Risk of Metabolic Complications in Patients with Solid Tumors Treated with mTOR inhibitors: Meta-analysis

SUNGYUB LEW[1,3] and RONALD S. CHAMBERLAIN[1,2,3]

[1]Department of Surgery, Saint Barnabas Medical Center, Livingston, NJ, U.S.A.;
[2]Department of Surgery, New Jersey Medical School, Rutgers University, Newark, NJ, U.S.A.;
[3]Saint George's University School of Medicine, St. George, Grenada, West Indies

Abstract. *Background/Aim: Numerous trials have described a wide variation of metabolic complications associated with the mammalian target of rapamycin inhibitors (mTORi). This analysis aimed to report and critically analyze the risks of mTORi-associated metabolic complications. Materials and Methods: A comprehensive search of all published phase II or III randomized controlled trials were investigated. Outcomes included were adverse effect profiles of hyperglycemia (HGC), hypertriglyceridemia (HTG), and hypercholesterolemia (HCE). Results: Sixteen phase II/III clinical trials were identified. The overall incidence of all-grade (AG) and high-grade (HG) metabolic complications associated with mTORi were 39.7% and 4.1% respectively. mTORi use was associated with an increased risk of AG (2.97 [2.25-3.92]) and HG HGC (4.08 [2.71-6.14]), AG (2.22 [1.70-2.89]) and HG HTG (1.88 [1.10-3.20]), and AG (2.48 [1.83-3.36]) and HG HCE (4.26 [2.30-7.90]). Conclusion: mTORi are associated with a significantly increased risk of AG and HG HGC, HTG, and HCE. Clinicians should be aware of these risks, perform regular monitoring, and consider alternative anti-neoplastic treatments or adjunctive pharmacological intervention if necessary.*

The mammalian target of rapamycin (mTOR) is a serine-threonine kinase that plays a vital role in phosphatidylinositol 3-kinase/Akt pathway that is involved in cell proliferation,

Correspondence to: Ronald S. Chamberlain, MD, MPA, FACS, Chairman and Surgeon-in-Chief, Department of Surgery, Saint Barnabas Medical Center, Professor of Surgery, Rutgers University, New Jersey Medical School (NJMS), 94 Old Short Hills Rd. Livingston, NJ 07039, U.S.A. Tel: +1 9733225195, Fax: +1 9733222471, e-mail: rchamberlain@barnabashealth.org

motility, metabolism, and angiogenesis (1, 2). mTOR inhibitors (mTORi) have been shown to inhibit tumor proliferations and angiogenesis in various *in vitro* tumor models (3). The Food and Drug Administration (FDA) has approved everolimus for the treatment of advanced renal cell carcinoma (RCC), pancreatic neuroendocrine tumor (pNET), advanced hormone receptor-positive, HER2-negative breast cancer and subependymal giant cell astrocytoma with or without association with tuberous sclerosis (3). Temsirolimus has been approved by FDA for the treatment of advanced RCC (4). Ridaforolimus has yet to be approved by FDA, but is currently in phase III clinical trials.

mTORi are associated with substantial side-effects including weight gain, hyperlipidemia, diarrhea, infection, fatigue, hypertension (5-7). In addition to these frequently reported adverse events, prior studies have also reported an increased risk of proteinuria, pulmonary toxicities, anemia, and impaired wound healing with mTORi therapy (8-10).

In a prior meta-analysis by Sivendran *et al*., significantly higher incidence and risk of metabolic complications were observed in patients administered mTORi: all-grade incidence 70% (95%CI=0.47-0.93], high-grade incidence 11% (95%CI=0.08-0.15), all-grade relative risk (RR) 2.93 (95%CI=2.33-3.70), and high-grade RR=4.58 (95%CI=2.86-7.34) respectively (11). That said, there existed several limitations to these analyses, including overestimation of the incidence of mTORi-associated hyperglycemia (HGL), hypertriglyceridemia (HTG) and hypercholesterolemia (HCE), since mTORi monotherapy and combinational therapy were analyzed together. Several recent large, randomized clinical trials have been completed since the previous meta-analysis with substantial variation in results. This study includes patients only receiving mTORi monotherapy alone in order to exclude the confounding impact of concomitant chemo- or immunotherapy for incidence analysis. In addition, to better understand the extent of the mTORi associated metabolic complications, an investigation of underlying malignancy type, dosage regimen, and comparison between mTORi rapamycin analogs were further explored.

This current meta-analysis provides an updated comprehensive analysis of the incidence and risk of high-grade HGL, HTG, and HCE with mTORi treatment, and a contemporary systematic review of mTORi treatment.

Materials and Methods

Data acquisition. Data abstraction, meta-analysis, and systemic review have been performed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guideline (12). A comprehensive literature search of PubMed, Google Scholar and the Cochrane Central Registry of Controlled Trials from January 1, 1966 to March 31, 2015 was conducted. Keywords included in the search were 'mTOR inhibitor', 'everolimus', 'afinitor', 'temsirolimus', 'torisel', 'ridaforolimus', 'deforolimus', 'cancer', and 'clinical trial'. The search was restricted to clinical trials in English. In case of duplicate publications, only the most recent and updated report of the clinical trial was included.

Study selection, data extraction, and clinical end-points. Clinical trials that met the following conditions were included in this study: (i) Phase II and III trials in patients with cancer; (ii) Participants assigned to treatment with everolimus, temsirolimus, or ridaforolimus; (iii) Events and sample size available for all-grade or high-grade hyperglycemia (HGL), hypertriglyceridemia (HTG), or hypercholesterolemia (HCE) (grade 3 and 4); (iv) Safety reporting of all- or high-grade hyperglycemia, hypertriglyceridemia, or hypercholesterolemia available. Analysis of the incidence of HGL, HTG, and HCE associated with mTORi were limited to trials in which participants were assigned to mTORi as a monotherapy.

The incidence of HGL, HTG, and HCE events in most included trials were recorded in accordance with Common Terminology Criteria for Adverse Events (CTCAE) version 3, which defines HGL as the following: (a) grade 1, upper normal limit (UNL) to 160 mg/dL, (b) grade 2, 160-250 mg/dL, (c) grade 3, 250-500 mg/dL and (d) grade 4, >500 mg/dL. CTCAE also defines HTG as: (a) grade 1, 1.0-2.0 times of UNL, (b) grade 2, 2.5-5.0 times of UNL, (c) grade 3, 5-10 times of the UNL, (d) grade 4, >10 times of UNL. Lastly, HCE is defined in CTCAE version 3 as the following: (a) grade 1, UNL-300 mg/dL, (b) grade 2, 300-400 mg/dL (c) grade 3, 400-500mg/dL (d) grade 4, > 500 mg/dL (13).

Assessment of RR includes only RCTs in which participants were randomly assigned to either mTORi versus placebo, mTORi plus best supportive care versus placebo plus best supportive care, or mTORi plus concurrent chemotherapy and/or immunotherapy versus chemotherapy and/or immunotherapy alone. In case of crossover studies, only data available prior to crossing over were used. If data prior to crossing over was not available, the study was excluded.

Statistical analysis. Incidence, RR and 95% CIs for all-grade (grade 1-4) and high-grade (grade 3-4) HGL, HTG, and HCE were calculated. RRs and CIs were calculated with data extracted only from randomized controlled studies and the adverse metabolic events in patients assigned to mTORi was compared to those assigned to control treatment in the same trial. To calculate 95% CIs, the variance of a log-transformed study-specific RR was derived using the delta method. To estimate the incidence, the number of patients with metabolic complications and the number of patients who received mTORi alone were extracted from selected single-arm and RCTs. The rate of adverse outcomes and
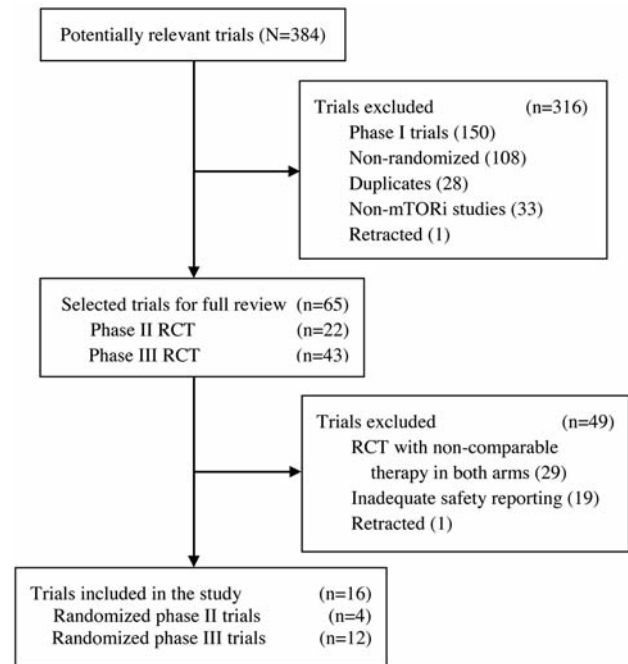

Figure 1. *CONSORT diagram of selection process for clinical trial inclusion in this meta-analysis.*

95% CIs were obtained from each trial. The traditional continuity corrections factor of 0.5 was adopted to calculate the RR and variance for the studies reporting zero events in any arm. In case of zero events in both groups, the RR were not calculable, and the study was excluded from the meta-analysis. Both the fixed-effect and random effects model were considered, depending on the heterogeneity of included studies, to calculate RRs and summary incidence. Cochrane's Q test with I^2 statistic were used to estimated statistical heterogeneity. An assumption of homogeneity was considered invalid for $p < 0.05$ or $I^2 > 50\%$. When substantial heterogeneity was not observed, the pooled estimate was calculated based on the fixed-effect model. When significant heterogeneity was observed, the pooled estimate calculated with a random-effects model was reported. The publication bias regarding the primary endpoint (RR of high-grade HGL, HTG, and HCE) was first visually evaluated funnel plot, and then quantified by Begg's, and Egger's tests. A two-tailed *p*-value of <0.05 was considered statistically significant. Statistical analysis was performed using the Comprehensive Meta-Analysis software Version 3 (Biostat, Englewood, NJ).

Results

Search results. The search strategy detailed above yielded 271 potentially relevant citations. The selection process excluded 224 citations. The study exclusion criteria are detailed in Figure 1. A total of 47 clinical trials were considered eligible for the meta-analysis. Among the 47 phase II and III trials, 15 trials involved randomized

treatment allocation, while 32 trials were single-arm trials. Of the 15 RCTs, 6 trials had placebo as a control and 9 trials had active treatment as the control arms. The metabolic adverse events in the included trials were reported in accordance with the CTCAE version 3. The baseline characteristics of each trial are depicted in Table I.

Overall incidence of adverse metabolic events. The analysis of metabolic event incidence included only mTORi monotherapy arms. The trials that involved concomitant chemotherapy and/or immunotherapy were excluded, given the possibility of confounding effects on blood pressure from concomitant therapy. A total of 1,754 mTORi-treated patients from both randomized and non-randomized studies were included. All-grade metabolic derangements occurred in 409 of 1,036 patients; 39.7% (95%CI=18.7-42.4). High-grade metabolic complications occurred in 73 of 1,754 patients; 4.1% (95%CI=1.7-6.9). For both all- and high-grade adverse metabolic events, there was significant heterogeneity between trials ($p<0.001$ and I2=88%) and a random-effects model was assumed.

Relative risk of adverse metabolic event events. The meta-analysis of the overall RR for all- and high-grade metabolic events included 15 RCTs. The control arm was best supportive care or chemotherapy and/or immunotherapy. The treatment arm was mTORi in addition to best supportive care or chemotherapy and/or immunotherapy. The RR of all-grade and high-grade metabolic events associated with mTORi compared to control was 2.53 (95%CI=2.15-2.97, $p<0.001$) and 3.29 (95%CI=2.47-4.14, $p=0.001$) respectively (Figures 2 and 3). A random-effects model was used for both all-grade and high-grade metabolic events since heterogeneity was found to be significant in both cases ($p<0.05$ and $I^2>50\%$).

Sub-group analyses. Given the potential risk of blood glucose, triglyceride, or cholesterol elevation occuring as a result of concomitant chemotherapeutic or immunotherapeutic agents, the impact of the control arm on RR of high-grade metabolic events with mTORi treatment was analyzed. Among 15 RCTs, 6 trials involved mTORi as a single agent and 9 trials used mTORi in combination with chemotherapeutic and/or immunotherapeutic agents. The RR of high-grade metabolic derangement in combination therapy was 3.19 (95%CI=2.29-4.46, $p<0.001$) and the RR of high-grade metabolic complications in mTORi monotherapy was 3.58 (95%CI=2.05-6.26, $p<0.001$). There was no difference observed in the RR of high-grade metabolic events between mTORi monotherapy and combination therapy ($p=0.835$) (Figure 3). The incidence and RR of high-grade metabolic events were further assessed by malignancy type and dosage regimen. The malignancy types studied were breast cancer (BC) and renal cell cancer (RCC). There was no difference in the incidence of the high-grade

metabolic complications varies between these two malignancies. There was no difference in the RR of high-grade metabolic events between RCC and non-RCC, and BC and non-BC. Metabolic events also did not differ by dosage of everolimus ($p=0.759$). Finally, no differences in the RR of high-grade metabolic events were observed between everolimus and temsirolimus ($p=0.835$) (Table II).

Publication bias. A funnel plot was used to qualitatively assess for publication bias. In addition, Egger's and Begg's tests were calculated to quantitatively access for publication bias. No evidence of publication bias for the primary outcome of HGL, HTG, and HCE were observed by Egger and Begg's test: HGL (Begg's test: $p=0.09$, Egger's test: $p=0.47$), HTG (Begg's test: $p=0.80$, Egger's test: $p=0.11$), and HCE (Begg's test: $p=0.76$, Egger's test: $p=0.91$) respectively.

Discussion

HGL, HTG, and HCE are common adverse events observed in clinical trials associated with mTOR inhibitor class medications. This study demonstrated that a high incidence of metabolic complications are associated with mTORi therapy in cancer patients (all-grade: 39% (95% CI=27.3-51.5)). The majority of mTORi-associated adverse metabolic events were grade I or II; however, high-grade metabolic complications in association with mTORi use were not infrequent (high-grade: 3.4% (95%CI=1.8-4.9)).

The exact mechanism of mTOR inhibitor-associated metabolic derangements is unclear. In a mouse model of type 2 diabetes, rapamycin was shown to increase insulin resistance and reduce beta cell function (14). Insulin is a key hormone regulating metabolism, clearance, and storage of both glucose and lipids. In a separate study of the effect of rapamycin on rat hepatocytes, rapamycin was shown to induce a fasting metabolic state by affecting fatty acid metabolism (15). Promotion of beta oxidation while decreasing influx of anabolic storage pathways induces fasting metabolic phenotype, where there is a preference for fatty acid as metabolic fuel and increased rate of lipolysis resulting in high serum fatty acids. Additionally, rapamycin has been shown to affect insulin-stimulated lipoprotein lipase (LPL) in a rat adipose cell (16). Finally, mTOR inhibitors also impair the clearance of lipid from blood rather than increasing hepatic synthesis by inhibition of insulin-stimulated LPL. The aforementioned mechanism of action of rapamycin in an animal model demonstrated interference with insulin signaling and simulating on insulin resistance also may partly explain the hyperglycemic state (17).

Currently, there exist no evidence-based guidelines for the management of mTOR inhibitor-induced hyperlipidemia or hyperglycemia. Although elevated triglyceride and LDL cholesterol are risk factors for the development of

Table I. *Characteristics of all clinical trials included in the current meta-analysis.*

Author	Year	Phase	Histology	N (enrolled)	Median (range)			Treatment arms	N (analyzed)	CTCAE version
					Age (years)	Treatment duration (months)	PFS (month)			
Zhu et al. (24)	2014	III	HCC	546	58 (23-84)	1.9 (0-7.9)	6.8 (4-8)	EVE 7.5 mg/d vs. placebo	202	3
Rini et al. (25)	2014	III	RCC	791	NR	11 (1-41)	11 (11-13)	TEM 25 mg/wk + BEV 10 mg q 2wk vs. IFN 9MIU 3/wk + BEV 10 mg q 2wk	375	3
Hutson et al. (26)	2014	III	RCC	512	53 (25-80)	2 (0-16.2)	2.8 (2.4-4.4)	TEM 25 mg/2k vs. SOR 400 mg BID	238	3
Andre et al. (27)	2014	III	BC	569	58 (31-81)	2.8	NR	EVE 5 mg/d + VR vs. placebo +VR	23	3
Yardley et al. (28)	2013	III	BC	724	65 (45-80)	1.5	3.8 (3.5-7.3)	EVE 10 mg/d + EXMST 25 mg/d vs. placebo + EXMST 25 mg/d	29	3
Ohtsu et al. (29)	2013	III	GC	656	58 (36-72)	NR	2.8	EVE 10 mg/d + BSC vs. placebo + BSC	36	3
Maas et al. (30)	2013	II	BC	39	56 (25-84)	4.6 (0.4-17.5)	11.4 (7.4-19.8)	EVE 10 mg/d vs. placebo	83	3
Demetri et al. (31)	2013	III	Sarcoma	702	57 (27-84)	0.3 (0.1-1.6)	7.4 (6.9-8.5)	RID 40 mg vs. Placebo	235	3
Wolff et al. (32)	2012	III	BC	1103	54 (31-84)	6.5 (5.7-7.3)	8.6 (8.2-10.3)	TEM 30 mg/d + LTZ 2.5 mg/d vs. Placebo + LTZ 2.5 mg/d	295	3
Baselga et al. (33)	2012	III	BC	720	57 (23-84)	3 (0.3-22)	5.7 (2.7-7)	EVE + EXMST vs. Placebo + EXMST	228	3
Yao et al.(34)	2011	III	PNET	407	61 (31-85)	4.3	3.6	EVE 10 mg/d + BSC vs. Placebo + BSC	473	3
Pavel et al. (35)	2011	III	NET	426	59 (25-83)	NR	7.8 (7.1-8.4)	EVE 10 mg/d + OTR 30 mg q28d vs. Placebo + OTR 30 mg q28d	384	3
Negrier et al. (36)	2011	II	RCC	128	59 (18-85)	NR	3.6 (2.8-4.1)	TEM 25 mg/wk + BEV 10 mg q 2wk vs. IFN 9MIU 3/wk + BEV 10mg q 2wk	526	3
Motzer et al. (37)	2010	II	RCC	411	52 (27-79)	3.8 (2.9-4.4)	5.4 (4.4-5.8)	EVE 10 mg/d + BSC vs. Placebo + BSC	217	3
Baselga et al. (38)	2009	II	BC	269	57 (30-78)	2.3 (0.3-5.6)	2.2 (1.9-2.3)	EVE 10 mg/d + LTZ 2.5 mg/d vs. Placebo + LET2.5 mg/d	137	3
Hudes et al. (39)	2007	III	RCC	408	57 (32-81)	7.2 (0.9-19.4)	7.3	TEM 25 mg/wk + IFN vs. IFN	208	3

N: Sample size; PFS: progression-free survival; BC: breast cancer; RCC: renal cell cancer; pNET: pancreatic neuroendocrine tumor; NET: neuroendocrine tumor; NR: not reported; EVE: everolimus; TEM: temsirolimus; RID: ridafolimus; IFN: interferon; BEV: bevacizumab; LTZ: letrozole; OTR: octreotide; EXMST:exemestane; VR: vinorelbine; SOR: sorafenib; BSC: best supportive care.
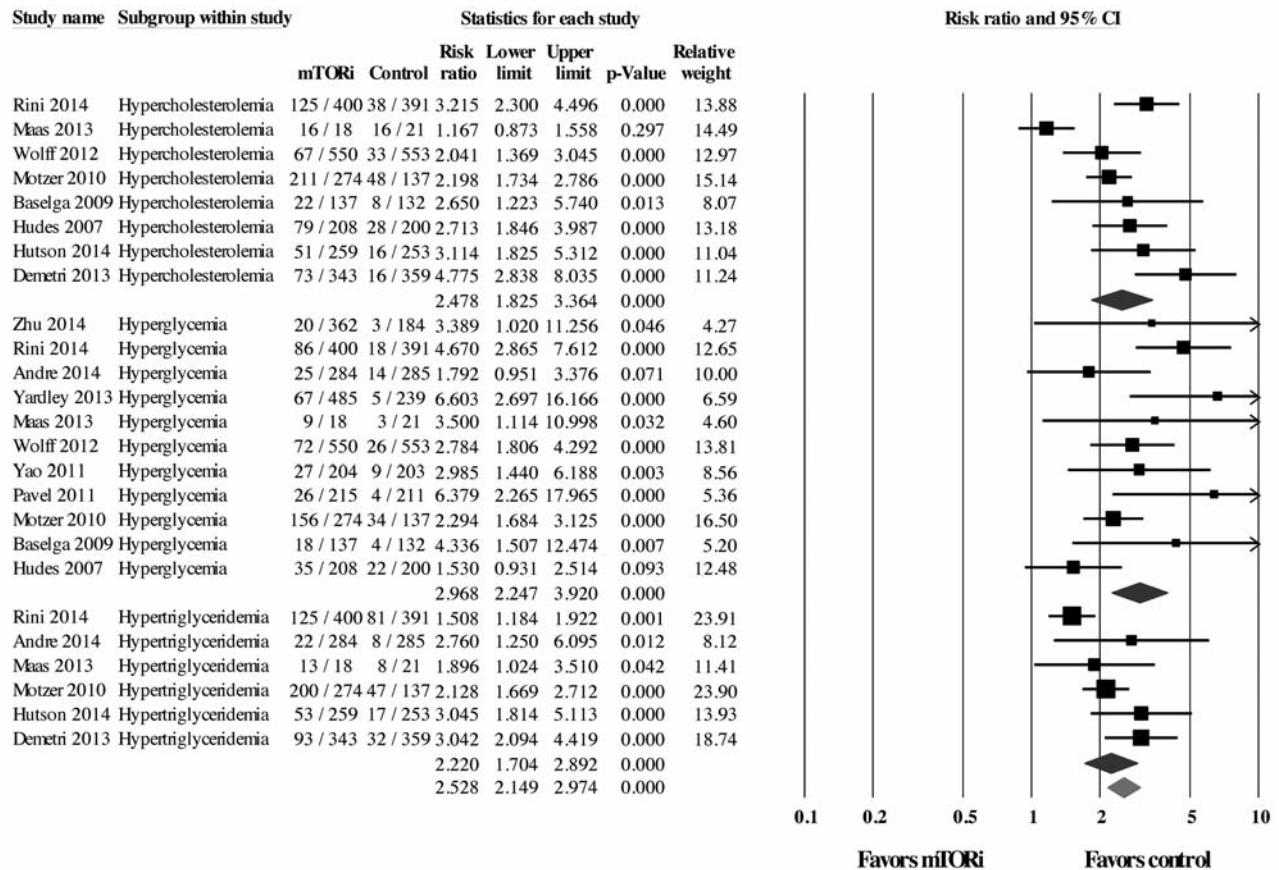
Study name	Subgroup within study	Statistics for each study						Risk ratio and 95% CI
		mTORi	Control	Risk ratio	Lower limit	Upper limit	p-Value	Relative weight
Rini 2014	Hypercholesterolemia	125 / 400	38 / 391	3.215	2.300	4.496	0.000	13.88
Maas 2013	Hypercholesterolemia	16 / 18	16 / 21	1.167	0.873	1.558	0.297	14.49
Wolff 2012	Hypercholesterolemia	67 / 550	33 / 553	2.041	1.369	3.045	0.000	12.97
Motzer 2010	Hypercholesterolemia	211 / 274	48 / 137	2.198	1.734	2.786	0.000	15.14
Baselga 2009	Hypercholesterolemia	22 / 137	8 / 132	2.650	1.223	5.740	0.013	8.07
Hudes 2007	Hypercholesterolemia	79 / 208	28 / 200	2.713	1.846	3.987	0.000	13.18
Hutson 2014	Hypercholesterolemia	51 / 259	16 / 253	3.114	1.825	5.312	0.000	11.04
Demetri 2013	Hypercholesterolemia	73 / 343	16 / 359	4.775	2.838	8.035	0.000	11.24
				2.478	1.825	3.364	0.000	
Zhu 2014	Hyperglycemia	20 / 362	3 / 184	3.389	1.020	11.256	0.046	4.27
Rini 2014	Hyperglycemia	86 / 400	18 / 391	4.670	2.865	7.612	0.000	12.65
Andre 2014	Hyperglycemia	25 / 284	14 / 285	1.792	0.951	3.376	0.071	10.00
Yardley 2013	Hyperglycemia	67 / 485	5 / 239	6.603	2.697	16.166	0.000	6.59
Maas 2013	Hyperglycemia	9 / 18	3 / 21	3.500	1.114	10.998	0.032	4.60
Wolff 2012	Hyperglycemia	72 / 550	26 / 553	2.784	1.806	4.292	0.000	13.81
Yao 2011	Hyperglycemia	27 / 204	9 / 203	2.985	1.440	6.188	0.003	8.56
Pavel 2011	Hyperglycemia	26 / 215	4 / 211	6.379	2.265	17.965	0.000	5.36
Motzer 2010	Hyperglycemia	156 / 274	34 / 137	2.294	1.684	3.125	0.000	16.50
Baselga 2009	Hyperglycemia	18 / 137	4 / 132	4.336	1.507	12.474	0.007	5.20
Hudes 2007	Hyperglycemia	35 / 208	22 / 200	1.530	0.931	2.514	0.093	12.48
				2.968	2.247	3.920	0.000	
Rini 2014	Hypertriglyceridemia	125 / 400	81 / 391	1.508	1.184	1.922	0.001	23.91
Andre 2014	Hypertriglyceridemia	22 / 284	8 / 285	2.760	1.250	6.095	0.012	8.12
Maas 2013	Hypertriglyceridemia	13 / 18	8 / 21	1.896	1.024	3.510	0.042	11.41
Motzer 2010	Hypertriglyceridemia	200 / 274	47 / 137	2.128	1.669	2.712	0.000	23.90
Hutson 2014	Hypertriglyceridemia	53 / 259	17 / 253	3.045	1.814	5.113	0.000	13.93
Demetri 2013	Hypertriglyceridemia	93 / 343	32 / 359	3.042	2.094	4.419	0.000	18.74
				2.220	1.704	2.892	0.000	
				2.528	2.149	2.974	0.000	

Figure 2. *Relative risk of all-grade metabolic events associated with mTORi versus control.*

Table II. *Incidence and relative risk of high-grade metabolic events stratified by type of malignancy.*

Stratification	Incidence (95% CI)	Difference (*p*-value)	Relative Risk (95% CI)	Difference (*p*-value)
RCC	4.9% (2.1-7.6)	0.221	3.33 (2.26-4.91)	0.71
Non-RCC	2.6% (2.1-7.6)		3.25 (2.12-4.97)	
BC	2.5% (0.7-4.3)	0.109	3.56 (1.96-6.49)	0.91
Non-BC	4.3% (0.3-5.6)		3.21 (2.32-4.38)	
Hyperglycemia	5.3% (4-6.6)	0.001	4.08 (2.71-6.14)	5.98
Hypertriglyceridemia	2.4% (0.8-4.2)		1.88 (1.10-3.20)	
Hypercholesterolemia	2% (0.6-3.4)		4.26 (2.30-7.90)	

BC: Breast cancer; Non-BC: Non Breast Cancer; RCC: renal cell cancer; Non-RCC: non-renal cell cancer.

cardiovascular disease, therapy is typically aimed at long-term risk reduction. The benefit of lipid-lowering agents in advanced cancer population whose life expectancy is short and who are under chemotherapy is unknown. As such, the overall goal of therapy should be management of short-term morbidity secondary to mTORi-induced metabolic complications rather than long-term cardiovascular risk reduction. Busaidy *et al*., suggested targeting a triglyceride level of below 300 mg/dL for patients with life expectancy of >1 year and triglyceride less than 500 mg/dL for those with life expectancy <1 year in only to decrease the risk of pancreatitis and cardiovascular events. Statin was recommended for hypertriglyceridemia <500 mg/dL, and single or a combination of fibrate, omega 3 acid, or niacin for triglyceride >500 mg/dL in those with estimated survival <1 year. In case of poor glycemic control, Busaidy *et al*. suggested a fasting glucose goal of <160 mg/dL, random
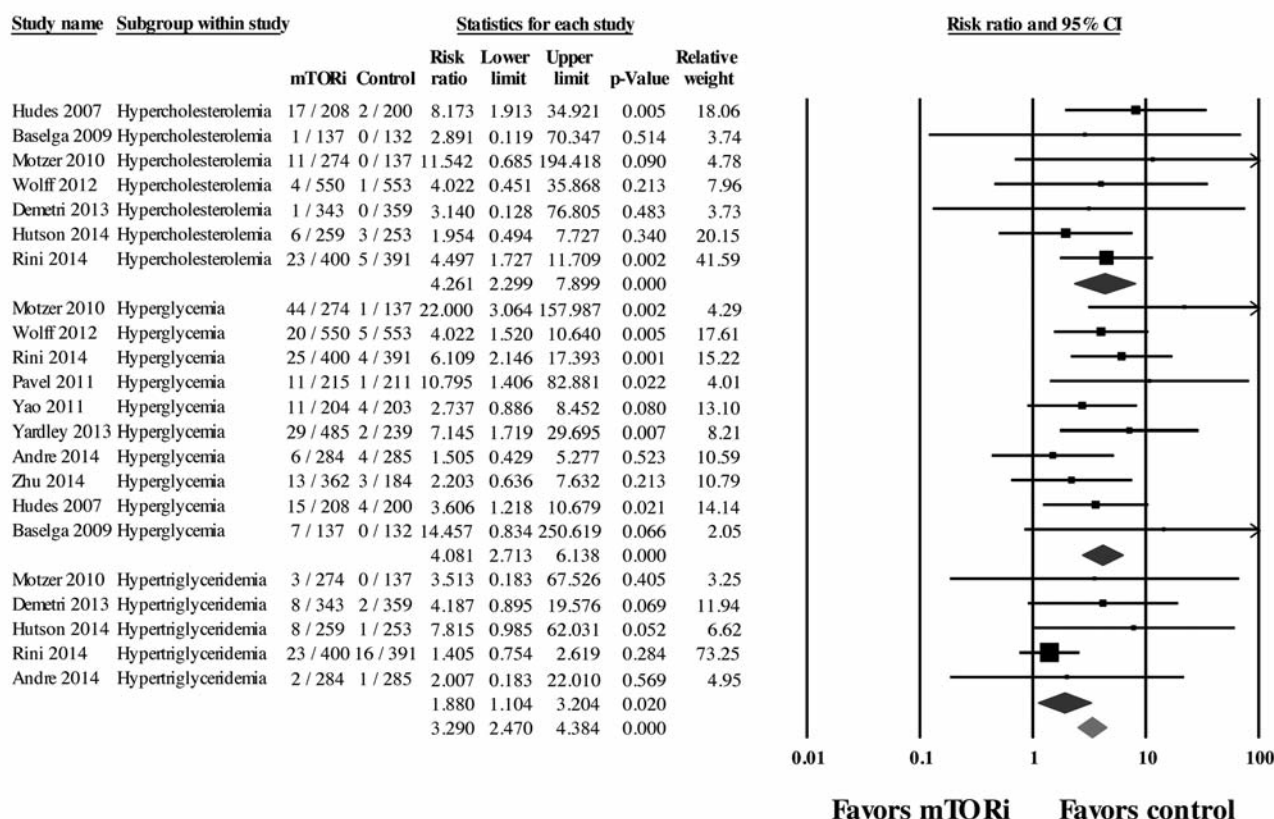
Study name	Subgroup within study			Statistics for each study					Risk ratio and 95% CI
		mTORi	Control	Risk ratio	Lower limit	Upper limit	p-Value	Relative weight	
Hudes 2007	Hypercholesterolemia	17 / 208	2 / 200	8.173	1.913	34.921	0.005	18.06	
Baselga 2009	Hypercholesterolemia	1 / 137	0 / 132	2.891	0.119	70.347	0.514	3.74	
Motzer 2010	Hypercholesterolemia	11 / 274	0 / 137	11.542	0.685	194.418	0.090	4.78	
Wolff 2012	Hypercholesterolemia	4 / 550	1 / 553	4.022	0.451	35.868	0.213	7.96	
Demetri 2013	Hypercholesterolemia	1 / 343	0 / 359	3.140	0.128	76.805	0.483	3.73	
Hutson 2014	Hypercholesterolemia	6 / 259	3 / 253	1.954	0.494	7.727	0.340	20.15	
Rini 2014	Hypercholesterolemia	23 / 400	5 / 391	4.497	1.727	11.709	0.002	41.59	
				4.261	2.299	7.899	0.000		
Motzer 2010	Hyperglycemia	44 / 274	1 / 137	22.000	3.064	157.987	0.002	4.29	
Wolff 2012	Hyperglycemia	20 / 550	5 / 553	4.022	1.520	10.640	0.005	17.61	
Rini 2014	Hyperglycemia	25 / 400	4 / 391	6.109	2.146	17.393	0.001	15.22	
Pavel 2011	Hyperglycemia	11 / 215	1 / 211	10.795	1.406	82.881	0.022	4.01	
Yao 2011	Hyperglycemia	11 / 204	4 / 203	2.737	0.886	8.452	0.080	13.10	
Yardley 2013	Hyperglycemia	29 / 485	2 / 239	7.145	1.719	29.695	0.007	8.21	
Andre 2014	Hyperglycemia	6 / 284	4 / 285	1.505	0.429	5.277	0.523	10.59	
Zhu 2014	Hyperglycemia	13 / 362	3 / 184	2.203	0.636	7.632	0.213	10.79	
Hudes 2007	Hyperglycemia	15 / 208	4 / 200	3.606	1.218	10.679	0.021	14.14	
Baselga 2009	Hyperglycemia	7 / 137	0 / 132	14.457	0.834	250.619	0.066	2.05	
				4.081	2.713	6.138	0.000		
Motzer 2010	Hypertriglyceridemia	3 / 274	0 / 137	3.513	0.183	67.526	0.405	3.25	
Demetri 2013	Hypertriglyceridemia	8 / 343	2 / 359	4.187	0.895	19.576	0.069	11.94	
Hutson 2014	Hypertriglyceridemia	8 / 259	1 / 253	7.815	0.985	62.031	0.052	6.62	
Rini 2014	Hypertriglyceridemia	23 / 400	16 / 391	1.405	0.754	2.619	0.284	73.25	
Andre 2014	Hypertriglyceridemia	2 / 284	1 / 285	2.007	0.183	22.010	0.569	4.95	
				1.880	1.104	3.204	0.020		
				3.290	2.470	4.384	0.000		

Favors mTORi   Favors control

Figure 3. *Relative risk of high-grade metabolic events associated with mTORi versus control.*

plasma glucose <200 mg/dL, or HbA1c <8% with oral agents to prevent acute symptoms and subacute complications of hyperglycemia (18).

The pinnacle of mTOR inhibitor therapy has yet to be reached. A number of clinical trials investigated the synergistic antitumor effect of mTOR and vascular endothelial growth factor (VEGF) inhibitors with improved outcomes (19). Dual mTOR and VEGF inhibitor therapy may have produced more complete VEGF signaling pathway inhibition or simultaneous inhibition of both pathways, thereby achieving better antitumor response (20). Despite the potential survival benefits, higher incidence of metabolic derangements was observed in dual mTOR and VEGF inhibitor therapies (21-23). Better identification of the patients at risk of treatment-related metabolic complications may provide improved management of patients enrolled in future dual therapy studies.

There are several limitations to the current meta-analysis. LDL is an important atherogenic component of cholesterol linked to increased risk of cardiovascular complications. That said, LDL level is not part of the adverse events included in CTCAE and often not reported in the clinical trial. The risk of cardiac complication can only be partially accessed with

triglyceride and total cholesterol level. In addition, the prevalence of the baseline HGL, HTG, and HCE is not well described in most clinical trials and may overestimate new onset mTORi-associated metabolic complications. Finally, significant heterogeneity was observed among the study population, malignancy type, and treatment regimen as well.

Despite its limitations, this study demonstrates that the use of mTORi is associated with a significant risk of developing all- and high-grade metabolic complications. The risk of adverse metabolic events does not differ by type of Rapamycin analog, type of malignancy treated, or when monotherapy or concomitant therapy is utilized. Early detection and effective management of HGL, HTG, and HCE may allow for more extensive use of mTORi therapy, especially in cancer patients with pre-existing metabolic comorbidities, and should limit treatment related toxicity.

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