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Invited Commentary

Evinacumab – The new kid on the block. Is it important for cardiovascular prevention?

1. What are angiopoietin-like proteins and what role do they play?

Angiopoietin-like proteins (ANGPTL) include the compounds ANGPTL1 through ANGPTL8 and belong to the vascular endothelial growth factor (VEGF) family [1–3].

ANGPTL3, ANGPTL4, and ANGPTL8 play an important role in terms of lipid metabolism. These proteins regulate the metabolism of triglyceride-rich lipoproteins (TRL) [4]. The main source of ANGPTL3 is liver, ANGPTL4 is from liver, adipose tissue, skeletal muscle, gut, heart and brain, and ANGPTL8 is from liver and adipose tissue. These proteins form a ANGPTL3-4-8 system that controls the availability of triglycerides depending on nutritional status, temperature, and physical activity [1–3,5].

Within white adipose tissue, lipoprotein lipase (LPL) activity is reduced by ANGPTL4 during fasting. In the heart, skeletal muscle, and brown adipose tissue, the activity of LPL after a meal is reduced by ANGPTL3 and ANGPTL8 (after a meal, the expression of ANGPTL8 is particularly increased, while the expression of ANGPTL3 is not dependent on the nutritional status) forming a heterodimer (ANGPTL8 is an activator of ANGPTL3). Thus, the ANGPTL3-4-8 system plays an important role in regulating triglyceride metabolism [1–3,5].

Fig. 1 summarizes the role of the ANGPTL3-4-8 system in the metabolism of triglyceride-rich lipoproteins.

2. Why is ANGPTL a promising drug target?

Dewey et al. reported that persons carrying the loss of function mutation of the *Angptl3* gene have decreased serum low density lipoprotein (LDL) and triglyceride concentrations, which translated into a 41% predicted reduction in the risk of coronary artery disease (aOR = 0.59; 95% CI: 0.41–0.85, $p = 0.004$) [6].

Considering the important role of ANGPTL3 in lipid metabolism and the beneficial cardiovascular effects of inhibiting this protein, industry has developed a drug that is a human anti-ANGPTL3 monoclonal antibody – evinacumab (RENG1500).

3. What is evinacumab?

Evinacumab (trade name Evkeeza® by Regeneron Pharmaceuticals) is a humanized IgG4 anti-ANGPTL3 monoclonal antibody that was registered earlier this year with the U.S. Food & Drug Administration (FDA) for the treatment of homozygous familial hypercholesterolaemia (HoHF) [7]. The European Medicines Agency recently approved Evinacumab for the treatment of HoHF [8].

4. How does evinacumab work?

Evinacumab reduces its activity by forming an immune complex with ANGPTL3. Evinacumab lowers LDL-cholesterol predominantly by increasing apoB-containing lipoprotein clearance from the circulation [9].

5. Evinacumab in the treatment of lipid disorders - what are the results?

In a double-blind, placebo-controlled phase III study, Raal et al. assessed the therapeutic efficacy of evinacumab in 65 patients with HoHF. The subjects were administered evinacumab intravenously at a dose of 15 mg/kg every 4 weeks or placebo. The mean baseline plasma LDL concentration was 255 mg/dl despite intensive lipid lowering treatment. After 24 weeks, a significant improvement in lipid parameters was demonstrated (Fig. 2.) [10]. Treatment with evinacumab is generally well tolerated and safe [11].

The results of clinical trials also indicate the beneficial effects of evinacumab in the treatment of resistant hypercholesterolaemia, heterozygous familial hypercholesterolaemia, and severe hypertriglyceridaemia [12–14]. Current studies with evinacumab are summarized in Table 1.

6. Conclusions and critical questions

The future of evinacumab seems a little different than that of other drugs used to treat severe hypercholesterolemia, such as PCSK9 inhibitors (alirocumab, evolocumab) or PCSK9 small interfering RNA particles (inclisiran). The latter two do not address hypertriglyceridemia. Thus, evinacumab could be the drug of choice, together with a statin, to treat mixed hyperlipidemia in very high cardiovascular risk patients. It could be the drug of choice for some patients in cardiovascular prevention, especially those with metabolic syndrome, diabetes, and hypertension occurring jointly. It might be helpful for some patients with atherogenic dyslipidemia. New clinical trials, however, are needed for broadening our experience with evinacumab in conjunction with ezetimibe, bempedoic acid, or even with PCSK9 inhibitors.

The critical questions for this drug are the following:

1. Will evinacumab be a better choice than PCSK9 blockade?
2. Will it change the way we treat hypertriglyceridemia?
3. What will be optimal algorithm for introducing this drug within the family of old and new hypolipemic drugs?

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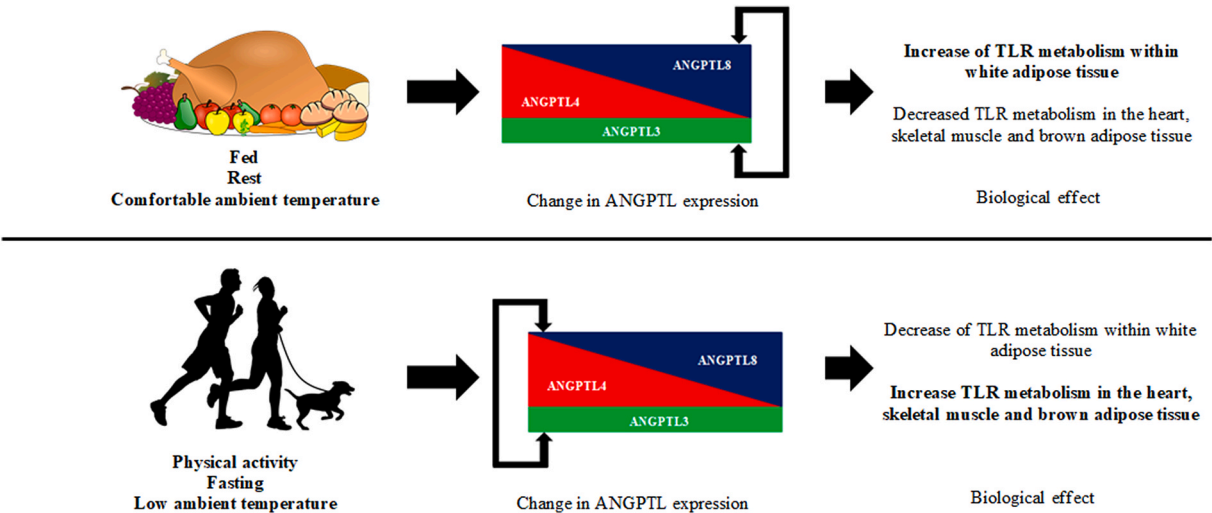


Fig. 1. ANGPTL3-4-8 system mechanism of action in the regulation of triglyceride-rich lipoprotein metabolism [1–3,5]. ANGPTL3 – angiopoetin-like protein 3; ANGPTL4 - angiopoetin-like protein 4; ANGPTL8 - angiopoetin-like protein 8; TLR - triglyceride-rich lipoprotein.

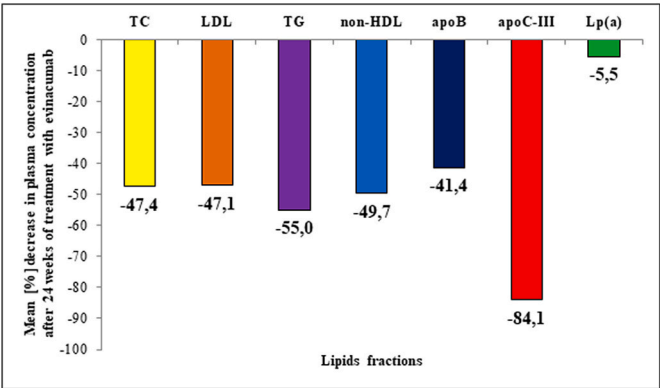


Fig. 2. Changes in lipids fractions during treatment with evinacumab. Adapted from F. Raal et al. [10]. TC – total cholesterol [mg/dl]; LDL – low density lipoprotein [mg/dl]; TG – trigliceryde [mg/dl]; non-HDL – cholesterol non-HDL (total cholesterol – HDL = non-HDL) [mg/dl]; apoB – apolipoprotein B [mg/dl]; apoC-III – apolipoprotein C-III [mg/dl]; Lp(a) – lipoprotein (a) [nmol/l].

Table 1
Current study using evinacumab. Source: [ClinicalTrials.gov](https://clinicaltrials.gov) (access: September 14, 2021).

Study title	Conditions	Status	Interventions	ClinicalTrials.gov Identifier
Efficacy and Safety of Evinacumab in Adult Patients With Severe Hypertriglyceridemia for the Prevention of Recurrent Acute Pancreatitis	Hypertriglyceridemia	Recruiting (estimated completion: 2024)	Evinacumab versus placebo	NCT04863014
Evaluate the Efficacy and Safety of Evinacumab in Pediatric Patients With Homozygous Familial Hypercholesterolemia	Homozygous Familial Hypercholesterolemia	Recruiting (estimated completion: 2023)	Evinacumab	NCT04233918

Declaration of competing interest

None declared.

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