Introduction

PCSK9: The promise of a new target in lipid management

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Cholesterol and Atherosclerosis

Nikolay Anichkov 1885-1964

Carrots and Salad

Lots of Egg Yolk
Residual CV Risk with Statin Therapy

![Bar chart showing the comparison of patients who suffered major CV events under control and statin therapy across various studies.](chart.png)

- **4S**: 28% (Control), 19% (Statin)
- **CARE**: 13.2% (Control), 10.2% (Statin)
- **LIPID**: 15.9% (Control), 12.3% (Statin)
- **HPS**: 11.8% (Control), 8.7% (Statin)
- **PROSPER**: 16.2% (Control), 14.1% (Statin)
- **ASCOT-LLA**: 3% (Control), 1.9% (Statin)
- **ALLHAT**: 8.1% (Control), 7.4% (Statin)
- **ASPEN**: 15% (Control), 13.7% (Statin)
- **WOSCOPS**: 7.9% (Control), 5.5% (Statin)
- **AFCAPS/TexCAPS**: 5.5% (Control), 3.5% (Statin)
- **CARDS**: 9% (Control), 5.8% (Statin)
- **TNT**: 10.9% (Control), 8.7% (Statin)

**Study Details**:
- **n = 4444** (4S)
- **n = 4159** (CARE)
- **n = 9014** (LIPID)
- **n = 20,536** (HPS)
- **n = 5804** (PROSPER)
- **n = 10,305** (ASCOT-LLA)
- **n = 10,355** (ALLHAT)
- **n = 2410** (ASPEN)
- **n = 6595** (WOSCOPS)
- **n = 6605** (AFCAPS/TexCAPS)
- **n = 2838** (CARDS)
- **n = 10,001** (TNT)
FH Patients at LDL Goal

Pijlman Atherosclerosis 2010; 209: 189-195
Mutations in *PCSK9* cause autosomal dominant hypercholesterolemia

Marianne Abifadel¹,², Mathilde Varret¹, Jean-Pierre Rabès¹,³, Delphine Allard¹, Khadija Ouguerram⁴, Martine Devillers¹, Corinne Cruaud⁵, Suzanne Benjannet⁶, Louise Wickham⁶, Danièle Erlich¹, Aurélie Derré¹, Ludovic Villéger¹, Michel Farnier⁷, Isabel Beucler⁸, Eric Bruckert⁹, Jean Chambaz¹⁰, Bernard Chanu¹¹, Jean-Michel Lecerf¹², Gerald Luc¹², Philippe Moulin¹³, Jean Weissenbach⁵, Annick Prat⁶, Michel Krempf⁴, Claudine Junien¹,³, Nabil G Seidah⁶ & Catherine Boileau¹,³
The Role of PCSK9 in the Regulation of LDL Receptor Expression
LDL Cholesterol and Coronary Heart Disease among Black Subjects by PCSK9$^{142X}$ or PCSK9$^{679X}$ Allele

Cohen NEJM 2006; 354:1264-72

No Nonsense Mutation (n=3278) No Nonsense Mutation (n=3278)

PCSK9$^{142X}$ or PCSK9$^{679X}$

PCSK9$^{142X}$ or PCSK9$^{679X}$ (N=85)

Frequency (%)

Coronary Heart Disease (%)

P=0.008

88%
Homozygous or Compound Heterozygous PCSK9 Mutations

• Very rare “loss of function” mutations
• Extremely low LDL-C (15mg/dL)
• Healthy and normal life span

Evolocumab in Hyperlipidemia as Add-On Therapy (DESCARTES Study)

Blom NEJM 2014; 370: 1809-1819
PCSK9 Inhibition: Current Status

- Reciprocal regulator of LDL levels with LDL receptors
- Can be blocked by therapy
- Huge potential for modification of LDL, atherogenesis and clinical complications
- Clinical trial programme for dose response, interval, safety, tolerability and four large outcome trials
- Novel approach to lower further LDL