Homozigot Ailesel Hiperkolesterolemi; Güncel Durum

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Editor-in Chief Balkan Medical Journal

OLGU

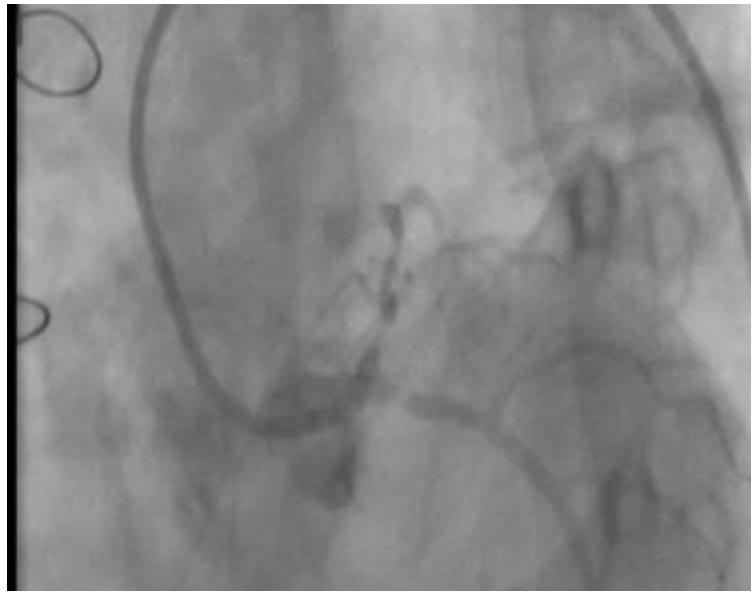
31 yaş K,

3 yaşında ksantom

15 yaş 2xCABG

Tekrarlayan MI

Statin-Ezetimib-Aferez



12 yaş K,

Senkop, GA

AKS

LDL:556

Aile öyküsü

2xCABG

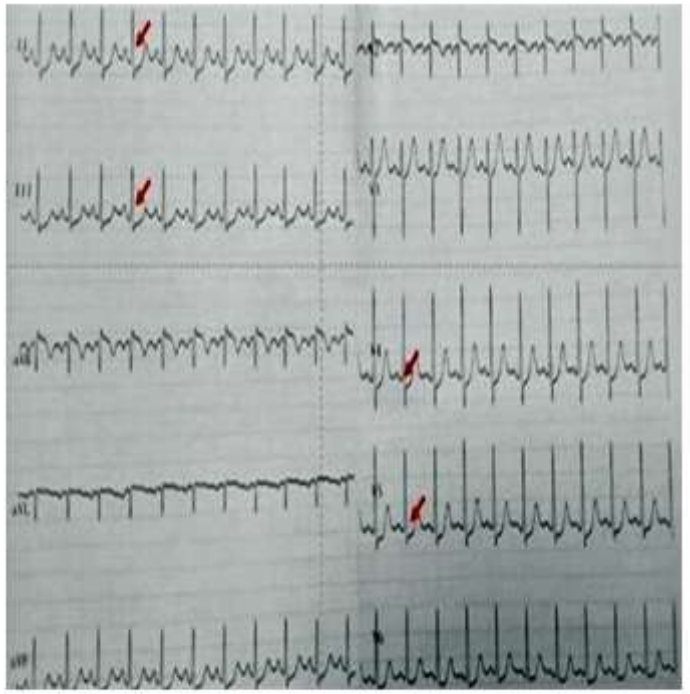


FIG. 1. Upon admission, electrocardiography showed an ST depression in the inferior leads and lateral precordial derivations.

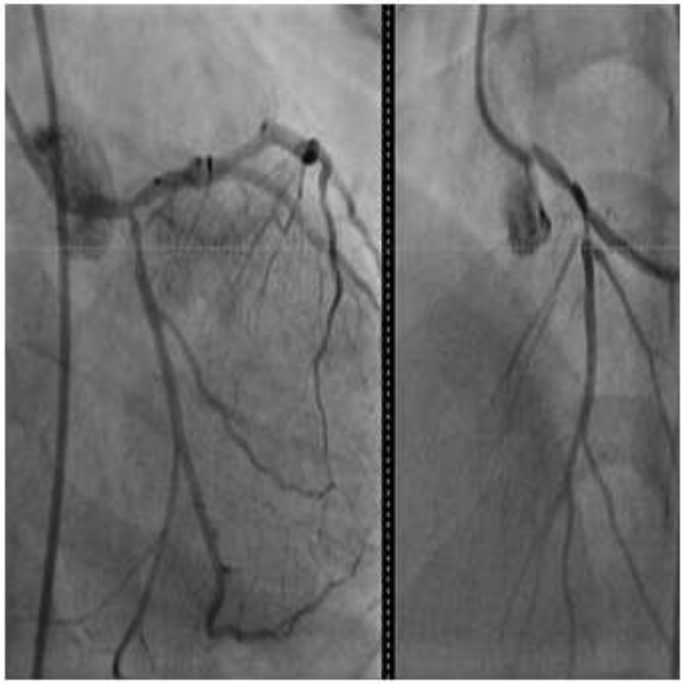


FIG. 3. Conventional coronary angiography revealed a significant occlusion of the left anterior descending artery and circumflex artery.

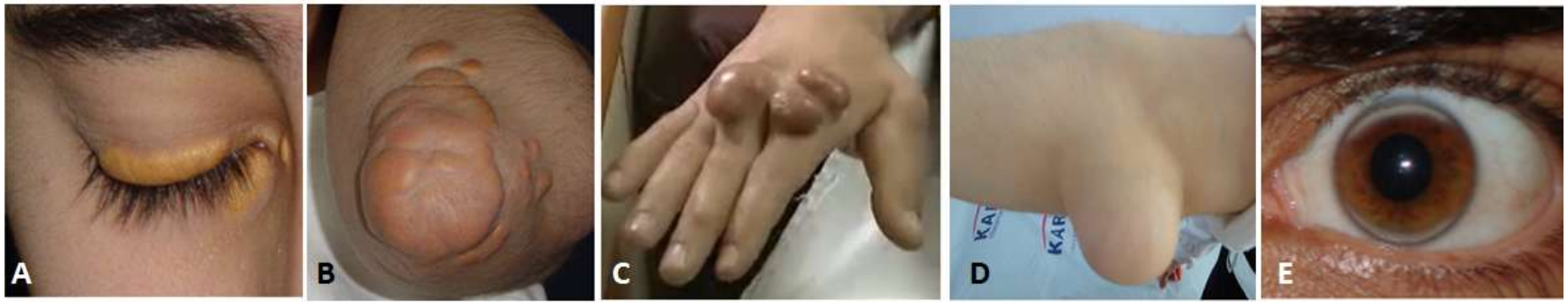
Balkan Med J 2018;35:208-11

Ailəvi hiperkolesterolemiya (FH)

çox yayılmış genetik xəstəlikdir (OD)

ilə xarakterizə olunur

- Yüksək xolesterol səviyyələri
- Erkən ateroskleroz
- Xolesterolun çökməsi



Kayıkçıoğlu M et al. Atherosklerosis 270 (2018) 42-48

Box 2 Updated criteria for the diagnosis of homozygous familial hypercholesterolaemia

Clinical criteria

- LDL-C criteria:
  Untreated LDL-C >10 mmol/L (>~400 mg/dL) is suggestive of HoFH requiring further investigation to confirm the diagnosis.
- Additional criteria:
  Cutaneous or tendon xanthomas before age of 10 years and/or
  untreated elevated LDL-C levels consistent with heterozygous FH in both parents*
  *In digenic form, one parent may have normal LDL-C levels and the other may have LDL-C levels consistent with HoFH.

Genetic criteria

- Genetic confirmation of bi-allelic pathogenic/likely pathogenic variants on different chromosomes at the *LDLR*, *APOB*, *PCSK9*, or *LDLRAP1* genes or ≥2 such variants at different loci (*Box 3*); for abbreviations for genetic nomenclature see below.

ABCG5, *ABCG8*: Genes encoding ATP-binding cassette subfamily G members 5 and 8
APOB: Gene encoding apolipoprotein B
LDLR: Gene encoding the low-density lipoprotein receptor
LDLRAP1: Gene encoding low-density lipoprotein receptor adaptor protein 1
LIPA: Gene encoding lysosomal acid lipase
PCSK9: Gene encoding proprotein convertase subtilisin/kexin type 9 protein (PCSK9)

European Heart Journal (2023) 44, 2277–2291
https://doi.org/10.1093/eurheartj/ehad197

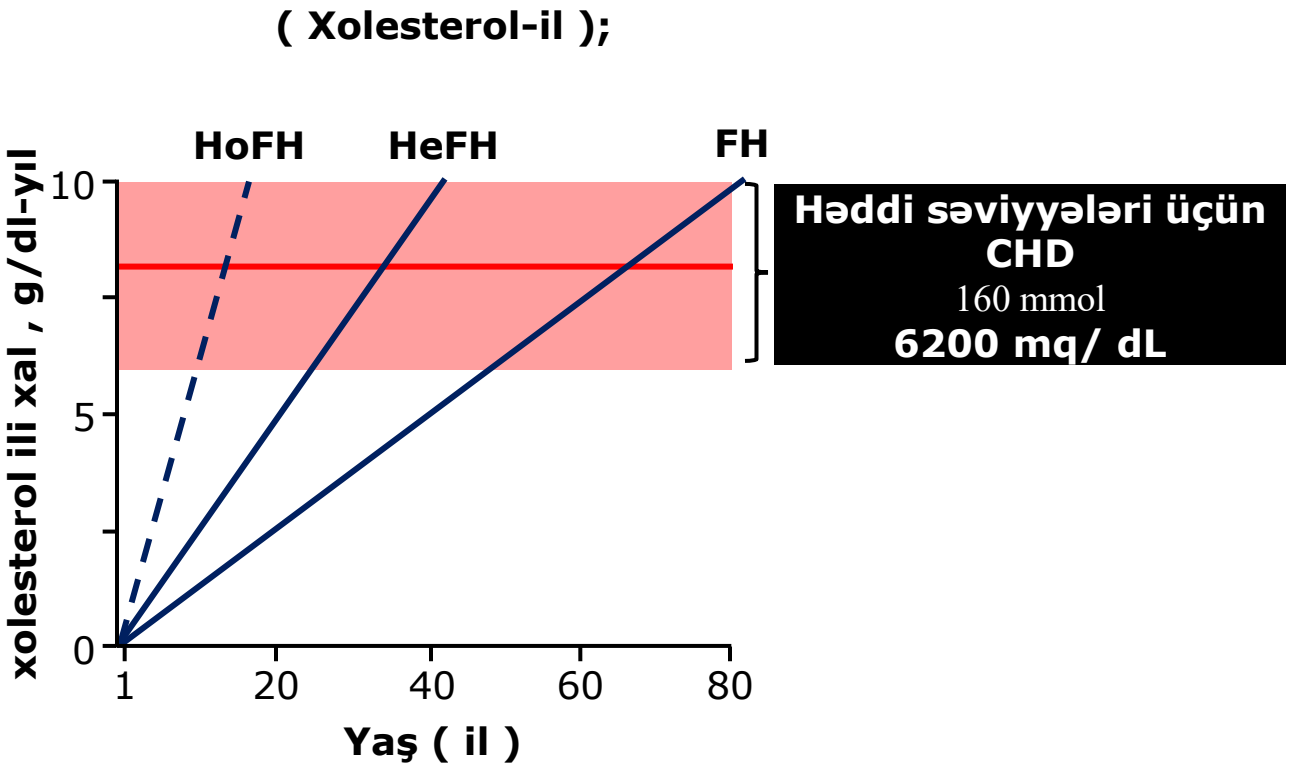
Tetkik Adı	Sonuç	Durum	Birim	Referans Aralığı / Karar Sınırı	Once
T.BILURUBIN	0,83		mg/dl	0.2 - 1.2	
D.BILURUBIN	0,34		mg/dl	0 - 0.5	
Na	139		mmol/L	136 - 145	
K	4,5		mmol/L	3.5 - 5.1	
AKŞ (Açlık Kan Şekeri)	90		mg/dl	70 - 105	
ÜRE	29		mg/dl	15 - 43	
KREATININ	0,67		mg/dl	0,57 - 1,11	
TRIGLISERID	64		mg/dl	0 - 200	
# **KOLESTEROL**	227	Y	**mg/dl**	**0 - 200**	
# **HDL-C**	74	Y	**mg/dl**	**50 - 60**	
LDL-C	100		mg/dl	0 - 130	
ALT	17		U/L	0 - 55	
AST	19		U/L	0 - 34	

AKŞ (Açlık Kan Şekeri)	88		mg/dL	74 - 106	97	97	83
ÜRE	37		mg/dL	17 - 49	35	29	18
KREATININ	0.81		mg/dL	0,5 - 0,9	0.77	0.71	0.62
# **URIK ASIT**	6.0	Y	**mg/dL**	**2,4 - 5,7**	5.0	4.5	4.8
TRIGLISERID	82		mg/dL	0 - 150 *	55	80	111
# **KOLESTEROL**	429	Y	**mg/dL**	**0 - 200 ***	255	236	207
HDL-C	89		mg/dL	50 - *	79	54	55
# **LDL-C**	327	Y	**mg/dL**	**0 - 130 ***	162	161	126
# **T.PROTEIN**	8.6	Y	**g/dl**	**6,4 - 8,3**	7.3	7.3	7.1
# T.PROTEIN_	86		g/L	64 - 83	73	73	71
ALBUMIN	5.2		g/dl	3,5 - 5,2	4.3	4.3	4.6
ALBUMIN_	52		g/L	35 - 52	43	43	46
ALT	15		U/L	0 - 33	10	6	8
AST	24		U/L	0 - 32	19	14	18

Secondary hyper-LDL cholesterolemia
Obesity
Nephrotic syndrome
Hypothyroidism
Diabetes mellitus
Cushing syndrome
Anorexia nervosa
Pheochromocytoma
Infectious
Diet related
Cholestatic liver disease
Inflammatory disease
Drug induced (steroids, cyclosporin)

FH ömür boyu xolesterola məruz qalır
FH insanları doğuşdan etibarən çox yüksək xolesterola məruz qoyur və beləliklə, həyatın əvvəlində CHD üçün ərəfəyə çatır.

LDL səviyyələri CV nəticəsini təyin edir!



Horton JD et al. J Lipid Res. 2009;50(Təchizat):S175

Familial hiperxolesterinemiya

Homozigot FH

1/160 000 - 1/320 000

Heterozigot FH

1/200 - 1/250

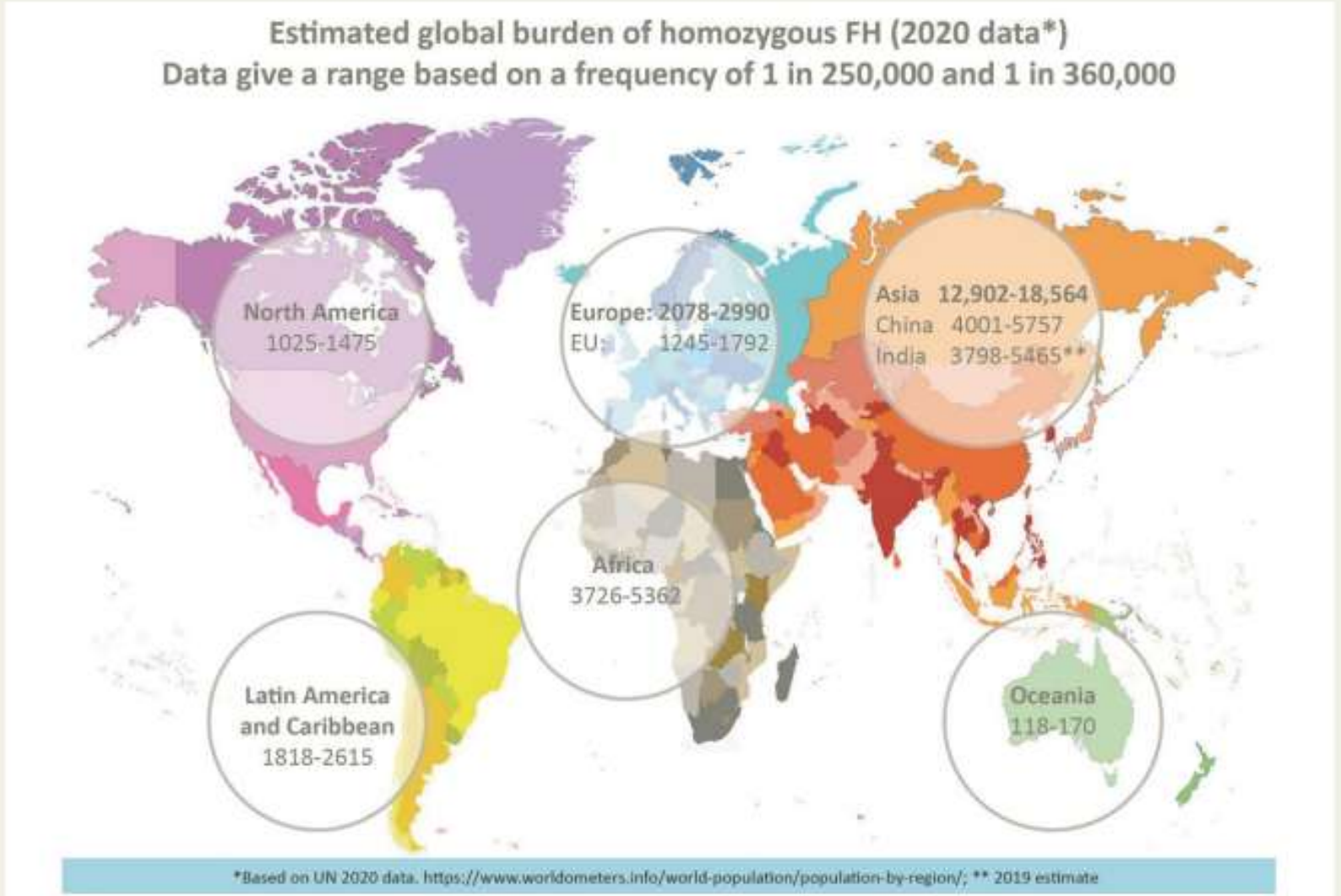
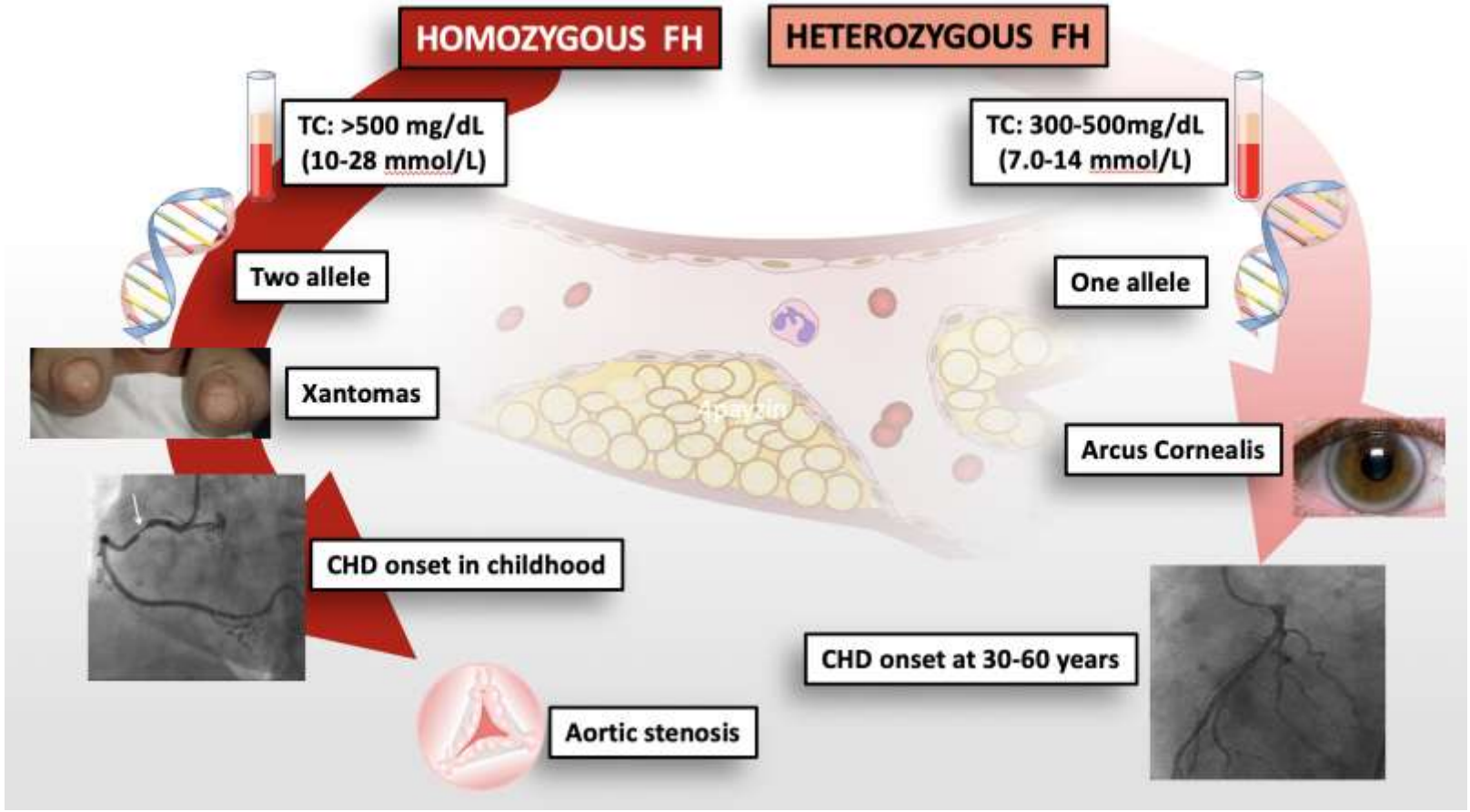


Figure 1 Estimated global prevalence of homozygous familial hypercholesterolaemia by United Nations world region, based on 2020 population data and estimates of homozygous familial hypercholesterolaemia prevalence ranging from 1:250 000 to 1:360 000.[10,11]

Doğuşdan bəri məcmu xolesterol məruz qalma vaxtından əvvəl CVD-yə səbəb olur

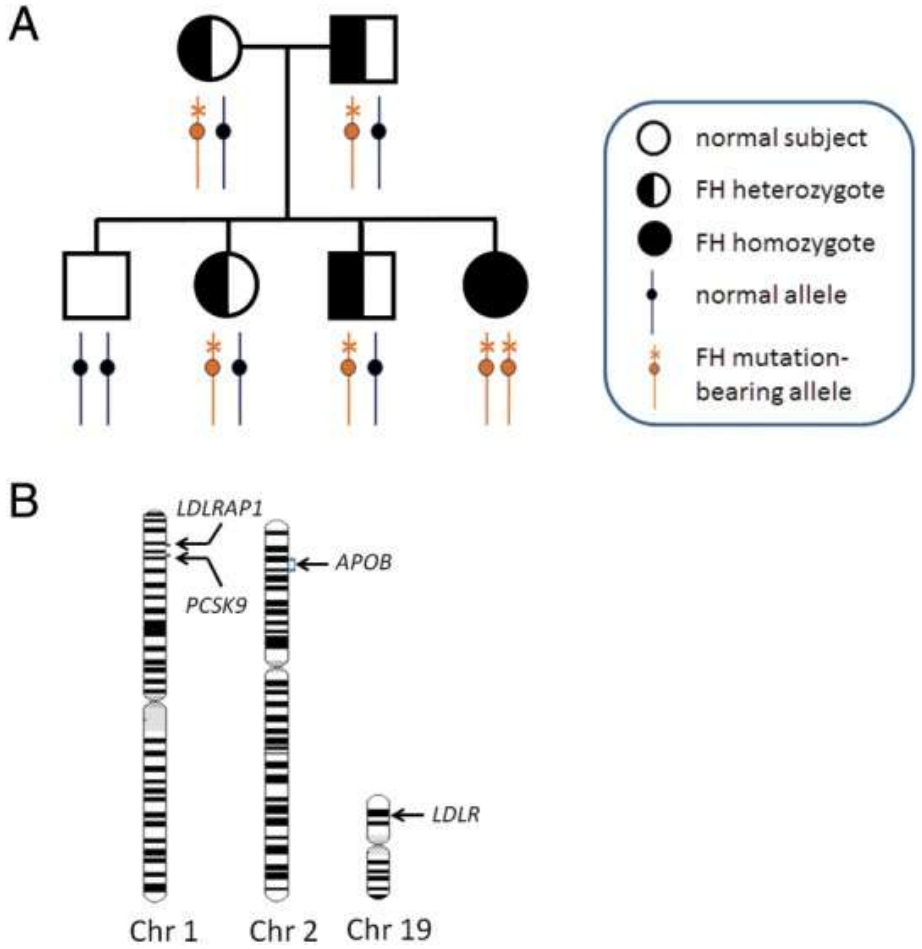


Ailəvi hiperkolesterolemiya: Qlobal yük və yanaşmalar.
Curr Cardiol Rep. 2021;23(10):151

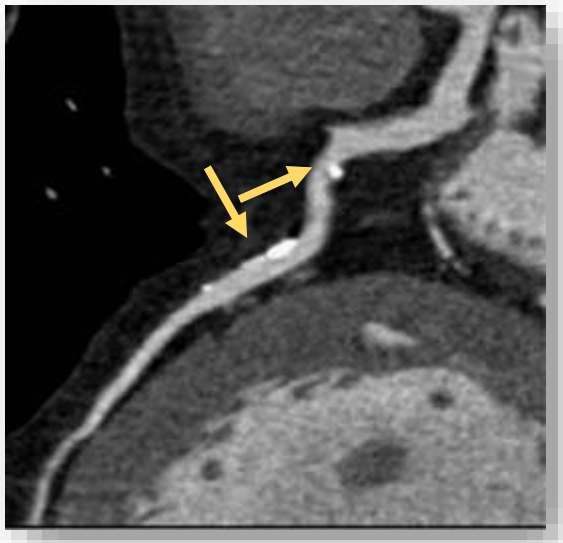
FH
ən çox plazmadan LDL hissəciklərini təmizləyən LDL-reseptoruna təsir edən genlərdəki mutasiyalarla əlaqədardır.

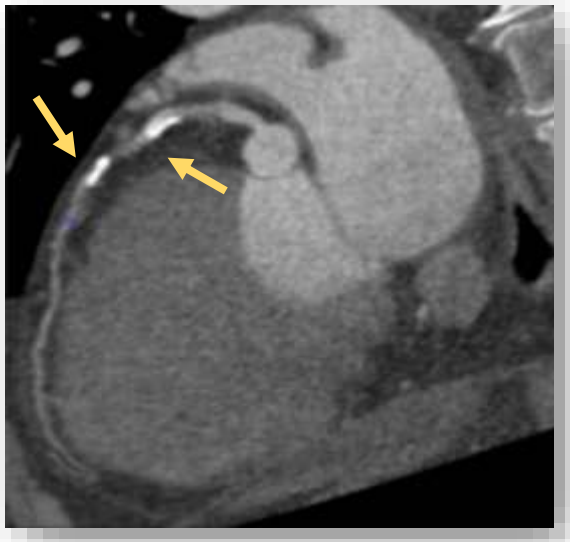
Genetic mutations

- LDL-R (80-90%)
- Apo-B
- PCSK9
- LDLRAP1
- others



Çox erkən CVD





8 yaş/o HoFH – müalicə olunmamış
Koronar damarların termoması

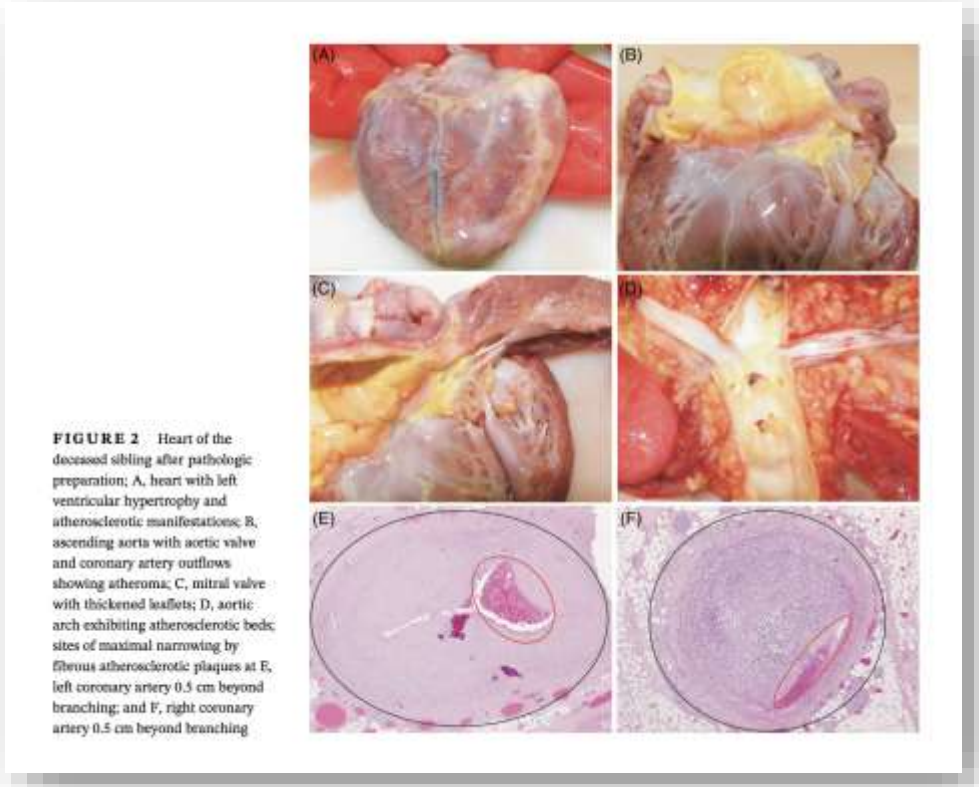


FIGURE 2 Heart of the deceased sibling after pathologic preparation; A, heart with left ventricular hypertrophy and atherosclerotic manifestations; B, ascending aorta with aortic valve and coronary artery outflows showing atheroma; C, mitral valve with thickened leaflets; D, aortic arch exhibiting atherosclerotic beds; sites of maximal narrowing by fibrous atherosclerotic plaques at E, left coronary artery 0.5 cm beyond branching; and F, right coronary artery 0.5 cm beyond branching

2 yaşlı oğlan HoFH səbəbiylə öldü

HoFH müalicəsi

- LDL hədəflərinə çatmaq lazımdır!
  - Mümkün qədər aşağı
  - Mümkün qədər tez

Table 3
Therapeutic Goals for FH in Children and Adolescents

Society	Country	Target LDL-C
National Institute for Health and Clinical Excellence[32]	United Kingdom	No specific LDL-C targets
Belgian consensus for FH treatment in children and young adults[33]	Belgium	• 10-14 years old: LDL-C <130 mg/dL (<7.2 mmol/l) and/or 30% reduction • 14-18 years old: LDL-C <130 mg/dL (<7.2 mmol/l) and/or 50% reduction
Pediatric guidelines on cardiovascular risk in children and adolescents[34]	USA	>10 years old: 50% reduction in LDL-C or LDL-C <130 mg/dL (<7.2 mmol/l)
Expert consensus of the European Atherosclerosis Society specific to children and adolescents (European Society of Cardiology)[15]	Europe	• 8-10 years old: 50% reduction in LDL-C • ≥10 years old: LDL-C <130 mg/dL (<7.2 mmol/l) (especially if CV risk factors are present)
International Atherosclerosis Society[13]	International	• LDL-C <100 mg/dl (<5.5 mmol/l) in the presence of additional ASCVD risk factors (primary prevention) • LDL-C <135 mg/dl (<7.5 mmol/l) or 50% reduction in the absence of additional risk factors for ASCVD

Abbreviations: ASCVD = atherosclerotic cardiovascular disease; FH = familial hypercholesterolemia; LDL-C = lipoprotein-cholesterol.

FH terapevtikləri

LDL-R bağlı

- Statinlər
- Ezetimibe
- Qətranlar
- Bempedoik turşu
- PCSK9 inh (Alirocumab, Evolocumab)
- siRNA(Inclirisan)

LDL-R bağlı olmayan

- Lomitapid
- Mipomersen
- Aferez
- ANGPLT3 inh
- Evinakumab (ANGPLT3 mab), iRNA
- Gemcabene, HDL autotransfuziya, AAV-8 əsaslı LDL-R gen əvəzedici terapiya
- Genomun redaktəsi (CRISPR-cas) – PCSK9 və ANGPLT3 hədəflənməsi (klinikadan əvvəlki inkişafın qabaqcıl mərhələlərində)

HoFH müalicəsi

<u>LDL-R-dən asılıdır</u>

- Statinlər
- Ezetimibe
- R esins
- **PCSK9 inh**
- Daxildir

Should we use PCSK9 inh in HoFH?

- PCSK9 inh could be effective in HoFH patients depending on the LDL-R activity
- LDL-C reduction varies ranging from 7% to 56%
- Patients with a response of 10–15% LDL-C reduction (or interval mean LDL) should continue PCSK9 inhibitors.

- *Kayikcioglu M. LDL Apheresis and Lp (a) Apheresis: A Clinician's Perspective. Curr Atheroscler Rep. 2021*
- *France M, et al; HEART UK statement on the management of HoFH in the United Kingdom. Atherosclerosis. 2016*

LDL-aferez

- Ən təsirli LDL azaldıcı terapiya
- LDL-R müstəqil
- Həyat xilasetmə
- Asan deyil , uyğunlaşa bilən terapiya
- Tezlik vacib (ideal həftəlik)
- başlaması : ideal yaş <6-7 yaş (çox əvvəllər)
- Əks halda Aorta stenoz irəliləmə qarşısını

A-HIT 1 – Türkiye Aferez registriyası
HoFH N=88

	il (min-maks)
İlk semptomda yaş ,	10±10 (0,5-45)
İlk xolesterolun ölçülməsində	12±11(1-45)
Diaqnoz yaşı	13±11 (1-50)
aferezin yaşı	21±12 (3-55)

2 il

8 il

Kayıkçıoğlu M et al. Ateroskleroz 270 (2018) 42-48

A-HIT 1
ballarının çoxu səmərəsiz LA ilə qarşılaşır və hədəflərə çata bilmir

The son 4 LA seansı 'LDL-C səviyyələri idi qeydə alınıb
Kroon düstur

Mg/ dL

4 son seansın orta seans öncəsi LDL	414±101 (205-518)
4 son seansın orta seansdan sonrakı LDL	133±44 (67-261)
Interval orta LDL	338±82 (168–561)
LDL məqsədə çatma (ESC 2016 Təlimatları)	5 xəstə (5,7%)

Yoxdur: ESC 2019-a görə

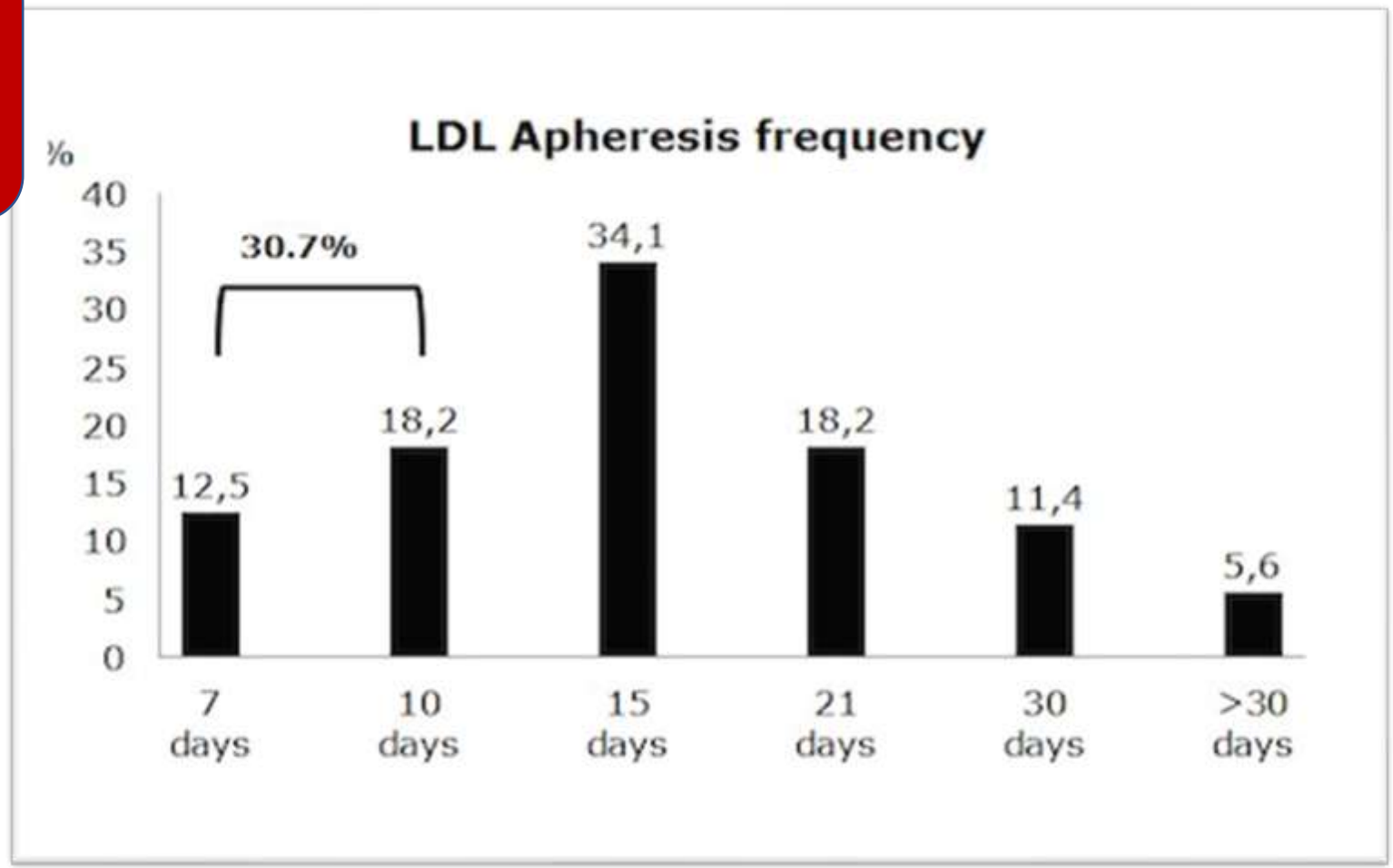
*c Kroon düsturu ilə hesablanır

LA, lipoprotein aferezi

LA seanslarının orta tezliyi : 19 (7-90) günlər

Yalnız 11 xəstə həftəlik LA keçirdi

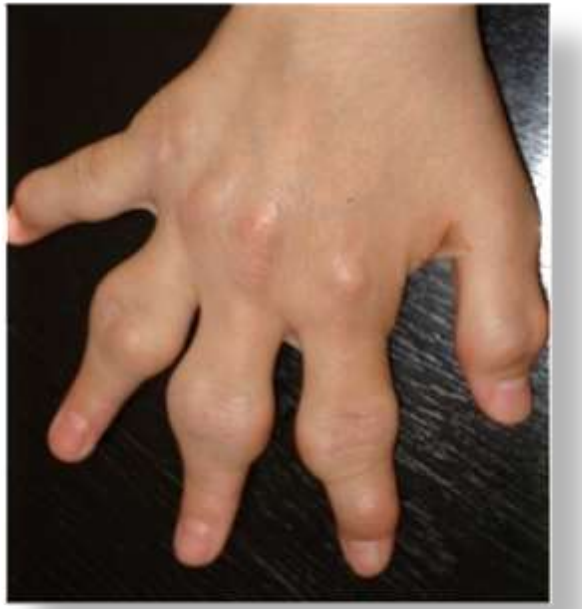
Aferez aralıq terapiyadır



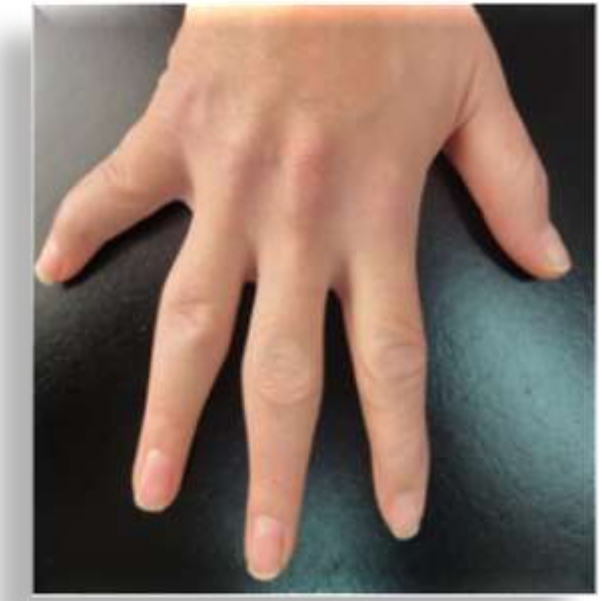
LA, lipoprotein aferezi

Kayıkçıoğlu M et al. Ateroskleroz 270 (2018) 42-48

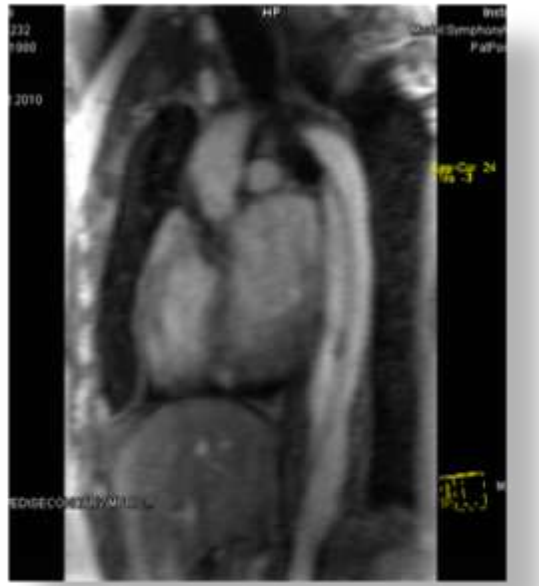
LDL aferez



Əsas xətt
13 yaş



2 -ci il



21 yaşında öldü
AS səbəbiylə HF

Kayıkçıoğlu M. Arch Turkish Cardiol 2014;42 Suppl 2:19-31

Qaraciyər Tx - son çarə müalicəsi

- əsasən qısamüddətli yaxşı nəticələr

Adv Ther (2022) 39:3042–3057
https://doi.org/10.1007/s12325-022-02131-3

CASE SERIES

Is Liver Transplant Curative in Homozygous Familial Hypercholesterolemia? A Review of Nine Global Cases

Mohammed Al Dubayee · Meral Kayikcioglu · Jeanine Roeters van Lennep · Nadia Hergli · Pedro Mata

Conclusions: Liver transplant did not enable attainment of recommended LDL-C targets in most patients with HoFH, and the majority of patients still required post-transplant LLT. Liver transplant was not curative in most of the patients with HoFH followed. Guidelines suggest that transplant is a treatment of last resort if contemporary treatments are not available or possible.

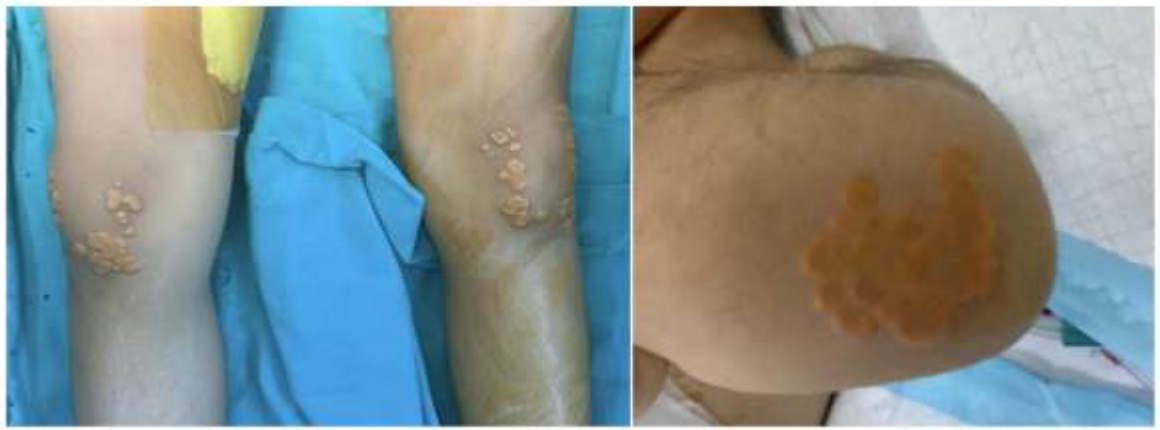


Fig 1. Bilateral multiloculated xanthomas on the knees and elbows preoperatively.

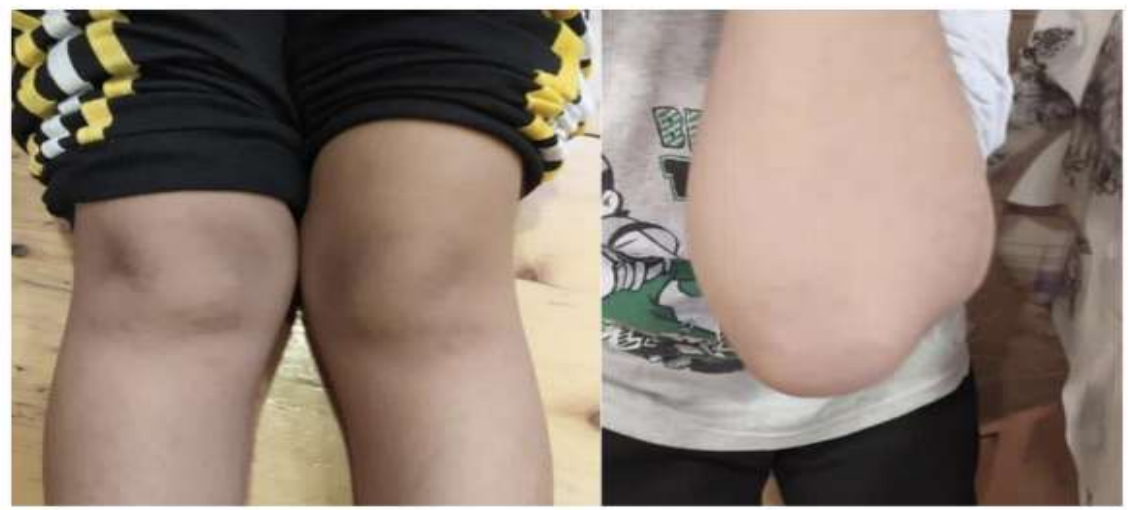
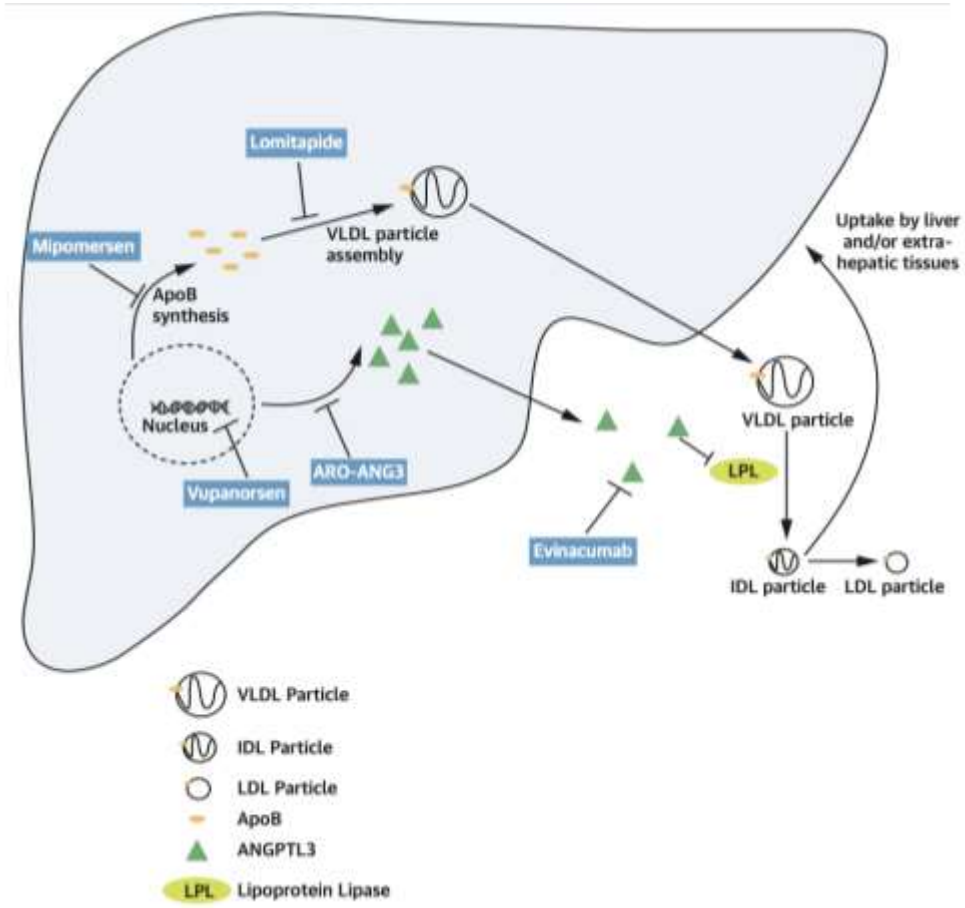


Fig 2. Xanthomas completely disappeared 1 year after the operation.

LDL-R bağlı olmayan

- Lomitapid
- Mipomersen
- Aferez
- ANGPLT3 inh
- Evinakumab (ANGPLT3 mab), iRNA
- Gemcabene, HDL autotransfuziya, AAV-8 əsaslı LDL-R gen əvəzedici terapiya
- Genomun redaktəsi (CRISPR-cas) – PCSK9 və ANGPLT3 hədəflənməsi (klinikadan əvvəlki inkişafın qabaqcıl mərhələlərində)



HoFH üçün anti-Apo B agentləri

Lomitapid

po

5-60 mq/gün

LDL reseptorlarından asılı olmayan təsir mexanizmi olan yeni nəsil güclü LL agenti

- apoB tərkibli trigliseridlərlə zəngin lipoproteinlərin sintezi üçün şaperon rolunu oynayan, membran vezikülləri arasında neytral lipidlərin daşınmasından məsul olan hüceyrə zülalı olan mikrosomal trigliserid ötürmə zülalını (MTTP) inhibə edir .

- qaraciyər və bağırsaqlarda

Lomitapid

po

5-60 mq/gün

EMA və FDA

Qarışıq terapiya zamanı müalicə hədəflərinə çata bilməyən HoFH olan böyüklər üçün təsdiq edilmişdir.

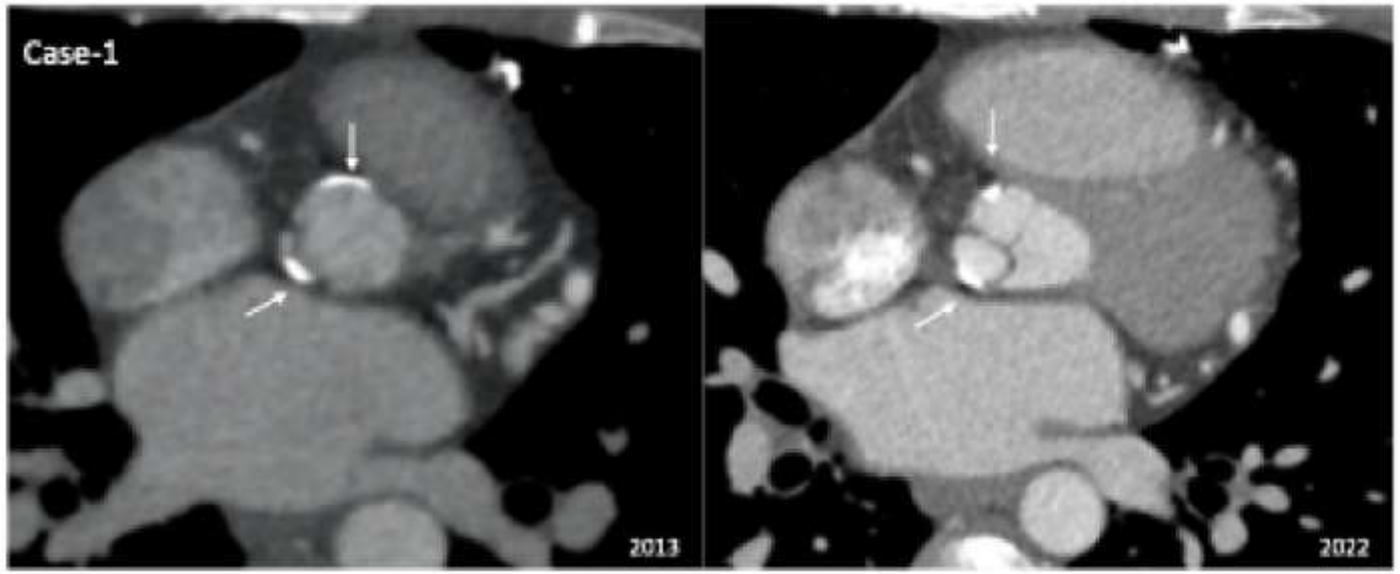
Uzun müddətli lomitapid müalicəsi (2.1-5.7 il) 19 HoFH böyüklərində LDL-xolesterol səviyyəsini orta hesabla 45.5% azaldır .

Real həyat sübutu; 246 həftəlik terapiya,

Xəstələrin 74%-i LDL hədəfinə 100 mq /dL çatmışdır

58% xəstələr 70 mq/dL hədəfləyir

(Blom *və b.* , 2017)



14
d 5 mq / gün
atin 80 mq / gün
nib 1 0 mq / gün

Noyabr 2022
Simptom aşağı səviyyədə pulsuz doza lomitapid və iki ayda bir aferez

CT nəticələri
Agatson-Xal : 0
Ateroma yoxdur irəliləmə

1994 2002 2004 2014 2019 2022

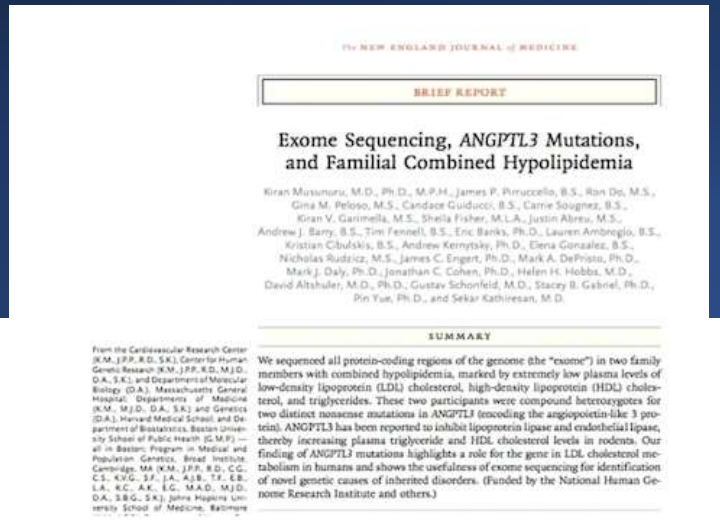
Noyabr 2013
CT nəticələri
Agatson-Xal : 0
Safen RCA grefti tıkanmış , yumşaqdır _ _ RCA ağzında 25 % stenoz lövhəsi .
Sonoqrafiya Tapıntılar
IMT : Sağ 1,3 mm Sol 1,5 mm
ATT: 9,4 mm

2014-cü ilin avqustu
Lomitapid doza titrləmə yuxarı üçün 20 mq/gün

Noyabr 2019
Sonoqrafiya Tapıntılar
IMT Sağ 0,8 mm, Sol 0,7 mm

Ön iclas : 130
Sessiyadan sonrakı LDL: 54
LDL intervalı orta : 55-65
İndi aferez haqqında hər 2 aydan bir

ANGPTL3 inhibitorları



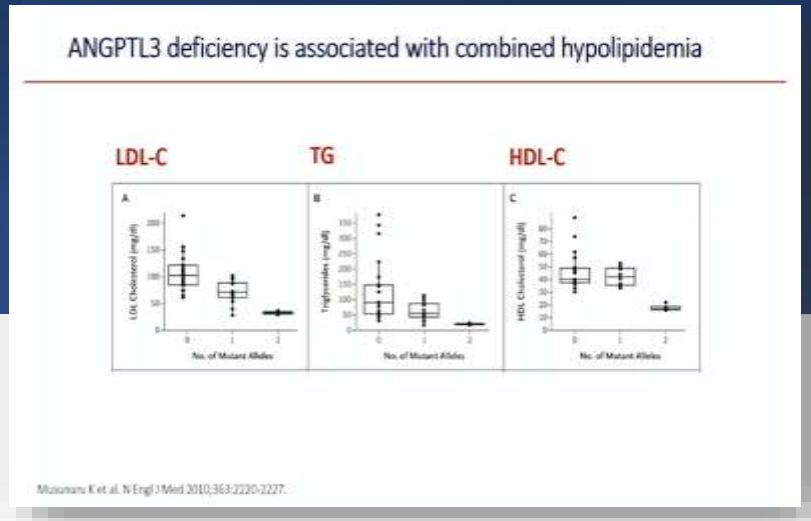
BRIEF REPORT

Exome Sequencing, *ANGPTL3* Mutations, and Familial Combined Hypolipidemia

Kiran Musunuru, M.D., Ph.D., M.P.H., James P. Pirruccello, B.S., Ron Do, M.S., Gina M. Peloso, M.S., Candace Guiducci, B.S., Carrie Sougnez, B.S., Kiran V. Garimella, M.S., Sheila Fisher, M.L.A., Justin Abreu, M.S., Andrew J. Barry, B.S., Tim Fennell, B.S., Eric Banks, Ph.D., Lauren Ambrogio, B.S., Kristian Cibulskis, B.S., Andrew Kernytsky, Ph.D., Elena Gonzalez, B.S., Nicholas Rudzicz, M.S., James C. Engert, Ph.D., Mark A. DePristo, Ph.D., Mark J. Daly, Ph.D., Jonathan C. Cohen, Ph.D., Helen H. Hobbs, M.D., David Altshuler, M.D., Ph.D., Gustav Schonfeld, M.D., Stacey B. Gabriel, Ph.D., Pin Yue, Ph.D., and Sekar Kathiresan, M.D.

SUMMARY

We sequenced all protein-coding regions of the genome (the "exome") in two family members with combined hypolipidemia, marked by extremely low plasma levels of low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides. These two participants were compound heterozygotes for two distinct nonsense mutations in *ANGPTL3* (encoding the angiopoietin-like 3 protein). ANGPTL3 has been reported to inhibit lipoprotein lipase and endothelial lipase, thereby increasing plasma triglyceride and HDL cholesterol levels in rodents. Our finding of *ANGPTL3* mutations highlights a role for the gene in LDL cholesterol metabolism in humans and shows the usefulness of exome sequencing for identification of novel genetic causes of inherited disorders. (Funded by the National Human Genome Research Institute and others.)



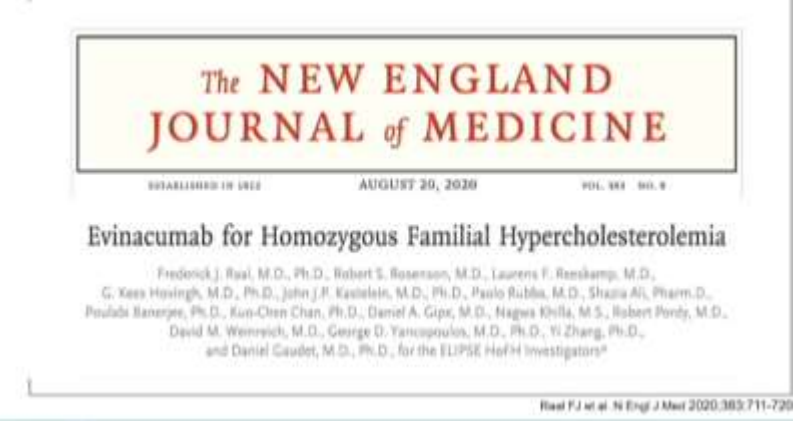
- ANGPTL3, 4 and 8 are important modulators of lipid metabolism;
- ANGPTL3 is a circulating protein synthesized in the liver that importantly modulates lipid-lipoprotein metabolism and has pleiotropic functions;
- The ANGPTL3 coding gene *(ANGPTL3)* is specifically expressed in the hepatocytes and its expression is regulated by LXR;
- Naturally occurring LoF variants the ANGPTL3 gene are associated with combined hypolipidemia and lower cardiovascular risk;

D. Gaudet-in izni ilə

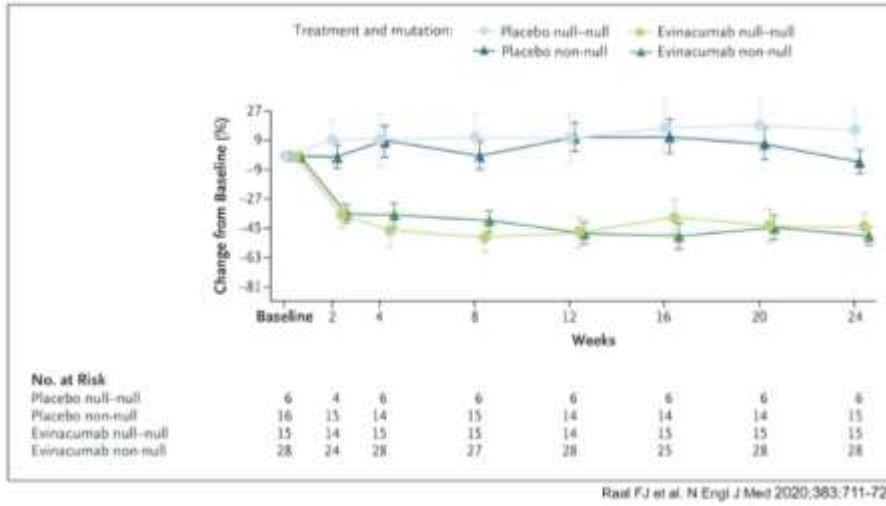
Evinakumab

iv. inf
15 mq/kq
aylıq

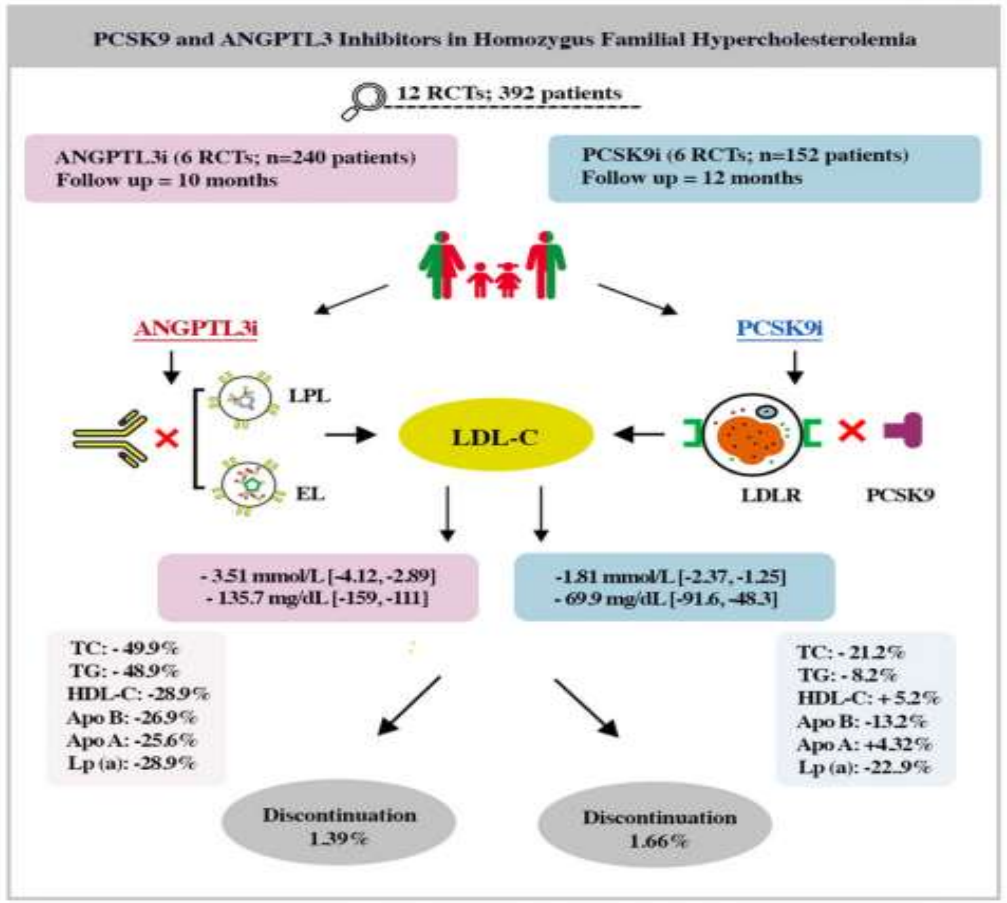
HOFH-də
Faza 3 Evinacumab null və qeyri-null

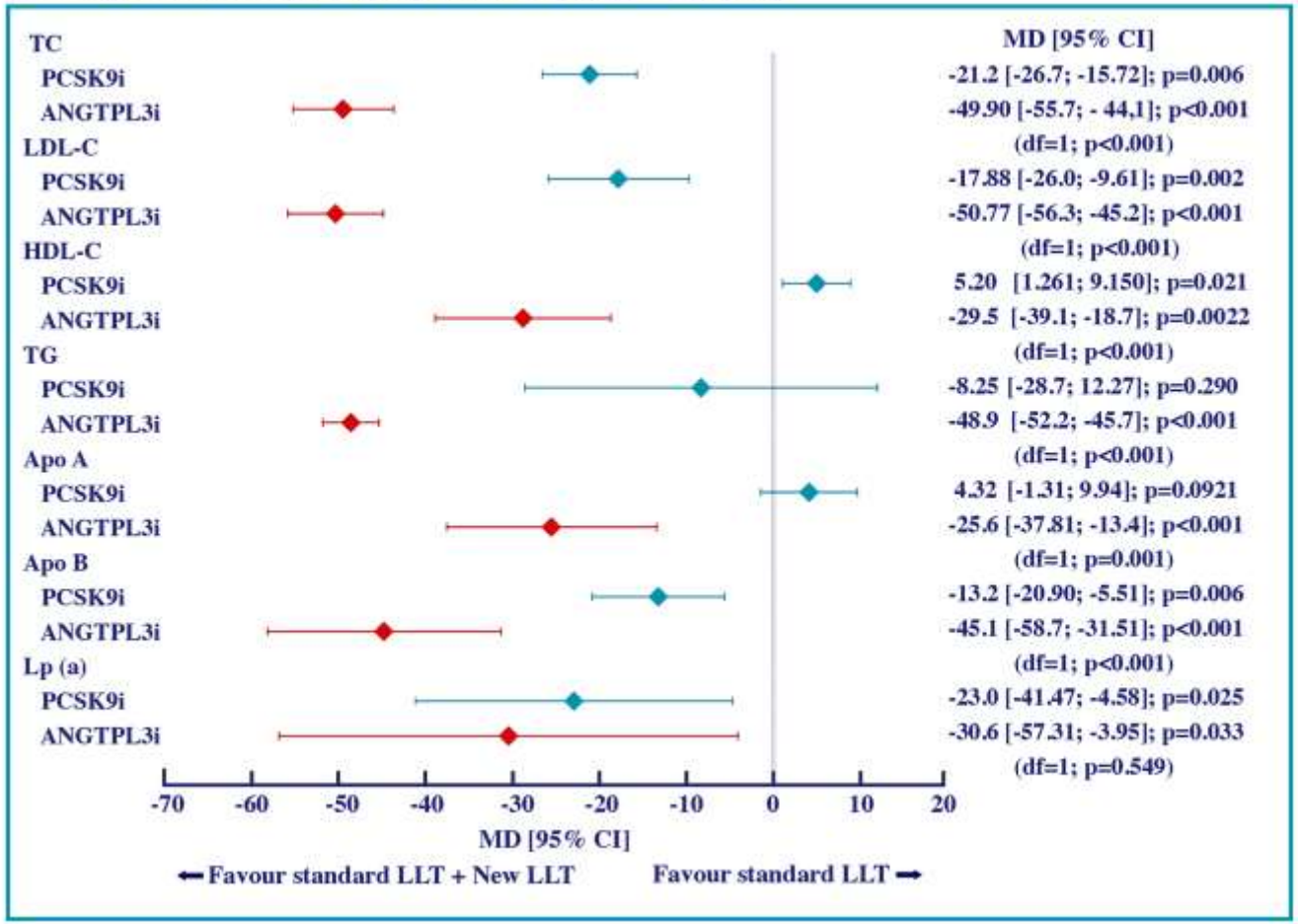


- HoFH olan xəstələr (n=65),
- evinakumab terapiyası xəstələrin 24 həftə ərzində LDL-C-nin 47% azalmasını təmin etdi



ANGPTL3 inhibition in homozygous familial hypercholesterolemia. N Engl J Med. 2017;377(3):296-297 Evinacumab for Homozygous Familial Hypercholesterolemia. N Engl J Med 2020; 383:711-720. doi: 10.1056/NEJMoa2004215





PCSK9 and ANGPTL3 Inhibitors in Homozygous Familial Hypercholesterolemia: A Meta-analysis of Randomized Clinical Trials. Drugs. 2026 Feb;86(2):231-242.

HoFH

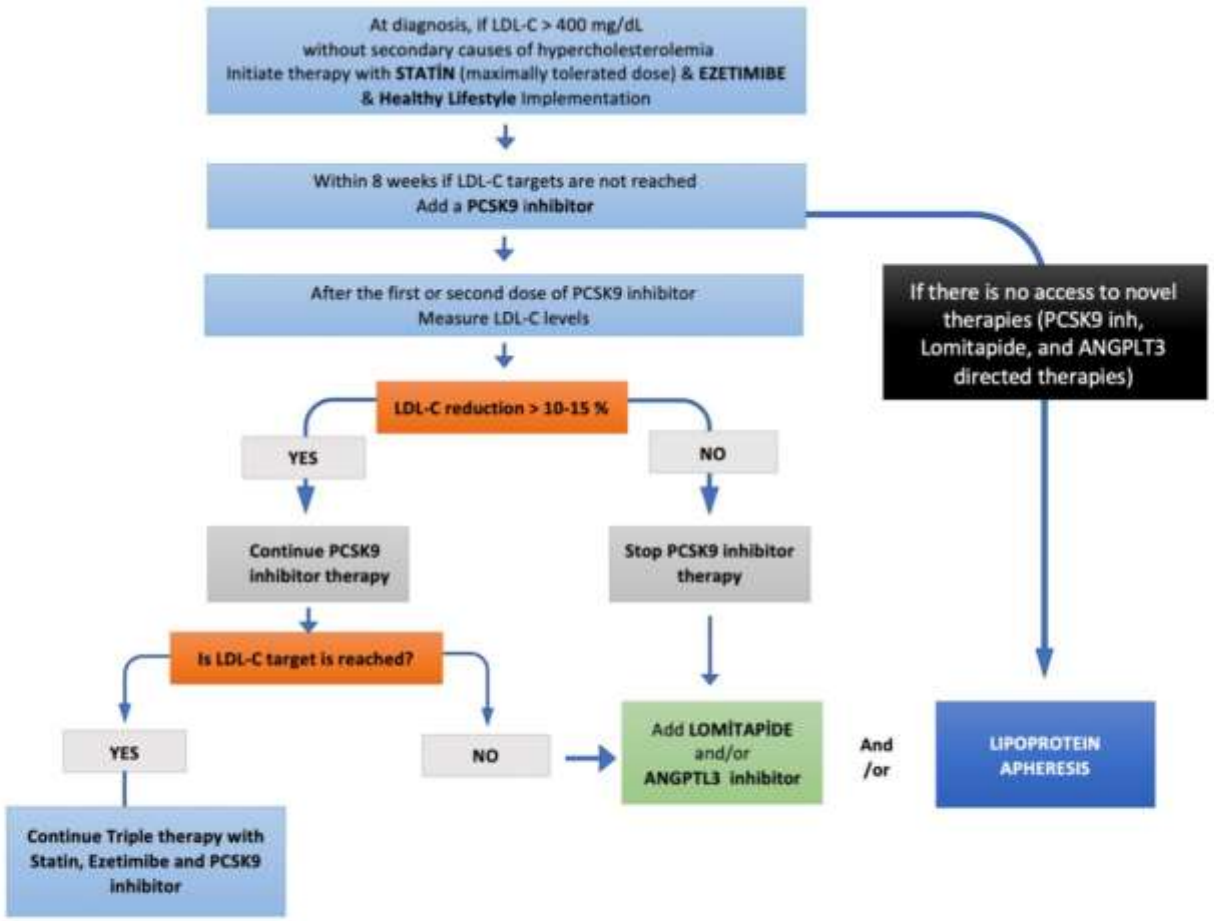


Figure 3. Step-by-step HoFH treatment algorithm.

Kayikcioglu M, Tokgozoglu L. Homozygous Familial Hypercholesterolemia-da Mövcud Müalicə Seçimləri. Əczaçılıq 2022 Dekabr ;16(1):64.

Worldwide experience of homozygous familial hypercholesterolaemia: retrospective cohort study

*Tycho R Tromp, Merel L Hartgers, G Kees Hovingh, Antonio J Vallejo-Vaz, Kausik K Ray, Handrean Soran, Tomas Freiberger, Stefano Bertolini, Mariko Harada-Shiba, Dirk J Blom, Frederick J Raal, Marina Cuchel, and the Homozygous Familial Hypercholesterolaemia International Clinical Collaborators**

	Overall (N=751)	High-income countries (n=398)	Non-high-income countries (n=353)
Age of familial hypercholesterolaemia diagnosis, years	12·0 (5·5–27·0); 18·0 (16·8–19·2)	16·0 (6·0–33·0); 20·7 (18·9–22·5)	10·0 (5·0–20·0); 15·1 (13·6–16·7)
Sex			
Female	389 (52·1%)	205 (51·5%)	184 (52·9%)
Male	362 (47·9%)	169 (47·1%)	193 (48·5%)
Xanthomas at diagnosis	516 (68·7%)	255 (64·1%)	261 (73·9%)
Body-mass index, kg/m²	24·0 (23·4–24·6)	24·0 (23·2–24·8)	24·0 (23·1–24·9)
Diabetes	23 (3·6%)	15 (5·2%)	8 (2·3%)
Hypertension	93 (14·5%)	41 (14·0%)	52 (14·9%)	
Chronic kidney disease	6 (1·2%)	5 (2·2%)	1 (0·4%)
Current smoker	43 (7·8%)	25 (8·7%)	18 (6·8%)
Previous smoker	54 (9·8%)	31 (10·8%)	23 (8·7%)
Lipids, mmol/L	..	..	..
Untreated			
Total cholesterol	16·2 (13·1–20·0); 16·8 (16·3–17·2)	15·5 (12·4–19·3); 16·4 (15·8–17·0)	17·2 (14·6–20·6); 17·6 (16·9–18·2)
LDL cholesterol	14·7 (11·6–18·4); 15·2 (14·8–15·6)	13·5 (10·4–17·2); 14·2 (13·6–14·9)	15·8 (12·9–19·2); 16·2 (15·6–16·7)

	Overall (N=534)	High-income countries (n=293)	Non-high-income countries (n=241)
Medication			
Statins	491 (91·9%)	262 (89·4%)	229 (95·0%)
Ezetimibe	342 (64·0%)	212 (72·4%)	130 (53·9%)
PCSK9 inhibitors	118 (22·1%)	76 (25·9%)	42 (17·4%)
Lomitapide	45 (8·4%)	40 (13·7%)	5 (2·1%)
Evinacumab*	13 (2·4%)	13 (4·4%)	0
Mipomersen	5 (0·9%)	0	5 (2·1%)
Bile acid sequestrants	33 (6·2%)	31 (10·6%)	2 (0·8%)
Fibrates	6 (1·1%)	2 (0·7%)	4 (1·7%)
Other†	17 (3·2%)	9 (3·1%)	8 (3·3%)
Lipoprotein apheresis‡	243/621 (39·1%)	118/293 (39·7%)	125/328 (38·1%)
Surgeries			
Liver transplantation	5 (0·8%)	4 (1·3%)	1 (0·3%)

Most recent*			
Total cholesterol	9·0 (5·8–13·0); 9·7 (9·3–10·1)	6·7 (4·9–9·1); 7·4 (7·0–7·9)	12·3 (8·9–15·4); 12·3 (11·7–12·9)
LDL cholesterol	7·7 (4·6–11·5); 8·3 (8·0–8·7)	4·9 (3·0–7·5); 5·7 (5·3–6·1)	10·1 (7·4–13·2); 10·5 (11·0–10·9)
LDL cholesterol below guideline-recommended goals†	42 (7·2%)	38 (14·6%)	4 (1·2%)
Lowest recorded level‡			
Total cholesterol	7·6 (4·9–11·1); 8·7 (8·2–9·1)	5·6 (4·1–7·6); 6·3 (5·9–6·7)	10·7 (7·9–14·7); 11·3 (10·7–11·9)
LDL cholesterol	6·6 (3·6–10·4); 7·5 (7·1–7·9)	3·9 (2·6–5·8); 4·7 (4·3–5·0)	9·3 (6·7–12·7); 9·8 (9·3–10·3)
LDL cholesterol below guideline-recommended goals†	64 (10·9%)	56 (21·4%)	8 (2·5%)
Genetic information available§	565 (75·2%)	367 (92·2%)	198 (56·1%)

www.thelancet.com **Published online January 28,, 2022 https://doi.org/10.1016/S0140-6736(21)02001-8**

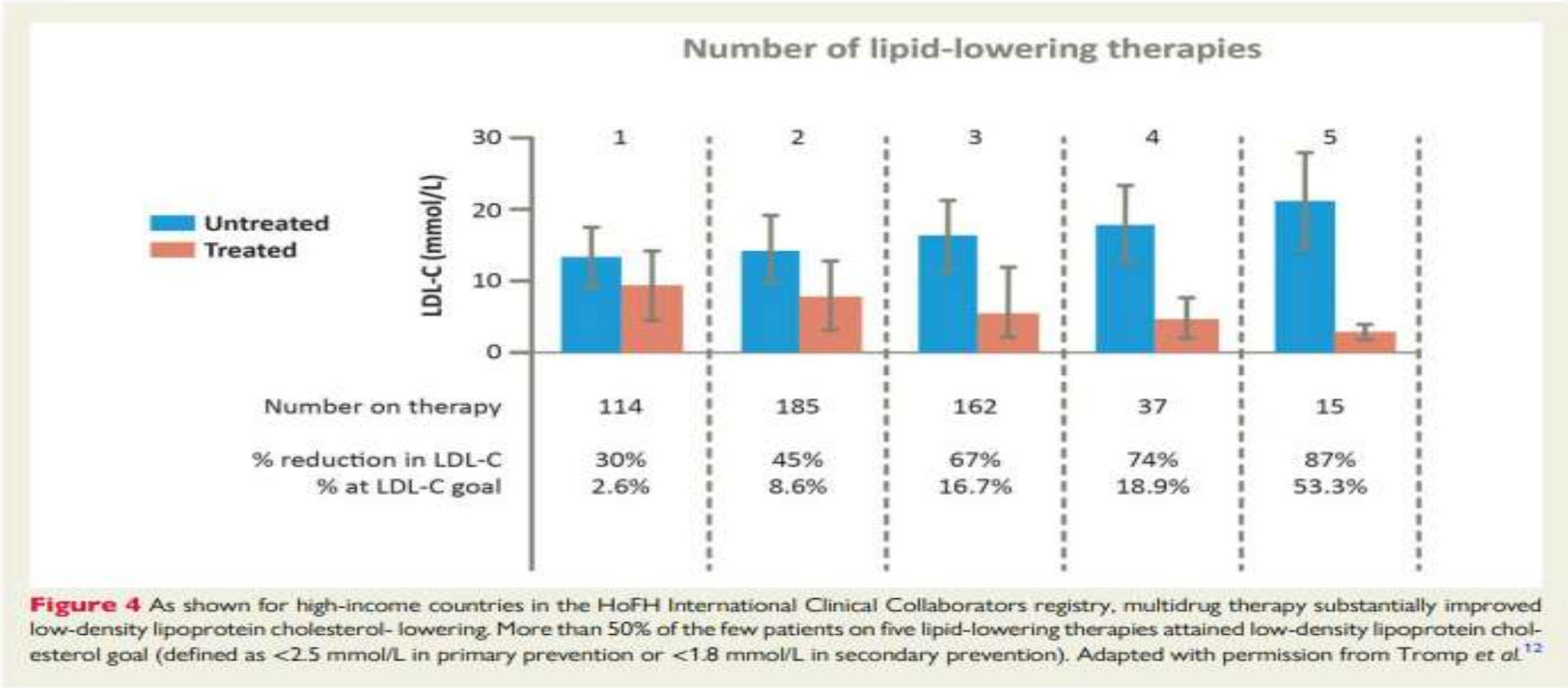


Figure 4 As shown for high-income countries in the HoFH International Clinical Collaborators registry, multidrug therapy substantially improved low-density lipoprotein cholesterol- lowering. More than 50% of the few patients on five lipid-lowering therapies attained low-density lipoprotein cholesterol goal (defined as <2.5 mmol/L in primary prevention or <1.8 mmol/L in secondary prevention). Adapted with permission from Tromp *et al*.[12]

Tromp TR, et al. Worldwide experience of homozygous familial hypercholesterolaemia: retros
cohort study. Lancet. 2022.

Bireyselleştirilmiş Tedavi

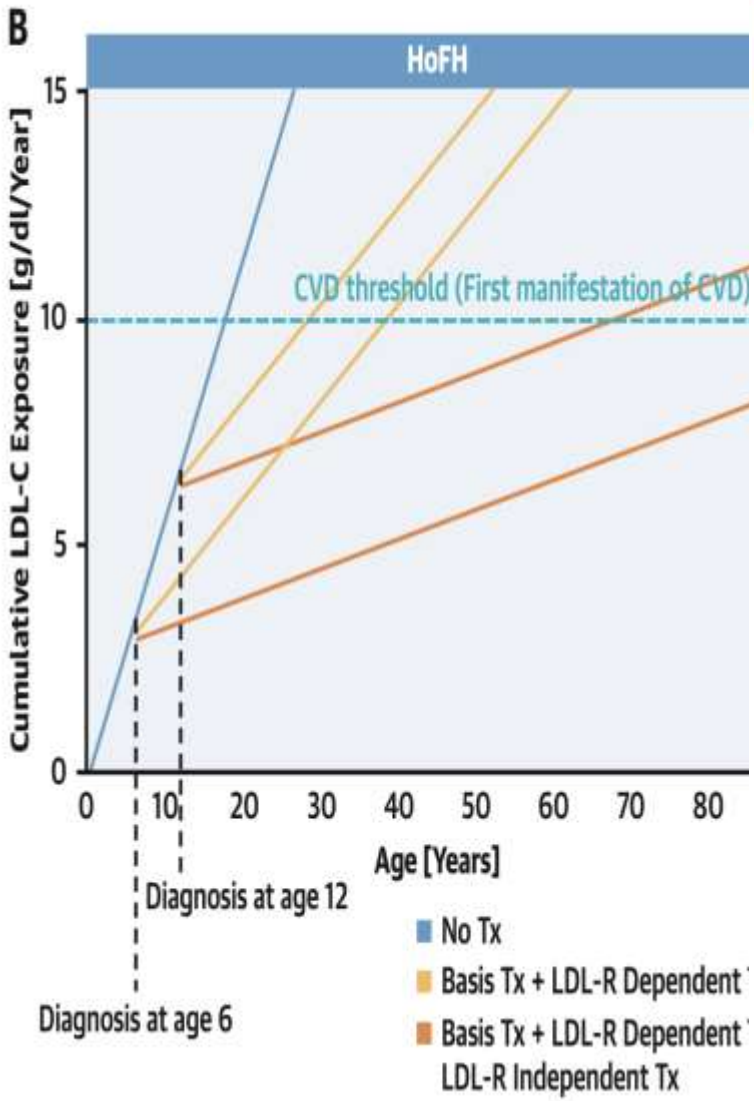
Table 1. Effect of lipid-lowering therapy on low-density lipoprotein cholesterol (LDL-C)

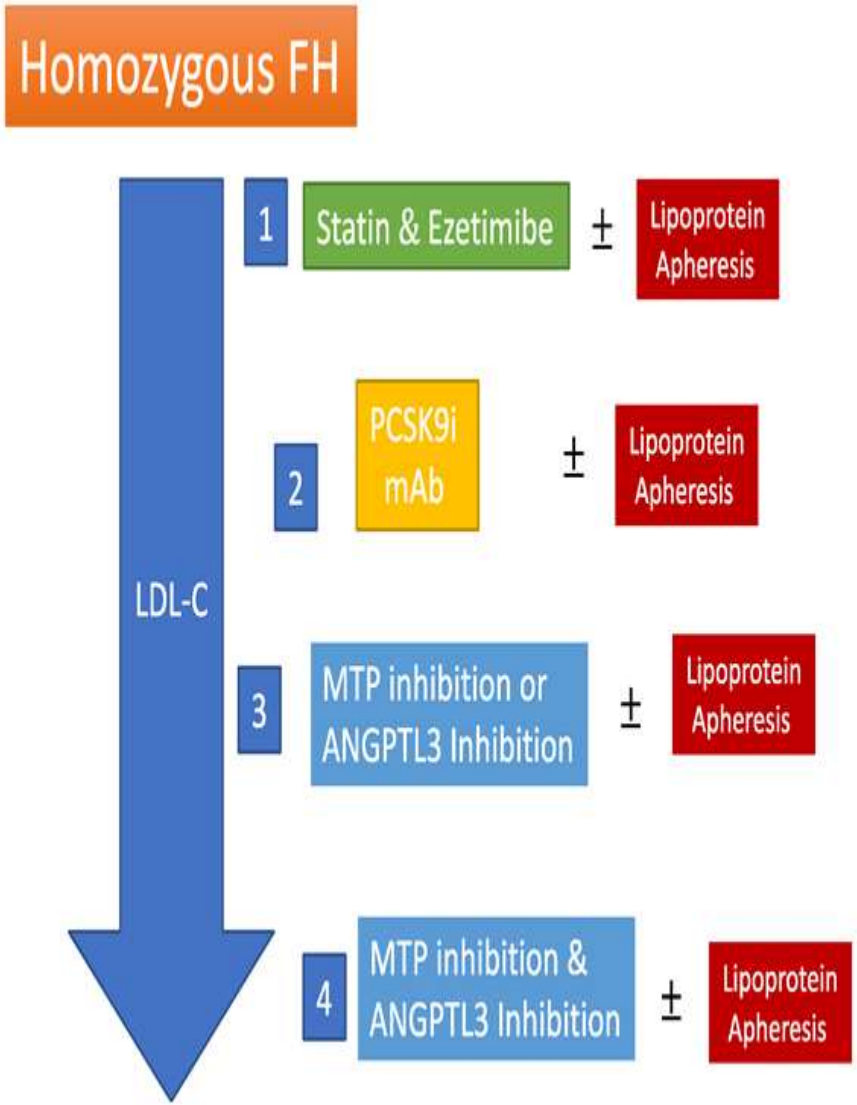
Treatment strategy	Without pharmacological treatment	Atorvastatin + ezetimibe	Atorvastatin + ezetimibe + alirocumab	Atorvastatin + ezetimibe + inclisiran	Rosuvastatin + ezetimibe + inclisiran	Rosuvastatin + ezetimibe + inclisiran + evinacumab
LDL-C [mg/dL]	670	168	128	100	89	49

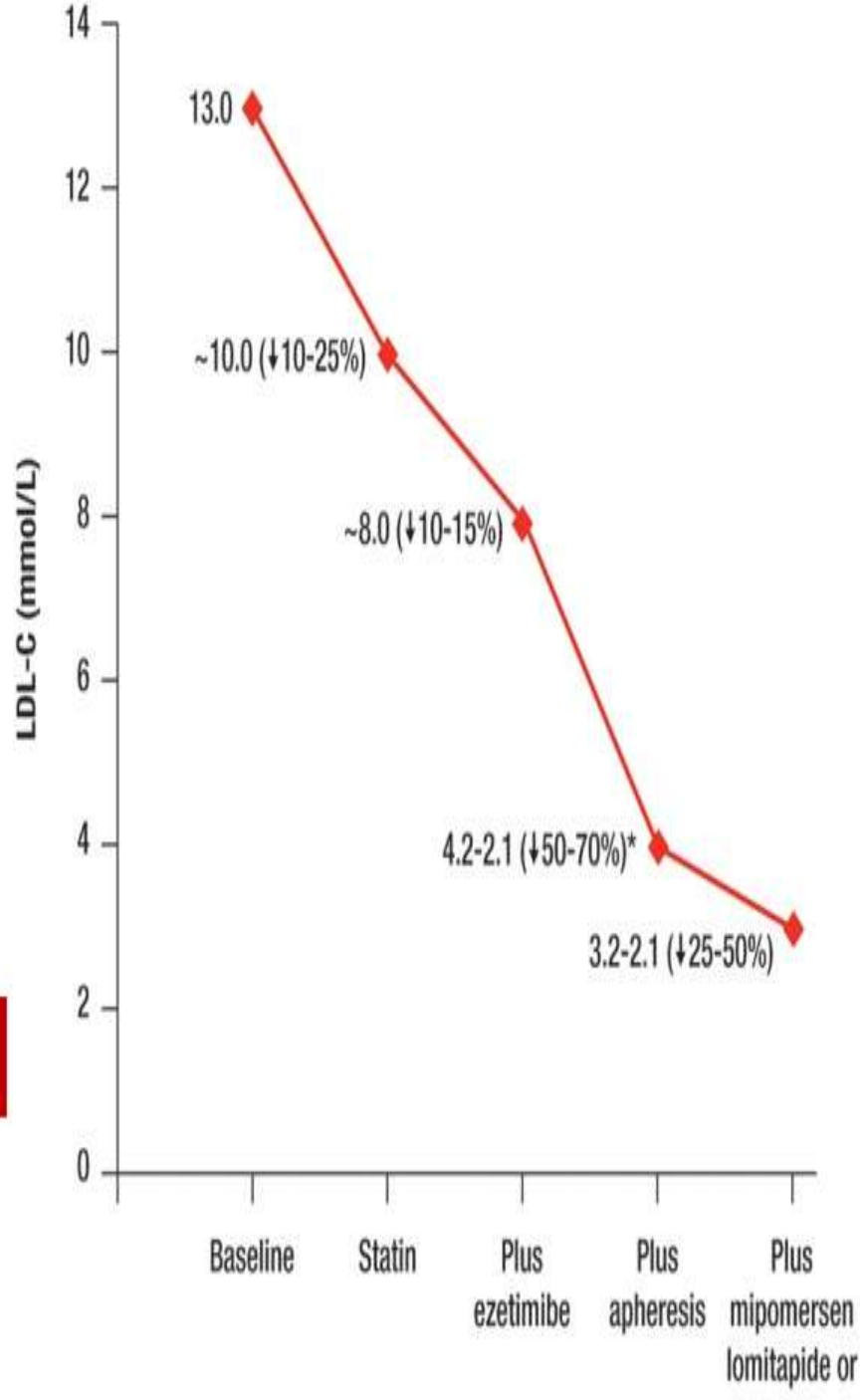
Endokrynol Pol. 2025;76(6):688-689. Achieving the impossible: effective reduction of low-density lipoprotein cholesterol (LDL-C) in a patient with homozygous familial hypercholesterolemia

Table 1
Comparative analysis of current HoFH therapies.

Agent	Mechanism of Action	LDL lowering effect (%)	Route and Dose	Effect on the Treatment of HoFH	Avilable RCT	Realword data	Side effects
Statins	Inhibiting HMG-CoA reductase and increasing LDL-R (Endo, 2010)	14–31 %	PO, Dose depends on the LDL-C target (Pang et al., 2020)	Cornerstone of LDL-C-lowering therapy in HoFH with limited efficacy (Pinal-Fernandez et al., 2018)	Statins resulted in a 27 % (95 % CI 23–30 %) reduction in major coronary events (Cheung et al., 2004)	Significant reduction of coronary heart disease events, hepatotoxicity and myotoxicity should be concerned (Pinal-Fernandez et al., 2018; Björnsson, 2017)	Liver damage and muscle damage,0.1 % incidence of ALT elevation (Björnsson, 2017; Chatzizisis et al., 2010)
Ezetimibe	Inhibiting the function of NPC1L1 (Jia et al., 2011)	5–14 %	PO, 10 mg/day (Kosoglou et al., 2005)	Second line therapy for HoFH lowers both LDL-C levels and ASCVD risk (Bays et al., 2001)	significantly reduced LDL cholesterol by an average of 18.58 % (95 % CI 19.67–17.48 %) (Pandor et al., 2009)	Moderate reduction of LDL-C in patients with high cholesterol absorption but low synthesis (Rosenblum et al., 1998)	Abdominal pain, diarrhea, headache, fatigue, 1.3 % incidence of ALT elevation (Kosoglou et al., 2005)
Evolocumab Alirocumab	Suppressing the function of the PCSK9 protein and increasing the number of LDL-R (Tomlinson et al., 2017)	Evolocumab 15–32 %; Alirocumab 26 %	Evalocumab, SC Biweekly 140 mg Alirocumab, SC Biweekly 75–150 mg (Henry et al., 2016; Manniello and Pisano, 2016)	Both are beneficial for HoFH patients with at least 2 % functional LDL-R (Ray et al., 2022)	The treatment significantly reduced LDL-C by 54.6 % (95 % CI 58.7–50.5 %) (Zhang et al., 2015)	Moderate LDL-C lowering has been demonstrated in HoFH, especially in patients with non-LA	Nasopharyngitis, URTI, headaches, back pain and muscle aches, 3.0 % incidence of ALT elevation (Markham, 2015a)
Inclisiran	Targeting *PCSK9* mRNA and inhibiting its translation (Nair et al., 2014)	12–37 %	SC, 284 mg on Days 1 and 90, then every 6 months (Lamb, 2021)	Improving compliance demonstrates potential for use in young individuals with HoFH (German and Shapiro, 2020)	Inclisiran reduced LDL-C levels by 50.42 % (95 % CI 44.70–56.15 %) (Basit et al., 2025)	Inclisiran could prevent numerous cardiovascular events, including acute coronary syndrome episodes and strokes (Wright et al., 2020)	Injection site erythema and injection site rash, 0.6 % incidence of ALT elevation (Koenig et al., 2024)
Bempedoic Acid	Inhibiting and ACLY reducing the production of cholesterol (Feng et al., 2020)	10 %	PO, 180 mg/day (Susekov et al., 2021)	Lowering LDL-C levels in cases of statin intolerance (Bilen and Ballantyne, 2016)	Bempedoic acid reduces total cholesterol by 16.50 % (95 % CI 13.97–19.21 %) (Filippo et al., 2023)	The safety is superior to statins, the effect on HoFH is limited	URTI, muscle spasms, anemia and elevated liver enzymes, 1.0 % incidence of ALT elevation (Banach et al., 2020)
Lomitapide	Inhibiting MTP and disrupting lipoprotein assembly (Cuchel et al., 2007)	24–57 %	10–60 mg/day (Perry, 2013)	Reducing the frequency of apheresis or serving as an alternative to apheresis (Abu-Farha et al., 2020)	Median liver fat content 10.20 % (95 % CI 8.30–14.70 %) (Blom et al., 2019)	Adjuvant therapy for adult patients with HoFH, combined with other LLT and LA (Noto et al., 2014)	Diarrhea, nausea, vomiting and stomach discomfort, 15.0 % incidence of ALT elevation (Perry, 2013)
Evinacumab	Inhibiting ANGPTL3 to reduce LDL-C levels (Deng et al., 2022)	47.1 %	IV 15 mg/kg every four weeks (Dingman et al., 2024)	Effective for patients with extremely low LDL-R levels (Gusarova et al., 2015)	Evinacumab significantly reduced LDL-C 33.12 % (95 % CI 48.64–17.61 %) (Jin et al., 2021)	Independent of LDL-R and well tolerated, it extends to the pediatric population	Common side effects and potential threats to the fetus, < 1.0 % incidence of ALT elevation (Stefanutti et al., 2024; Olatunji et al., 2024; Watts et al., 2023)


B
HoFH
CVD threshold (First manifestation of CVD)
Cumulative LDL-C Exposure [g/dl/Year]
15
10
5
0
0
10
20
30
40
50
60
70
80
Age [Years]
Diagnosis at age 12
Diagnosis at age 6
No Tx
Basis Tx + LDL-R Dependent
Basis Tx + LDL-R Dependent
LDL-R Independent Tx


Homozygous FH
LDL-C
1
Statin & Ezetimibe
±
Lipoprotein Apheresis
2
PCSK9i mAb
±
Lipoprotein Apheresis
3
MTP inhibition or ANGPTL3 Inhibition
±
Lipoprotein Apheresis
4
MTP inhibition & ANGPTL3 Inhibition
±
Lipoprotein Apheresis


LDL-C (mmol/L)
14
12
10
8
6
4
2
0
13.0
~10.0 (↓10-25%)
~8.0 (↓10-15%)
4.2-2.1 (↓50-70%)*
3.2-2.1 (↓25-50%)
Baseline
Statin
Plus ezetimibe
Plus apheresis
Plus mipomersen lomitapide or

TEŞEKKÜRLER

Prof.Dr. Meral Kayıkçıoğlu’na teşekkür ederim.