Erasmus MC
University Medical Center Rotterdam

Nieuwe therapeutische ontwikkelingen

Jan Danser, Professor of Pharmacology
Division of Vascular Medicine and Pharmacology
Department of Internal Medicine
Erasmus MC, Rotterdam, The Netherlands

Amersfoort, 1 februari 2019

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

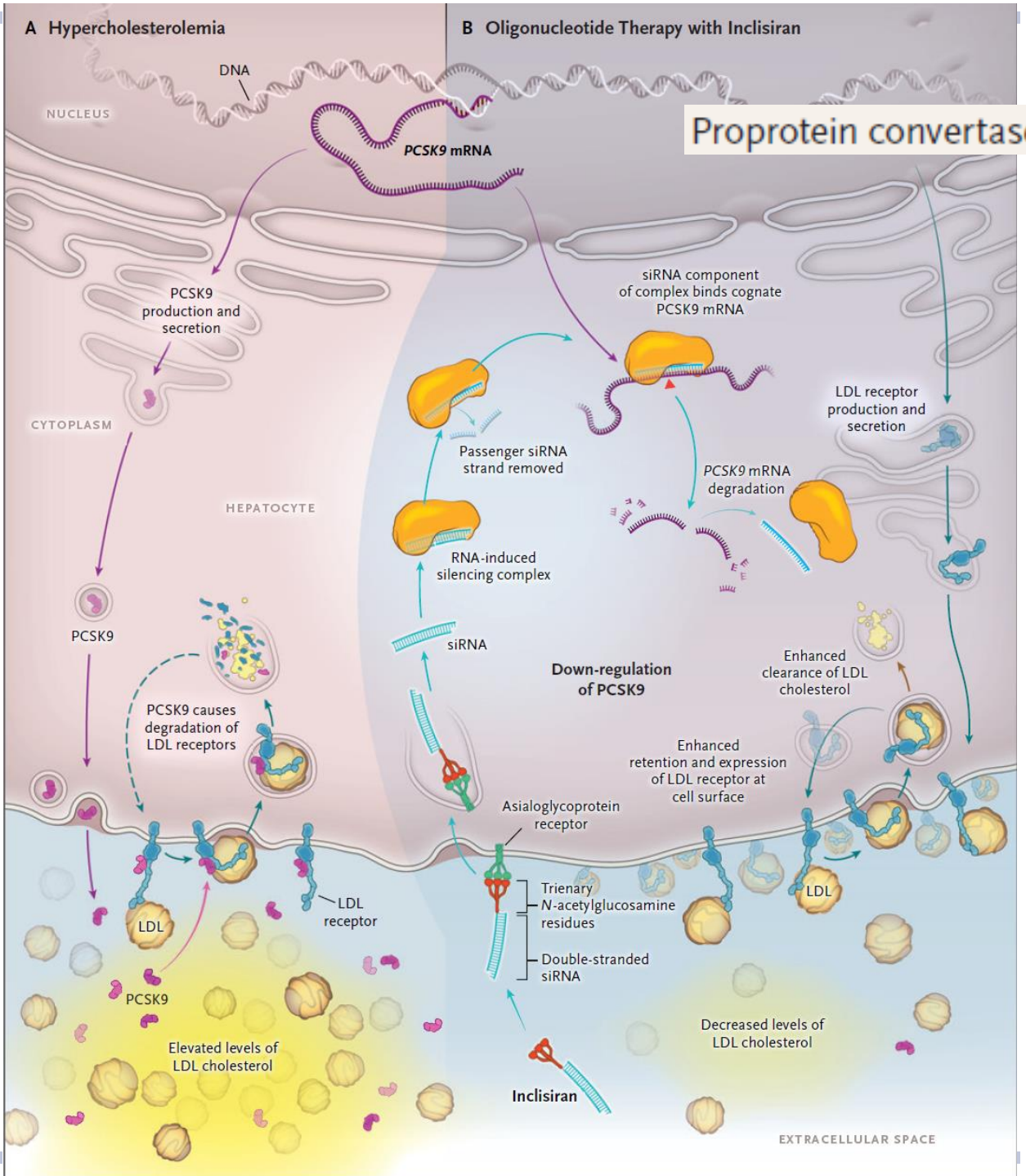
FRONTIERS IN MEDICINE

Treating Disease at the RNA Level with Oligonucleotides

Arthur A. Levin, Ph.D.

From Research and Development, Avidity Biosciences, La Jolla, CA. Address reprint requests to Dr. Levin at art.levin@aviditybio.com.

N Engl J Med 2019;380:57-70.
DOI: 10.1056/NEJMra1705346



Proprotein convertase subtilisin–kexin type 9 (PCSK9)

PCSK9 breekt de LDL receptor af → minder binding LDL → LDL concentratie stijgt

oplossing: zorg dat PCSK9 niet meer gemaakt wordt:

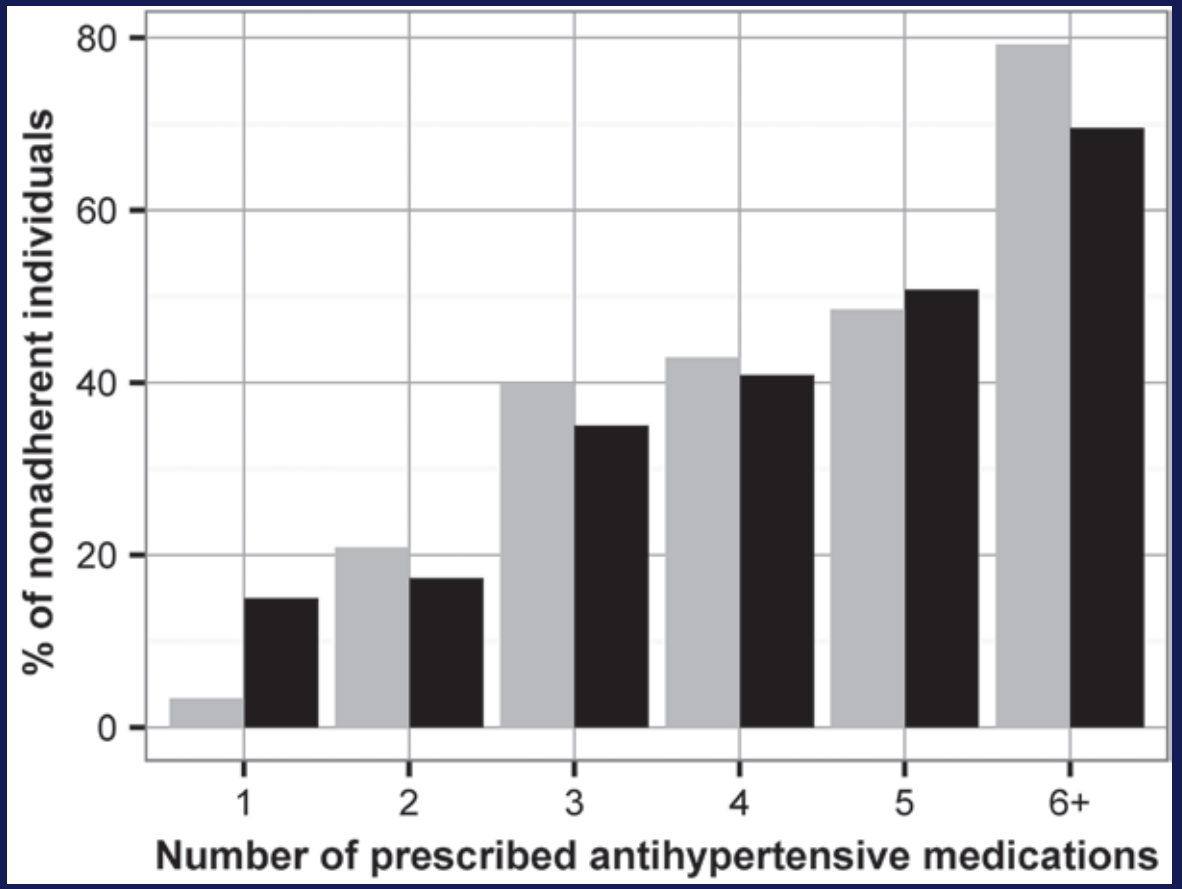
siRNA targeten naar de lever

1 injectie per half jaar!

Erasmus MC

Treatment ‘’resistance’’ in hypertension

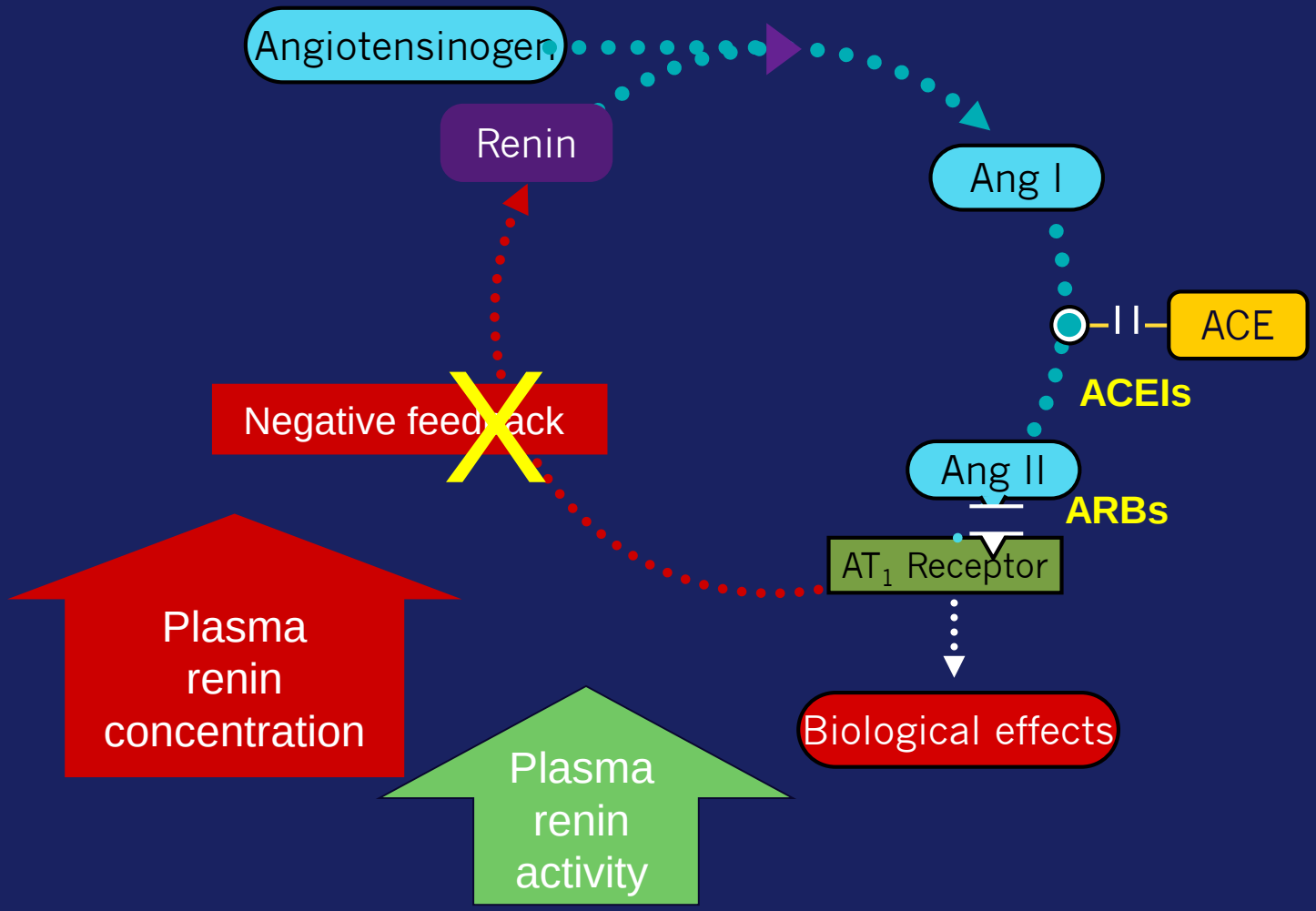
- non-initiation (24%)
- non-persistence (50% at 1 year)
- poor execution



grey: UK, black: Czech Republic

Gupta et al., *Hypertension* 2017

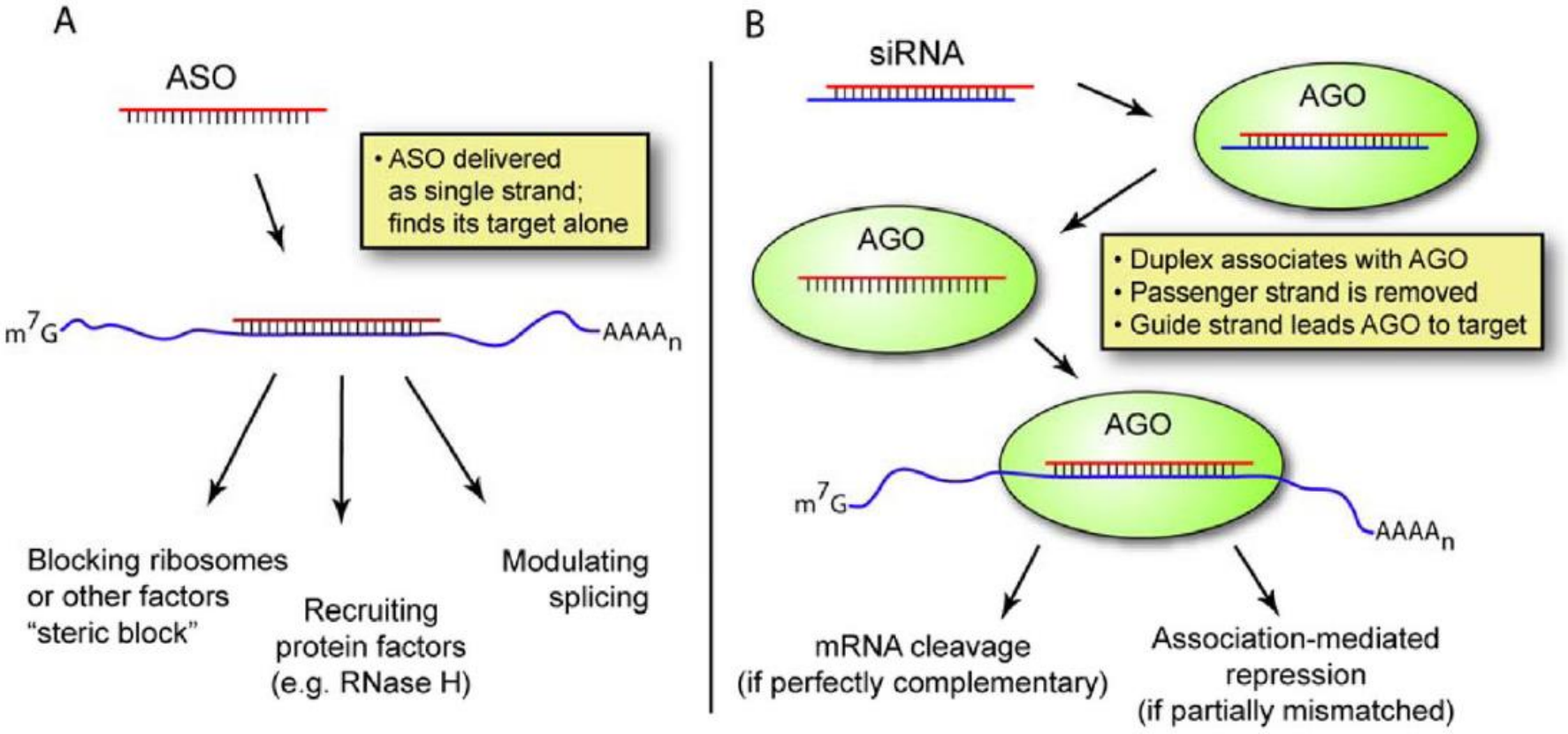
Renin-angiotensin system (RAS) blockers and the negative feedback loop



Do we need more than one RAS blocker?

- the more RAS blockade, the better: > blood pressure lowering, less proteinuria, less post-MI remodelling, etc.?
- ONTARGET, SUPPORT, and NEPHRON-D suggested otherwise: no further reduction in MI, stroke, and hospitalization!
- yet, more side effects: hypotension and renal dysfunction (dialysis, doubling serum creatinine, hyperkalemia), although proteinuria diminished and the albumin excretion rate increased less in the combination treatment group

Angiotensinogen: antisense oligonucleotide (ASO) vs. siRNA

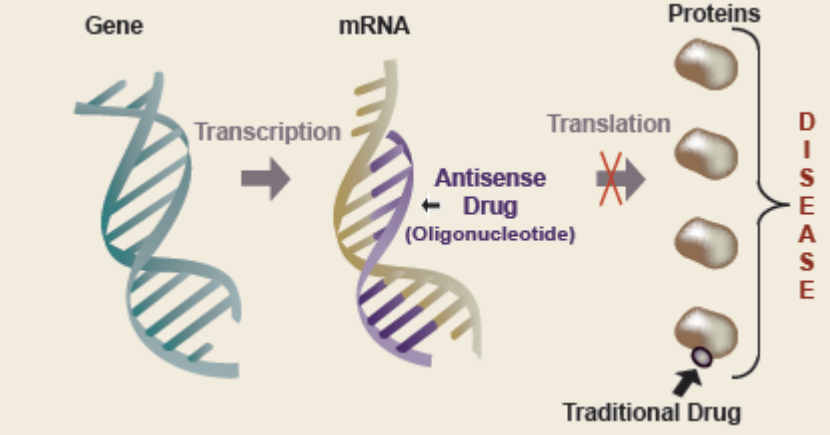


Watts & Corey, *J Pathol* 2012

AGO, Argonaute

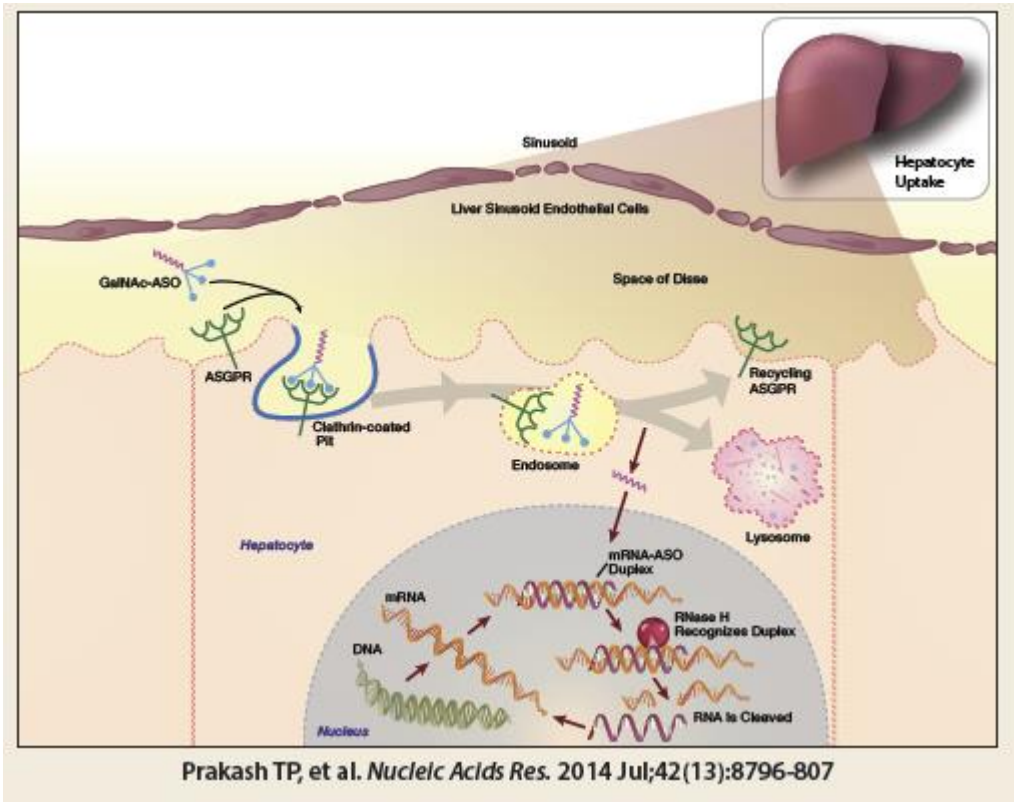
Erasmus MC

Antisense Oligonucleotide/siRNA



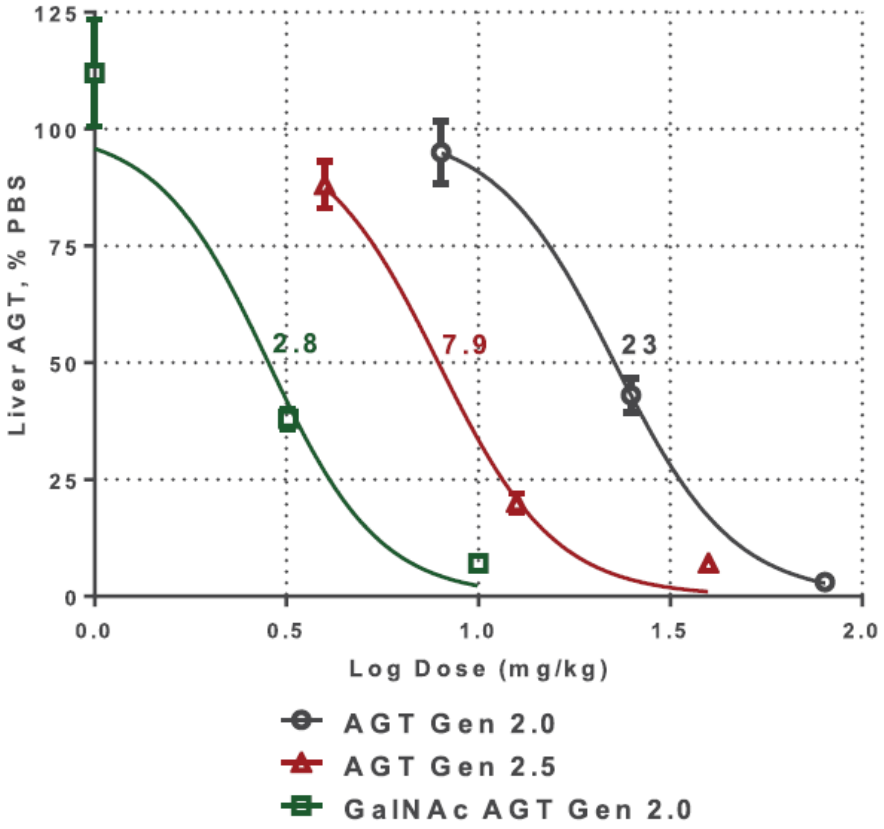
angiotensinogen is exclusively (?) generated in the liver: how to target to this organ?

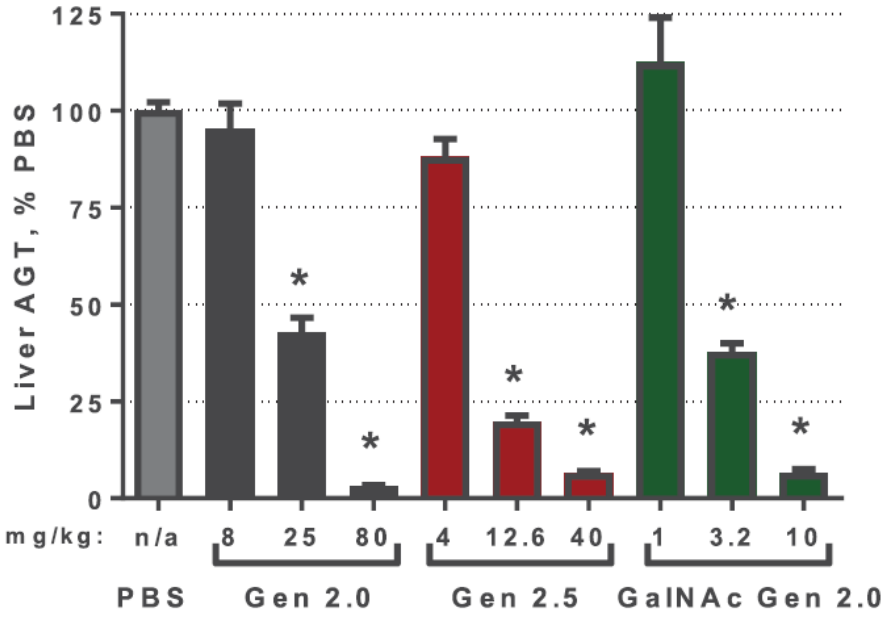
- asialoglycoprotein receptor is a C-type lectin which is abundantly expressed by hepatocytes (> 0.5 million receptors/cell)
- high specificity for N-acetyl-galactosamine (GalNAc)-terminated oligosaccharides
- one receptor can internalize 250 GalNac-conjugated molecules during its lifetime: ideal way to transport oligonucleotide into hepatocytes!



Prakash TP, et al. *Nucleic Acids Res.* 2014 Jul;42(13):8796-807

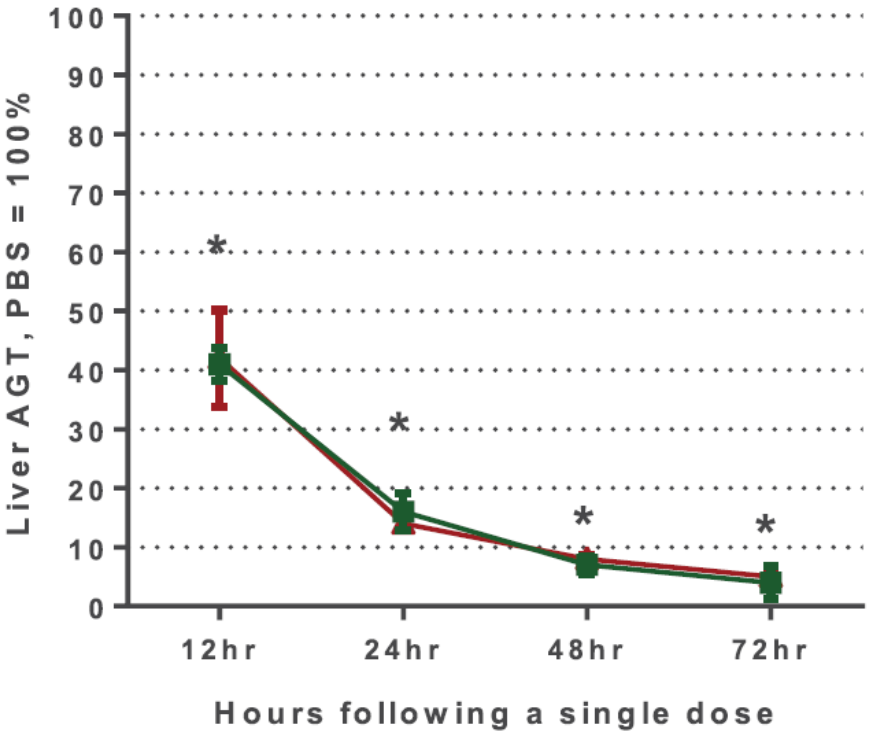
AGT ASO: effect of liver-targeting

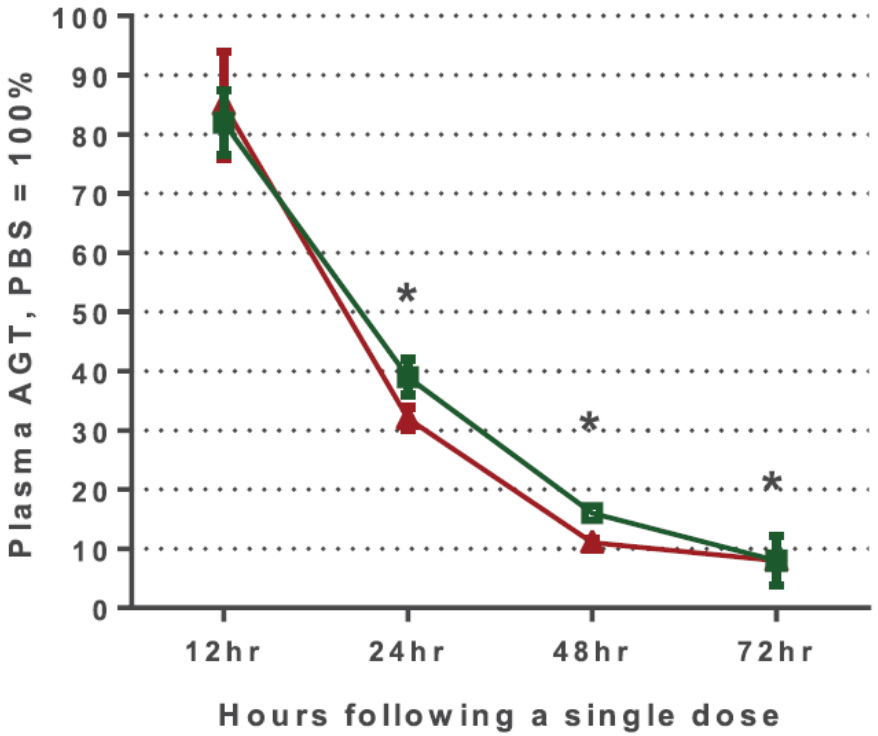




Mullick et al., *Hypertension* 2017

AGT ASO: rapid suppression of liver AGT synthesis





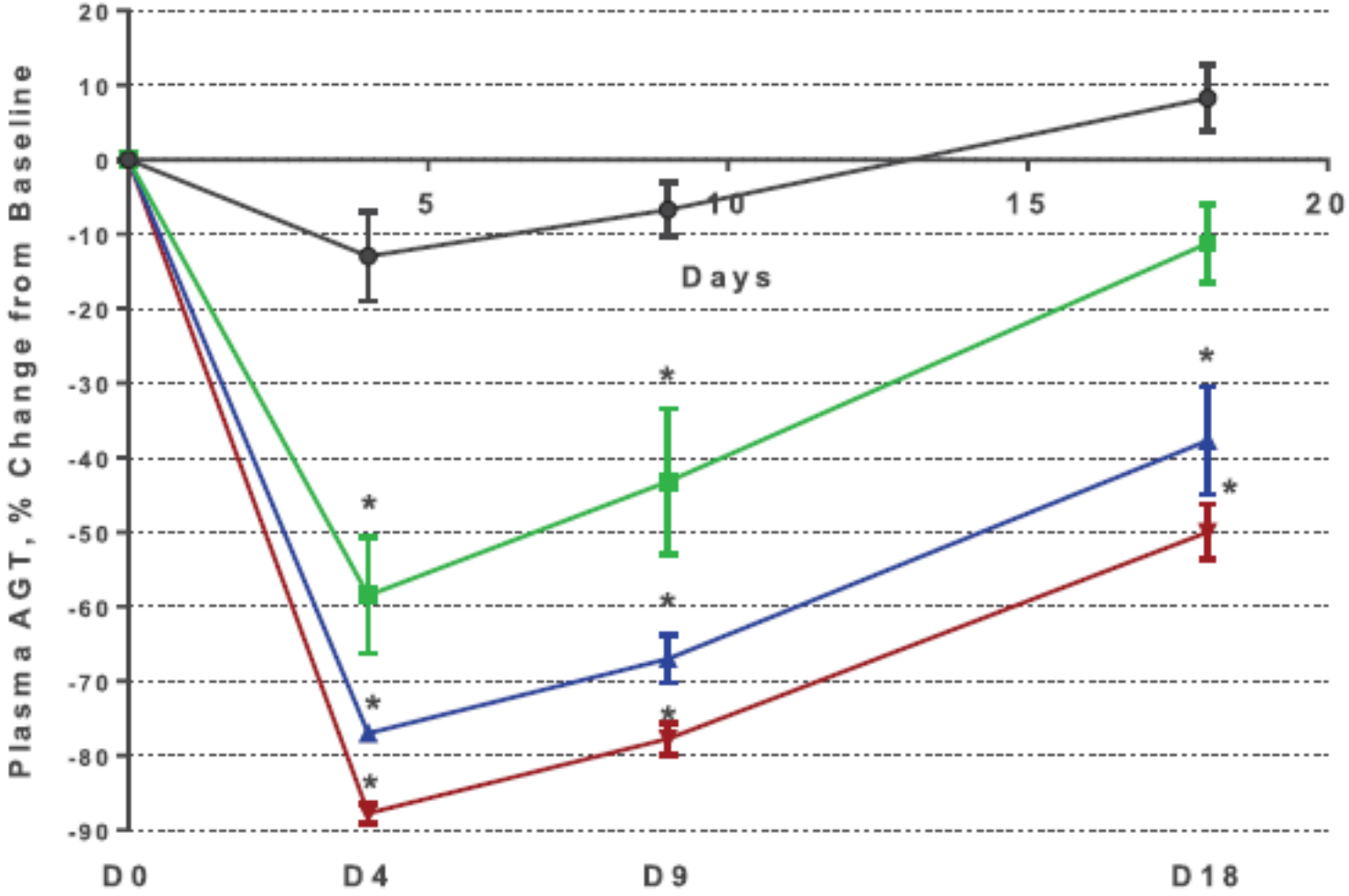
AGT Gen 2.5
GalNAc AGT Gen 2.0

Mullick et al., *Hypertension* 2017

Erasmus MC
University Medical Center Rotterdam

Prolonged AGT suppression with GalNac ASO

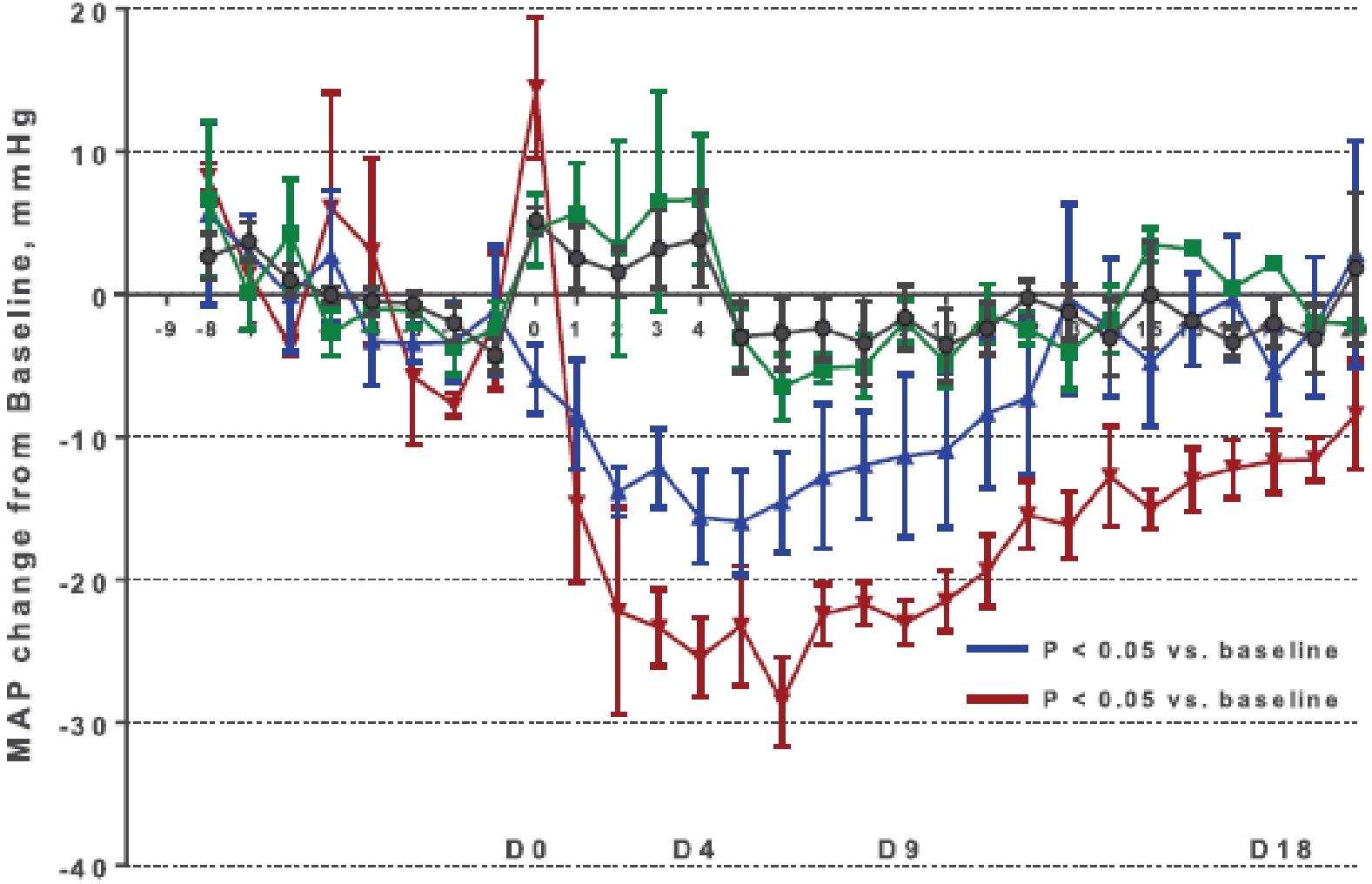
2.5, 5, 10 or 20 mg/kg



Mullick et al., *Hypertension* 2017

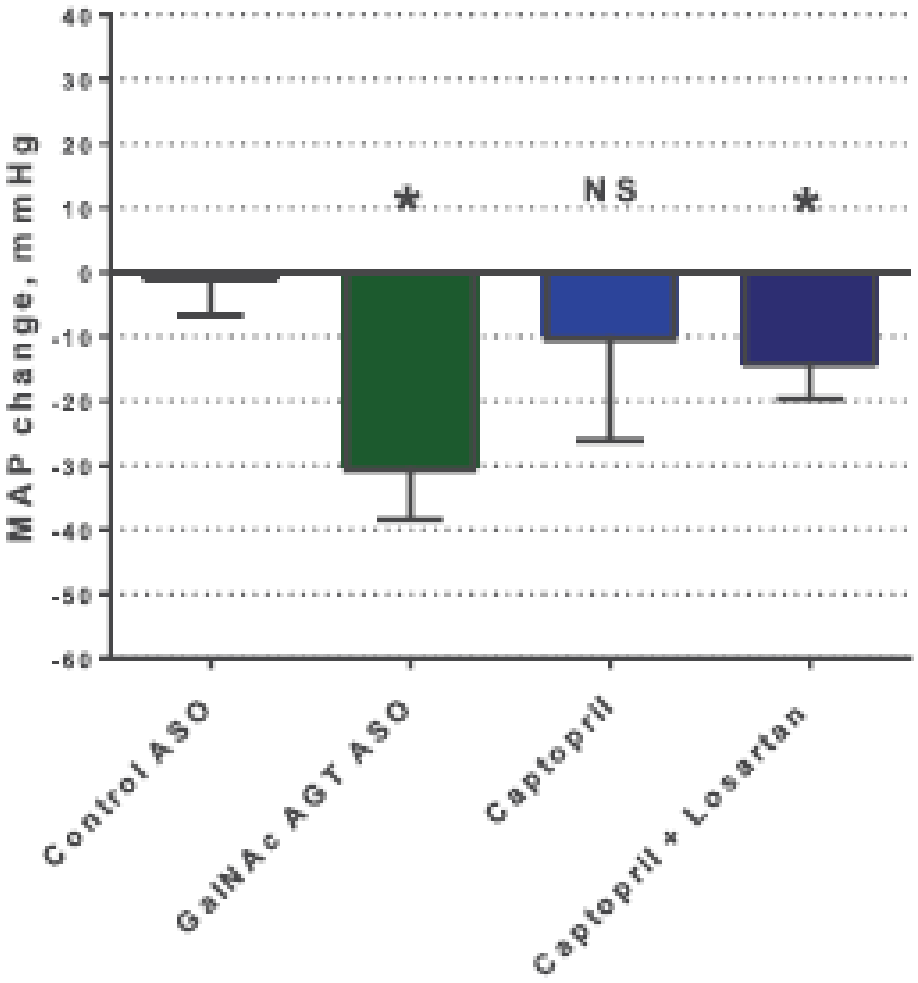
Erasmus MC
University Medical Center Rotterdam

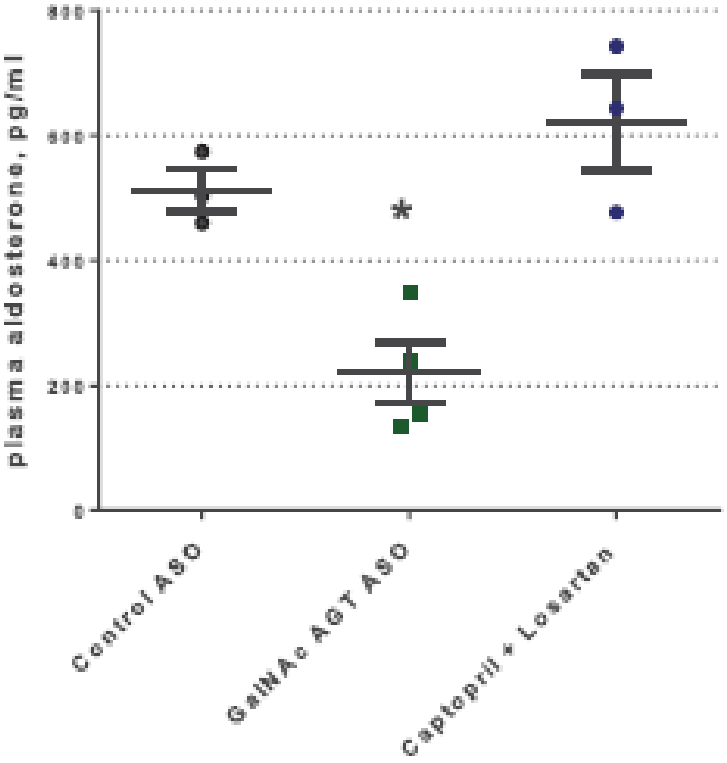
Dose-dependent BP-lowering effect of GalNac ASO in SHR (2.5, 5, 10,& 20 mg/kg)



Mullick et al., *Hypertension* 2017

GalNac AGT ASO acts in RAS blocker-resistant SHR fed 8% salt

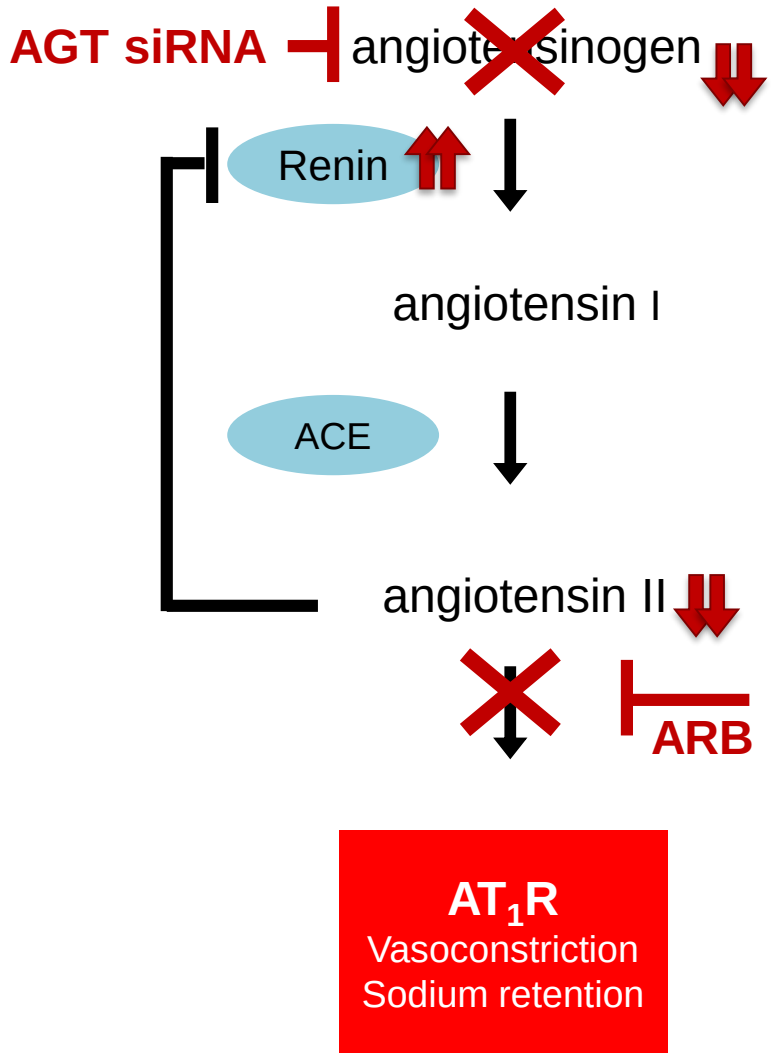




Mullick et al., *Hypertension* 2017

Erasmus MC
University Medical Center Rotterdam

Summary and conclusions



- AGT siRNA gives a similar BP reduction as valsartan and captopril,

  → **non-inferior to ARB or ACEi**

- but with a lower dosing frequency

  → **novel treatment opportunity for apparent treatment resistant HT**

- Combination therapy has a synergistic effect on BP, cardiac damage and kidney function

  → **models of heart failure and kidney damage**

Erasmus MC
University Medical Center Rotterdam