Research Article

Elevated Triglycerides (≥ 150 mg/dL) and High Triglycerides (200–499 mg/dL) Are Significant Predictors of Hospitalization for New-Onset Kidney Disease: A Real-World Analysis of High-Risk Statin-Treated Patients

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Keywords

Triglycerides · Kidney disease · Cardiovascular disease · Diabetes · Hospitalization

Abstract

Background: Dyslipidemia in kidney disease (KD) involves increased levels of triglycerides (TG) and TG-rich lipoproteins, with only minor changes in low-density lipoprotein cholesterol. The increasing prevalence of diabetic KD and the shared atherogenic lipid profile between KD and diabetes underscore the importance of understanding dyslipidemia in these patients. Previous studies suggest an association between elevated TG and new-onset KD. Additional data are needed to better define the relationship between hypertriglyceridemia and new-onset KD. **Objective:** To evaluate the real-world impact of elevated and high TG on risk of KD in high-risk statin-treated patients. **Methods:** This retrospective administrative claims analysis of the Optum Research Database included statin-treated patients (age ≥ 45 years) with diabetes and/or atherosclerotic cardiovascular disease who were followed for ≥ 6 months. Cohorts included patients with elevated TG (≥ 150 mg/dL; $n = 27,471$) or high TG (200–499 mg/dL; subgroup of elevated TG cohort; $n = 13,411$), and a comparator cohort (TG < 150 mg/dL and high-density lipoprotein cholesterol > 40 mg/dL; $n = 32,506$). The probability of hospitalization for new-onset KD was calculated post hoc from multivariate analyses controlled for patient characteristics and comorbidities using a Cox proportional hazards model. **Results:** The rate of hospitalization for new-onset KD was 31% higher in the elevated-TG cohort (hazard ratio [HR],

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1.311; 95% confidence interval [CI], 1.228–1.401; $p < 0.001$) and 45% higher in the high-TG cohort (HR, 1.451; 95% CI, 1.339–1.572; $p < 0.001$) compared with the respective comparator cohorts. **Conclusions:** In a real-world analysis of statin-treated patients with high cardiovascular risk, both elevated TG (≥ 150 mg/dL) and high TG (200–499 mg/dL) were significant predictors of hospitalization for new-onset KD, identifying hypertriglyceridemia as a potential KD risk factor.

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Introduction

Patients with chronic kidney disease have increased cardiovascular (CV) morbidity and mortality [1–3]. Chronic kidney disease is an independent risk factor for CV disease [4, 5] and is defined as a coronary heart disease risk equivalent by the American Heart Association [6] and National Kidney Foundation [7]. Patients with chronic kidney disease are more likely to die from accelerated CV disease than from renal failure [5, 8]. The higher CV risk in patients with chronic kidney disease is due partly to the high prevalence of conventional CV risk factors such as hypertension and diabetes, but other mechanisms, such as oxidative stress, inflammation, dyslipidemia, anemia, and disordered mineral metabolism also contribute [5, 9]. The chronic inflammatory state in patients with chronic kidney disease promotes all phases of atherothrombosis, including early cell adhesion and endothelial dysfunction, matrix and collagen degradation, smooth muscle cell proliferation, increased platelet reactivity, plaque rupture, thrombosis, and the development of vascular calcification [10]. Although cholesterol-lowering therapy with statins consistently reduces CV risk in the general population, it has less CV benefit in patients with chronic kidney disease, particularly patients on dialysis [11–13]. The dyslipidemia in chronic kidney disease encompasses an atherogenic profile characterized by increased levels of triglycerides (TG) and TG-rich lipoproteins, low levels of high-density lipoprotein cholesterol (HDL-C), with only minor changes in low-density lipoprotein cholesterol (LDL-C) [14, 15]. Plasma TG are increased in the early stages of kidney disease, with the highest levels present in patients on dialysis [16]. The precise biochemical mechanisms underlying these changes are as yet poorly characterized.

TG-rich remnant lipoproteins are also elevated in patients with type 2 diabetes mellitus [17] and are predictive of CV events in patients with chronic kidney disease and diabetes [18]. Patients with diabetes harbor a residual risk of kidney disease, despite control of hypertension and hyperglycemia. One of the factors responsible for this residual risk is diabetic dyslipidemia; the risk for microvascular complications in diabetic patients is not mitigated by LDL-C lowering alone but also requires modification of other lipid subfractions [19]. Previous studies also suggest that elevated TG are an independent risk factor for development of new-onset kidney disease in non-hypertensive patients with diabetes [20, 21].

The increasing prevalence of diabetic kidney disease and the shared atherogenic lipid profile between kidney disease and diabetes underscore the importance of understanding the role of dyslipidemia in these patients. High-risk statin-treated patients with elevated TG and generally controlled LDL-C are commonly encountered in clinical practice and are increasing in number because of the increasing prevalence of diabetes and obesity [22]. Additional data are needed on the role of hypertriglyceridemia in new-onset kidney disease.

The purpose of this retrospective analysis of a large medical claims database was to evaluate the real-world impact of hypertriglyceridemia on risk of new-onset kidney disease in high-risk statin-treated patients.

Methods

Study Design

The study design has been described previously [23, 24]. The Optum Research Database, which includes >160 million individuals, was used for this retrospective analysis. Patients ≥ 45 years, with documented diabetes and/or atherosclerotic CV disease (ASCVD) were included if they had filled at least 1 prescription for a statin between January 1, 2010 and December 31, 2010, and had at least 6 months of baseline data prior to the first statin claim; the use of any niacin-based product (over-the-counter niacin, Niaspan, Simcor, Advicor, etc.) was an exclusion criterion due to niacin's lack of effect on CV events and its association with serious adverse events in large randomized clinical studies [25, 26]. Patients were followed for at least 6 months from the index date to the earliest of the following events: end of the study (March 31, 2016), date of disenrollment from the insurance plan, or death.

Study Cohorts

Study cohorts were evaluated based on the following lipid levels at the most recent laboratory visit prior to the index date: the elevated-TG cohort included patients with TG ≥ 150 mg/dL, the high-TG sub-cohort included patients with TG 200–499 mg/dL, and the comparator cohort included patients with TG <150 mg/dL and HDL-C >40 mg/dL.

Endpoints

The primary endpoint was the frequency of major CV events (a composite of CV-related death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularization, or unstable angina) in the follow-up period. Secondary endpoints were health-care costs (in USD) and resource utilization in the follow-up period. This analysis of rates of hospitalization for new-onset kidney disease was post hoc and was defined as hospitalization in the follow-up period for kidney disease in patients with no kidney disease at baseline. New-onset kidney disease, including end-stage renal disease, was identified by diagnosis codes (online suppl. Table 1, available at www.karger.com/doi/10.1159/000502511) in the first or second position indicating an inpatient stay for kidney disease in patients for whom no diagnostic code for kidney disease was identified during the baseline period.

Statistical Analysis

All study variables were analyzed descriptively and reported for the overall study sample, as well as stratified and statistically compared by cohort. Mean and standard deviation were provided for all continuous variables; descriptive techniques that account for the length of observation time, such as per patient per month, were used for analyses of health care cost and resource utilization. Statistical comparison tests included Rao-Scott test and chi-square test for categorical measures and *t* test and analysis of variance for continuous measures. Multivariate pre-match analyses used a Cox proportional hazards model to calculate hazard ratios (HR) for time-to-event analyses. A *p* value <0.05 was considered statistically significant.

A matched comparator study cohort similar to the analysis cohort, but without elevated or high TG, was created using a propensity score analysis by controlling for confounding relationships. This method of balancing cohorts assumes that the distribution of observed baseline covariates is similar between the elevated-TG cohort and comparator cohort. The estimated propensity score is the predicted probability of treatment derived from a fitted logistic regression model in which the cohort indicator is regressed on predetermined baseline characteristics resulting in matched sets of patients from the 2 cohorts. Propensity score matching was performed using a greedy match algorithm [27]. The procedure used attempts to match each case to a single control based on the propensity score's first 8 digits (estimated using logistic regression), then 7 digits, and so on, until a match occurred. The closest available match ("nearest neighbor") was used. Ties were resolved randomly. A maximum allowed propensity score difference ("caliper") of 0.01 between the matched case-control pairs was imposed a priori. Once a match was identified, it was not reconsidered and the control was removed from the available match pool. The final sample of cases successfully matched to controls was retained for analysis. The final list of variables included in the propensity score model was determined following review of pre-matching descriptive analyses of patient characteristics and other pre-index measures, including age, gender, insurance type, region, baseline medical cost, LDL-C level relative to the median, if available, baseline use of statins, fibrates, or omega-3 fatty acids, and the following diagnoses: ASCVD, diabetes, stroke, hypertension, renal disease, and peripheral artery disease. Patients in the elevated-TG cohort were matched in a 1:1 ratio to the comparator cohort. Those who were not matched were not included in the descriptive analyses.

Fig. 1. Patient disposition. **a** Elevated TG cohort and comparator. **b** High-TG cohort and comparator. * Population used for multivariate analyses. † Population used for patient characteristics and other analyses. HDL-C, high-density lipoprotein cholesterol; TG, triglycerides [23, 24].

Fig. 2. Effects of triglycerides on hospitalization for new-onset kidney disease in statin-treated patients with high cardiovascular risk (multivariate analysis). Hospitalization for new-onset kidney disease was analyzed as inpatient stay for kidney disease in the follow-up period in patients without evidence of baseline kidney disease. Covariates included TG cohort, age (45–54, 55–64, ≥ 65), gender, insurance coverage type, geographic region of enrollment, baseline clinical characteristics (diabetes, ASCVD, LDL-C laboratory result in relation to median), and baseline medication use (fibrates, prescription omega-3s, both, and neither). * Elevated TG ≥ 150 mg/dL (*n* = 27,471) vs. comparator: TG < 150 mg/dL and HDL-C > 40 mg/dL (*n* = 32,506). † High TG 200–499 mg/dL (*n* = 13,411) vs. comparator: TG < 150 mg/dL and HDL-C > 40 mg/dL (*n* = 32,506).

Results

Patients

Approximately 1.6 million statin-treated patients were identified from the Optum Research Database. Figure 1 shows patient disposition. The inclusion and exclusion criteria were applied, resulting in 27,471 patients in the elevated-TG cohort (23,181 after propensity matching) and 13,411 patients in the high-TG sub-cohort (10,990 after propensity matching). There were 32,506 patients in the comparator cohort before propensity matching. Baseline demographic and clinical characteristics showed no clinically important differences between

Table 1. Patient demographics, characteristics, and baseline comorbidities [22, 23]

	Elevated TG* (n = 23,181)	Comparator* (n = 23,181)	p value	High TG† (n = 10,990)	Comparator† (n = 10,990)	p value
Age, years	62.2±9.6	62.6±9.9	<0.001	61.7±9.6	62.2±9.9	<0.001
Female	11,518 (49.7)	11,467 (49.5)	0.244	5,433 (49.4)	5,424 (49.4)	0.769
Insurance type						
Commercial	15,823 (68.3)	15,855 (68.4)	0.461	7,589 (69.1)	7,571 (68.9)	0.556
Medicare	7,358 (31.7)	7,326 (31.6)	0.461	3,401 (30.9)	3,419 (31.1)	0.556
Duration of follow-up, months	41.4±23.7	42.5±23.9	<0.001	41.3±23.8	42.1±23.9	0.018
Baseline‡ lipid profile, mg/dL						
TG	220.31±77.4	97.9±28.9	<0.001	263.8±60.2	98.2±29.2	<0.001
LDL-C	104.6±41.1	100.9±35.0	<0.001	106.1±43.2	101.7±34.7	<0.001
HDL-C	42.3±10.2	55.1±12.2	<0.001	40.4±9.3	55.0±12.4	<0.001
Total cholesterol	190.2±46.6	175.4±38.8	<0.001	198.2±47.9	176.3±38.6	<0.001
Non-HDL-C§	147.9±44.2	120.4±36.5	<0.001	157.9±45.2	121.2±36.3	<0.001
Baseline comorbidities						
Diabetes	19,392 (83.7)	19,478 (84.0)	0.017	9,326 (84.86)	9,375 (85.30)	0.048
ASCVD	6,915 (29.8)	6,800 (29.3)	0.009	3,185 (28.98)	3,141 (28.58)	0.156
Myocardial infarction	495 (2.1)	411 (1.8)	0.003	235 (2.14)	189 (1.72)	0.020
Stroke	750 (3.2)	674 (2.9)	0.005	349 (3.18)	323 (2.94)	0.177
Angina	1,225 (5.3)	1,179 (5.1)	0.284	571 (5.20)	554 (5.04)	0.562
Coronary revascularization	600 (2.6)	506 (2.2)	0.002	299 (2.72)	213 (1.94)	<0.001
Peripheral artery disease	3,384 (14.6)	3,317 (14.3)	0.104	1,561 (14.20)	1,550 (14.10)	0.704
Heart failure	1,258 (5.4)	1,088 (4.7)	<0.001	626 (5.70)	519 (4.72)	<0.001
Atrial fibrillation	1,133 (4.9)	989 (4.3)	0.001	527 (4.80)	472 (4.29)	0.070
Hypertension	18,346 (79.1)	18,375 (79.3)	0.462	8,678 (78.96)	8,723 (79.37)	0.106
Renal disease	2,832 (12.2)	2,782 (12.0)	0.196	1,322 (12.03)	1,314 (11.96)	0.767

Data are presented as mean ± standard deviation or n (%). Rao-Scott test was used for binary measures. Robust standard errors were used for continuous measures. * Elevated TG ≥150 mg/dL and matched comparator with TG <150 mg/dL and HDL-C >40 mg/dL. † High TG 200–499 mg/dL and matched comparator with TG <150 mg/dL and HDL-C >40 mg/dL. ‡ Baseline period excludes index date. § Calculated by subtracting HDL-C result from total cholesterol. This value was not calculated unless patients had both HDL-C and total cholesterol laboratory result in period. ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; TG, triglycerides.

the elevated-TG cohort or high-TG sub-cohorts and their matched comparators, other than an expected difference in baseline lipid levels due to study entry requirements (Table 1). The elevated-TG cohort and its propensity-matched comparator cohort were comparable for mean age (62.2 vs. 62.6 years), sex distribution (49.7% vs. 49.5% female), and baseline comorbid conditions (diabetes, 83.7% vs. 84.0%; ASCVD, 29.8% vs. 29.3%; peripheral arterial disease, 14.6% vs. 14.3%; hypertension, 79.1% vs. 79.3%; and renal disease, 12.2% vs. 12.0%). Similar baseline results were found in the analysis of the high-TG sub-cohort and its propensity-matched comparator.

Impact of TG on Hospitalization for New-Onset Kidney Disease

The rate of hospitalization for new-onset kidney disease was 31% higher in the elevated-TG cohort (HR, 1.311; 95% confidence interval [CI], 1.228–1.401; $p < 0.001$) and 45% higher in the high-TG sub-cohort (HR, 1.451; 95% CI, 1.339–1.572; $p < 0.001$) compared with the respective comparators (Fig. 2).

Discussion

This real-world analysis of administratively derived data from more than 45,000 statin-treated patients with high CV risk in the Optum Research Database found that both elevated TG (≥ 150 mg/dL) and high TG (200–499 mg/dL) were significant predictors of hospitalization for new-onset kidney disease, with 31 and 45% higher risk in these 2 cohorts, respectively. These data are consistent with previous studies reporting that elevated TG are an independent risk factor for development of kidney disease in high-risk patients [20, 21]. Although the current study population included a large proportion of statin-treated patients with diabetes and/or hypertension, the presence of elevated or high TG conferred an added risk of developing kidney disease, substantiating previous findings that an atherogenic phenotype contributes to microvascular complications, including kidney disease, in high-risk patients [19]. Moreover, statin therapy was insufficient to meaningfully attenuate this augmented risk for developing renal dysfunction [19].

The high- and elevated-TG thresholds were chosen to align with the ATP III definitions of hypertriglyceridemia (200–499 mg/dL) and metabolic syndrome (>150 mg/dL), respectively [28]. In our previous analyses of these patient populations, we showed that statin-treated patients at high CV risk and with elevated or high TG had poorer CV and health economic outcomes than comparators with TG <150 and HDL-C >40 mg/dL [23, 24]. The overall risk of a major CV event was 26% higher in the elevated-TG cohort versus the comparator cohort after controlling for baseline characteristics and comorbidities (HR, 1.258; 95% CI, 1.185–1.335; $p < 0.001$) [24]. This elevated-TG cohort also incurred 11.8% higher mean monthly direct health care costs (USD 1,438 vs. USD 1,270; $p < 0.001$) which, when extrapolated across the variable follow-up time, resulted in an annual direct cost difference of USD 47 million or an annual direct cost difference of USD 200 million per 100,000 patients [24]. Likewise, multivariate analyses in the high-TG sub-cohort showed a 34.9% higher rate of major CV events versus the comparators (HR, 1.349; 95% CI, 1.225–1.485; $p < 0.001$) [23]. Mean monthly direct health care costs were 14.5% higher in the high-TG cohort (USD 1,462 vs. USD 1,279; $p < 0.001$), which extrapolated to an annual direct cost difference of USD 24 million or an annual direct cost difference of USD 220 million per 100,000 patients [23]. A 13.4% higher likelihood of inpatient stays in the elevated-TG cohort (33.5% vs. 30.5%; $p < 0.001$) and 16.7% in the high-TG sub-cohort (34.0% vs. 30.4%; $p < 0.001$) may have contributed to the increased health care costs [23, 24]. It should be noted that since there is some overlap between the elevated- and high-TG cohorts, the higher point estimates reported for the high-TG sub-cohort do not necessarily represent a dose-response relationship; however, the results remain robust at either threshold.

This analysis was designed only to assess the clinical and health economic burden of elevated TG despite generally controlled LDL-C. It was not designed to assess the potential effects of any add-on therapy. A strength of this real-world study is that the data source encompassed a large number of patients encountered in clinical practice, and the results therefore may reflect actual use in real-world community settings more accurately than evidence from clinical trials [29, 30]. Some drawbacks of claims data are that they may not be generalizable, they are subject to entry errors, missing data, and uncertainty about internal validity [31], and they do not capture costs to patients such as transportation and missed work days. Additionally, it is important to note that the results reported herein must be interpreted with caution, as small differences may be statistically significant due to the large sample size but have little or no clinical relevance.

In conclusion, this real-world claims database study showed that both elevated and high TG were significant predictors of hospitalization for new-onset kidney disease, identifying hypertriglyceridemia as a potential risk factor for kidney disease. These data substantiate

previous studies reporting that elevated TG are an independent risk factor for development of new-onset kidney disease in high-risk patients [20, 21]. As the prevalence and burden of kidney disease continue to increase, especially in patients with diabetes, further study is warranted to assess whether lowering TG in patients with elevated or high TG will be associated with a reduced risk of kidney disease. Prospective CV outcomes trials of similar patient populations may shed light on hypertriglyceridemia in diabetes and kidney disease.

Statement of Ethics

The authors have no ethical conflicts to disclose. No patient's identity or medical records were disclosed for the purposes of this study.

Disclosure Statement

Peter P. Toth is a consultant and/or speaker for Amarin Pharma Inc, Amgen, Kowa, Novo-Nordisk, Regeneron, and Sanofi. Sephy Philip and Craig Granowitz are employees and stock shareholders of Amarin Pharma Inc. Michael Hull is an employee of Optum.

Funding Sources

This study was funded by Amarin Pharma Inc, Bedminster, NJ. Medical writing assistance was provided by Peloton Advantage, LLC, Parsippany, NJ, and funded by Amarin Pharma Inc.

Author Contributions

Study design: all authors. Data analysis/interpretation: all authors. Critical revision and review of the manuscript: all authors. Project/data management: M.H., S.P. Statistical analyses: all authors. Approval of final draft for submission: all authors.

References

- 1 Astor BC, Hallan SI, Miller ER 3rd, Yeung E, Coresh J. Glomerular filtration rate, albuminuria, and risk of cardiovascular and all-cause mortality in the US population. *Am J Epidemiol*. 2008 May;167(10):1226–34.
- 2 Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, et al.; Chronic Kidney Disease Prognosis Consortium. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet*. 2010 Jun;375(9731):2073–81.
- 3 van der Velde M, Matsushita K, Coresh J, Astor BC, Woodward M, Levey A, et al.; Chronic Kidney Disease Prognosis Consortium. Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. *Kidney Int*. 2011 Jun;79(12):1341–52.
- 4 Jellinger PS, Handelsman Y, Rosenblit PD, Bloomgarden ZT, Fonseca VA, Garber AJ, et al. American Association of Clinical Endocrinologists and American College of Endocrinology guidelines for management of dyslipidemia and prevention of cardiovascular disease. *Endocr Pract*. 2017 Apr;23 Suppl 2:1–87.
- 5 Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, Jafar TH, Heerspink HJ, Mann JF, et al. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. *Lancet*. 2013 Jul;382(9889):339–52.
- 6 Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, et al.; American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation*. 2003 Oct;108(17):2154–69.
- 7 Kidney Disease Outcomes Quality Initiative (K/DOQI) Group. K/DOQI clinical practice guidelines for management of dyslipidemias in patients with kidney disease. *Am J Kidney Dis*. 2003 Apr;41(4 Suppl 3):I–IV, S1–91.

- 8 Keith DS, Nichols GA, Gullion CM, Brown JB, Smith DH. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. *Arch Intern Med*. 2004 Mar;164(6):659–63.
- 9 Epstein M, Vaziri ND. Statins in the management of dyslipidemia associated with chronic kidney disease. *Nat Rev Nephrol*. 2012 Feb;8(4):214–23.
- 10 Cherney DZ, Lytvyn Y, McCullough PA. Cardiovascular risk reduction in patients with chronic kidney disease: potential for targeting inflammation with canakinumab. *J Am Coll Cardiol*. 2018 May;71(21):2415–8.
- 11 Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, et al.; SHARP Investigators. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet*. 2011 Jun;377(9784):2181–92.
- 12 Barylski M, Nikfar S, Mikhailidis DP, Toth PP, Salari P, Ray KK, et al.; Lipid and Blood Pressure Meta-Analysis Collaboration Group. Statins decrease all-cause mortality only in CKD patients not requiring dialysis therapy—a meta-analysis of 11 randomized controlled trials involving 21,295 participants. *Pharmacol Res*. 2013 Jun;72:35–44.
- 13 Wanner C, Krane V, März W, Olschewski M, Mann JF, Ruf G, et al.; German Diabetes and Dialysis Study Investigators. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med*. 2005 Jul;353(3):238–48.
- 14 Bulbul MC, Dägel T, Afsar B, Uluşu NN, Kuwabara M, Covic A, et al. Disorders of lipid metabolism in chronic kidney disease. *Blood Purif*. 2018;46(2):144–52.
- 15 Choudhury D, Tuncel M, Levi M. Disorders of lipid metabolism and chronic kidney disease in the elderly. *Semin Nephrol*. 2009 Nov;29(6):610–20.
- 16 Ferro CJ, Mark PB, Kanbay M, Sarafidis P, Heine GH, Rossignol P, et al. Lipid management in patients with chronic kidney disease. *Nat Rev Nephrol*. 2018 Dec;14(12):727–49.
- 17 Krauss RM. Lipids and lipoproteins in patients with type 2 diabetes. *Diabetes Care*. 2004 Jun;27(6):1496–504.
- 18 Sidney S, Quesenberry CP Jr, Jaffe MG, Sorel M, Nguyen-Huynh MN, Kushi LH, et al. Recent trends in cardiovascular mortality in the United States and public health goals. *JAMA Cardiol*. 2016 Aug;1(5):594–9.
- 19 Toth PP, Simko RJ, Palli SR, Koselleck D, Quimbo RA, Cziraky MJ. The impact of serum lipids on risk for microangiopathy in patients with type 2 diabetes mellitus. *Cardiovasc Diabetol*. 2012 Sep;11(1):109.
- 20 Russo GT, De Cosmo S, Viazzi F, Pacilli A, Ceriallo A, Genovese S, et al.; AMD-Annals Study Group. Plasma triglycerides and HDL-C levels predict the development of diabetic kidney disease in subjects with type 2 diabetes: The AMD Annals Initiative. *Diabetes Care*. 2016 Dec;39(12):2278–87.
- 21 Tao-Chun L. Hypertriglyceridemia is a residual risk factor associated with new-onset DKD in type 2 diabetic patients without hypertension [abstract 536-P]. *Diabetes*. 2017;66 suppl 1:A140.
- 22 Palmer MK, Toth PP. Trends in lipids, obesity, metabolic syndrome, and diabetes mellitus in the United States: an NHANES analysis (2003–2004 to 2013–2014). *Obesity (Silver Spring)*. 2019 Feb;27(2):309–14.
- 23 Toth PP, Granowitz C, Hull M, Liassou D, Anderson A, Philip S. High triglycerides are associated with increased cardiovascular events, medical costs, and resource use: a real-world administrative claims analysis of statin-treated patients with high residual cardiovascular risk. *J Am Heart Assoc*. 2018 Aug;7(15):e008740.
- 24 Toth PP, Philip S, Hull M, Granowitz C. Association of elevated triglycerides with increased cardiovascular risk and direct costs in statin-treated patients. *Mayo Clin Proc*. Accepted 2019. <https://doi.org/10.1016/j.mayocp.2019.03.028>.
- 25 Guyton JR, Slee AE, Anderson T, Fleg JL, Goldberg RB, Kashyap ML, et al. Relationship of lipoproteins to cardiovascular events: the AIM-HIGH Trial (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides and Impact on Global Health Outcomes). *J Am Coll Cardiol*. 2013 Oct;62(17):1580–4.
- 26 Landray MJ, Haynes R, Hopewell JC, Parish S, Aung T, Tomson J, et al.; HPS2-THRIVE Collaborative Group. Effects of extended-release niacin with laropiprant in high-risk patients. *N Engl J Med*. 2014 Jul;371(3):203–12.
- 27 Parsons LS. Reducing bias in a propensity score matched-pair sample using greedy matching techniques [poster 214–26]. *Proceedings of the 26th Annual SAS Users Group International Conference*; 2001; Long Beach, CA.
- 28 National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002 Dec;106(25):3143–421.
- 29 Jarow JP, LaVange L, Woodcock J. Multidimensional evidence generation and FDA regulatory decision making: defining and using “real-world” data. *JAMA*. 2017 Aug;318(8):703–4.
- 30 Sherman RE, Anderson SA, Dal Pan GJ, Gray GW, Gross T, Hunter NL, et al. Real-world evidence - what is it and what can it tell us? *N Engl J Med*. 2016 Dec;375(23):2293–7.
- 31 Berger ML, Sox H, Willke RJ, Brixner DL, Eichler HG, Goettsch W, et al. Good practices for real-world data studies of treatment and/or comparative effectiveness: recommendations from the Joint ISPOR-ISPE Special Task Force on Real-World Evidence in Health Care Decision Making. *Value Health*. 2017 Sep;20(8):1003–8.