

# Aldose Reductase Catalyzes Reduction of Lipid Oxidation Products and AGE Precursors and Protects against Early Atherosclerotic Lesions



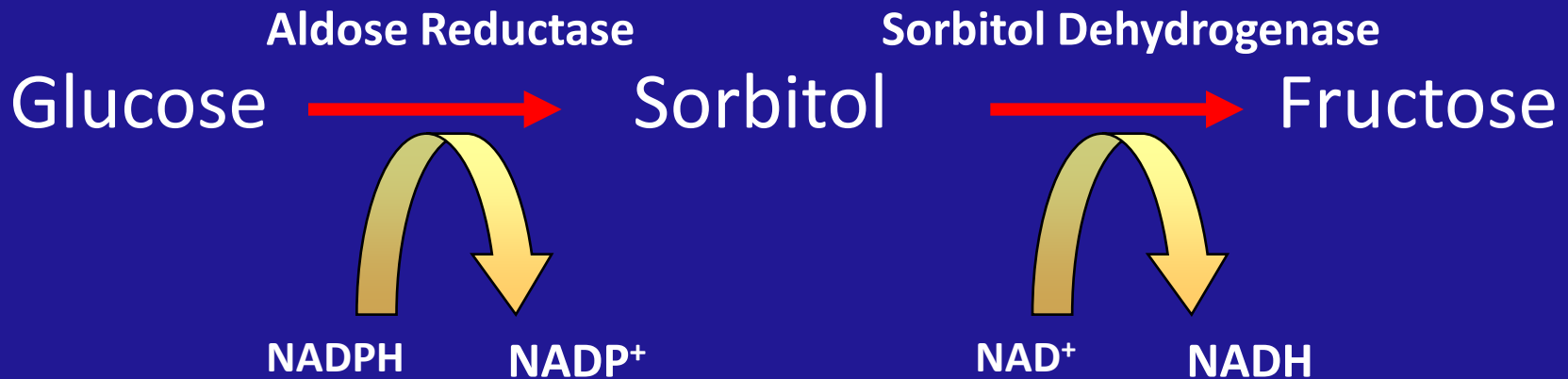
Oleg A. Barski

Diabetes and Obesity Center

University of Louisville

# Aldose Reductase and Glucose Metabolism

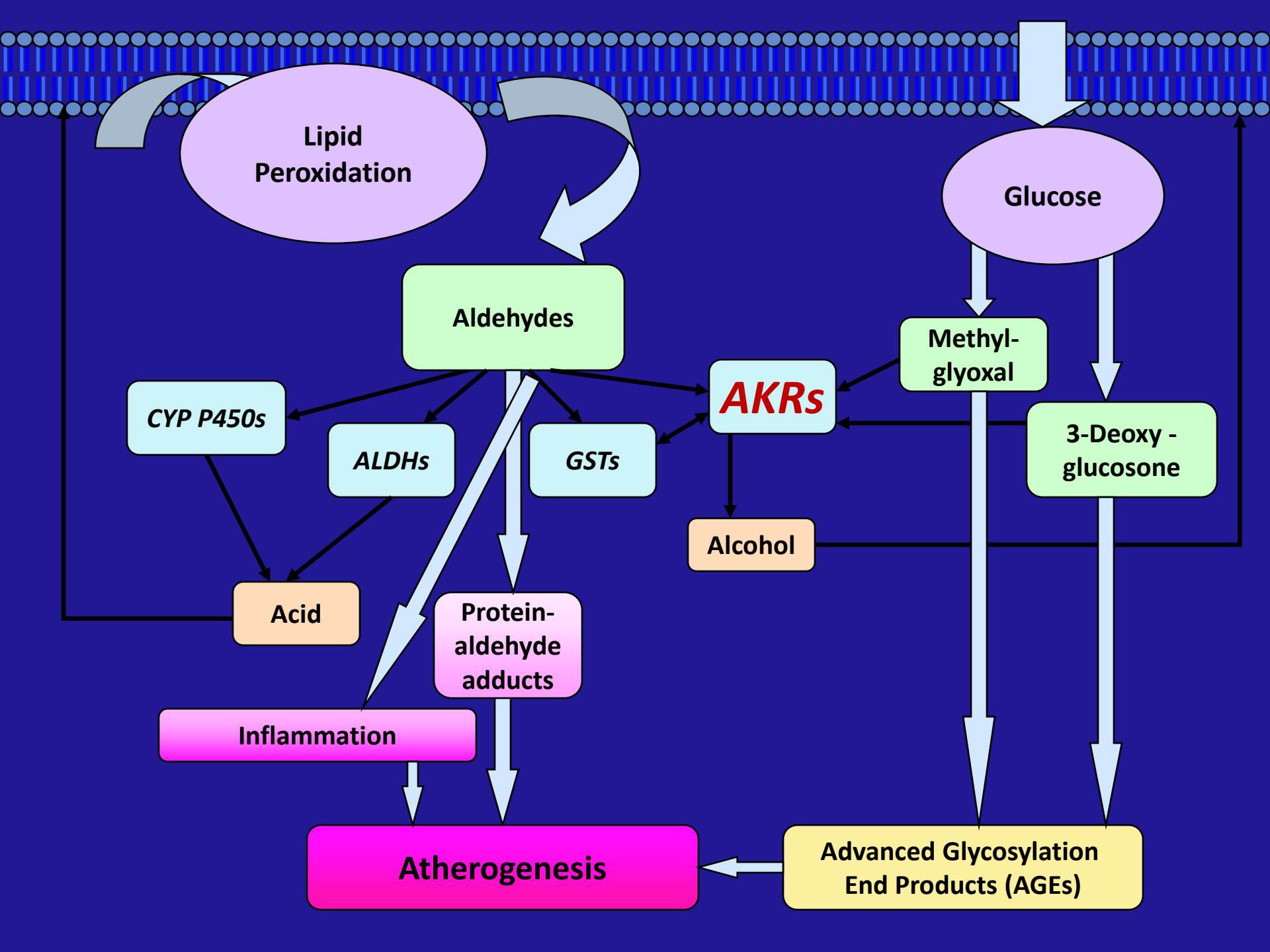
## Polyol Pathway



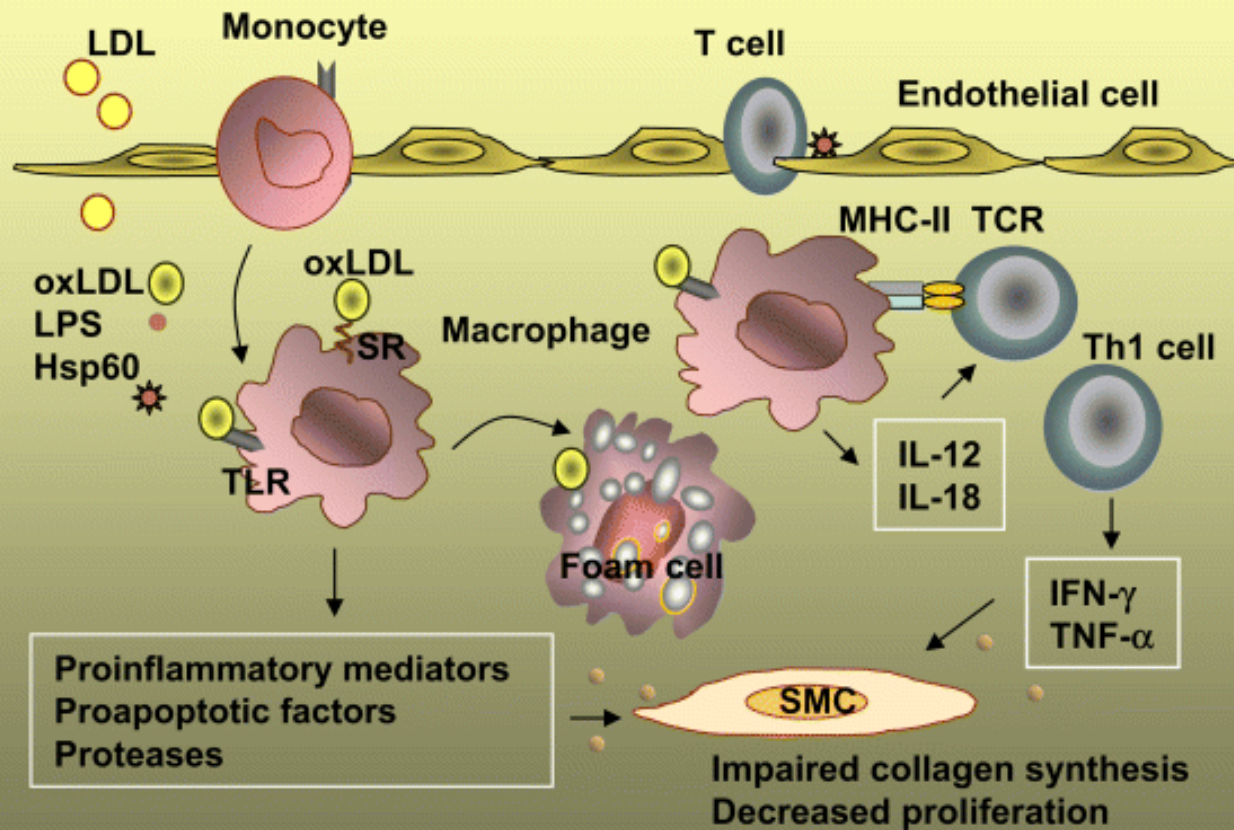
$$K_m = 200\text{mM}$$

$$k_{\text{cat}} = 1 \text{ sec}^{-1}$$

Uncontrolled sorbitol accumulation in tissues is a contributing factor to the development of diabetic complications



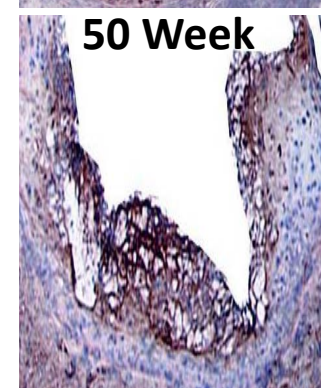
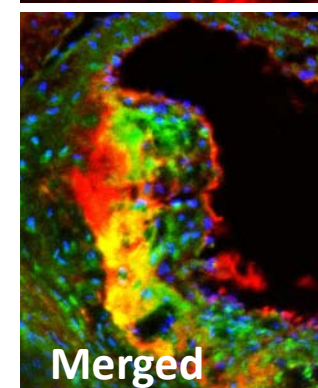
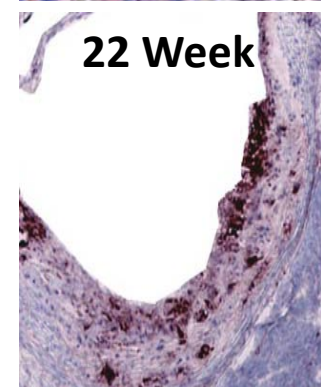
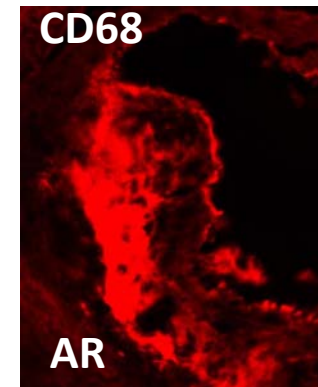
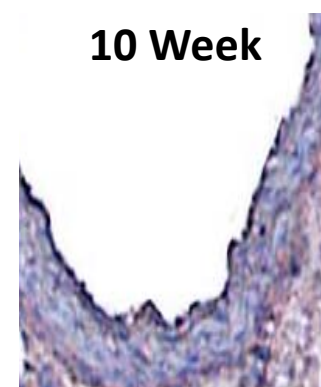
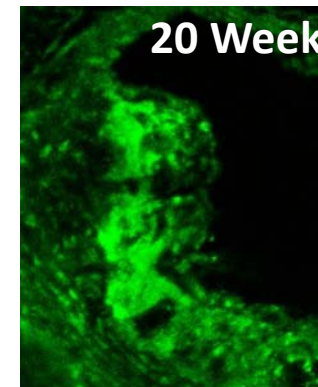
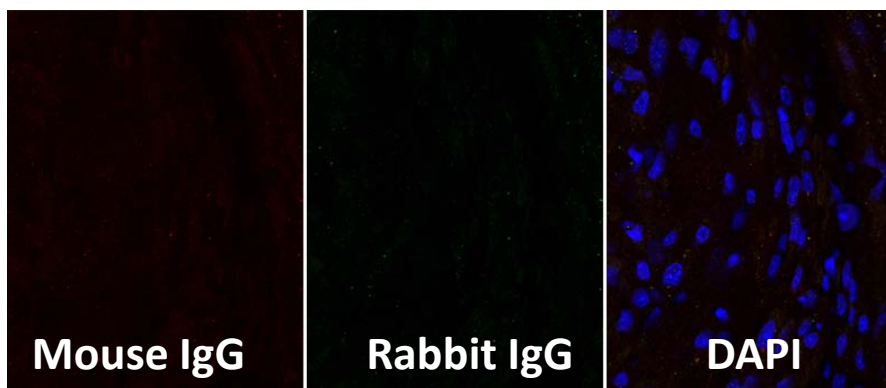
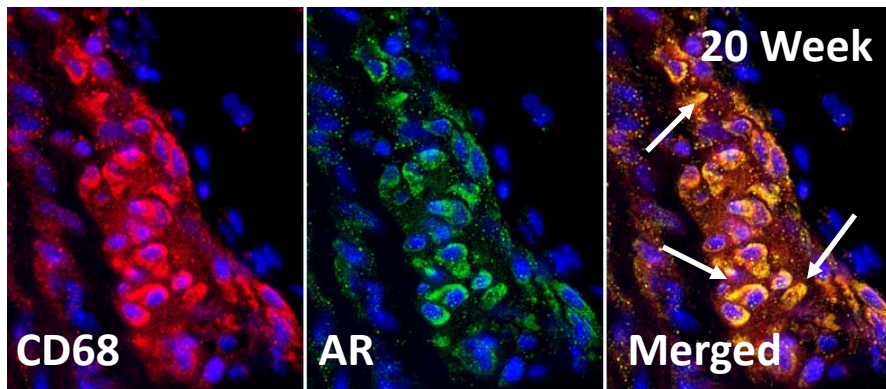
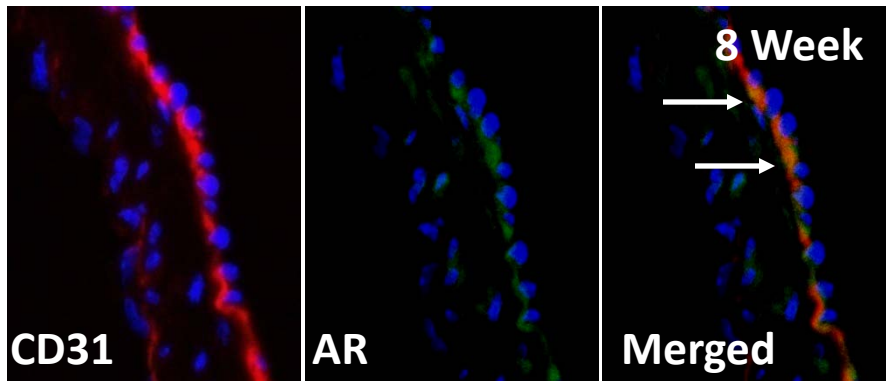
# Oxidized Lipids Promote Atherosclerosis



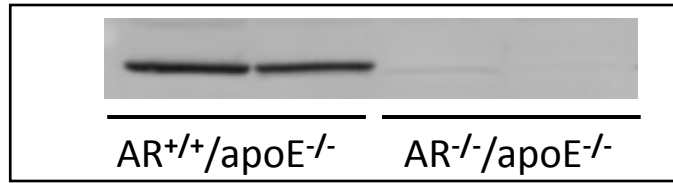
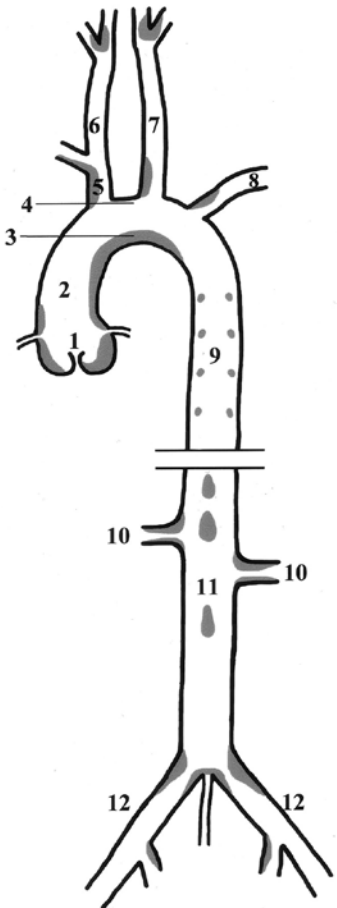
# Expression of AR in Atherosclerotic Lesions

## Innominate Artery

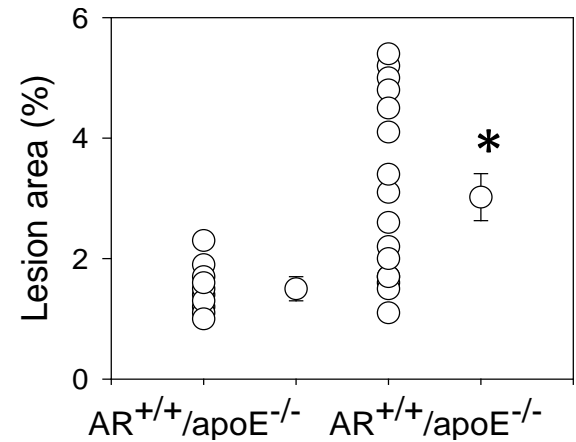
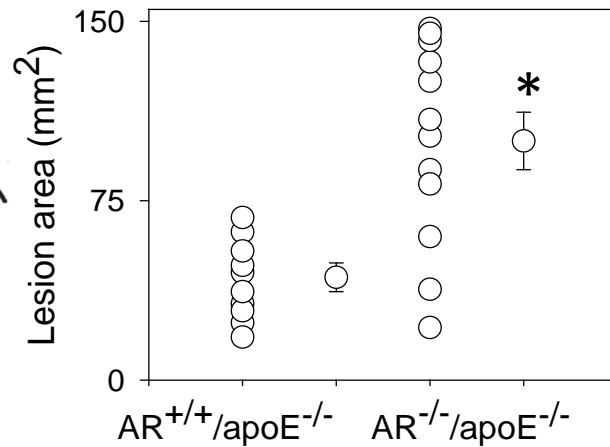
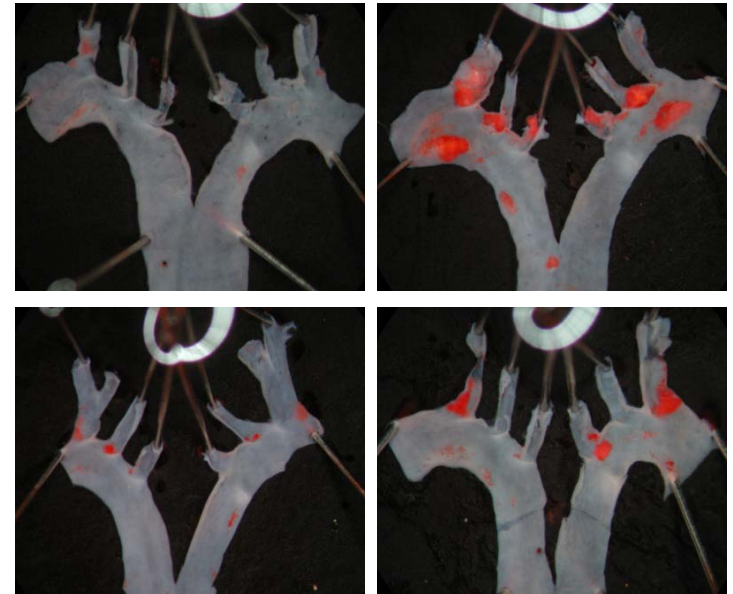
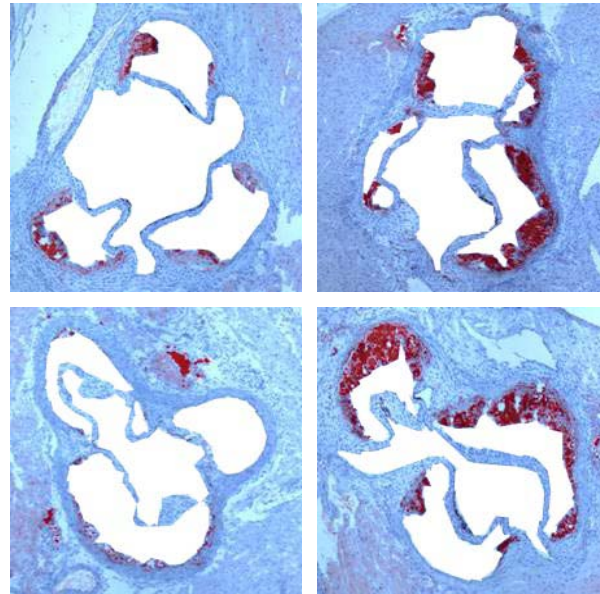
## Aortic Valve



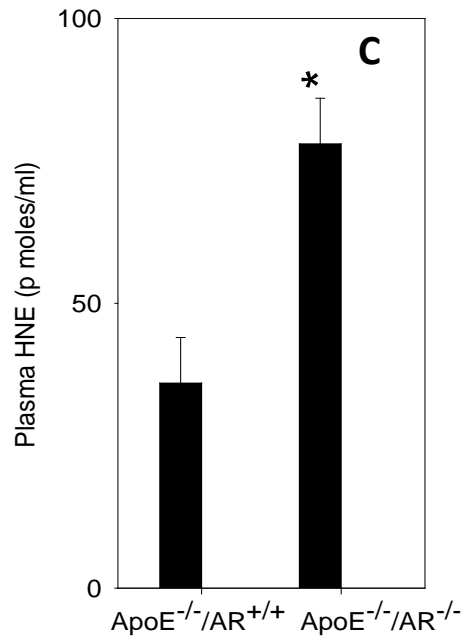
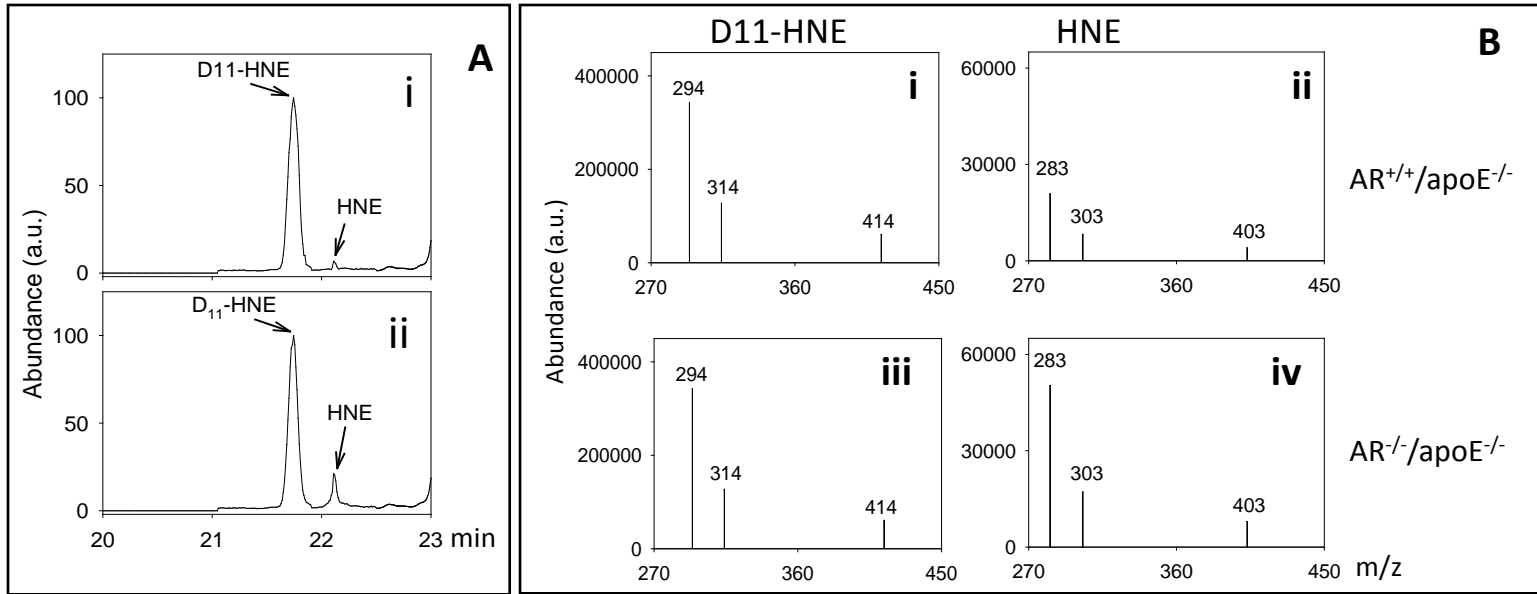
# Genetic Ablation of AR Increases Early Atherosclerotic Lesion Formation



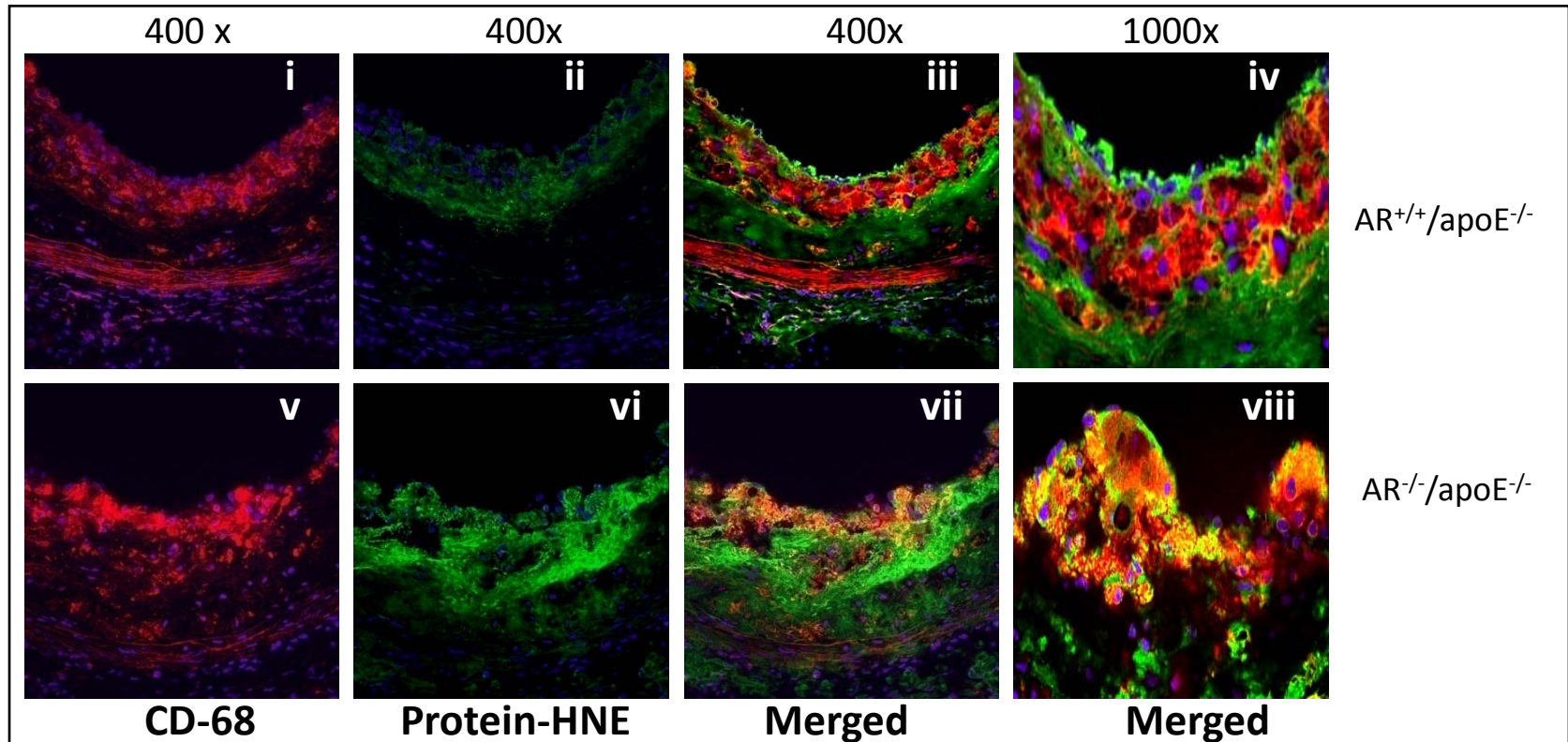
Eight week old mice maintained on high fat diet for 4 weeks



# Genetic Ablation of AR Increases the Concentration of HNE in the Plasma



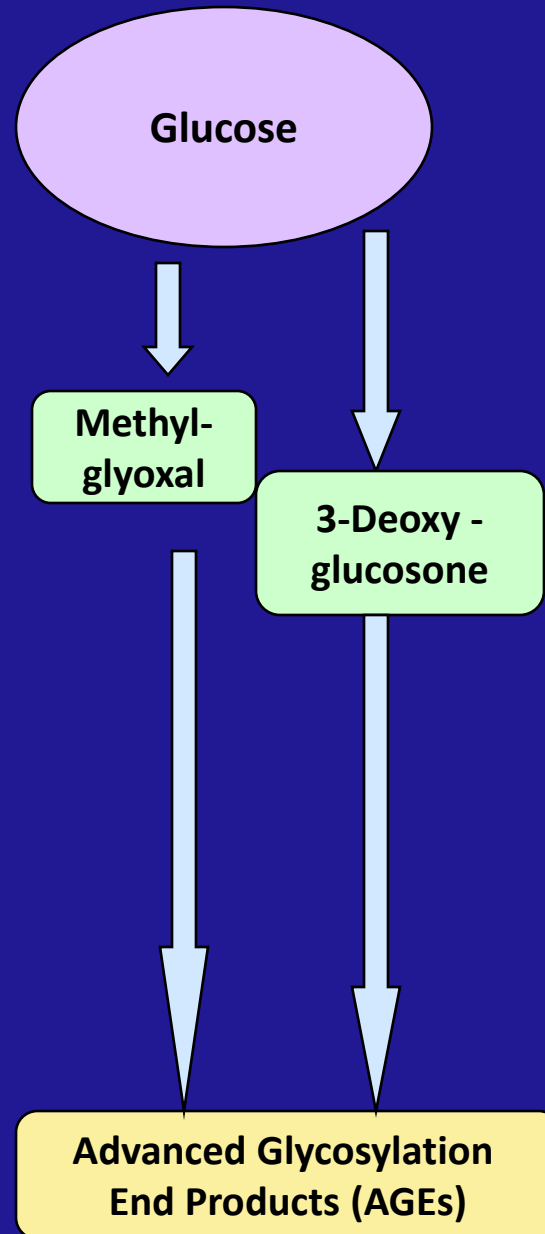
# Genetic Ablation of AR Increases the Accumulation of Protein-HNE Adducts in Atherosclerotic Lesions



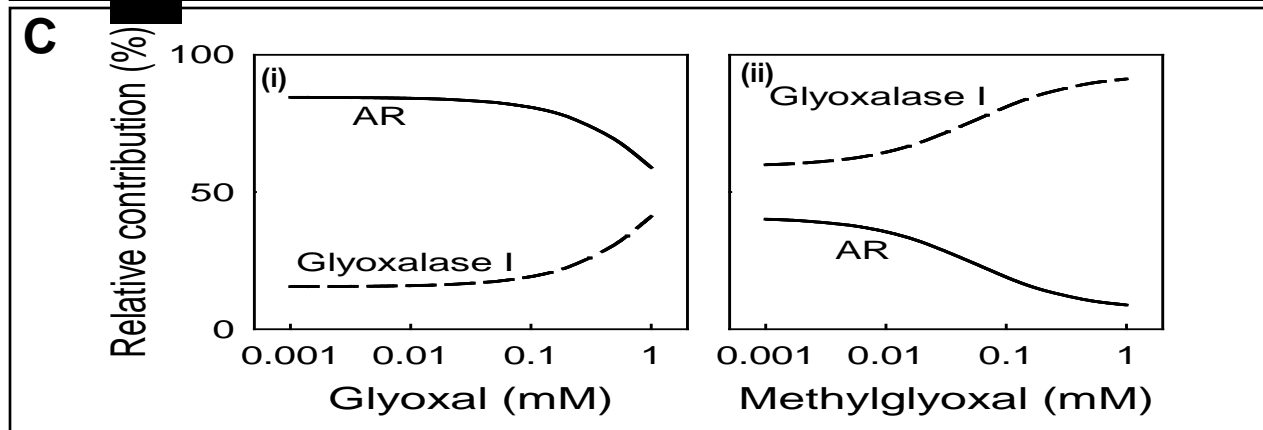
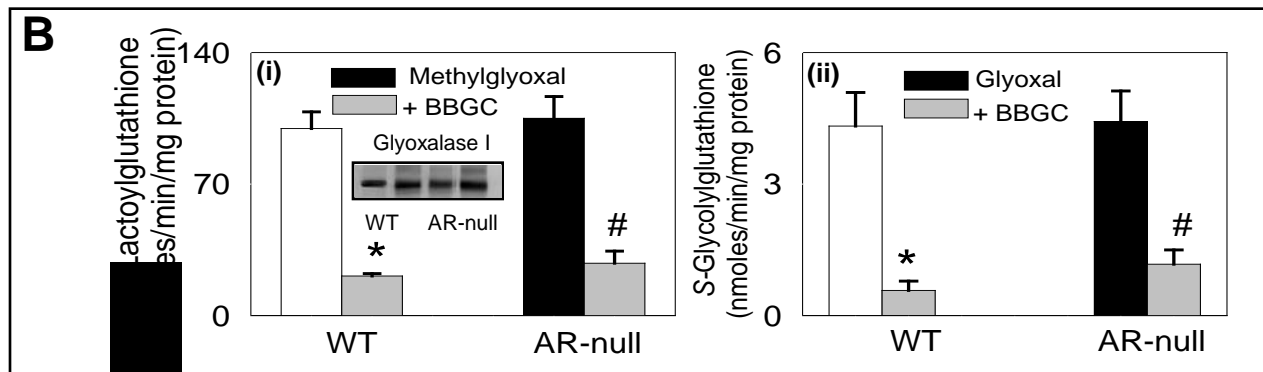
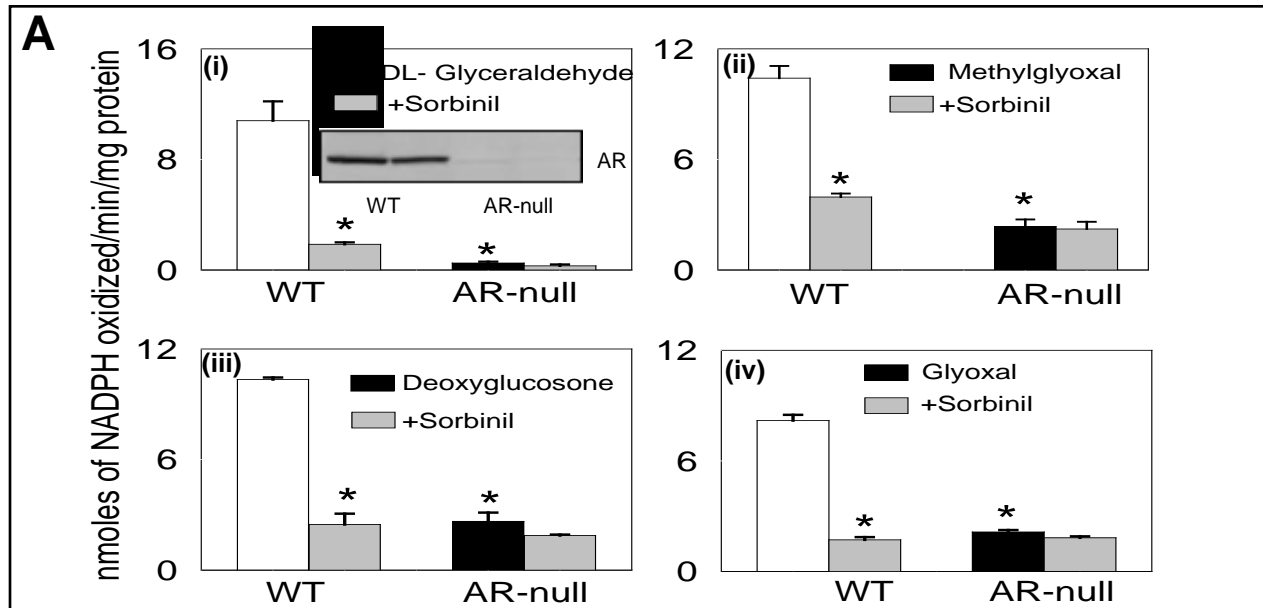
Eight week old mice maintained on high fat diet for 12 weeks.

Inhibition of AR increases the accumulation of aldehyde-protein adducts in atherosclerotic lesions and enhances lesions formation

# Oxidation of Glucose Generates AGE-Precursors

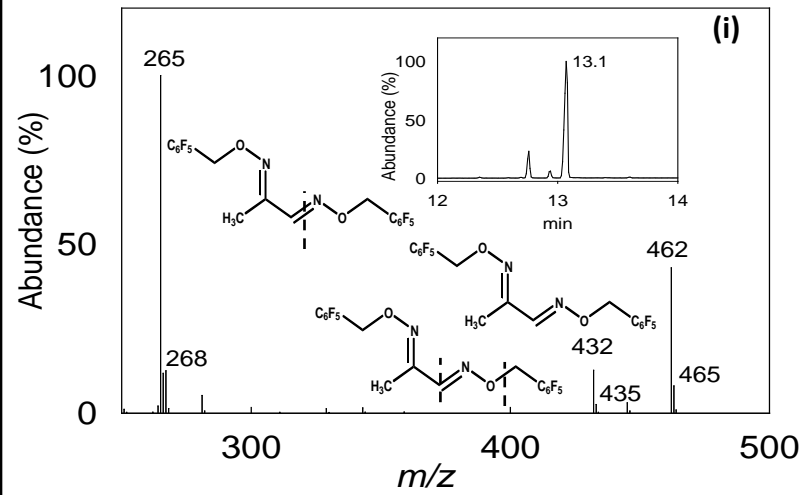


# Contribution of AR to the metabolic pathways of AGE precursors



# AR Catalyzes the Reduction of Methylglyoxal in EC

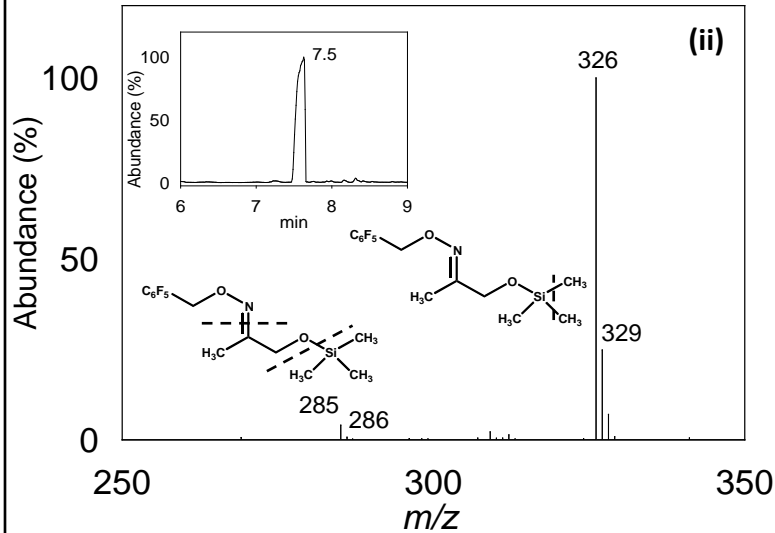
**A**



*m/z*

462=C7H2F5NO-12C3H4NOC7H2F5  
432=C7H2F5NO-12C3H3H2F5  
265=C7H2F5NO-12C3H3

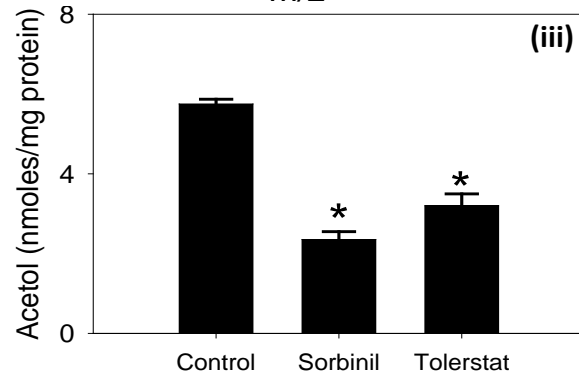
465=C7H2F5NO-13C3H4NOC7H2F5  
435=C7H2F5NO-13C3H3H2F5  
268=C7H2F5NO-13C3H3



*m/z*

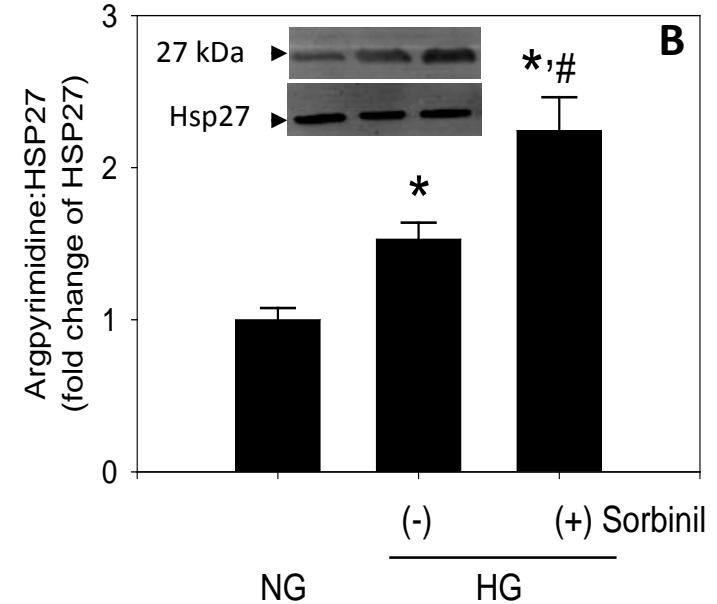
326=C7H2F5NO12C3H4OSi(C H3)2  
285=C7H2F5NO Si(CH3)3

329=C7H2F5NO13C3H4OSi(C H3)2  
286=C7H2F5 HNOSi(CH3)3



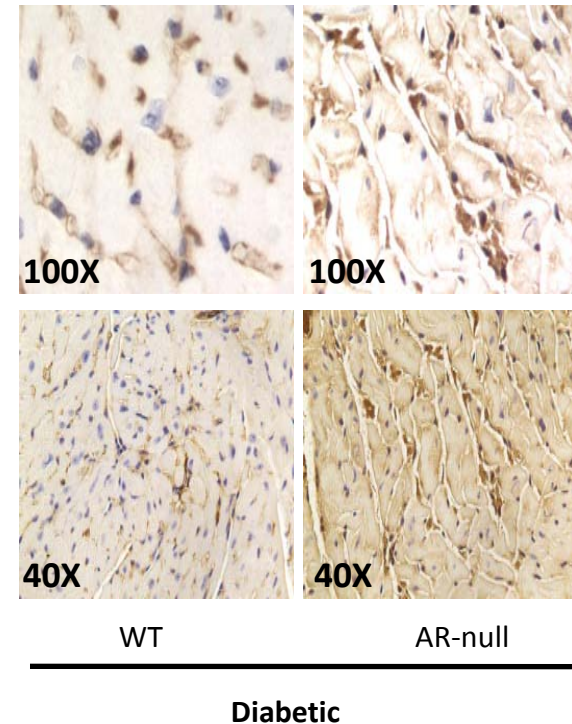
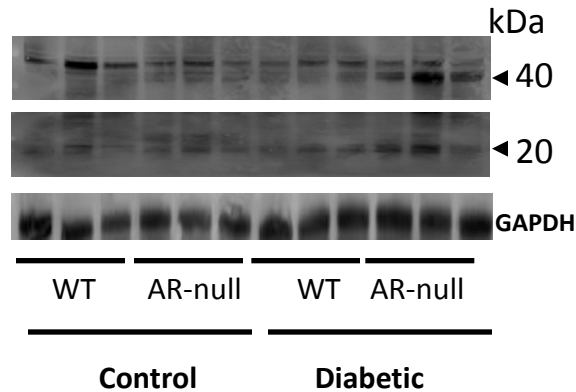
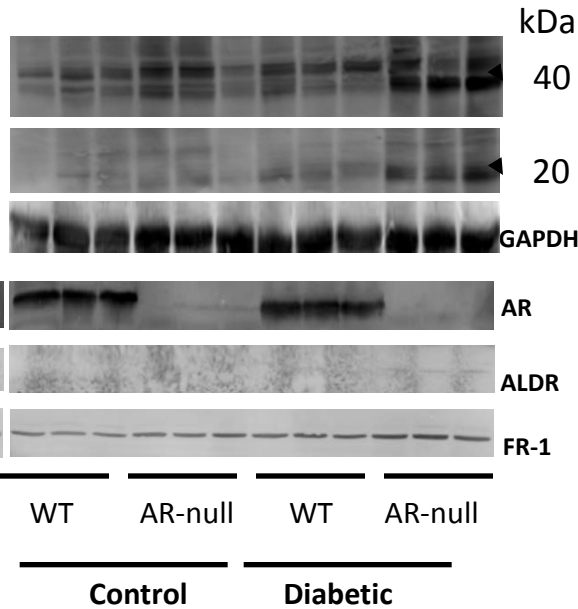
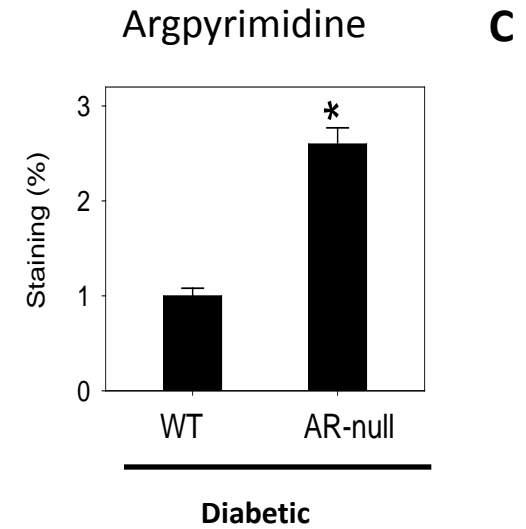
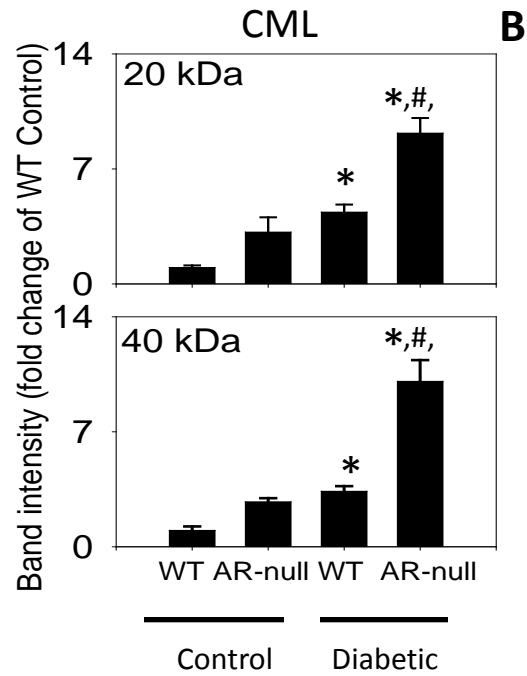
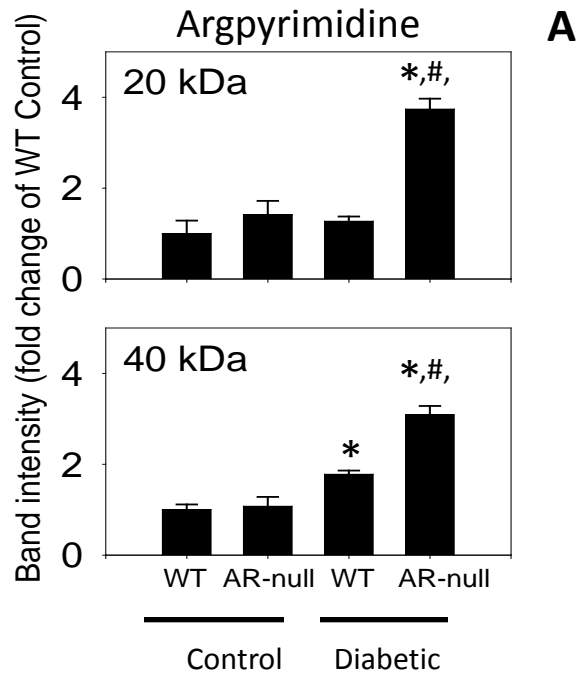
HUVEC incubated with 1mM methylglyoxal for 24 h

HUVEC maintained in 20mM glucose for 7 days

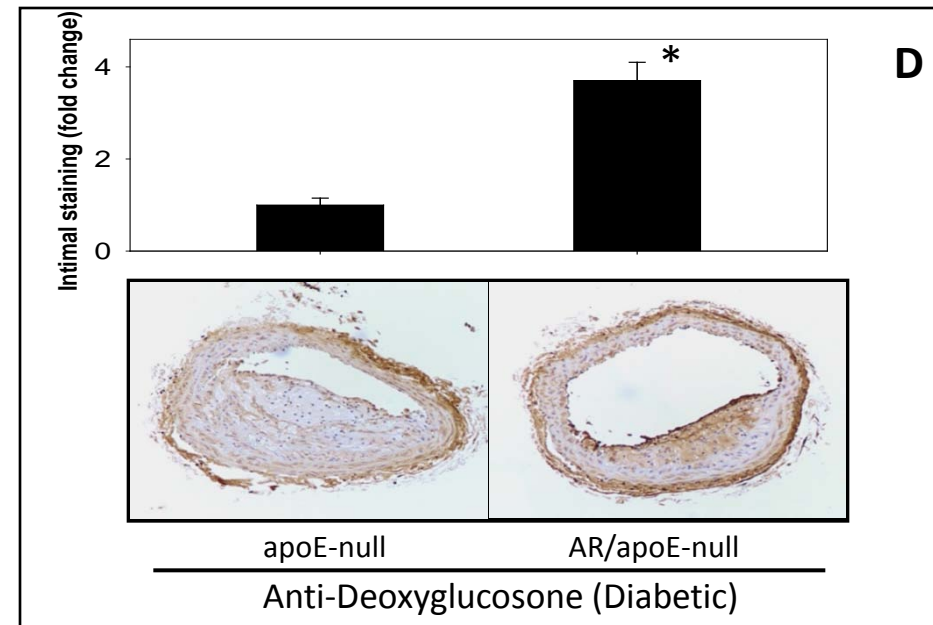
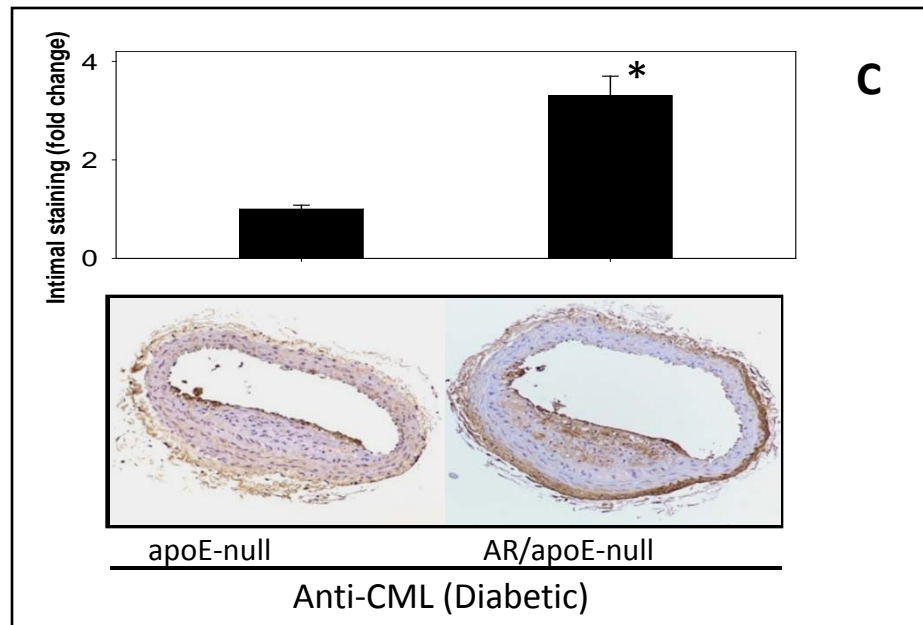
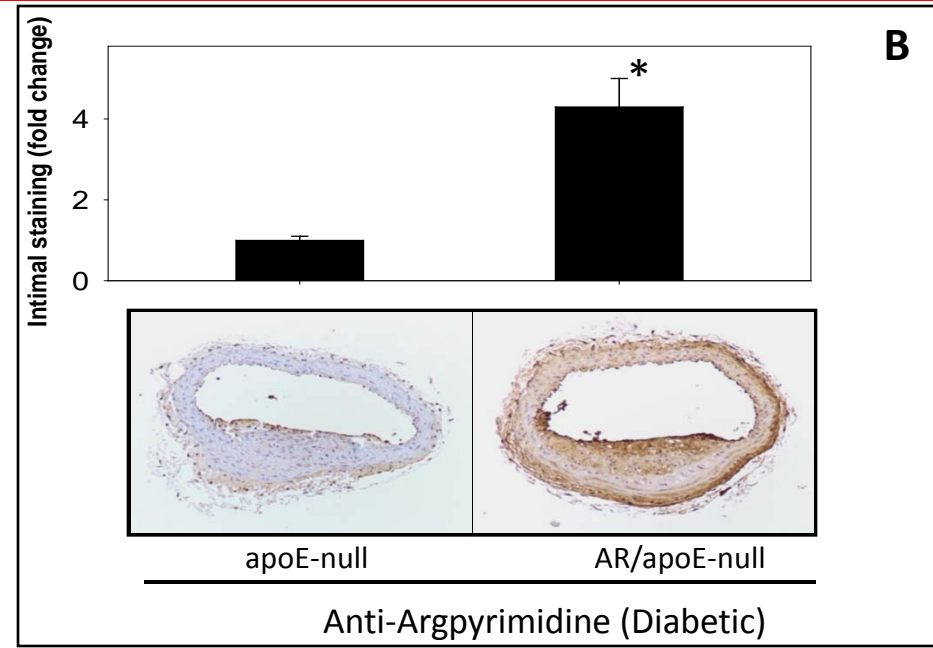
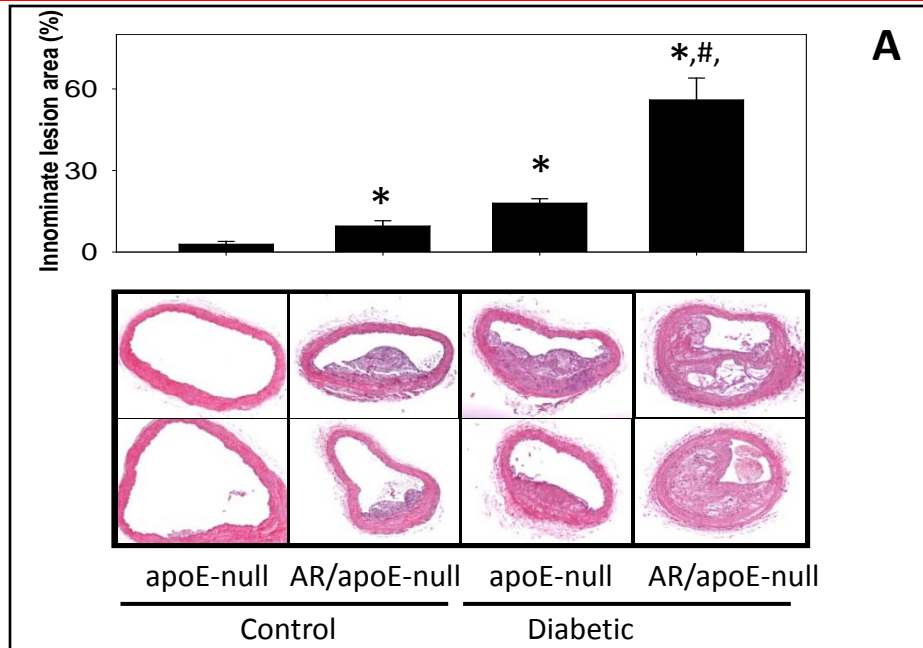


**Inhibition of AR enhances high glucose-induced AGE formation in EC.**

# Genetic Ablation of AR Increases the Accumulation of AGEs in the Heart



# Genetic Ablation of AR Increases the Accumulation of AGEs in Innominate Lesions



# Conclusion

Reduction of reactive aldehydes by aldose reductase protects against

- a) early atherosclerotic lesion formation and
- b) AGE accumulation in diabetes

# Acknowledgments

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# Diabetes and Obesity Center

