the toripalimab–axitinib group, IPTW adjustment showed a consistent trend toward improved IRC-assessed progression-free survival among patients receiving lipid-lowering therapy, though not statistically significant (HR 0.62, 95% CI 0.38–1.04; P=0.068), whereas overall survival remained significantly associated with reduced risk of death (HR 0.48, 95% CI 0.26–0.88; P=0.018).

In the sunitinib group, no significant association was observed for either PFS (HR 0.91, 95% CI 0.61–1.36; P=0.641) or OS (HR 0.72, 95% CI 0.42–1.25; P=0.246), and these IPTW-adjusted findings were directionally consistent with univariable and multivariable Cox analyses. Additional sensitivity and diagnostic analyses, including BMI-excluded models (Table S1, Figure S1), interaction analyses (Table S2), and IPTW balance diagnostics (Table S5), supported the robustness of the main findings.

3.5 Objective response and disease control according to lipid-lowering therapy use

The association between lipid-lowering therapy and tumor response was evaluated using logistic regression analysis separately within each treatment arm (Supplementary Table S7). In treatment-stratified analyses, lipid-lowering therapy was not significantly associated with ORR or DCR in either the toripalimab plus axitinib group or the sunitinib group.

These findings suggest that lipid-lowering therapy was not significantly associated with tumor shrinkage or disease control within either treatment arm. The observed survival signal, particularly the OS association in the toripalimab plus axitinib group, may therefore not be primarily explained by improved objective tumor response.

3.6 Post hoc analyses according to lipid-lowering therapy class and lipid biomarkers

Among 113 lipid-lowering therapy (LLT) users, 91 (80.5%) received statins, 22 (19.5%) non-statins, and 19 (16.8%) combination therapy; median statin dose was 20 mg/day (Supplementary Tables S3 and S8).

Post hoc analyses by LLT class and baseline lipid biomarkers (Table S8) showed no stable difference in IRC-assessed PFS or OS between statin and non-statin users, suggesting the survival signal was not clearly attributable to a statin-specific effect. Baseline total cholesterol showed no consistent association with outcomes. Among LLT users, baseline triglycerides (TG) were evaluated using the 1.7 mmol/L cutoff within each treatment arm (Tables S8 and S4).

In the toripalimab–axitinib group, TG ≥ 1.7 mmol/L was associated with shorter PFS versus < 1.7 mmol/L (HR 3.21, 95% CI 1.29–8.03; $P=0.009$), while OS was not significant (HR 1.90, $P=0.242$). In the sunitinib group, the direction reversed: TG ≥ 1.7 mmol/L was associated with more favorable PFS (HR 0.43, 95% CI 0.20–0.94; $P=0.030$) and OS (HR 0.29, 95% CI 0.10–0.85; $P=0.016$).

Given the small sample size, treatment-stratified subgroups, and opposite directions between groups, these TG findings are post hoc and hypothesis-generating, not evidence that TG directly mediates the LLT–survival association.

4. Discussion

In this post hoc analysis of the phase III RENOTORCH trial, recorded oral lipid-lowering therapy use was associated with more favorable survival outcomes in patients with advanced RCC, with the most consistent signal observed for OS. This association was primarily apparent in patients receiving toripalimab plus axitinib, in whom lipid-lowering therapy remained significantly associated with improved OS after both multivariable Cox regression and IPTW adjustment. By contrast, no significant association with IRC-assessed PFS or OS was observed in the sunitinib group. These findings suggest that lipid-lowering therapy use may be linked to long-term outcomes in patients receiving immunotherapy-based combination therapy, although the results should be interpreted as hypothesis-generating rather than causal.

The treatment landscape of advanced RCC has been substantially reshaped by ICI-based combinations, including dual immune checkpoint blockade and PD-1/PD-L1 inhibitors combined with VEGF/VEGFR-targeted therapy [7–12,49,50]. The RENOTORCH trial further demonstrated that toripalimab plus axitinib improved clinical outcomes compared with sunitinib as first-line treatment for advanced RCC [13]. However, treatment benefit remains heterogeneous, and clinical factors associated with durable survival remain incompletely understood. Established prognostic frameworks, including MSKCC and IMDC-related models, have provided important tools for risk stratification in metastatic RCC, particularly in patients treated with cytokine-based or VEGF-targeted therapies [44–48]. Nevertheless, these models do not directly account for concomitant medication use or lipid/metabolic factors. In recent years, increasing attention has been paid to concomitant medications, which may influence immunotherapy outcomes through effects on the gut microbiome, systemic inflammation, metabolic pathways, and the tumor immune microenvironment [17–20].

A notable feature of the present analysis is that lipid-lowering therapy was associated more consistently with OS than with short-term tumor response. In the toripalimab plus axitinib group, the association with IRC-assessed PFS showed a favorable but non-significant trend, whereas the OS association remained statistically significant after adjustment. Moreover, lipid-lowering therapy was not significantly associated with ORR or DCR in either treatment arm. This pattern suggests that the observed OS signal is unlikely to be explained simply by greater tumor shrinkage or improved short-term disease control. Instead, lipid-lowering therapy use may reflect longer-term host-related factors, including metabolic status, cardiovascular risk management, inflammatory regulation, or immune-metabolic interactions.

The medication-class analysis further refines the interpretation of our findings. Among patients with recorded lipid-lowering therapy use, statins were the predominant agents; however, no stable difference in PFS or OS was observed between statin and non-statin users. Therefore, although statins provide a biologically plausible framework through inhibition of the mevalonate pathway, effects on protein prenylation, and anti-inflammatory or immunomodulatory properties [21–26], the present dataset does not support attributing the observed survival association to a clearly identifiable statin-specific effect. This may reflect limited sample size, heterogeneous drug exposure, combination lipid-lowering therapy, or the possibility that lipid-lowering therapy use partly represents broader metabolic management rather than a single drug-class effect.

The lipid biomarker findings should also be interpreted cautiously. Blood lipid metabolism includes cholesterol, triglycerides, phospholipids, fatty acids, and lipoprotein particles [21,51]. Therefore, total cholesterol represents only one component of lipid metabolism and should not be equated with overall lipid status. In the present analysis, baseline TC was not consistently associated with survival outcomes. Among lipid-lowering therapy users, TG-stratified analyses showed treatment-context-dependent patterns, with TG ≥ 1.7 mmol/L associated with shorter PFS in the toripalimab plus axitinib group but more favorable PFS and OS in the sunitinib group. Given the small subgroup sample size, opposite directions between treatment groups, and multiple nominal comparisons, these TG findings should be regarded as exploratory rather than evidence that TG directly mediates the association between lipid-lowering therapy and survival.

The biological plausibility of a relationship between lipid-lowering therapy and outcomes of ICI-based treatment remains relevant. Dysregulated cholesterol metabolism has been shown to affect CD8 + T-cell exhaustion, antigen presentation, and tumor immune escape, whereas modulation of cholesterol metabolism may enhance antitumor immune responses [27–29]. More broadly, lipid metabolic reprogramming can remodel the tumor microenvironment by influencing tumor-cell energy supply, membrane synthesis, lipid signaling, macrophage polarization, myeloid-derived suppressor cell activity, and T-cell function [52]. Advanced RCC is also a vascular and immunologically active tumor, and anti-VEGF therapy may normalize tumor vasculature, reduce immunosuppressive cell infiltration, and enhance T-cell trafficking, thereby supporting immune checkpoint blockade [40–43]. Within this context, lipid-lowering therapy may influence long-term outcomes through systemic inflammatory and immune-metabolic pathways, although this mechanism remains indirect in the present dataset.

Previous studies evaluating statins or other concomitant medications in patients receiving ICIs have produced inconsistent results across tumor types, treatment settings, medication exposure definitions, and study designs [17–20,30–34]. In RCC, several reports and meta-analyses have suggested potential

associations between statin use and improved survival, but most evidence has come from retrospective or real-world cohorts [35–38]. The present study adds to this literature by leveraging data from a randomized phase III trial with standardized treatment protocols, follow-up, and outcome assessment. Nevertheless, because lipid-lowering therapy use was not randomized, these results should not be interpreted as evidence that lipid-lowering therapy itself causes improved survival.

Several limitations should be acknowledged. First, lipid-lowering therapy use was defined according to recorded medication use and may be affected by indication bias and residual confounding despite multivariable adjustment and IPTW analysis. Second, patients receiving lipid-lowering therapy differed from non-users in metabolic and cardiovascular comorbidities, which may reflect underlying differences in host metabolic status. Third, detailed information on treatment timing, duration, adherence, dose intensity, and longitudinal lipid changes was limited, and medication exposure could not be modeled as a dynamic pharmacologic intervention. Fourth, statin-versus-non-statin comparisons and TG subgroup analyses involved small sample sizes and multiple nominal comparisons.

5. Conclusion

In conclusion, recorded oral lipid-lowering therapy use was associated with improved survival outcomes in patients with advanced RCC in this post hoc analysis of the RENOTORCH trial, with the most consistent association observed for OS in patients receiving toripalimab plus axitinib.

Lipid-lowering therapy was not associated with improved ORR or DCR, suggesting that the observed OS signal was not primarily explained by short-term objective tumor response. In addition, no stable survival difference was observed between statin and non-statin lipid-lowering therapy users, and baseline TC was not consistently associated with outcomes. TG-related findings among lipid-lowering therapy users were suggestive but showed opposite directions between treatment groups, supporting cautious interpretation.

Overall, these findings suggest a potential relationship between lipid-lowering therapy, lipid metabolism, and long-term outcomes in patients receiving systemic therapy for advanced RCC.

Declarations

Ethics approval and consent to participate

This study was a post hoc analysis based on data from the phase III RENOTORCH trial. The RENOTORCH trial was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and applicable regulatory requirements. The study protocol and all amendments were approved by the institutional review boards or ethics committees at participating centers. All patients provided written informed consent before enrollment.

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Declaration of competing interests

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Author contributions

Yabo Zhai and Xiaowen Wu contributed to study conception and design, data analysis, interpretation of results, and drafting of the manuscript. Xieqiao Yan and Juan Li contributed to data collection, data verification, and interpretation of clinical findings. Yihao Zhu, Xuwen Li, Jianguo Zheng, and Xinghang Dai contributed to data curation, statistical review, and manuscript revision. Nianzeng Xing, Jun Guo, Xiongjun Ye, and Xinan Sheng contributed to study supervision, clinical interpretation, project administration, and critical revision of the manuscript. All authors reviewed and approved the final version of the manuscript.

Data availability statement

The data analyzed in this study were obtained from the RENOTORCH clinical trial database. Individual patient-level data are not publicly available due to clinical trial data protection policies and applicable regulatory requirements. Data access may be considered upon reasonable request and subject to approval by the trial sponsor and relevant regulatory or institutional requirements.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this manuscript, the authors used ChatGPT for language editing and improving readability. The authors reviewed and edited the content and take full responsibility for the final version of the manuscript.

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Figures

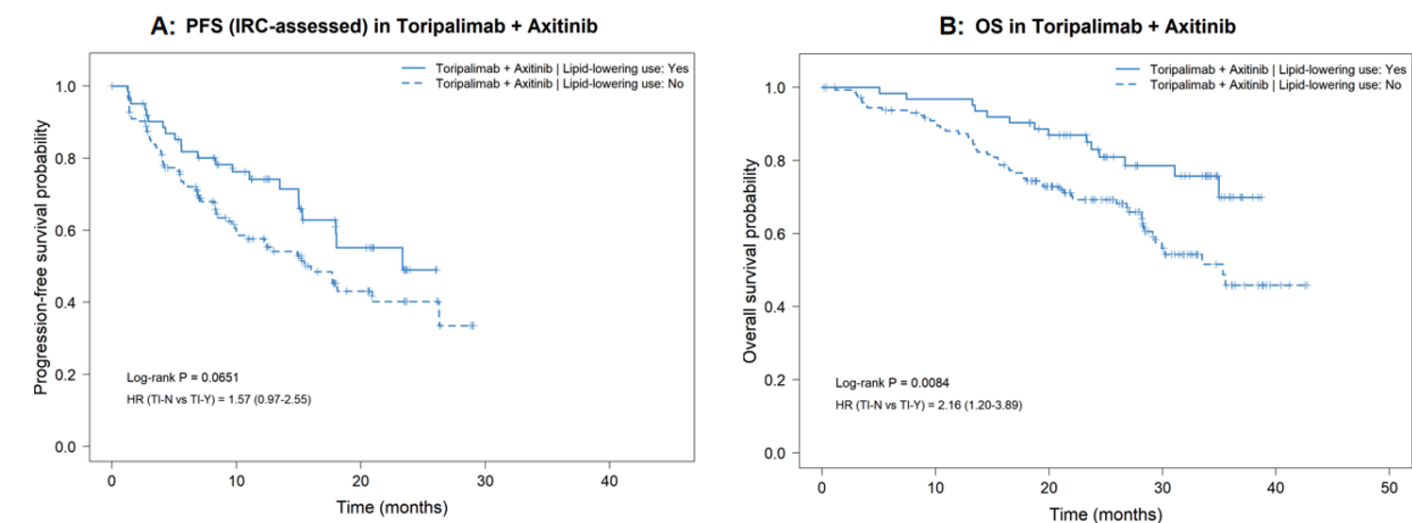


Figure 1

Survival outcomes according to lipid-lowering therapy use in the toripalimab plus axitinib group.

(A) IRC-assessed progression-free survival. (B) Overall survival. P values were calculated using the log-rank test. HRs and 95% CIs were estimated using Cox proportional hazards models.

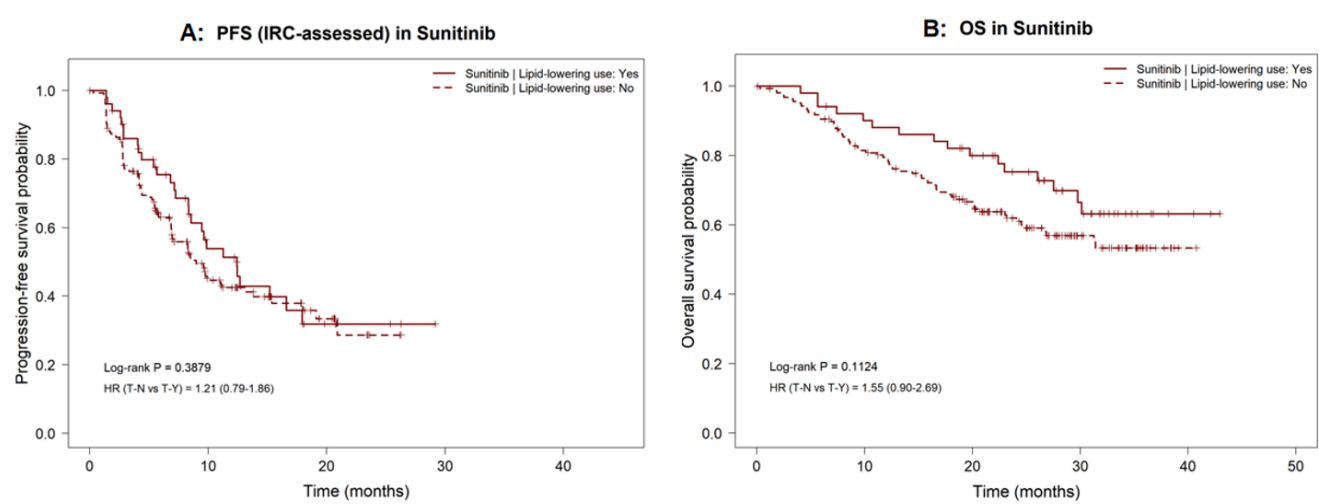


Figure 2

Survival outcomes according to lipid-lowering therapy use in the sunitinib group.

(A) IRC-assessed progression-free survival. (B) Overall survival. P values were calculated using the log-rank test. HRs and 95% CIs were estimated using Cox proportional hazards models.

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