Title: Real-world Insights into Evolocumab Use in Patients with Hyperlipidemia Across Five Countries: Analysis from the ZERBINI Study

Authors: Milan Gupta, MD;[a] Rajvi J. Wani, PhD, MS;[b] Khalid Al Faraidy, MD;[c] Jean Bergeron, MD, MSc;[d] Eduardo Contreras, MD;[e] Angel Alberto Garcia Peña, MD;[f] G. B. John Mancini, MD;[g] Francisco Padilla, MD;[h] Abel Alberto Pavia Lopez, MD;[i] Kiran Philip, MD, MBA;[j] Johnny Wu, MS, MA;[j] Erin S. Mackinnon, PhD[b]

Affiliations:

[a]Department of Medicine, University of Toronto & the Canadian Collaborative Research Network, 3 Conestoga Dr., Suite 200, Brampton, ON, L6Z 4N5, Canada

[b]Amgen Canada Inc., 6775 Financial Dr., #300, Mississauga, ON, L5N 0A4, Canada

[c]Interventional Cardiology, King Fahad Military Medical City, Main Hospital Building No 111, Abqaiq Rd., ICT Department PO Box 946, Dhahran, 31932 Saudi Arabia

[d]Departments of Medicine and of Laboratory Medicine, Centre Hospitalier Universitaire de Québec-Université Laval, 2705 boulevard Laurier, C-00-224, Québec, Québec, G1V 4G2, Canada

[e]Clinica de Occidente – Angiografia de Occidente, Cl. 18 Nte. #5-34, San Vicente, Cali, Valle del Cauca, Colombia

[f]Division of Cardiology, Hospital Universitario San Ignacio, Pontificia Universidad Javeriana, Kra 7° #40-62, Bogotá, Colombia

[g]Centre for Cardiovascular Innovation, Division of Cardiology, Department of Medicine, University of British Columbia, 6th floor, 2635 Laurel St., Vancouver, BC, V5Z 1M9, Canada

[h]Clinical and Interventional Research, Cardiovascular Center Chapalita, TARASCOS 3469-517 Guadalajara, Jalisco, Mexico

[i]Clinical and Interventional Cardiology, Centro Medico ABC, Sur 136 No. 116, Col. Las Americas, Alvaro Obregon, 01120, Mexico City, Mexico

[j]Amgen Inc., One Amgen Center Drive, Thousand Oaks, California, CA, 91320, USA

Corresponding author: Erin S. Mackinnon: emackinn@amgen.com, +1-(647) 919-0453 6775 Financial Dr., Suite 300, Mississauga, ON L5N 0A4

Supplementary Information

Supplementary Material

Table S1: ZERBINI Study Investigators

Country	Name	Institution and City
Canada	Hoag, Gordon, N	Discovery Clinical Services, Victoria
	Mancini, Giovanni Battista John	Centre for Cardiovascular Innovation - The University of British Columbia (UBC), Vancouver
	Manjoo, Priya	Victoria Endocrinoloy, Victoria
	Ahooja, Vineeta	Heart Health Institute, Scarborough
	Curnew, Gregory, P	Dr. Greg Curnew MD, Office of, Hamilton
	Gupta, Milan, K	Brampton Research Associates, Brampton
	McPherson, Phyllis Ruth	University of Ottawa - Heart Institute (UOHI) (Institut de Cardiologie de L'Universite d'Ottawa), Ottawa
	Pandey, A. Shekhar	Cambridge Cardiac Care Centre, Cambridge
	Bergeron, Jean	Clinique des maladies lipidiques de Québec (CMLQ Inc.), Québec City
	Gaudet, Daniel	ECOGENE-21, Chicoutimi
	Hamet, Pavel	Clinique de recherche Medpharmgene, Montréal
	Tsoukas, George, M	Applied Medical Informatics Research Inc. (A.M.I.R.), Montréal
Colombia	Leal, Janeth	IPS Universitaria, Servicios de Salud, Universidad de Antioquia, Medellin
	Roman Gonzalez, Alejandro	Hospital Universitario San Vicente De Paul, Medellin
	Martinez, Erika	Colsanitas, Barranquilla
	Manzur Jattin, Fernando Gabriel	Centro de Diagnostico Cardiologico LTDA, Cartagena
	Hoyos Perez, Carlos Arturo	Asociacion IPS Medicos Internistas de Caldas, Manizales
	Burgos Martinez, Eduardo Antonio	FUNCENTRA IPS Fundacion centro de excelencia en enfermedades cronicas no transmisibles, Monteria
	Alberto Garcia, Angel	Hospital Universitario San Ignacio, Bogota
	Gomez Lopez, Efrain Alonso	Fundacion Clinica Abood-Shaio / Fundacion Abbod Shaio, Bogota
	Lugo Pena, Julian Rodrigo	Clinicos IPS, Bogota
	Roncancio, Heidy	Cardiocolombia, Bogota
	Trout Guardiola, Guillermo, O	T Y C Inversiones S A S, Santa Marta
	Marin Sanchez, Alejandro	Megacentro Pinares, Pereira
	Contreras Zuniga, Eduardo	Clinica Occidente Cali, Cali
	Vesga, Carlos	Fundacion Valle del Lili, Cali
Kuwait	Akbar, Mousa	Al Sabah Hospital, Safat
	AlDashti, Rajaa	Al-Amiri Hospital (Sabah AlAhmed Cardiac Center), Kuwait City

	AlJarallah, Mohamed	Al-Amiri Hospital (Sabah AlAhmed Cardiac Center), Kuwait City
Mexico	Llamas Esperon, Guillermo Antonio	Hospital Cardiologica Aguescalientes, Aguascalientes
	Munoz Beltran, Leocadio Gerardo	Hospital Angeles Ciudad Juarez / Private office, Ciudad Juarez
	Nevarez Ruiz, Luis Alejandro, A	Investigacion en Salud y Metabolismo S.C., Chihuahua
	Robles Ramirez, Carlos	Hospital Angeles Torreon, Torreón
	Pavia Lopez, Abel Alberto	Sanatorio Durango, Mexico City
	Sierra Galan, Lilia Mercedes	Hospital ABC Santa Fe, Mexico City
	Padilla Padilla, Francisco, G	Centro Francisco Gerardo Padilla Padilla Cardiología Clínica e Intervención., Guadalajara
	Salas Llamas, Jose Pascual	Centro Diagnostico Cardiovascular, Guadalajara
	Guadarrama Arasi, Jose Luis	Centro Medico Toluca, Barrio San
	Sauque Reyna, Leobardo	Instituto de Diabetes, Obesidad y Nutricion S.C. Coordinacion, Cuernavaca
	Garcia Cantu, Elias Alberto	Centro de Investigacion Clinica Aplicada, Monterrey,
	Garcia Castillo, Armando	Cardiolink Clin Trials, S.C., Monterrey
	Garcia Hernandez, Pedro Alberto	Hospital Universitario Dr Jose E Gonzalez, Monterrey
	Alcocer Gamba, Marco, A	Centro de Estudios Clinicos de Queretaro (CECLIQ), Queretaro
Saudi Arabia	AlFaraidy, Khaled	King Fahad Military Medical Complex in Dhahran, Dhahran
	AlShehri, Mohamed	Khamis Meshhet Military Hospital, Khamis Mesheet
	AlQudaimi, Ahmed	Saud Albabtain Cardiac Center, Dammam
	AlNouri, Fahad	Prince Sultan Cardiac Center, Riyadh
	Awan, Zuhier	King Abdulaziz University Hospital, Jeddah
	Hussein Abdeen, Gamal	North West Armed Forces King Salman Hospital, Tabuk

Table S2: Reimbursement Criteria for Evolocumab per Country Included in the ZERBINI Study

Country	Reimbursement in primary prevention patients (FH)	Reimbursement in secondary prevention patients (established ASCVD)

Canada	HeFH:
	• LDL-C ≥2.0 mmol/L for secondary prevention or <50% reduction from untreated baseline, after:
	  ○ Maximally tolerated dose of statins + ezetimibe, OR
	  ○ Ezetimibe for at least 3 months or documented statin intolerance
	• Public access in all provinces and private reimbursement.
	
	HoFH:
	• After last 2 lipid-lowering therapies.
	• Public (1/10 provinces) and private reimbursement.
		• ASCVD on maximally tolerated dose of statins or with documented statin intolerance with LDL-C not at goal.
		• Covered by >90% of private payers with no public access.

Mexico	• HeFH or HoFH on maximally tolerated dose of statins +/- ezetimibe with LDL-C not at goal. • Private and public (public limited at time of study).	• ASCVD on maximally tolerated dose of statins +/- ezetimibe with LDL-C not at goal. • Private and public (public limited at time of study).
Colombia	• HeFH (adults) and HoFH (since 13 years) with LDL-C not at goal. • Covered by health system when HMO approves its use.	• ASCVD on maximally tolerated dose of statins +/- ezetimibe with LDL-C not at goal. • Covered by health system when HMO approves its use.
Saudi Arabia	• HeFH or HoFH on maximally tolerated dose of statins +/- ezetimibe with LDL-C not at goal. • Covered by both government and private payers.	• ASCVD on maximally tolerated dose of statins +/- ezetimibe with LDL-C not at goal (private institutions) and >100 mg/dL (Ministry of Health hospitals). • Covered by both government and private payers.
Kuwait	• HeFH or HoFH on maximally tolerated dose of statins +/- ezetimibe with LDL-C not at goal. • Covered by both government and private payers.	• ASCVD on maximally tolerated dose of statins +/- ezetimibe with LDL-C not at goal and >70 mg/dL. • Covered by both government and private payers.

ASCVD: atherosclerotic cardiovascular disease; HeFH: heterozygous familial hypercholesterolemia; HMO: Health Maintenance Organization; HoFH: homozygous familial hypercholesterolemia; LDL-C: low-density lipoprotein cholesterol.

Table S3: Sensitivity Analysis of LDL-C Outcomes in Evolocumab Completers vs. the Full Cohort

Median (IQR) LDL-C Concentration in Patients with Both Baseline & 1-12 Month Follow-up Measures	Completers[a]	Full Cohort[b]
	N=330	N=417
Baseline		
mmol/L	3.5 (2.8-4.4)	3.6 (2.8-4.4)
mg/dL	135.3 (108.3-170.2)	139.2 (108.3-170.2)
1-12 months follow-up		
mmol/L	1.3 (0.9-2.1)	1.0 (0.6-1.8)
mg/dL	50.3 (34.8-81.2)	38.7 (23.2-69.6)
Median (IQR) LDL-C Concentration in Patients with Baseline, 1-6 Month & 7-12 Month Follow-up Measures	**N=170**	**N=215**
Baseline		
mmol/L	3.7 (2.9-4.6)	3.7 (2.9-4.5)
mg/dL	143.1 (112.1-177.9)	143.1 (112.1-174.0)
1-6 months follow-up		
mmol/L	1.3 (0.7-2.0)	1.1 (0.7-1.8)
mg/dL	50.3 (27.1-77.3)	42.5 (27.1-69.6)
7-12 months follow-up		
mmol/L	1.4 (0.8-2.1)	1.3 (0.8-2.2)
mg/dL	54.1 (30.9-81.2)	50.3 (30.9-85.1)

[a]Data represent patients who remained on evolocumab at the end of the 12-month study follow-up period, with an LDL-C measure at baseline (measured within 6 months prior to initiation of evolocumab) and their mean LDL-C measure during the indicated follow-up timeframes; [b]Data represent patients with an LDL-C measure at baseline (measured within 6 months prior to initiation of evolocumab) and their minimum LDL-C measure during the indicated timeframes over the 12-month follow-up period.

IQR: interquartile range; LDL-C: low-density lipoprotein cholesterol.

Table S4: Lipid-lowering Therapy Usage at Baseline Across Studied Countries

LLT n (%)	Overall (N=578)	North America		South America	Middle East	
		Canada (N=131)	Mexico (N=108)	Colombia (N=114)	Saudi Arabia (N=155)	Kuwait (N=70)
Statin[a]	437 (75.6)	73 (55.7)	64 (59.3)	93 (81.6)	147 (94.8)	60 (85.7)
Ezetimibe (without statin)	39 (6.7)	19 (14.5)	3 (2.8)	13 (11.4)	3 (1.9)	1 (1.4)
Ezetimibe + statin	168 (29.1)	51 (38.9)	8 (7.4)	50 (43.9)	45 (29.0)	14 (20.0)
Bile acid sequestrant	16 (2.8)	14 (10.7)	0 (0.0)	2 (1.8)	0 (0.0)	0 (0.0)
Other LLT[b]	25 (4.3)	4 (3.1)	9 (8.3)	5 (4.4)	1 (0.6)	6 (8.6)
Reported statin intolerance	206 (35.6)	81 (61.8)	48 (44.4)	39 (34.2)	12 (7.7)	26 (37.1)
Number of statins reported intolerant to:	**(N=206)**	**(N=81)**	**(N=48)**	**(N=39)**	**(N=12)**	**(N=26)**
1	119 (57.8)	27 (33.3)	43 (89.6)	17 (43.6)	12 (100)	20 (76.9)
2	39 (18.9)	21 (25.9)	3 (6.3)	10 (25.6)	0 (0.0)	5 (19.2)
3	35 (17.0)	23 (28.4)	2 (4.2)	9 (23.1)	0 (0.0)	1 (3.8)
≥4	13 (6.3)	10 (12.3)	0 (0.0)	3 (7.7)	0 (0.0)	0 (0.0)

[a]Any patient on a statin; [b]Other LLT included Epacor, Fibrates, and Niacin.

LLT: Lipid-lowering therapy.

Table S5: LDL-C Measurement Incidence & Characteristics Over Study Period

Incidence of LDL-C Measurements	**N=578 n (%)**
Baseline LDL-C measurement[a]	
Yes	539 (93.3)
No	39 (6.7)
≥1 follow-up LDL-C measurement[b]	
Yes	445 (77.0)
No	133 (23.0)
Median (IQR) number of LDL-C measurements	1 (1-2)
Follow-up LDL-C Measurement Characteristics	**N=445**
Median (IQR) number of LDL-C measurements	2 (1-3)
Frequency of LDL-C measurements, n (%)	
1	174 (39.1)
2[b]	129 (29.0)
≥3[b]	142 (31.9)
Median (IQR) days from evolocumab initiation to LDL-C measurement, days	
First measure	87 (46-148)
Last measure	247 (153-315)

[a]The last LDL-C measured within six months prior to initiation of evolocumab was regarded as the baseline LDL-C;

[b]In patients with multiple LDL-C measures during the 12-month follow-up period, their minimum value was used for analysis.

IQR: interquartile range; LDL-C: low-density lipoprotein cholesterol.

Table S6: LDL-C Reductions from Baseline Over Study Period in the Full Study Cohort (N=417)[a]

LDL-C Reduction from Baseline	N=417 n (%)
≥30%	372 (89.2)
≥50%	317 (76.0)
≥80%	115 (27.6)
Any reduction	406 (97.4)
No reduction[b]	11 (2.6)

[a]Data represent patients with an LDL-C measure at baseline (measured within 6 months prior to initiation of evolocumab) and their minimum LDL-C measure during the 12-month study follow-up period; [b]Three of the 11 patients with no LDL-C reduction discontinued evolocumab and 1 patient missed 2 consecutive doses (28 days of no drug). 6 of the 11 patients had unknown FH status.

FH: familial hypercholesterolemia; LDL-C: low-density lipoprotein cholesterol.

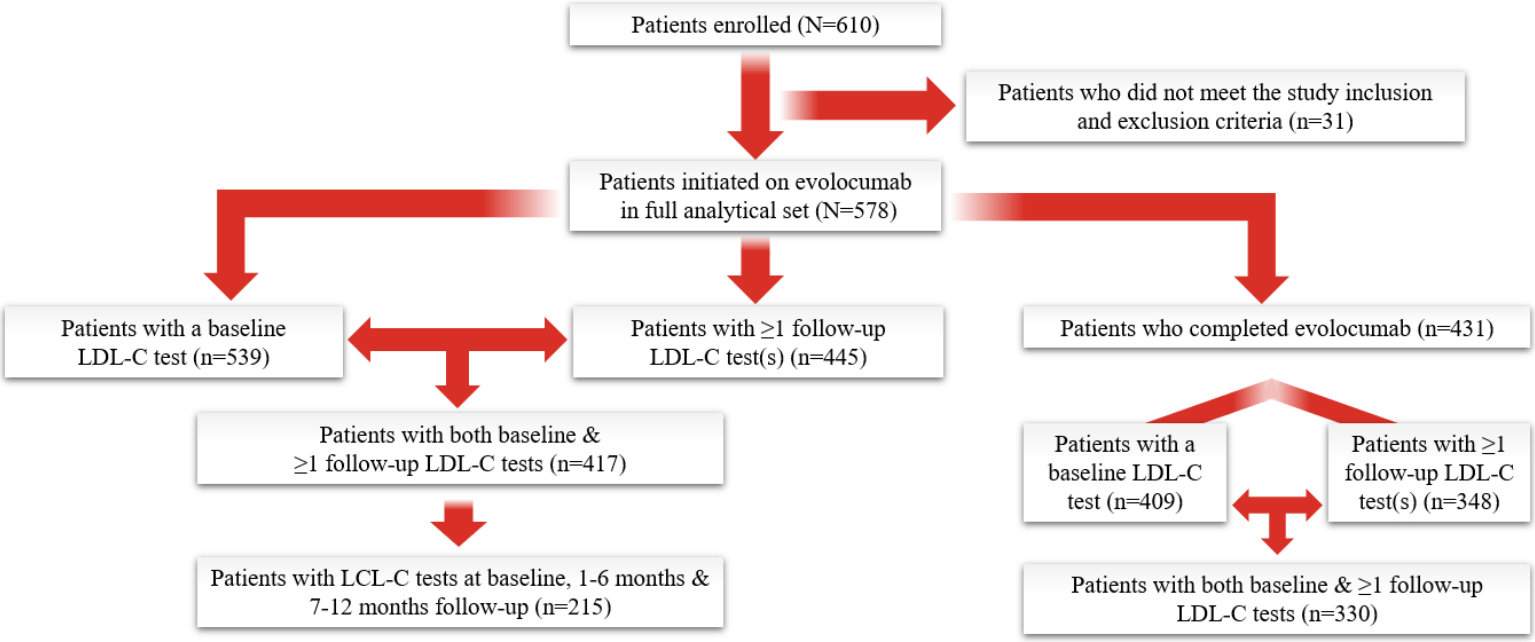
Table S7: Treatment Emergent Adverse Drug Reactions by System Organ Class and Preferred Term in Descending Frequency (N=579)

System Organ Class Preferred Term	Total (N = 579) n (%)
Musculoskeletal and connective tissue disorders	**6 (1.0)**
Myalgia	3 (0.5)
Arthralgia	1 (0.2)
Back pain	1 (0.2)
Muscle discomfort	1 (0.2)
Nervous system disorders	**6 (1.0)**
Dizziness	4 (0.7)
Headache	3 (0.5)
Balance disorder	1 (0.2)
General disorders and administration site conditions	**4 (0.7)**
Chest pain	1 (0.2)
Fatigue	1 (0.2)
Illness	1 (0.2)
Puncture site haematoma	1 (0.2)
Respiratory, thoracic and mediastinal disorders	**4 (0.7)**
Catarrh	1 (0.2)
Dyspnoea	1 (0.2)
Sinus congestion	1 (0.2)
Throat irritation	1 (0.2)
Infections and infestations	**3 (0.5)**
Influenza	2 (0.3)
Sinusitis	1 (0.2)
Skin and subcutaneous tissue disorders	**3 (0.5)**
Pruritus	1 (0.2)
Rash	1 (0.2)
Skin lesion	1 (0.2)
Gastrointestinal disorders	**2 (0.3)**
Dyspepsia	1 (0.2)
Nausea	1 (0.2)

Table S8: Full List of Ethics Committees

Site Country	PI Full Name	Site No	Site Member Organization	EC Full Name	Ethical Approval Numbers
Colombia	Burgos Martinez, Eduardo Antonio	32730001	FUNCENTRA IPS Fundacion centro de excelencia en enfermedades cronicas no transmisibles	Research Ethics Committee of the Mental Hospital of Antioquia E.S.E.	
Colombia	Gomez Lopez, Efrain Alonso	32730002	Fundacion Clinica Abood-Shaio / Fundacion Abbod Shaio	Research Ethics Committee Abood Shaio Foundation	
Colombia	Leal, Janeth	32730003	IPS Universitaria, Servicios de Salud, Universidad de Antioquia	Universitaria IPS Research and Ethics Committee	
Colombia	Roman Gonzalez, Alejandro	32730004	Hospital Universitario San Vicente De Paul	Research Ethics Committee San Vicente Paul Hospital Foundation	
Colombia	Vesga, Carlos	32730007	Fundacion Valle del Lili	Comite de Etica en Investigacion Biomedica of Fundacion Valle del Lili	
Colombia	Contreras Zuniga, Eduardo	32730010	Clinica Occidente Cali	Ethics Committee on Human Reasearch Angiografia de Occidente S.A.	
Colombia	Marin Sanchez, Alejandro	32730015	Megacentro Pinares	Comite Regional de Etica en Investigacion Clinica del Eje Cafetero (CREICEC)	
Colombia	Alberto Garcia, Angel	32730017	Hospital Universitario San Ignacio	Institutional Research and Ethics Committee of the Pontifical Xavierian University School of Medicine	
Colombia	Trout Guardiola, Guillermo, O	32730022	T Y C Inversiones S A S	Research Ethics Committee of the Mental Hospital of Antioquia E.S.E.	
Colombia	Manzur Jattin, Fernando Gabriel	32730023	Centro de Diagnostico Cardiologico LTDA	El Comite de Etica en Investigacion del Centro de Diagnostico Cardiologico para la investigacion biomedica	
Colombia	Martinez, Erika	32730024	Colsanitas	El Comite de Etica en Investigaciones del Oriente	

Figure S1: ZERBINI Study Patient Sample Size Flowchart



LDL-C: low-density lipoprotein cholesterol.

Figure S2: Study Schema

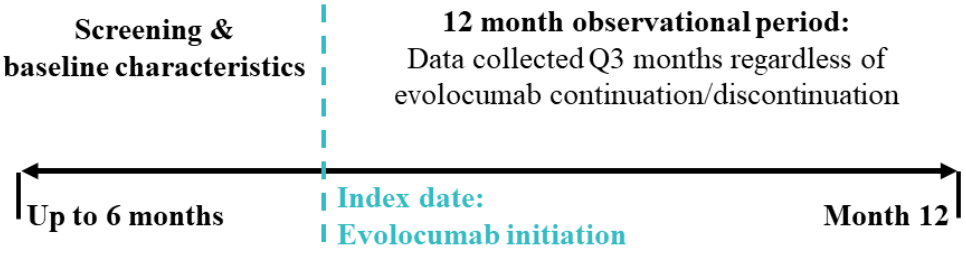
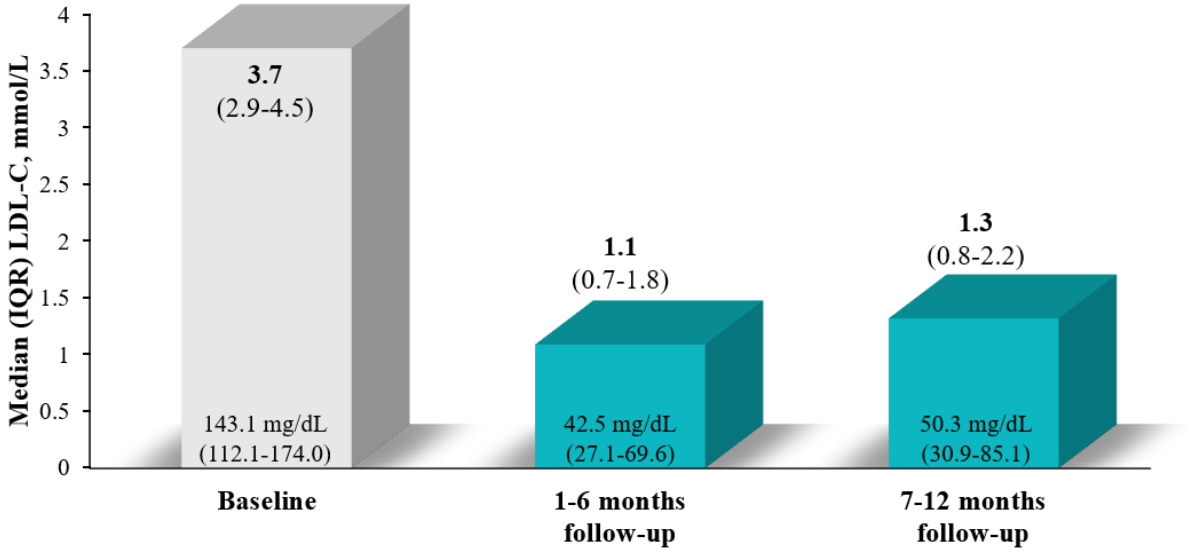


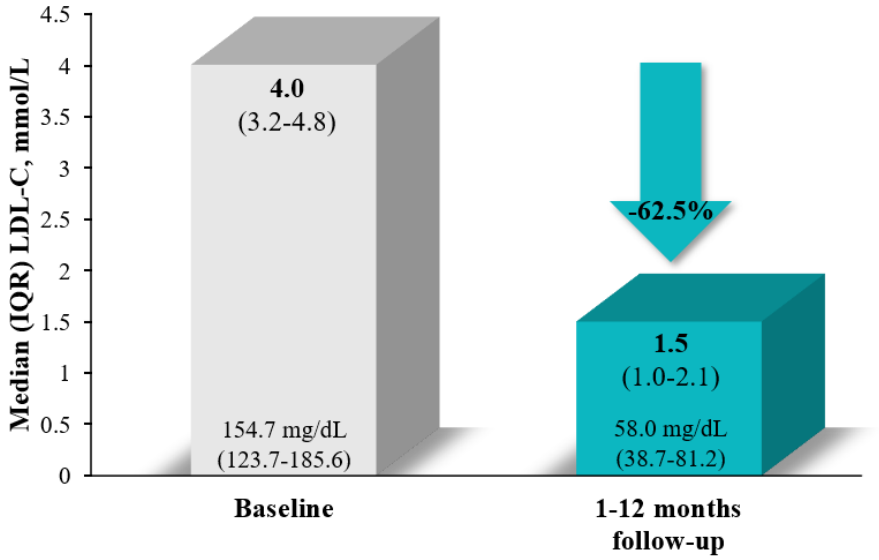
Figure S3: Median LDL-C Concentrations at Baseline and Over Study Period in the Full Study Cohort (N=215)*



*Data represent patients with an LDL-C measure at baseline (measured within 6 months prior to initiation of evolocumab) and their minimum LDL-C measure during the indicated timepoints over the 12-month follow-up period.

IQR: interquartile range; LDL-C: low-density lipoprotein cholesterol.

Figure S4: Median LDL-C Concentrations at Baseline and Follow-up in Patients on Evolocumab Monotherapy (N=63)*



*Data represent patients with an LDL-C measure at baseline (measured within 6 months prior to initiation of evolocumab) and their minimum LDL-C measure during the 12-month follow-up period.

IQR: interquartile range; LDL-C: low-density lipoprotein cholesterol.