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EDIT-401: A potentially transformative investigational *in vivo* CRISPR gene editing medicine upregulates LDLR and meaningfully reduces LDL-C in non-human primates

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Disclosures

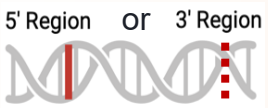
- Paul Wrighton is an employee and equity holder of Editas Medicine, Inc.

Editas' differentiated *in vivo* gene editing upregulation strategy

Functional Upregulation

Differentiated use of CRISPR nuclease-based technology

Edit
non-coding, regulatory
regions



to *upregulate* a wild-type allele or functional homolog

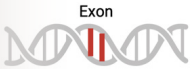
- **Treats diseases by increasing the level of disease-mitigating protein**
- **Does not alter sequence of naturally occurring protein**

Other Approaches

Edit
coding
regions

Knockdown of disease-causing protein

Gene correction of disease-causing protein



CRISPR, clustered regularly interspaced short palindromic repeats.

ASCVD is a serious disease with significant opportunity for a transformative therapy to reduce LDL-C

ASCVD is driven by **cholesterol-rich** plaque accumulation in the arteries

- ASCVD is the primary cause of morbidity and mortality globally,[1] including in patients with heterozygous familial hypercholesterolemia (HeFH), a genetic disease primarily related to loss of function mutations in *LDLR* gene[2]
- The link between lower LDL-C and reduced ASCVD risk is well established[1]
- ~75% of patients with ASCVD do not meet LDL-C goals[3,4]
- Standard of care requires multiple therapies and lifelong administration[1]

Robust, lifelong reduction of LDL-C provides maximal benefit[5,6]

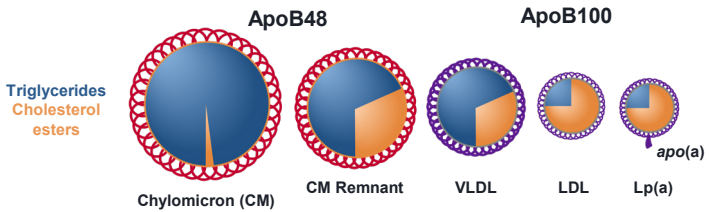
ASCVD, atherosclerotic cardiovascular disease; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor.

1. Arnett DK *et al. Circulation* 2019; 140 (11): e596–e646. 2. Gidding SS *et al. J Am Heart Assoc* 2025;14:e038458. 3. Gu J *et al. Am J Prev Cardiol* 2022; 10: 100336.
4. Klimchak AC *et al. Am J Prev Cardiol* 2020; 1: 100010. 5. Cohen JC *et al. N Engl J Med* 2006; 354 (12): 1264–1272. 6. Gaba P *et al. Circulation.* 2023; 147 (16): 1192–1203.

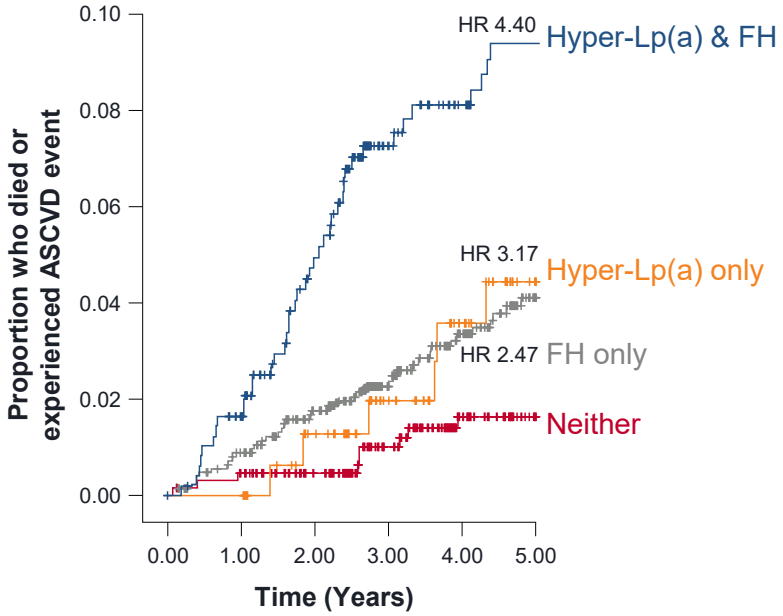
LDL-C, ApoB, and Lp(a) are key risk factors for ASCVD

ASCVD Risk Factors

- **LDL-C** is the foundational marker of ASCVD risk[1]
- **ApoB** captures all atherogenic particles – CM, remnants, VLDL, LDL, Lp(a) – and lowering ApoB consistently reduces ASCVD risk[2]
- **Lp(a)** adds *independent* risk beyond LDL-C or ApoB[3,4]
- Newer dyslipidemia guidelines suggest measuring **ApoB and Lp(a) in addition to LDL-C**[1]



Lp(a) Risk & Familial Hypercholesterolemia (FH)[5]



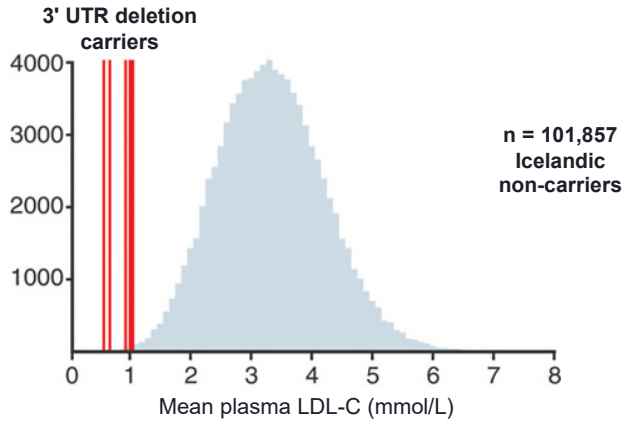
Hyper-Lp(a) defined as plasma Lp(a) concentration >50 mg/dL[5].
Apo(a), apolipoprotein(a); ApoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; CM, chylomicron; FH, familial hypercholesterolemia; HR, hazard ratio; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); VLDL, very low-density lipoprotein.

1. Blumenthal RS et al. *J Am Coll Cardiol* 2026; 87(19): 2624-2757. 2. Glavinovic T *et al. J Am Heart Assoc* 2022; 11 (20): e025858. 3. Nordestgaard BG *et al. Lancet* 2024; 404 (10459): 1255–1264. 4. Sniderman AD *et al. Eur Heart J* 2025; 46 (27): 2702–2704. 5. Loh *et al. Front Genet* 2022; 13: 905941.

Therapeutic strategy of LDLR upregulation for LDL-C reduction is informed by human genetics

Seven Icelandic family members were identified as carriers of partial *LDLR* 3' UTR deletion[1]

Plasma LDL-C levels[1]



Impact on carriers[1]

LDL-C:

- **0.35–1.87 mmol/L (13–72 mg/dL)** plasma levels
- **Mean 74% lower** in carriers compared to non-carriers

LDLR:

- **1.5- to 2.5-fold** higher surface LDLR*

Safety:

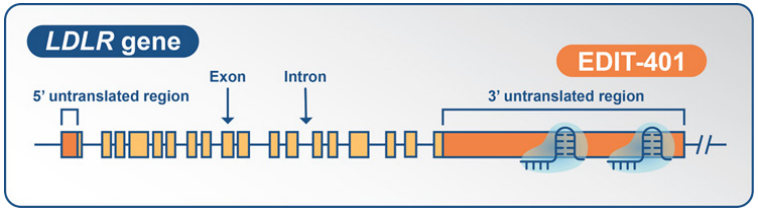
- No adverse events

*Noted value was for lymphocytes. Liver LDLR values are unknown.
3' UTR, three prime untranslated region; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor.

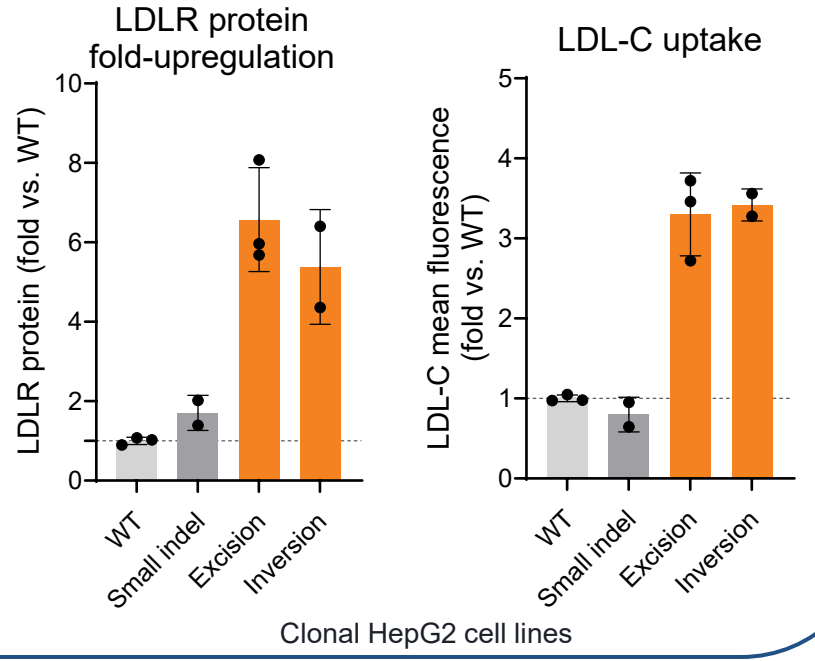
1. Bjornsson *et al. Circ Genom Precis Med* 2021; 14 (1): e003029.

CRISPR/Cas9 and dual gRNA-based strategy with LNP delivery creates a potent approach to LDLR upregulation for LDL-C reduction

- CRISPR/Cas9 nuclease and dual gRNAs disrupt negative regulatory elements in the 3' UTR, increasing mRNA stability
- Functional editing events are the result of targeted excisions or inversions



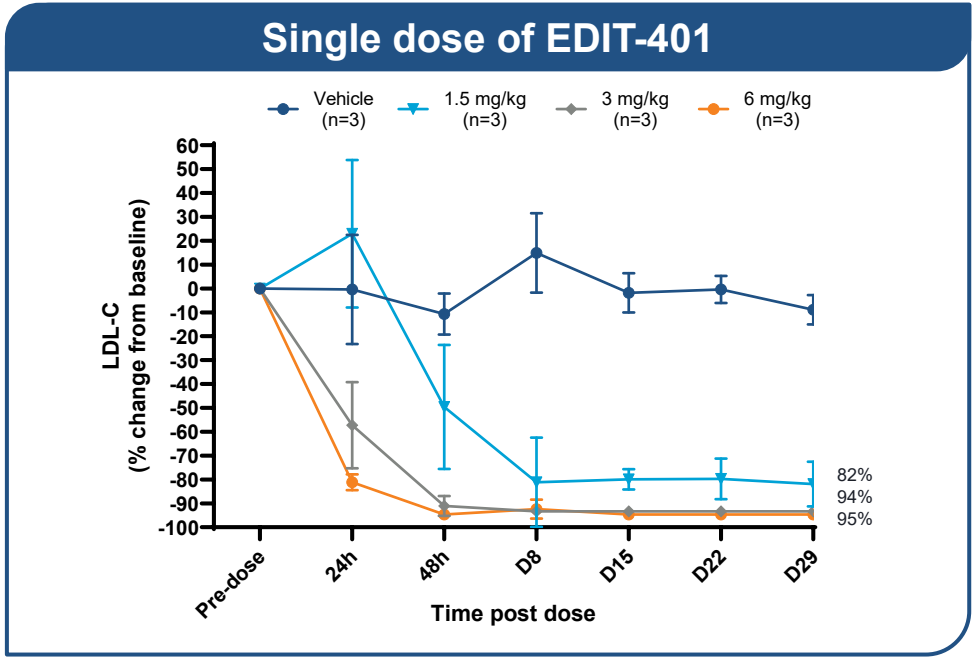
Functional edits increase LDLR protein expression and LDL-C uptake



3' UTR, three prime untranslated region; Cas9, CRISPR-associated protein 9; CRISPR, clustered regularly interspaced short palindromic repeats; HepG2, hepatoma G2; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; WT, wild-type.

EDIT-401 achieved >90% mean LDL-C reduction by upregulating LDLR

EDIT-401, CRISPR/Cas9 nuclease, and dual gRNAs for LDLR upregulation encapsulated in a GalNAc conjugated LNP administered to non-human primates; Dose Range Finding (DRF) study data shown.



- >90% mean LDL-C reduction across all dosed NHPs
- Rapid LDL-C reduction observed
- Consistent data across multiple independent studies

Pre-dose LDL-C was averaged across two timepoints to account for variability in measurements. Day 1 defined as day of dosing. Mean values are shown +/- SD. Values below lower limit of quantitation assigned as LLoQ/2.
Cas9, CRISPR-associated protein 9; CRISPR, clustered regularly interspaced short palindromic repeats; D, day; DRF, dose range finding; GalNAc, N-acetylgalactosamine; h, hour; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; LNP, lipid nanoparticle; LLoQ, lower limit of quantification; NHP, non-human primate; SD, standard deviation.
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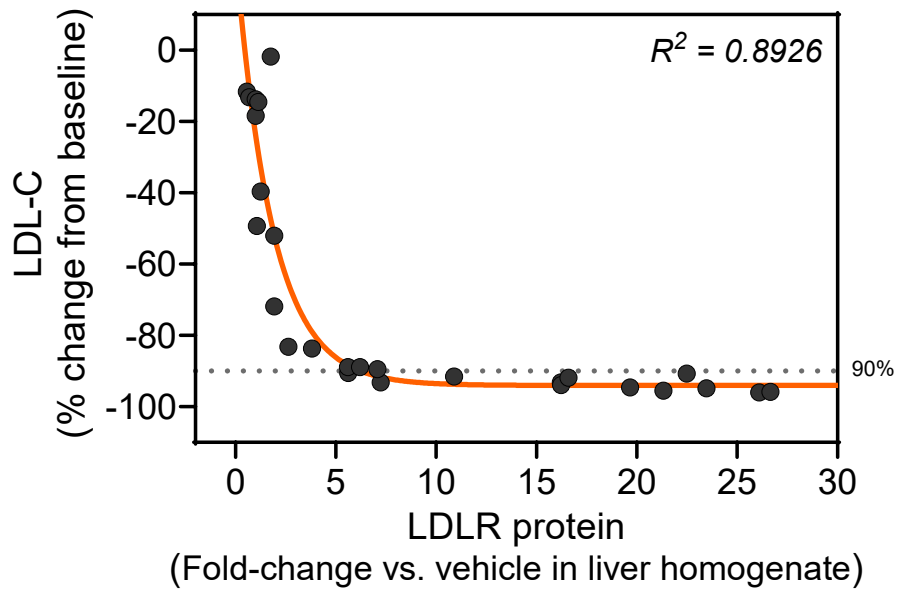
EDIT-401 enables increase in LDLR protein levels needed to achieve ≥90% LDL-C reduction in NHPs

LDL-C reduction correlated with LDLR protein upregulation



- ≥6-fold mean increase in LDLR protein in liver resulted in ≥90% LDL-C reduction in NHPs

LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; NHP, non-human primate.
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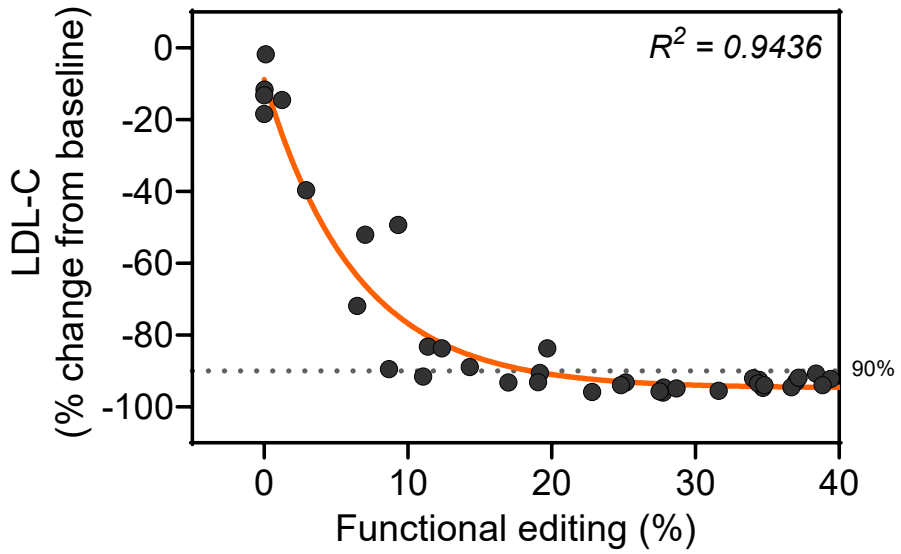
EDIT-401 therapeutic strategy requires only a moderate level of functional editing to demonstrate ≥90% LDL-C reduction in NHPs

LDL-C reduction correlated with functional editing



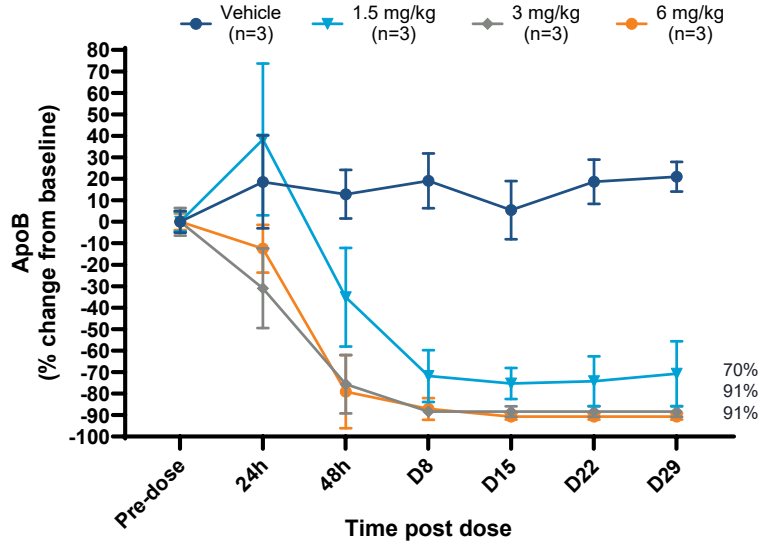
- Approximately 10%–40% functional editing can lead to the LDLR protein increase resulting in ≥90% LDL-C reduction in NHPs

Functional editing: Percent of alleles containing targeted excisions or inversions from bulk liver. LDL-C reduction from final D29 timepoint.
D, day; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; NHP, non-human primate.
LNPs licensed from Genevant Sciences Corporation.

EDIT-401 achieved up to ~90% mean ApoB reduction

EDIT-401, CRISPR/Cas9 nuclease, and dual gRNAs for LDLR upregulation encapsulated in a GalNAc conjugated LNP administered to non-human primates; Dose Range Finding (DRF) study data shown

Single dose of EDIT-401



- Dose-dependent ApoB reduction
- Rapid ApoB reduction observed
- Reduction in ApoB correlates with LDL-C reduction

Pre-dose ApoB was averaged across one or two timepoints to account for variability in measurements. Mean values are shown +/- SD. Values below lower limit of quantitation assigned as LLoQ/2.

ApoB, apolipoprotein B; Cas9, CRISPR-associated protein 9; CRISPR, clustered regularly interspaced short palindromic repeats; D, day; GalNAc, N-acetylgalactosamine; h, hour; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; LNP, lipid nanoparticle; LLoQ, lower limit of quantification.

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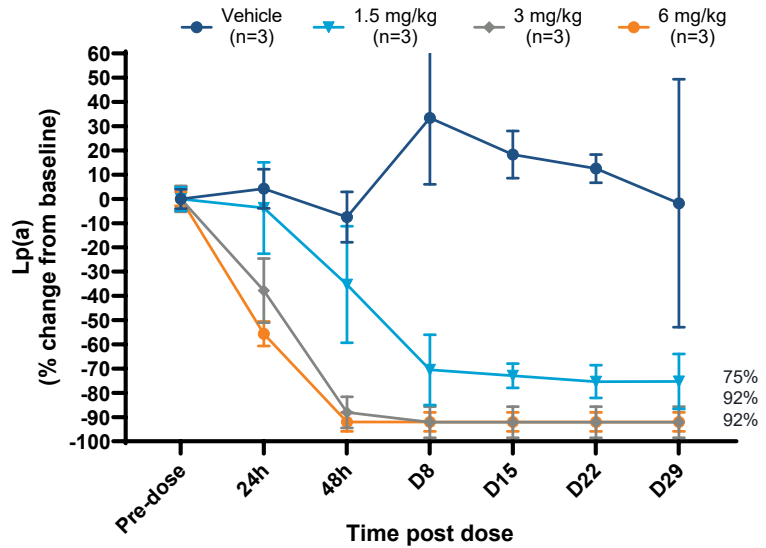
EDIT-401 achieved up to ~90% mean Lp(a) reduction

EDIT-401, CRISPR/Cas9 nuclease, and dual gRNAs for LDLR upregulation encapsulated in a GalNAc conjugated LNP administered to non-human primates; Dose Range Finding (DRF) study data shown

Single dose of EDIT-401



- Dose-dependent Lp(a) reduction
- Rapid Lp(a) reduction observed
- Reduction in Lp(a) correlates with LDL-C and ApoB reductions
- NHP baseline Lp(a) values approximate elevated CVD risk in humans[1]

Pre-dose Lp(a) was averaged across one or two timepoints to account for variability in measurements. Mean values are shown +/- SD. Values below lower limit of quantitation assigned as LLoQ/2. Animal baseline Lp(a) values with a range of ~22–159 mg/dL.

ApoB, apolipoprotein B; LLoQ, lower limit of quantification; Cas9, CRISPR-associated protein 9; CRISPR, clustered regularly interspaced short palindromic repeats; CVD, cardiovascular disease; D, day; GalNAc, N-acetylgalactosamine; h, hours; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; LNP, lipid nanoparticle; Lp(a), lipoprotein(a).

LNPs licensed from Genevant Sciences Corporation.

1. Irvine A *et al. Front Cardiovasc Med* 2026; 12: 1710557.

Summary

- EDIT-401 combines Editas' drug development expertise and Genevant's LNP to deliver a **differentiated therapeutic strategy of functional LDLR upregulation**
- Low to moderate functional editing of *LDLR* alleles leads to **≥6-fold mean increase LDLR protein** in the NHP liver
- A single dose of EDIT-401 achieved **>90% mean LDL-C reduction and up to ~90% mean ApoB and Lp(a) reductions** in NHPs
- LDLR upregulation with EDIT-401 translates to a **potentially transformative medicine to reduce LDL-C**, **ApoB**, **and Lp(a)**
- Encouraging preclinical data supports advancing EDIT-401 towards a **first-in-human clinical trial on track to be initiated in 2026**

Robust, long-term reductions of LDL-C, ApoB, *and* Lp(a) may be needed to provide maximum clinical benefit[1–4]

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ApoB, apolipoprotein B; LDLR, low-density lipoprotein receptor; LDL-C, low-density lipoprotein cholesterol; LNP, lipid nanoparticle; Lp(a), lipoprotein(a); NHP, non-human primate.

1. Vuorio A *et al. J Intern Med* 2020; 287 (1): 2–18. 2. Cohen *et al. N Engl J Med* 2006; 354: 1264–272. 3. Gaba *et al. Circulation* 2023; 147 (16): 1192–1203. 4. Glavinovic T *et al. J Am Heart Assoc* 2022; 11 (20): e025858.

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Thank you!