Review Article

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2026.65.010206

Small Interfering RNA Therapeutics for Severe Hypertriglyceridemia: Mechanisms, Clinical Evidence, and Therapeutic Implications

Fu Jingjia[1], Jiang Tao[2]* and Jiang Hongwei[1]*

[1]*Luoyang Key Laboratory of Clinical Multiomics and Translational Medicine, Henan Key Laboratory of Rare Diseases, Endocrinology and Metabolism Center, The First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology, China*

[2]*Department of Laboratory Medicine, The First Affiliated Hospital of Henan University of Science and Technology, China*

***Corresponding author:** Jiang Tao, Department of Laboratory Medicine, The First Affiliated Hospital of Henan University of Science and Technology, Luoyang 471003, China

Jiang Hongwei, Luoyang Key Laboratory of Clinical Multiomics and Translational Medicine, Henan Key Laboratory of Rare Diseases, Endocrinology and Metabolism Center, the First Affiliated Hospital and College of Clinical Medicine of Henan University of Science and Technology, Luoyang 471003, China

ARTICLE INFO

Received: April 14, 2026

Published: May 05, 2026

Citation: Fu Jingjia, Jiang Tao and Jiang Hongwei. Small Interfering RNA Therapeutics for Severe Hypertriglyceridemia: Mechanisms, Clinical Evidence, and Therapeutic Implications. Biomed J Sci & Tech Res 65(3)-2026. BJSTR. MS.ID.010206.

ABSTRACT

Severe hypertriglyceridemia (sHTG) is a clinically heterogeneous disorder characterized by marked accumulation of triglyceride-rich lipoproteins, recurrent or persistent chylomicronemia, and a high risk of acute pancreatitis, together with broader metabolic and cardiovascular consequences. Conventional treatment includes strict dietary restriction, correction of secondary causes, fibrates, omega-3 fatty acids, glycemic control, and supportive measures during pancreatitis; however, durable triglyceride control remains difficult in familial chylomicronemia syndrome, multifactorial chylomicronemia syndrome, and very severe hypertriglyceridemia. Small interfering RNA (siRNA) therapeutics have emerged as a promising advance because they enable long-acting, hepatocyte-directed silencing of genes involved in triglyceride metabolism, particularly apolipoprotein C-III and angiopoietin-like protein 3. This review summarizes the pathophysiological basis of sHTG, the mechanistic rationale for RNA interference, and the current clinical evidence for APOC3- and ANGPTL3-targeted siRNA therapies. The most mature evidence supports plozasiran, which has demonstrated profound and durable triglyceride lowering, improvement in lipoprotein profiles, and potential reduction in recurrent pancreatitis risk. ANGPTL3-targeting agents, including zodasiran and solbinsiran, further broaden the therapeutic landscape by combining triglyceride lowering with favorable effects on apoB-containing lipoproteins, although disease-specific evidence in sHTG is still limited. Overall, siRNA therapeutics represent an important step toward precision treatment of severe triglyceride disorders.

Keywords: Severe Hypertriglyceridemia; Familial Chylomicronemia Syndrome; Small Interfering RNA; Apolipoprotein C-III; ANGPTL3; Plozasiran; Zodasiran; Solbinsiran; Pancreatitis; Precision Medicine

Abbreviations: ANGPTL3: Angiopoietin-Like Protein 3; APOC3: Apolipoprotein C-III; ASCVD: Atherosclerotic Cardiovascular Disease; ASO: Antisense Oligonucleotide; FCS: Familial Chylomicronemia Syndrome; GalNAc: N-Acetylgalactosamine; LDL-C: Low-Density Lipoprotein Cholesterol; LPL: Lipoprotein Lipase; MCS: Multifactorial Chylomicronemia Syndrome; non-HDL-C: Non-High-Density Lipoprotein Cholesterol; RNAi: RNA Interference; siRNA: Small Interfering RNA; sHTG: Severe Hypertriglyceridemia; TG: Triglyceride; TRL: Triglyceride-Rich Lipoprotein; VLDL: Very-Low-Density Lipoprotein

Introduction

Severe hypertriglyceridemia is not a single disease entity but rather a syndrome arising from different combinations of genetic susceptibility, impaired lipolysis, remnant accumulation, hepatic overproduction of triglyceride-rich lipoproteins, and environmental or metabolic stressors [1-8]. In routine clinical practice, fasting triglyceride concentrations of at least 500 mg/dL are commonly used to define severe hypertriglyceridemia, whereas concentrations above 880-1000 mg/dL are typically associated with clinically relevant chylomicronemia and sharply increased pancreatitis risk [1-6]. The clinical stakes are high. In addition to recurrent abdominal pain and eruptive xanthomas in some patients, severe triglyceride elevation is a well-established cause of acute pancreatitis and is often associated with recurrent attacks, intensive care utilization, and substantial morbidity [5,6,9,10]. The biology of sHTG is closely linked to defects in the lipoprotein lipase pathway. Familial chylomicronemia syndrome is the classic monogenic form and usually reflects bi-allelic pathogenic variants in LPL, APOC2, APOA5, GPIHBP1, or LMF1, leading to profound impairment of chylomicron clearance [3,7,8,11]. However, true FCS is rare. Most patients seen in specialist lipid clinics have multifactorial chylomicronemia syndrome or severe polygenic hypertriglyceridemia, in which common and rare genetic variants interact with insulin resistance, obesity, alcohol use, medications, hypothyroidism, pregnancy, or poorly controlled diabetes [1-4,7,8,10,12].

This distinction has practical importance because many conventional triglyceride-lowering therapies rely, at least in part, on residual LPL function and therefore are frequently inadequate in FCS and variably effective in multifactorial disease [1-4,9,11]. For many years, treatment has centered on dietary fat restriction, elimination of secondary causes, fibrates, omega-3 fatty acids, and acute supportive strategies such as insulin infusion or apheresis in selected pancreatitis settings [1-6,10]. While these measures remain essential, they often do not provide durable biochemical control or reliable pancreatitis prevention in the highest-risk patients. Against this background, RNA-based therapeutics have emerged as one of the most important innovations in lipidology because they allow selective silencing of hepatic genes that regulate triglyceride metabolism upstream of the clinical phenotype [13-19].

Objective of the Work

The objective of this review is to provide a current knowledge regarding small interfering RNA therapeutics for severe hypertriglyceridemia, with emphasis on molecular rationale, pharmacologic platform, key clinical trial evidence, therapeutic positioning, and remaining translational challenges. Particular attention is given to APOC3- and ANGPTL3-directed agents, especially plozasiran, zodasiran, and solbinsiran, because these programs currently define the leading edge of RNA interference therapy for severe triglyceride disorders [18-35].

Pathophysiological Basis of Severe Hypertriglyceridemia and the Therapeutic Rationale for RNA Interference

Triglyceride-rich lipoprotein metabolism is governed by a dynamic balance among intestinal chylomicron production, hepatic VLDL secretion, intravascular lipolysis, and clearance of remnants by hepatic receptors [1-4,7,8,36]. LPL is central to this network because it hydrolyzes triglycerides in chylomicrons and VLDL, thereby facilitating clearance of large triglyceride-rich particles. When the LPL pathway is severely impaired, chylomicrons accumulate even in the fasting state, producing the biochemical and clinical phenotype of chylomicronemia [3,7,8,11]. Two hepatic proteins are especially relevant to modern targeted therapy. APOC3 inhibits LPL-mediated lipolysis and interferes with hepatic remnant clearance, thereby amplifying the persistence of triglyceride-rich lipoproteins in the circulation [9,11,13,14,17-19,36]. Elevated APOC3 therefore contributes both to extreme triglyceride elevation and to persistence of remnant particles. ANGPTL3 also acts as an inhibitor of lipoprotein lipase and endothelial lipase and influences multiple lipid fractions, including triglycerides, LDL-related parameters, and remnant burden [13,14,18,19,29-35].

Importantly, these proteins are synthesized in the liver, which makes them highly suitable targets for hepatocyte-directed RNA silencing. This molecular logic is particularly compelling in FCS and related severe phenotypes. In FCS, dietary management remains indispensable, but APOC3 inhibition offers a way to improve triglyceride metabolism through mechanisms that are at least partly independent of fully intact LPL activity, including enhanced remnant clearance [9,11,20-28,36]. In multifactorial chylomicronemia and mixed dyslipidemic forms of severe hypertriglyceridemia, targeting APOC3 or ANGPTL3 may also improve the broader lipoprotein phenotype, with potential relevance for pancreatitis prevention and cardiometabolic risk modification [9,13,14,18,19,29-35,36]. Thus, RNA interference is not simply another triglyceride-lowering strategy; it directly addresses key upstream regulators of disease biology.

RNA Interference Platform and Pharmacologic Considerations

Small interfering RNA therapeutics are typically double-stranded oligonucleotides designed to exploit the endogenous RNA-induced silencing complex. Once internalized, the guide strand directs sequence-specific cleavage of the target messenger RNA, resulting in prolonged suppression of protein production [15,16,24]. In lipid therapeutics, the major technical advance enabling clinical translation has been GalNAc conjugation, which promotes selective uptake into hepatocytes through the asialoglycoprotein receptor [24,29,31,37]. This feature offers two major advantages: high potency in the liver and infrequent subcutaneous dosing. The pharmacologic profile of siRNA

differs in clinically meaningful ways from other triglyceride-lowering modalities. Because hepatocyte uptake is efficient and intracellular silencing is durable, meaningful target suppression can often be maintained with dosing intervals of several months [24,31,32]. This is relevant for chronic diseases in which adherence to weekly or more frequent therapy is difficult.

Moreover, hepatic targeting minimizes systemic distribution and may contribute to a favorable tolerability profile compared with older systemic nucleic acid approaches [13,14,24,37]. At a practical level, the siRNA platform also supports phenotype-specific targeting. APOC3-directed agents may be preferred when pancreatitis prevention and chylomicronemia control are the dominant priorities, while ANGPTL3-directed agents may be particularly attractive when severe hypertriglyceridemia coexists with mixed dyslipidemia, elevated apoB-containing particles, or broader residual cardiometabolic risk [9,13,14,18,19,29-35,36]. These distinctions remain provisional, but they illustrate why understanding the platform is important for clinical positioning rather than merely for drug development.

APOC3-Directed siRNA Therapeutics

Plozasiran: Mechanistic Basis and Developmental Significance

Among currently available RNA interference programs for severe triglyceride disorders, plozasiran is the most clinically advanced and the most relevant to immediate practice. Plozasiran is a GalNAc-conjugated siRNA that suppresses hepatic APOC3 synthesis and thereby reduces circulating apoC-III concentrations, enhances triglyceride-rich lipoprotein catabolism, and improves clearance of remnant particles [20-28]. Because apoC-III is a central regulator of chylomicron and VLDL persistence, this target is especially important in patients with severe hypertriglyceridemia, recurrent pancreatitis, and FCS [9,11,18,19,36]. The therapeutic logic for plozasiran is supported by both mechanistic and clinical literature. Reviews focused on FCS and anti-apoC-III strategies have consistently emphasized that apoC-III is one of the most actionable molecular nodes in severe triglyceride disorders, in part because its inhibition may remain beneficial even in settings where the classical LPL pathway is profoundly compromised [9,11,18,19,21,22,36]. This is one reason why APOC3-directed therapy has become central to the modern management discussion for FCS.

Clinical Evidence for Plozasiran in Severe Hypertriglyceridemia

The SHASTA-2 randomized trial marked a major step forward by showing that plozasiran produced large reductions in triglycerides in adults with severe hypertriglyceridemia, with additional improvements in apoC-III and related lipid parameters [20]. These results were important not merely because they confirmed biochemical efficacy, but because they established that deep triglyceride lowering could be achieved with a quarterly siRNA regimen in a phenotype directly relevant to pancreatitis risk. Subsequent work expanded the clinical picture. Detailed lipoprotein analysis demonstrated that APOC3 silencing with plozasiran favorably altered lipoprotein particle size and number, suggesting that the effect of the drug extends beyond simple fasting triglyceride reduction and may reshape the atherogenic remnant phenotype [21]. This broader lipoprotein remodeling is particularly relevant in patients whose disease lies at the interface between severe hypertriglyceridemia and mixed dyslipidemia.

The phase 3 PALISADE program further elevated the importance of plozasiran by focusing on persistent chylomicronemia and clinically meaningful outcomes [22]. The resulting evidence linked profound triglyceride lowering to reduced pancreatitis burden, helping move the field beyond surrogate biochemistry toward event-related clinical benefit. This shift is critical because severe hypertriglyceridemia therapy has historically suffered from a mismatch between biochemical improvements and hard clinical outcomes. More recently, a post hoc analysis of PALISADE specifically reported prevention of recurrent pancreatitis in adults with very severe hypertriglyceridemia [23]. Although post hoc evidence requires cautious interpretation, it directly addresses one of the most important clinical questions in this field. In parallel, first-approval summaries and expert reviews have consolidated the translational significance of plozasiran, culminating in its approval in the United States for adults with familial chylomicronemia syndrome [24,25]. This approval is a milestone for both RNA interference therapeutics and rare lipid disease management.

Safety and Practical Experience with Plozasiran

Early-phase and supportive studies suggest that plozasiran has a generally manageable tolerability profile. Phase 1 data in Chinese healthy volunteers confirmed expected pharmacokinetic and pharmacodynamic behavior, including durable apoC-III and triglyceride lowering after subcutaneous administration [26]. Population pharmacokinetic modeling further supports flexible dosing considerations across healthy volunteers and patients with FCS, severe hypertriglyceridemia, and mixed hyperlipidemia [27]. These studies are not substitutes for long-term outcomes research, but they strengthen confidence in the platform. Case-based observations also provide important clinical nuance. Reported use during pregnancy in a woman with FCS highlights the kind of complex real-world scenarios that specialists increasingly face as targeted therapies become available [28]. Conversely, a case of apparent poor response due to pseudohypertriglyceridemia caused by a glycerol kinase variant underscores the importance of diagnostic rigor before labeling a patient as treatment refractory [38]. These reports are not definitive efficacy studies, but they illustrate how precision therapeutics and precision diagnosis must evolve together.

ANGPTL3-Directed siRNA Therapeutics

Zodasiran

ANGPTL3 inhibition represents a complementary therapeutic strategy in severe triglyceride disorders. Whereas APOC3 targeting is most strongly aligned with chylomicronemia and pancreatitis prevention, ANGPTL3 silencing may have broader effects on triglycerides, remnant lipoproteins, and apoB-containing particles [13,14,18,19]. Zodasiran is the leading ANGPTL3-directed RNA interference therapeutic currently evaluated in human lipid disorders. In a randomized trial involving patients with mixed hyperlipidemia, zodasiran substantially reduced triglycerides together with non-HDL-C, LDL-C, and other atherogenic parameters [29]. Although this population was not restricted to severe hypertriglyceridemia, the results demonstrated that ANGPTL3 silencing can deliver a broader lipid-lowering signature than therapies aimed solely at triglycerides. This characteristic may prove valuable in patients whose severe triglyceride elevation coexists with elevated remnant cholesterol and mixed dyslipidemia. The final report of the phase 1 basket trial extended these observations by showing that zodasiran lowers both cholesterol and triglycerides across hyperlipidemic phenotypes [30]. These early-stage data reinforce the biologic versatility of ANGPTL3 inhibition. However, compared with plozasiran, the evidence base for zodasiran in dedicated FCS or very severe hypertriglyceridemia populations remains limited, and its ultimate role in pancreatitis prevention is not yet established.

Solbinsiran

Solbinsiran is another GalNAc-conjugated siRNA targeting ANGPTL3. Preclinical and early human studies demonstrated effective ANGPTL3 inhibition and favorable lipid changes, supporting continued clinical development [31]. Subsequently, the phase 2 PROLONG-ANG3 trial showed durable efficacy in adults with mixed dyslipidemia, further validating the concept that long-acting ANGPTL3 silencing can provide clinically meaningful lipid lowering with infrequent dosing [32]. For severe hypertriglyceridemia specialists, the main question is whether the broader lipid profile improvements seen with ANGPTL3 inhibition will translate into a specific role for patients with very high triglycerides, mixed dyslipidemia, metabolic syndrome, or residual apoB-remnant risk. At present, solbinsiran remains promising but less directly validated in the severe chylomicronemia setting than plozasiran [31,32].

Therapeutic Landscape, Comparators, and Clinical Positioning

siRNA therapeutics should be interpreted within the broader treatment landscape of severe triglyceride disorders. Conventional therapies remain indispensable. Dietary fat restriction, abstinence from alcohol, improved glycemic control, and withdrawal of secondary aggravating medications continue to form the foundation of care [1-6]. In acute pancreatitis settings, insulin-based approaches and, in selected centers, apheresis may still have a role [6,39]. Thus, siRNA therapeutics are not replacements for metabolic management; rather, they fill the longstanding gap where conventional strategies fail to provide durable disease control. Comparison with antisense oligonucleotides is also important. APOC3-directed antisense approaches, including volanesorsen and newer ligand-conjugated agents, established proof of principle that apoC-III is a valid target in FCS and severe hypertriglyceridemia [22,23,36]. However, siRNA therapeutics may offer practical advantages in dosing frequency and, potentially, tolerability, though cross-trial comparisons must be made carefully. In this sense, plozasiran represents not the beginning of apoC-III therapeutics, but the maturation of the field toward a more clinically convenient RNA platform [9,11,13,14,22,23,36].

From a patient-selection perspective, not all severe hypertriglyceridemia phenotypes are identical. True FCS, multifactorial chylomicronemia, severe polygenic hypertriglyceridemia, and mixed dyslipidemia with severe triglyceride elevation differ in biology and therapeutic goals [1-4,7,8,10-12,18,19]. Patients with recurrent pancreatitis and persistent chylomicronemia are currently the clearest candidates for APOC3-directed siRNA. By contrast, patients with severe triglyceride elevation plus broader apoB-remnant excess may ultimately derive additional benefit from ANGPTL3-directed approaches, although dedicated outcome data remain insufficient [29-35,40]. Given the rapidly evolving therapeutic landscape, a structured summary may help clarify the relative positioning of currently available and emerging approaches. The major siRNA therapeutics relevant to severe hypertriglyceridemia, together with important comparator strategies, are summarized in Table 1. Key clinical studies supporting the current evidence base for APOC3- and ANGPTL3-directed siRNA therapies are outlined in Table 2. Finally, phenotype-based practical considerations for selecting siRNA therapy in severe triglyceride disorders are presented in Table 3.

Table 1: Major siRNA therapeutics relevant to severe hypertriglyceridemia.

Agent	Target	Clinical Stage/Setting	Main Lipid Effects	Current Significance
Plozasiran	APOC3	Phase 2-3; approved in the United States for adults with FCS	Profound TG lowering, apoC-III reduction, improved lipoprotein particle profile	Most mature siRNA program for severe triglyceride disorders and pancreatitis-oriented care [20-28]
Zodasiran	ANGPTL3	Early clinical development in hyperlipidemia/mixed hyperlipidemia	TG lowering plus broader reductions in atherogenic cholesterol parameters	Promising for mixed dyslipidemic phenotypes; dedicated sHTG data still limited [29,30]
Solbinsiran	ANGPTL3	Early to mid-stage development in mixed dyslipidemia	Durable TG lowering with broader ANGPTL3-mediated lipid effects	Potential role where severe TG elevation coexists with remnant/apoB burden [31,32]
APOC3-directed ASO comparators	APOC3	Approved or advanced programs in FCS/sHTG	Lower TG and apoC-III, but platform-specific tolerability considerations	Important mechanistic comparators that helped validate apoC-III as a target [22,23,36]
Conventional therapy	Multiple metabolic pathways	Standard of care across phenotypes	Variable TG lowering, strong dependence on adherence and residual pathway function	Remains foundational but often insufficient alone in FCS or recurrent pancreatitis [1-6]

Table 2: Representative clinical studies shaping the current siRNA evidence base.

Study/Program	Population	Intervention	Main Findings	Clinical Implication
SHASTA-2 [20]	Adults with severe hypertriglyceridemia	Plozasiran	Large and durable TG lowering with marked apoC-III reduction	Established proof that quarterly APOC3 siRNA can control severe triglyceride phenotypes
Lipoprotein particle analysis [21]	Hypertriglyceridemia	Plozasiran	Improved lipoprotein particle size and number	Suggests benefit beyond fasting TG alone
PALISADE [22]	Persistent chylomicronemia/FCS-related phenotype	Plozasiran	Deep TG lowering and reduced pancreatitis burden	Shifted field toward clinically meaningful outcomes
Post hoc pancreatitis analysis [23]	Adults with very severe hypertriglyceridemia	Plozasiran	Prevention of recurrent pancreatitis episodes	Supports pancreatitis-oriented therapeutic positioning
NEJM zodasiran trial [29]	Mixed hyperlipidemia	Zodasiran	Lowered TG and multiple atherogenic lipid parameters	Highlights broader lipid effects of ANGPTL3 silencing
PROLONG-ANG3 [32]	Mixed dyslipidemia	Solbinsiran	Durable ANGPTL3 suppression and lipid lowering	Suggests future utility in broader cardiometabolic phenotypes

Table 3: Practical clinical considerations for selecting siRNA therapy in severe triglyceride disorders.

Clinical Scenario	Primary Goal	Preferred Molecular Logic	Key Caveat	Practical Implication
Confirmed familial chylomicronemia syndrome	Prevent pancreatitis and maintain long-term chylomicron control	APOC3 inhibition	Continued strict diet remains essential	Plozasiran currently has the strongest evidence and regulatory relevance [22-28]
Multifactorial chylomicronemia with recurrent pancreatitis	Reduce TG excursions and recurrence burden	APOC3 inhibition, with correction of secondary causes	Phenotype can fluctuate with diabetes, alcohol, obesity, and medications	Combine targeted therapy with aggressive metabolic management [1-6,9,11]
Severe TG elevation plus mixed dyslipidemia	Improve TG and broader remnant/apoB burden	ANGPTL3 inhibition	Severe sHTG-specific outcome data remain limited	Zodasiran or solbinsiran may become attractive as evidence matures [29-32]
Apparent nonresponse to targeted therapy	Clarify diagnosis	Reassess analytic and genetic confounders	Pseudohypertriglyceridemia can mimic treatment failure	Confirm phenotype before escalating therapy [38]
Pregnancy or other complex special situations	Balance maternal risk and limited evidence	Case-by-case specialist decision	Evidence is still sparse	Individualized multidisciplinary evaluation is required [28]

Discussion

The current wave of siRNA therapeutics has changed the intellectual framework of severe hypertriglyceridemia management. Historically, the field was defined by the limitations of lifestyle therapy, fibrates, and omega-3 fatty acids, especially in FCS and recurrent chylomicronemia [1-6,9,11]. The clinical reality was often one of partial biochemical control, repeated pancreatitis, and frustrating mismatch between therapeutic effort and disease stability. In contrast, RNA interference allows direct intervention at molecular regulators that sit upstream of the phenotype, which is why the recent emergence of plozasiran has had such disruptive importance [20-28]. A 2026 updated meta-analysis of randomized studies further supported this platform-level signal by showing significant reductions in triglycerides, non-HDL-C, VLDL-C, apoB, and remnant cholesterol with siRNA therapy overall, while also suggesting differential lipid signatures between APOC3- and ANGPTL3-directed programs [41]. A second major advance is the shift from biochemical endpoints toward clinically relevant outcomes. Triglyceride reduction remains the core surrogate marker, but pancreatitis prevention is the true outcome that matters most in patients with persistent chylomicronemia [5,6,9,11]. The available evidence for plozasiran is notable because it begins to connect profound and durable triglyceride lowering with reduced recurrent pancreatitis burden [22,23]. Even if longer and broader confirmatory datasets are still needed, this connection represents a meaningful maturation of the field.

Nevertheless, several uncertainties remain. First, the optimal sequencing of APOC3- versus ANGPTL3-directed therapy is not yet established. Second, real-world implementation will require better phenotyping so that FCS, multifactorial chylomicronemia, and mixed dyslipidemic severe hypertriglyceridemia are not inappropriately grouped together [3,7,8,10-12,42]. Third, long-term safety and durability beyond trial horizons remain important questions for all RNA therapeutics, especially as these agents are introduced earlier in the disease course. Fourth, the relationship between profound triglyceride lowering and longer-term ASCVD reduction remains incompletely defined, particularly for patients whose predominant risk lies in remnant cholesterol and apoB-related burden rather than pancreatitis alone [9,18,19,29-35,40]. Another important point is that siRNA therapeutics should not be interpreted as stand-alone solutions. The biology of severe hypertriglyceridemia is too heterogeneous for any single pharmacologic intervention to replace dietary control, diabetes management, weight reduction, and correction of secondary factors [1-6]. In this respect, the best current model is precision combination care: accurate diagnosis, lifestyle intervention, secondary-cause correction, and molecular therapy aligned with the dominant disease mechanism.

Conclusion

Small interfering RNA therapeutics represent one of the most important contemporary advances in the treatment of severe hypertriglyceridemia. By selectively silencing hepatic APOC3 or ANGPTL3, these agents move clinical management beyond nonspecific triglyceride lowering toward direct control of the molecular drivers of chylomicronemia and remnant accumulation [7,8,13-17,18,19]. The strongest current evidence supports plozasiran, which has demonstrated profound and durable triglyceride lowering, favorable effects on lipoprotein profiles, evidence for pancreatitis risk reduction, and first regulatory approval for adults with familial chylomicronemia syndrome [20-28]. ANGPTL3-directed agents such as zodasiran and solbinsiran further broaden the therapeutic horizon and may ultimately be especially useful in phenotypes where severe triglyceride elevation coexists with mixed dyslipidemia and elevated remnant burden [29-32]. Future studies should focus on long-term safety, phenotype-specific treatment algorithms, real-world implementation, and the extent to which pancreatitis-oriented molecular therapy can also modify broader cardiometabolic risk. Taken together, current evidence indicates that severe hypertriglyceridemia is entering an era in which targeted RNA therapeutics can be integrated into clinically meaningful precision care [43,44].

Acknowledgement

None.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this review.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Gouni Berthold I, Schwarz J, Berthold HK (2023) Updates in Drug Treatment of Severe Hypertriglyceridemia. Curr Atheroscler Rep 25(10): 701-709.
2. Malick WA, Do R, Rosenson RS (2023) Severe hypertriglyceridemia: Existing and emerging therapies. Pharmacol Ther 251: 108544.
3. Dron JS, Hegele RA (2020) Genetics of Hypertriglyceridemia. Front Endocrinol (Lausanne) 11: 455.
4. Hernandez P, Passi N, Modarressi T, Vivek Kulkarni, Meshal Soni, et al. (2021) Clinical Management of Hypertriglyceridemia in the Prevention of Cardiovascular Disease and Pancreatitis. Curr Atheroscler Rep 23(11): 72.
5. Yang AL, McNabb Baltar J (2020) Hypertriglyceridemia and acute pancreatitis. Pancreatology 20(5): 795-800.
6. Garg R, Rustagi T (2018) Management of Hypertriglyceridemia Induced Acute Pancreatitis. Biomed Res Int 2018: 4721357.
7. Abedi AH, Yildirim Simsir I, Bayram F, Huseyin Onay, Su Ozgur, et al. (2023) Genetic Variants Associated with Severe Hypertriglyceridemia: LPL, APOC2, APOA5, GPIHBP1, LMF1, and APOE. Turk Kardiyol Dern Ars 51(1): 10-21.
8. Alves M, Laranjeira F, Correia da Silva G (2024) Understanding Hypertriglyceridemia: Integrating Genetic Insights. Genes (Basel) 15(2): 190.

9. Weijs BM, Oostveen RF, Kraaijenhof JM, Stroes ESG (2025) Targeting apolipoprotein C-III: a game changer for pancreatitis prevention in severe hypertriglyceridemia. Curr Opin Endocrinol Diabetes Obes 32(3): 126-132.
10. Suzuki T, Kurano M, Isono A, Takuya Uchino, Yohei Sayama, et al. (2024) Genetic and biochemical analysis of severe hypertriglyceridemia complicated with acute pancreatitis or with low post-heparin lipoprotein lipase mass. Endocr J 71(5): 447-460.
11. Brinton EA, Eckel RH, Gaudet D, Ballantyne CM, Baker BF, et al. (2025) Familial chylomicronemia syndrome and treatments to target hepatic APOC3 mRNA. Atherosclerosis 403: 119114.
12. Shamsudeen I, Hegele RA (2022) Safety and efficacy of therapies for chylomicronemia. Expert Rev Clin Pharmacol 15(4): 395-405.
13. Nurmohamed NS, Dallinga Thie GM, Stroes ESG (2020) Targeting apoC-III and ANGPTL3 in the treatment of hypertriglyceridemia. Expert Rev Cardiovasc Ther 18(6): 355-361.
14. Tomlinson B, Wu QY, Zhong YM, Li YH (2024) Advances in Dyslipidaemia Treatments: Focusing on ApoC3 and ANGPTL3 Inhibitors. J Lipid Atheroscler 13(1): 2-20.
15. Tirronen A, Hokkanen K, Vuorio T, Yla Herttuala S (2019) Recent advances in novel therapies for lipid disorders. Hum Mol Genet 28(R1): R49-R54.
16. Gaudet D, Brisson D (2015) Gene-based therapies in lipidology: current status and future challenges. Curr Opin Lipidol 26(6): 553-565.
17. Hegele RA (2022) APOC3 Interference for Familial Chylomicronaemia Syndrome. touchREV Endocrinol 18(2): 82-83.
18. Patel J, Shah S, Reddy A, Prajapati D, Pandya A, et al. (2026) Novel Approaches to Lipid Management: Beyond Statins and PCSK9 Inhibitors. J Clin Med Res 18(3): 121-141.
19. Izar MC, Fonseca FAH (2025) Novel Therapeutics for Familial Chylomicronemia Syndrome. Curr Atheroscler Rep 27(1): 51.
20. Gaudet D, Pall D, Watts GF, Nicholls SJ, Rosenson RS, et al. (2024) Plozasiran (ARO-APOC3) for Severe Hypertriglyceridemia: The SHASTA-2 Randomized Clinical Trial. JAMA Cardiol 9(7): 620-630.
21. Ballantyne CM, Gaudet D, Rosenson RS, Hegele RA, Zhou R, et al. (2025) Effect of Targeting ApoC-III With Plozasiran on Lipoprotein Particle Size and Number in Hypertriglyceridemia. J Am Coll Cardiol 85(19): 1839-1854.
22. Watts GF, Rosenson RS, Hegele RA, Goldberg IJ, Gallo A, et al. (2025) Plozasiran for Managing Persistent Chylomicronemia and Pancreatitis Risk. N Engl J Med 392(2): 127-137.
23. Loomba R, de Madaria E, Afghani E, Singh VK, Leeper NJ (2026) Clinical Trial: Plozasiran Prevents Recurrent Pancreatitis in Adults with Very Severe Hypertriglyceridemia-Results of a Post Hoc Analysis of the Phase 3 PALISADE Study. Aliment Pharmacol Ther 63(9): 1236-1245.
24. Syed YY (2026) Plozasiran: First Approval. Drugs 86(5): 753-758.
25. Hang S, Hegele RA (2026) The evaluation of plozasiran for the treatment of familial chylomicronemia syndrome. Expert Rev Endocrinol Metab, p. 1-10.
26. Wang F, You D, Niu X, Shi J, Li Y, et al. (2025) Safety, pharmacokinetics and pharmacodynamics of Plozasiran in Chinese healthy volunteers. Cardiovasc Diabetol 24(1): 399.
27. Ousey J, Jomphe C, Ta A, Gosselin NH, Shi J (2025) Population Pharmacokinetic Modeling of Subcutaneous Plozasiran in Healthy Volunteers and Patients with Familial Chylomicronemia Syndrome, Severe Hypertriglyceridemia, and Mixed Hyperlipidemia. J Clin Pharmacol 65(11): 1485-1496.
28. Larouche M, Brisson D, Roy N, Grenon C, Poirier P, et al. (2025) Course of Pregnancy in a Woman with Familial Chylomicronemia Syndrome Treated with Plozasiran, a Small Interfering RNA Against ApoC3. JIMD Rep 67(1): e70052.
29. Rosenson RS, Gaudet D, Hegele RA, Ballantyne CM, Nicholls SJ, et al. (2024) Zodasiran, an RNAi Therapeutic Targeting ANGPTL3, for Mixed Hyperlipidemia. N Engl J Med 391(10): 913-925.
30. Watts GF, Scott R, Sullivan D, Baker J, Clifton P, et al. (2026) Zodasiran for cholesterol and triglyceride lowering in patients with hyperlipidemia: final report of phase 1 basket trial. Nat Med 32(4): 1432-1443.
31. Ray KK, Linnebjerg H, Michael LF, Shen X, Ma X, et al. (2025) Effect of ANGPTL3 Inhibition with Solbinsiran in Preclinical and Early Human Studies. J Am Coll Cardiol 85(19): 1803-1818.
32. Ray KK, Oru E, Rosenson RS, Jones J, Ma X, et al. (2025) Durability and efficacy of solbinsiran, a GalNAc-conjugated siRNA targeting ANGPTL3, in adults with mixed dyslipidaemia (PROLONG-ANG3): a double-blind, randomised, placebo-controlled, phase 2 trial. Lancet 405(10489): 1594-1607.
33. Tomlinson B (2025) An up-to-date review of emerging biologic therapies for hypercholesterolemia. Expert Opin Biol Ther 25(1): 69-78.
34. Larouche M, Khoury E, Brisson D, Gaudet D (2023) Inhibition of Angiopoietin-Like Protein 3 or 3/8 Complex and ApoC-III in Severe Hypertriglyceridemia. Curr Atheroscler Rep 25(12): 1101-1111.
35. Zhang R (2025) ANGPTL3/8: one target, multiple lipid disorders. Trends Mol Med 32(4): 323-325.
36. Tsimikas S (2025) Anti-apoC-III Therapies and Implications for Treatment of Pancreatitis and Cardiovascular Disease. Curr Atheroscler Rep 27(1): 103.
37. Prakash TP, Mullick AE, Riney S, Yu J, Nikan M, et al. (2025) Discovery of long-acting APOC3 siRNA for treating patients with hypertriglyceridemia. Nucleic Acids Res 53(20): gkaf1063.
38. Larouche M, Ballantyne C, Dufour J, Brisson D, Given B, et al. (2025) Glycerol Kinase Gene Variant as a Cause of Pseudohypertriglyceridemia and Apparent Poor Response to Plozasiran. JCEM Case Rep 3(8): luaf146.
39. Gubensek J, Buturovic Ponikvar J, Romozi K, Ponikvar R (2023) The role of apheresis and insulin therapy in hypertriglyceridemic acute pancreatitis-a concise review. BMC Gastroenterol 23: 122.
40. Varbo A, Benn M, Tybjaerg Hansen A, Nordestgaard BG (2013) Remnant cholesterol as a causal risk factor for ischemic heart disease. J Am Coll Cardiol 61(4): 427-436.
41. Gao Y, Bai Y, Mu X, Pang X (2026) Efficacy and safety of small interfering RNA therapies for hypertriglyceridemia and mixed dyslipidemia: an updated systematic review and meta-analysis. Front Pharmacol 17: 1736821.
42. De Luca C, Ciciola P, D Errico G, Di Taranto MD, Fortunato G, et al. (2025) Genetic Assessment and Clinical Correlates in Severe Hypertriglyceridemia: A Systematic Review. Genes (Basel) 16(11): 1377.
43. Hansen SEJ, Madsen CM, Varbo A, Anne Tybjaerg Hansen, Borge G Nordestgaard (2021) Genetic variants associated with increased plasma levels of triglycerides, via effects on the lipoprotein lipase pathway, increase risk of acute pancreatitis. Clin Gastroenterol Hepatol 19(8): 1652-1660.
44. Esan O, Wierzbicki AS (2020) Volanesorsen in the Treatment of Familial Chylomicronemia Syndrome or Hypertriglyceridaemia: Design, Development and Place in Therapy. Drug Des Devel Ther 14: 2623-2636.

ISSN: 2574-1241

DOI: 10.26717/BJSTR.2026.65.010206

Jiang Tao and Jiang Hongwei. Biomed J Sci & Tech Res

Submission Link: https://biomedres.us/submit-manuscript.php