Cardiovascular Outcomes and Efficacy of the PCSK9 Inhibitor Evolocumab in Persons with Type 1 Diabetes Mellitus: Insights from FOURIER Trial

Yu Mi Kang[1,2], Robert P. Giugliano[1], Xinhui Ran[1], Prakash Deedwania[3], Gaetano M. De Ferrari[4], Jyothis T. George[5], Ioanna Gouni-Berthold[6], Gabriel Paiva da Silva Lima[5], Yehuda Handelsman[7], Basil S. Lewis[8], E. Magnus Ohman[5], Huei Wang[5], J. Antonio G. López[5], Maria Laura Monsavo[5], Marc S. Sabatine[1] and Lawrence A. Leiter[9]

[1]TIMI Study Group, Brigham and Women's Hospital and Harvard Medical School, Boston, MA; [2]Division of Endocrinology, Diabetes, and Hypertension, Brigham and Women's Hospital and Harvard Medical School, Boston, MA; [3]University of California San Francisco Fresno, Fresno, CA; [4]University of Pavia, and IRCCS Fondazione Policlinico San Matteo, Pavia, Italy; [5]Global Development, Amgen Inc.; [6]Center for Endocrinology, Diabetes and Preventive Medicine, University of Cologne, Cologne, Germany; [7]Metabolic Institute of America, Tarzana, CA.; [8]Lady Davis Carmel Medical Center and the Technion-Israel Institute of Technology, Haifa, Israel; [9]Li Ka Shing Knowledge Institute of St Michael's Hospital, University of Toronto, Toronto, ON, Canada.

Background and Aims

- Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death in people with type 1 diabetes mellitus (T1DM).
  - The rising prevalence of T1DM in older adults (≥65 yeas) further underscores the urgency of effective cardiovascular (CV) risk reduction strategies.
- Multiple clinical guidelines emphasize the importance of optimal glycemic control and suggest optimization of CV risk factors such as dyslipidemia and hypertension.
  - Due to the limited availability of T1DM-dedicated randomized trials, data extrapolated from observational studies or trials in individuals with type 2 diabetes mellitus (T2DM).
  - Consequently, guidelines differ in specific recommendations in dyslipidemia management in persons with T1DM.
- In Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor evolocumab effectively reduced LDL cholesterol and major adverse cardiovascular events (MACE) in adults with ASCVD.
  - However, their efficacy in individuals with T1DM has not been well studied.
- **Therefore, we aimed to assess the efficacy of evolocumab in individuals with T1DM enrolled in the FOURIER trial.**

Methods

Study Design and Participants

- The FOURIER trial was an event-driven, randomized, double-blind, placebo-controlled study that enrolled 27,564 adults aged 18-85 years with stable ASCVD (Figure 1).
- Based on dedicated questions in the case report form, patients were categorized as T1DM, T2DM, or not having diabetes.
  - Insulin therapy was required to be categorized as T1DM for confirmatory purposes.

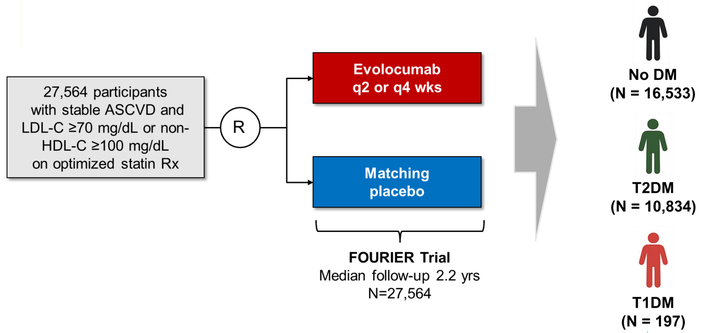


Figure 1. FOURIER Trial Schema

Methods (continued)

Endpoints

- The primary endpoint of the FOURIER study was the composite of CV death, myocardial infarction (MI), stroke, hospitalization due to unstable angina, or coronary revascularization.
- The key secondary endpoint was a composite of cardiovascular death, MI, or stroke.
- A clinical events committee categorized the causes of death and adjudicated all cardiovascular events while unaware of treatment assignment and lipid measurements.

Statistical Analyses

- The time from randomization to the first occurrence of any event in the composite endpoints were evaluated in the intention-to-treat population.
- Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using a stratified Cox proportional hazards model, accounting for randomization strata (screening LDL-C levels and geographic region).
  - Kaplan-Meier event rates and absolute risk reduction (ARR) were reported at 2.5 years.
- The association between diabetes types and CV risk was explored in the placebo arm in Cox proportional hazard models, accounting for clinical covariates and randomization strata
- Interaction terms were included to evaluate potential effect modification by diabetes subgroup on treatment outcomes.

Results

Table 1. Baseline Characteristics by Diabetes Type

Characteristics	No DM (N = 16,533)	T2DM (N = 10,834)	T1DM (N = 197)	P-value
Age (years)	63 (56-69)	63 (57-69)	58 (53-64)	<0.001
Male	76.8%	73.5%	131 (66.5%)	<0.001
White race	88.5%	79.9%	89.3%*	<0.001
Region				<0.001
-Asia Pacific	12.3%	16.5%	7.6%	
-Europe	66.7%	57.2%	56.9%	
-Latin America	5.7%	8.2%	1.0%	
-North America	15.4%	18.1%	34.5%	
BMI (kg/m^2)	28.0 (25.4-31.1)	30.1 (27.0-33.7)	29.0 (25.4-32.4)	<0.001
Hypertension	75.3%	87.5%	82.2%	<0.001
Current smoker	32.3%	22.0%	24.4%¶	<0.001
Duration of DM	N/A	5.6 (1.9-11.4)	27.8 (12.4-38.2)	<0.001
Insulin use	N/A	23.3%	100.0%	N/A
Prior MI	82.7%	78.9%	72.1%	<0.001
High-intensity statin	70.9%	66.8%	72.1%*¶	<0.001
HbA1c (%)	5.7 (5.4-5.9)	6.7 (6.1-7.8)	8.4 (7.4-9.5)	<0.001
HbA1c (mmol/mol)	39 (36-41)	50 (43-62)	68 (57-80)	<0.001
eGFR (ml/min/1.73m^2)	75.6 (64.9-87.2)	74.8 (61.3-87.8)	71.2 (56.7-86.9)	<0.001
Urine albumin (mg/L)	5 (3-13)	11 (3-45)	14 (4-94)¶	<0.001
LDL cholesterol (mg/dL)	92.5 (80.5-109.5)	90.0 (78.0-107.0)	95.0 (81.0-111.5)*	<0.001
HDL cholesterol (mg/dL)	45.5 (38.5-54.5)	41.0 (35.0-49.0)	46.5 (38.0-57.0)*	<0.001
Lipoprotein (a) (nmol/L)	40.0 (14.0-169.0)	33.0 (11.0-155.5)	39.0 (12.0-152.0)*¶	<0.001
hsCRP (mg/L)	1.6 (0.8-3.2)	2.1 (1.0-4.2)	2.2 (1.2-3.9)	<0.001

Values are %, or median (Q1-Q3). *P≥0.05 for difference between T1DM and No DM groups; ¶P≥0.05 for difference between T1DM and T2DM groups. Abbreviations: BMI: body mass index; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; HDL: high-density lipoprotein; hsCRP: high-sensitivity C-reactive protein; LDL: low-density lipoprotein; MI: myocardial infarction; T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus

Results

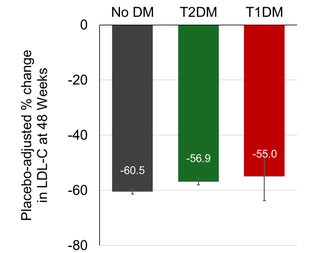
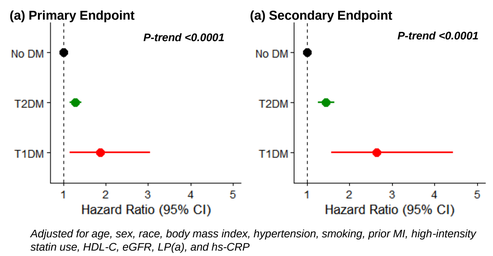


Figure 2. LDL-C Changes at 48 Weeks



Adjusted for age, sex, race, body mass index, hypertension, smoking, prior MI, high-intensity statin use, HDL-C, eGFR, LP(a), and hs-CRP

Figure 3. Risk of MACE by Diabetes Types

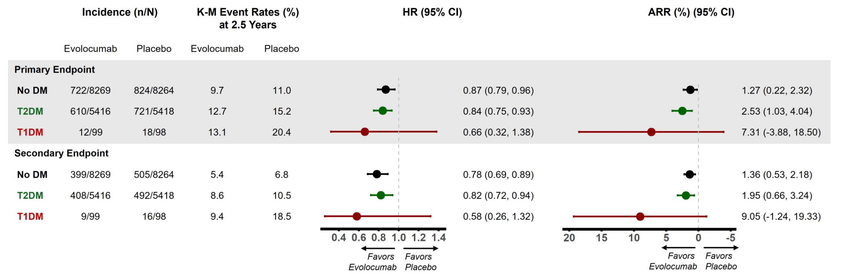


Figure 4. : Risk of MACE at 2.5 Years by Diabetes Types

Conclusions

- Intensive LDL-C lowering with evolocumab was associated with a trend towards reduced cardiovascular risk among individuals with T1DM on statin therapy.
- These findings provide much-needed evidence to guide lipid management in this high-risk population and may help inform future updates to currently inconsistent clinical guidelines.
- Further LDL-C lowering studies are warranted to guide care for persons with T1DM at high cardiovascular risk.

Disclosure Information

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@YumiKangEndo
@TIMIStudyGroup
@BrighamEndo