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Methodological Concerns Regarding Cardioprotective Effects of PCSK9 Inhibition in Diabetic Rats

LETTER TO THE EDITOR

To the Editor,

We read with interest the recent article by Zhang et al[1] investigating the cardioprotective effects of alirocumab and atorvastatin in a rat model of type 2 diabetes mellitus (T2DM) with myocardial ischemia-reperfusion (I/R) injury. While the findings are potentially valuable, we wish to raise several methodological concerns that fundamentally affect the interpretation and validity of the conclusions.

First, the induction of T2DM using 150 mg/kg streptozotocin is unusually high. As detailed in a comprehensive practical guide, the standard dose range for establishing a T2DM model in rats is 25 to 35 mg/kg, administered after a high-fat diet to induce partial beta-cell dysfunction.[2] Doses of 50 to 65 mg/kg are reserved for inducing type 1 diabetes, while doses exceeding 65 mg/kg cause near-complete and irreversible beta-cell ablation.[2] The 150 mg/kg dose is therefore overwhelmingly toxic and would produce a phenotype consistent with severe type 1 diabetes, not T2DM.[1] This is corroborated by the authors' own data showing significantly reduced insulin and C-peptide levels in diabetic rats. The mechanistic claims regarding metabolic modulation must be reconsidered given that the observed beta-cell destruction is likely irreversible.

Second, the absence of a sham-operated control group represents a critical oversight. The non-diabetic I/R and T2DM+I/R groups underwent thoracotomy with coronary ligation, while the "Control" group consisted of naive animals. Without a sham group undergoing thoracotomy without ligation, it is impossible to distinguish inflammatory and metabolic changes attributable to true I/R injury from those resulting from surgical trauma alone.

Third, the 2-hour reperfusion duration is relatively shorter to show apoptotic and inflammatory changes to peak following I/R injury. The authors' TUNEL and caspase-3 data at 2 hours may not capture the full extent of injury or the true therapeutic efficacy of the interventions. Evidence for longer reperfusion indicates that many key apoptotic and inflammatory pathways continue to evolve beyond 2 hours.[3]

Fourth, the finding that atorvastatin downregulates PCSK9 expression is biologically paradoxical. Careskey et al demonstrated conclusively that atorvastatin (40 mg/day) significantly increases circulating PCSK9 levels in humans by 34% compared with baseline and placebo.[4] This occurs because statins upregulate SREBP-2, a transcription factor that activates both the LDL receptor and PCSK9 genes.[4] The authors present their contradictory finding as "novel evidence" without mechanistic explanation, implying potential errors in assay design or data interpretation.[1]

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Finally, no pharmacokinetic bridging data are provided to justify whether the 10 mg/kg/week alirocumab dose in rats achieves plasma concentrations comparable to therapeutic human doses.[1] Without measured drug levels, extrapolation to clinical efficacy remains speculative.

While the study addresses an important clinical question, these methodological limitations collectively compromise the translational reliability of the findings.

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