Erasmus MC
University Medical Center Rotterdam

Overgebleven risico op hart-en vaatziekten in patiënten met Familiaire Hypercholesterolemia, wat nu?

Annette Galema-Boers, MANP

24-11-2017

Clinic for dyslipidemias and
inherited cardiovascular diseases

Disclosure belangen spreker	Annette Galema-Boers
Potentiele belangenverstrengeling:	Nee
Voor bijeenkomst mogelijk relevante relaties [1]	Nee
• Sponsoring of onderzoeksgeld[2]	Ja: Amgen en Sanofi
• Honorarium of andere (financiële) vergoeding[3]	Nee
• Aandeelhouder[4]	Nee
• Andere relatie, namelijk …[5]	NVT

Familiaire Hypercholesterolemie (FH)

- Hoog risico op premature Hart-en Vaat Ziekten (HVZ)
- Lipiden verlagende therapie en leefstijl-interventie effectief in HVZ preventie bij FH patiënten
- Patienten ontwikkelen nog steeds HVZ tijdens lipidenverlagende therapie (LVT)

Methode

Cohort studie (1988-2016) van alle opeenvolgende volwassen FH patiënten behandeld met LVT op onze lipidenpolikliniek in het Erasmus MC.

Data collectie:

- Demographische factoren
- Cardiovasculaire events
- LVT en lipiden parameters
- Cardiovasculaire risicofactoren

Table 1 General characteristics of FH patients according to CV event on LLT

Table 1
General characteristics of FH patients according to CV event at maximum tolerated LLT

	Total n=812	CV event on LLT n=98 (12%)	No CV event on LLT n=714 (88%)	P
Age* (years) mean ± SD	46.4±15.2	51.1±11.0	45.8±15.6	**0.001**
Women, n(%)	434 (53)	47 (48)	387 (54)	0.25
Caucasian Ethnicity, n(%)	757 (93)	89 (91)	668 (94)	0.31
Cardiovascular risk factors, n(%)				
Ever smoker	347 (43)	63 (64)	284 (40)	**<0.001**
Current smokers*	126 (16)	31 (32)	95 (13)	**<0.001**
BMI mean ± SD	26.5±4.6	27.7±4.0	26.3±4.6	**0.004**
Hypertension	228 (28)	68 (69)	160 (22)	**<0.001**
DM type 1 and 2	34 (4)	12 (12)	22 (3)	**<0.001**
Family history premature CVD	341 (42)	57 (58)	284 (40)	**0.001**
History of CVD before LLT	90 (11)	30 (31)	60 (8)	**<0.001**
FH genetic mutation, n(%)				
LDL receptor mutations	547 (67)	66 (67)	481 (67)	0.99
Apo B mutation	62 (8)	8 (8)	54 (8)	0.83
FH clinical criteria	203 (25)	24 (25)	179 (25)	0.90

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Table 1 General characteristics of FH patients according to CV event on maximum tolerated LLT

	Total n=812	CV event on LLT n=98 (12%)	No CV event on LLT n=714 (88%)	P
Lipid lowering therapy* n(%)				
Maximum LLT	492 (61)	64 (65)	428 (60)	0.31
Maximum tolerated LLT	239 (29)	26 (27)	213 (30)	0.50
Treated Lipid values*, mean ± SD				
Total cholesterol (mmol/l)	5.4±1.6	6.0±1.5	5.3±1.6	**<0.001**
LDL cholesterol (mmol/l)	3.6±1.5	4.2±1.4	3.5±1.5	**<0.001**
HDL cholesterol (mmol/l)	1.4±0.4	1.3±0.4	1.4±0.4	**<0.001**
Triglyceride (mmol/l)	1.3±0.8	1.6±1.0	1.3±0.7	**<0.001**
LDL-c < 2.5 mmol/l, n(%)	151 (19)	8 (9)	142 (20)	**0.008**

LDL=low density lipoprotein; HDL= high density lipoprotein; CVD= cardiovascular disease;
BMI= body mass index; DM= diabetes mellitus; LLT= lipid lowering therapy *At 31-03-2016 or first event

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HDL cholesterol (mmol/l)	1.4±0.4	1.3±0.4	1.4±0.4	**<0.001**
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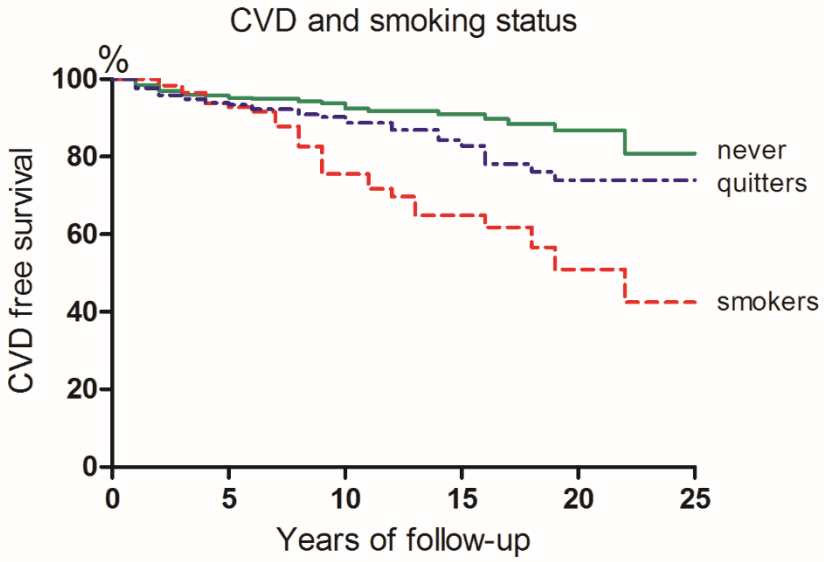
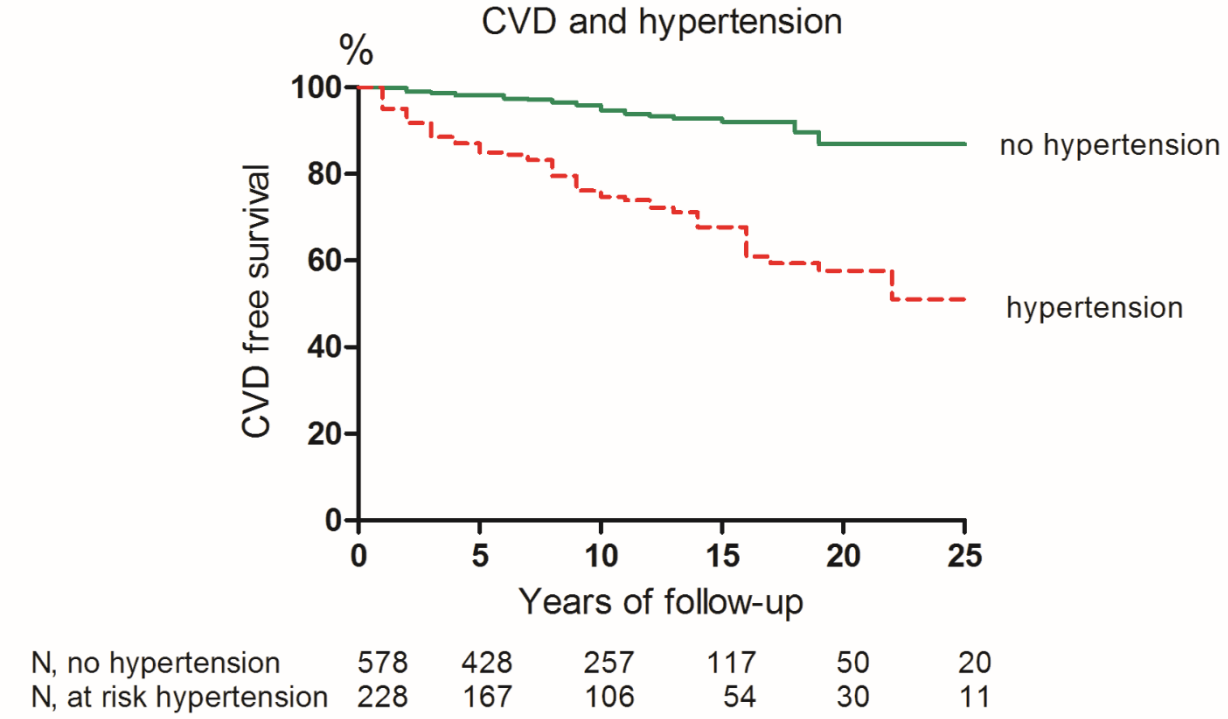
CVD free survival of FH patients and smoking status



N, never Smokers	465	330	198	90	40	13
N, at risk Quitters	220	174	120	58	32	13
N, at risk Smokers	126	90	44	22	8	1

CVD free survival of FH patients and hypertension.



Associations between determinants and cardiovascular events

	Adjusted* **(OR, 95%CI)**	**P**
Age (years)	1.07 (1.04-1.10)	**<0.001**
Gender	1.07 (0.61-1.86)	0.81
Cardiovascular risk factors		
Never smokers	1	
Current smokers	3.86 (1.93-7.70)	**<0.001**
Quit smokers> 1 year	1.20 (0.65-2.19)	0.56
DM type 1 and 2	2.27 (0.94-5.51)	0.07
BMI	1.00 (0.95-1.06)	0.95
History of hypertension	2.91 (1.64-5.17)	**<0.001**
Family history premature CVD	1.80 (1.06-3.04)	**0.029**
History of CVD before LLT	2.22 (1.17-4.19)	**0.014**
Treated lipid values		
Triglyceride >2.0 mmol/l	0.77 (0.38-1.55)	0.47
HDL-cholesterol <1.0 mmol/l	4.35 (2.19-8.65)	**<0.001**
LDL-cholesterol > 2.5 mmol/l	3.61 (1.53-8.49)	**0.003**

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LDL-cholesterol > 2.5 mmol/l	3.61 (1.53-8.49)	**0.003**

Table 2 Characteristics of FH patients according to a second cardiovascular event

	Second event on LLT n=30	No second event on LLT n=68	P
Age* (years) mean ± SD	55.7±10.2	57.5±11.2	
Women, n(%)	13 (43)	34 (50)	
Caucasian Ethnicity, n(%)	25 (83)	64 (94)	
Cardiovascular risk factors, n(%)			
Current smokers*	10 (33)	7 (10)	**0.006**
BMI, mean ± SD	27.3±4.3	27.9±3.8	
History of hypertension	25 (83)	43 (63)	**0.047**
DM	3 (10)	9 (13)	
Family history premature CVD	18 (60)	39 (57)	
History of CVD before LLT	11 (37)	19 (28)	
FH Pathogenic mutation, n(%)			
LDL receptor mutation,	20 (67)	46 (68)	
Apo B mutation	3 (10)	5 (7)	
Clinical grounds	7 (23)	17 (25)	

Table 2 Characteristics of FH patients according to a second cardiovascular event

	Second event on LLT n=30	No second event on LLT n=68	P
Lipid lowering therapy* n(%)			
No statin; intolerant	1 (3)	4 (6)	
Maximum therapy, n(%)	19 (63)	46 (68)	
Maximum tolerated therapy, n(%)	8 (27)	17 (25)	
Treated lipid values*, mean ± SD			
LDL cholesterol (mmol/l) mean ± SD	3.8±1.6	3.6±1.6	
LDL-c < 1.8 mmol/l, n(%)	1 (3)	6 (9)	
LDL-c < 2.5 mmol/l, n(%)	6 (21)	15 (23)	

LDL= low density lipoprotein; CVD= cardiovascular disease; BMI= body mass index; DM= diabetes mellitus
LLT= lipid lowering therapy *At 31-03-2016 or second event

Conclusie

- Patiënten met FH en LVT ontwikkelen nog steeds HVZ;12%

  61% max therapie en 29% max tolereerbare therapie

- 1/3 (31%) ontwikkelde een tweede event.

- Beinvloedbare risicofactoren; roken en hypertensie

  Lipiden parameters; hoog LDL-c, laag HDL-c

  Leeftijd, HVZ in voorgeschiedenis bij pat zelf of familie

Conclusie

- 1. **Leefstijl-interventie** blijft noodzakelijk
- 2. Optimaliseren lipiden verlagende therapie
- 3. Patienten niet op streefwaarden LDL-c, kandidaat voor PCSK9 inhibitors.

*PCSK9-remmers zijn geïndiceerd voor de behandeling van hypercholesterolemie. **Belangrijk:** PCSK9-remmers is niet geïndiceerd voor de preventie van cardiovasculaire events bij patiënten met een (zeer) hoog CV risico.

Indicatie voor PCSK9 remmer Erasmus MC

- Patiënten met Familiaire Hypercholesterolemie **en** max therapie **en** voldoende hoog risico op HVZ
  - Primaire preventie LDL-c > 4.0 mmol/l
  - Secundaire preventie LDL-c >3.0 mmol/l
- Patiënten met hypercholesterolemie en meerdere events.

- Patiënten met Diabetes Mellitus en event.

- Patiënten met een CV event/FH en een statine intolerantie

  Ezetimibe verplicht

Ondergetekende, cardioloog of vasculair internist, heeft *PCSK9 remmer* voorgeschreven aan deze verzekerde:			kolom 1*	kolom 2*
1	met hypercholesterolemie die bij behandeling met maximaal verdraagbare statine en in combinatie met ezetimibe niet de behandeldoelstelling bereikt in overeenstemming met de richtlijnen die in Nederland door de desbetreffende beroepsgroepen zijn aanvaard.	□ JA, ga naar 2 □ NEE		XO
2	en met voldoende hoog risico:	□ JA, ga naar 2a □ NEE		XO
2a	heterozygote familiaire hypercholesterolemie patiënt	□JA ga naar 3 □NEE, ga naar 2b		
2b	patiënt met een doorgemaakt cardiovasculair event én een recidief cardiovasculair event	□ JA ga naar 3 □ NEE, ga naar 2c		
2c	patiënt met diabetes mellitus type 2 én een doorgemaakt cardiovasculair event	□ JA, ga naar 3 □ NEE, ga naar 2d		
2d	patiënt met een doorgemaakt cardiovasculair event én echte statineintolerantie die is vastgesteld en gedocumenteerd	□ JA, ga naar 3 □ NEE		XO
3	in combinatie met zowel statine als ezitimibe	□ JA □ NEE, ga naar 4	12	
4	in combinatie met enkel ezitimibe: er is sprake van gedocumenteerde statineintolerantie: statine-geassocieerde spierpijn voor tenminste drie verschillende statines vastgesteld volgens het stroomschema en de criteria beschreven door EAS/ESC consensus (European Heart Journal 2015; 36:1012-22)	□ JA □ NEE	12	XO

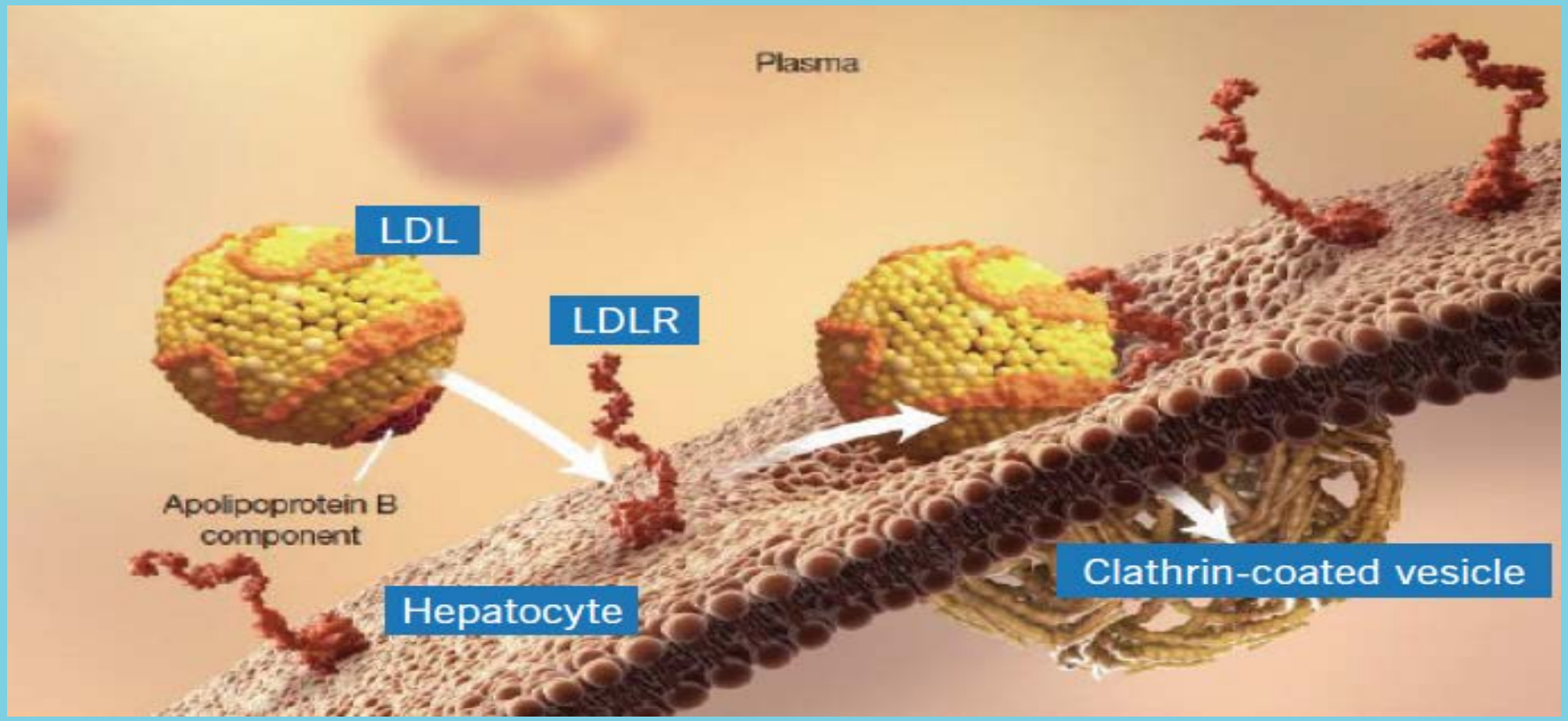
Twee PCSK9 remmers op de markt

Evolocumab

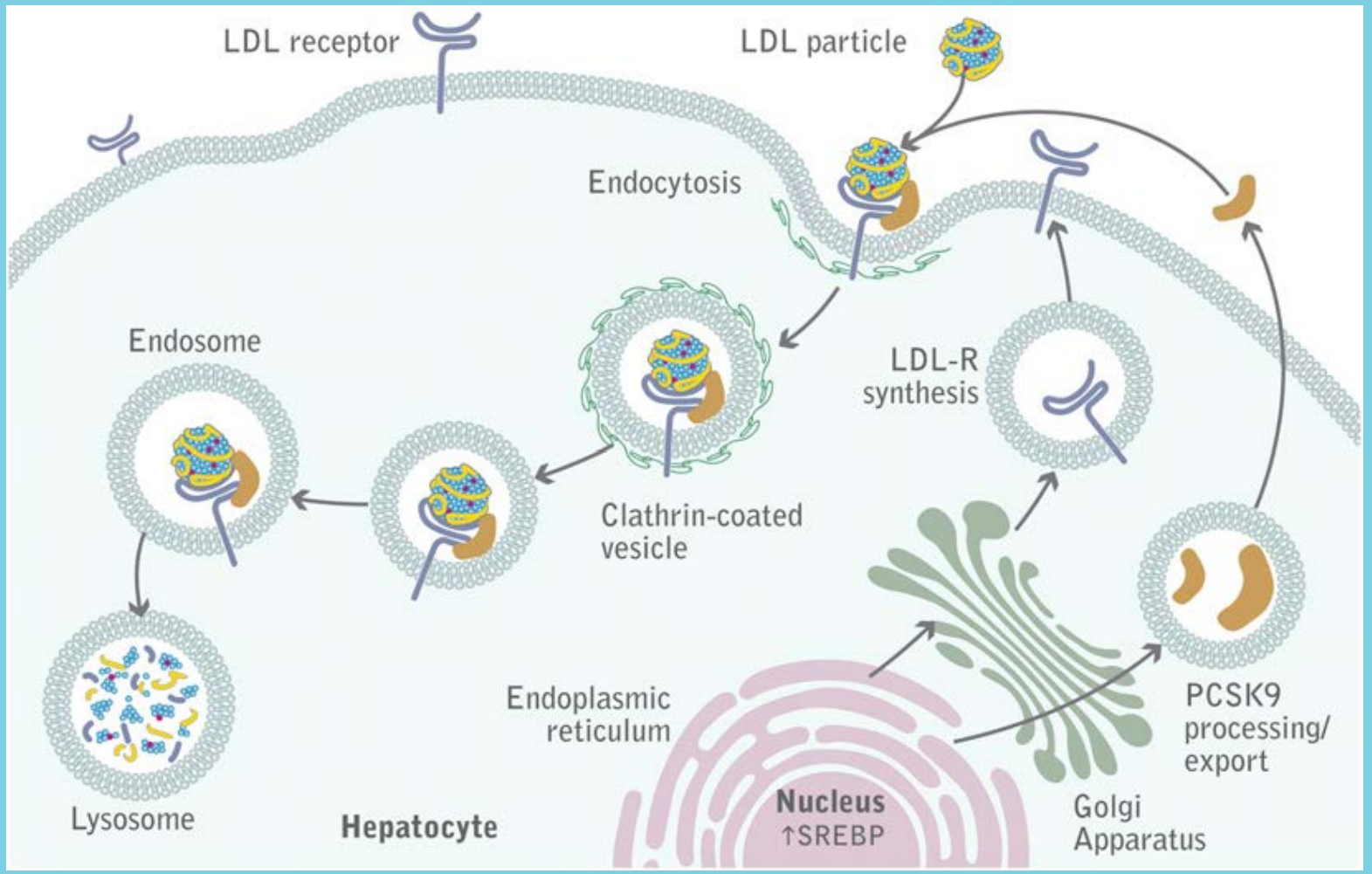
Alirocumab

De werking PCSK9 remmers

- LDL-c wordt gebonden aan de LDL receptoren op de levercel
- LDL-R aangemaakt door de lever en statines



Proprotein convertase subtilisin/kexin type 9



Lambert et al. JLR 2012 2515-2524

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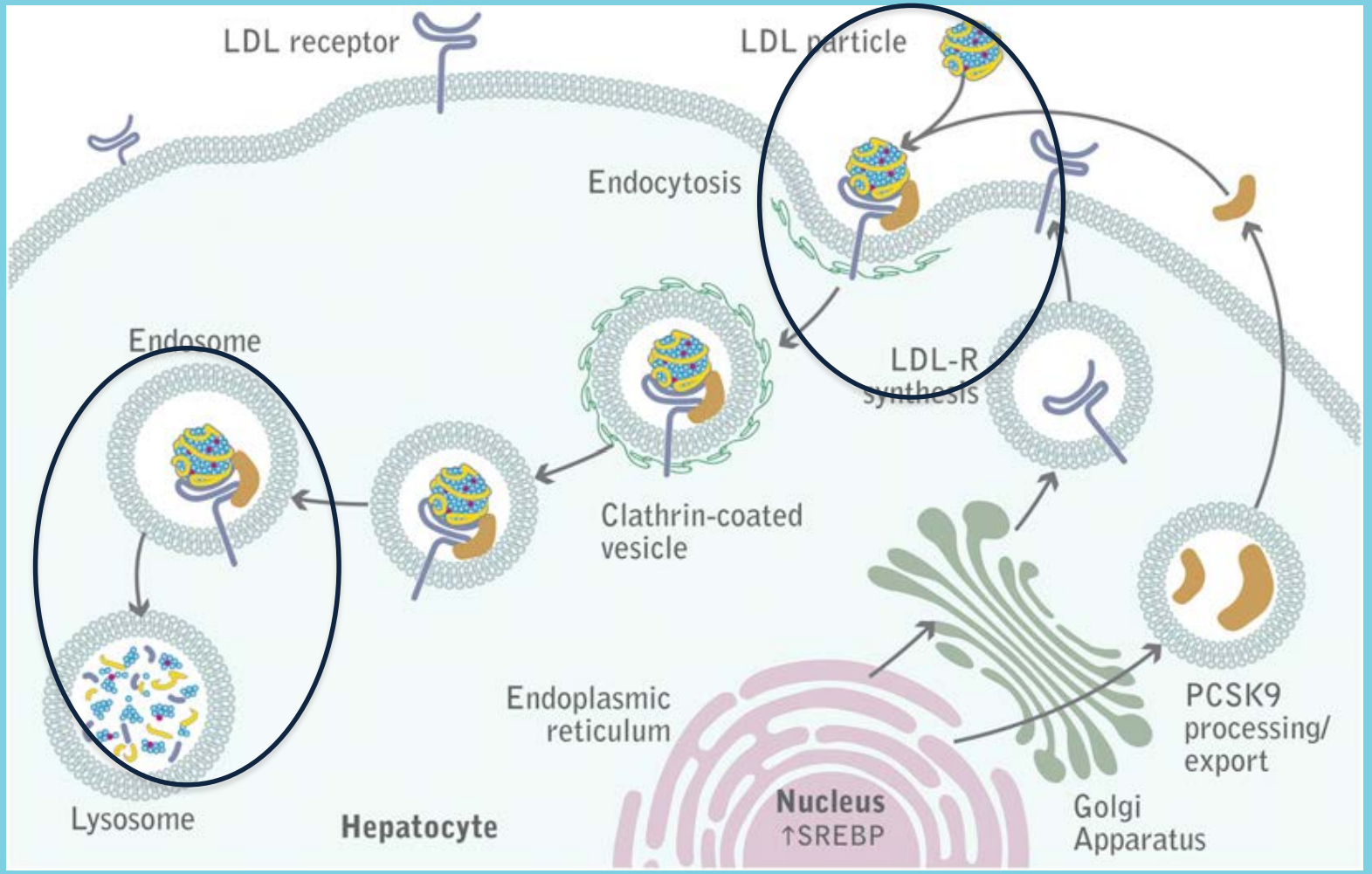
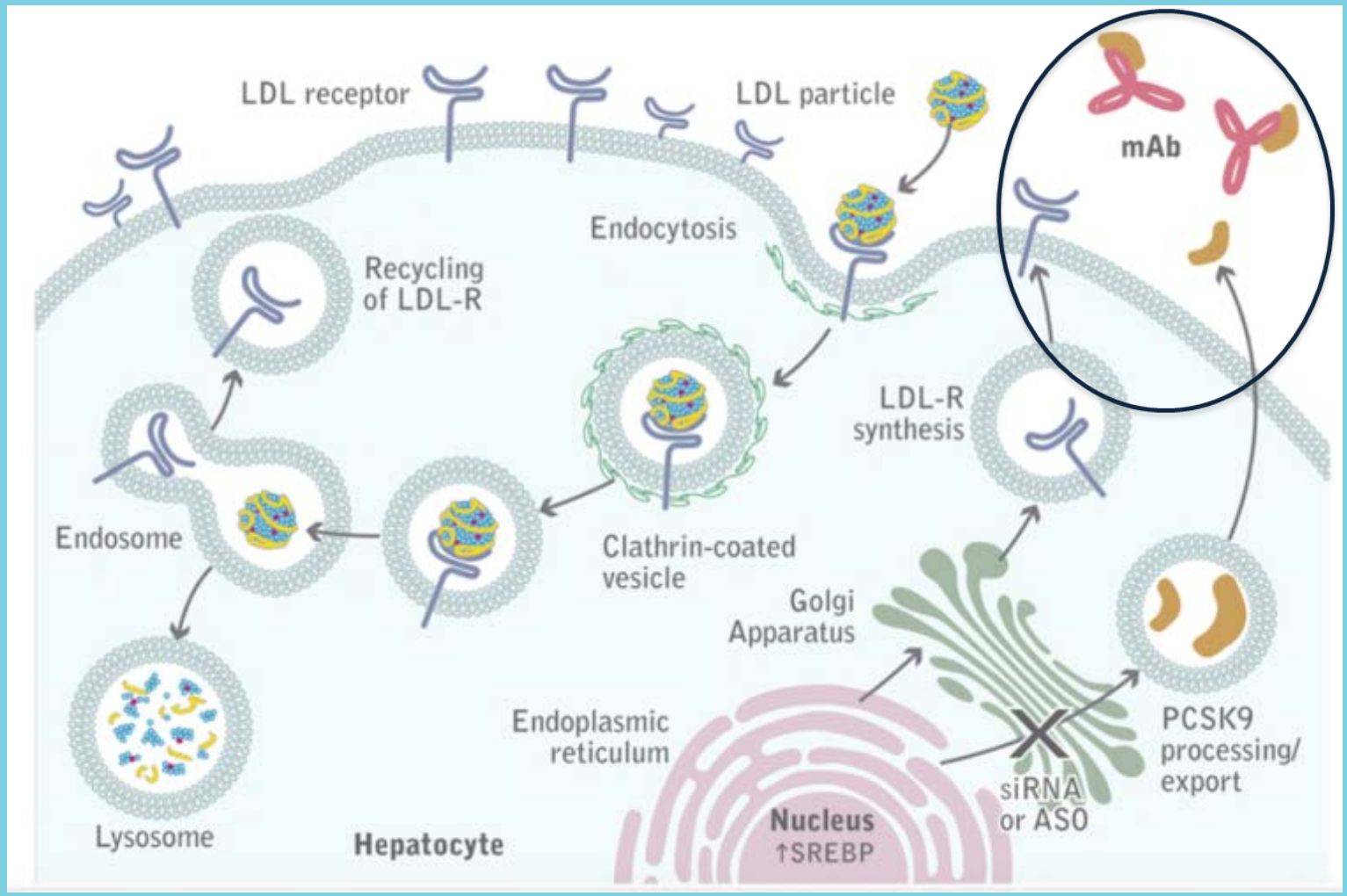


Lambert et al. JLR 2012 2515-2524

Monoclonale antistoffen

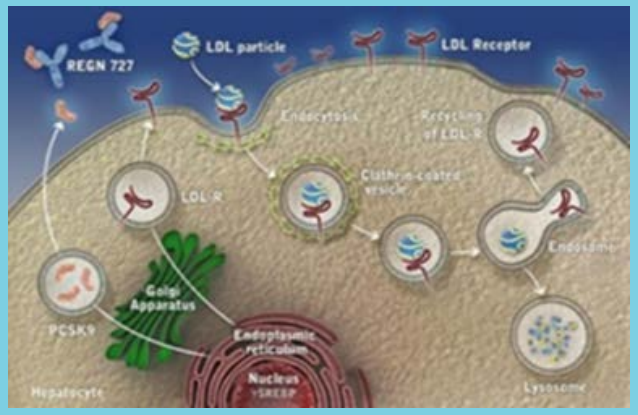


Lambert et al. JLR 2012 2515-2524

Eerste resultaten met PCSK9 remming in de praktijk

N=83 op PCSK9 remmers

General characteristics of FH patients before starting PCSK9 inhibition N=83	
Age (years) mean±SD	55.1±11.6
Women, n(%)	39 (47)
History of CVD, n(%)	50 (60)
Smokers current, n(%)	4 (5)
Diabetes Mellitus, n(%)	11 (13)
Hypertension, n(%)	33 (40)
Heterozygous FH, n(%)	65 (78)
Homozygous FH	4 (5)
Clinical FH	14 (17)



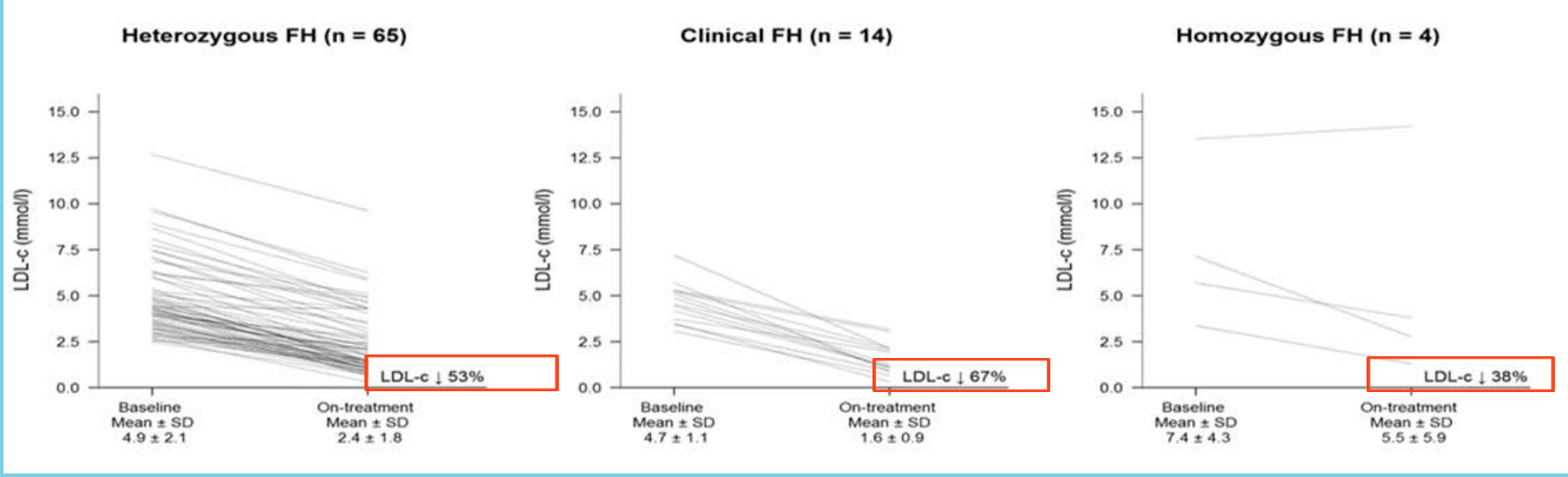
- Instructies aan patiënten door VS
- Groepsverband
- Partners welkom
- Retour poli na 6 weken voor bloedafname en bijwerkingen

Galema-Boers et al. Journal Clinical Lipidology. 2017 May - Jun;11(3):674-681

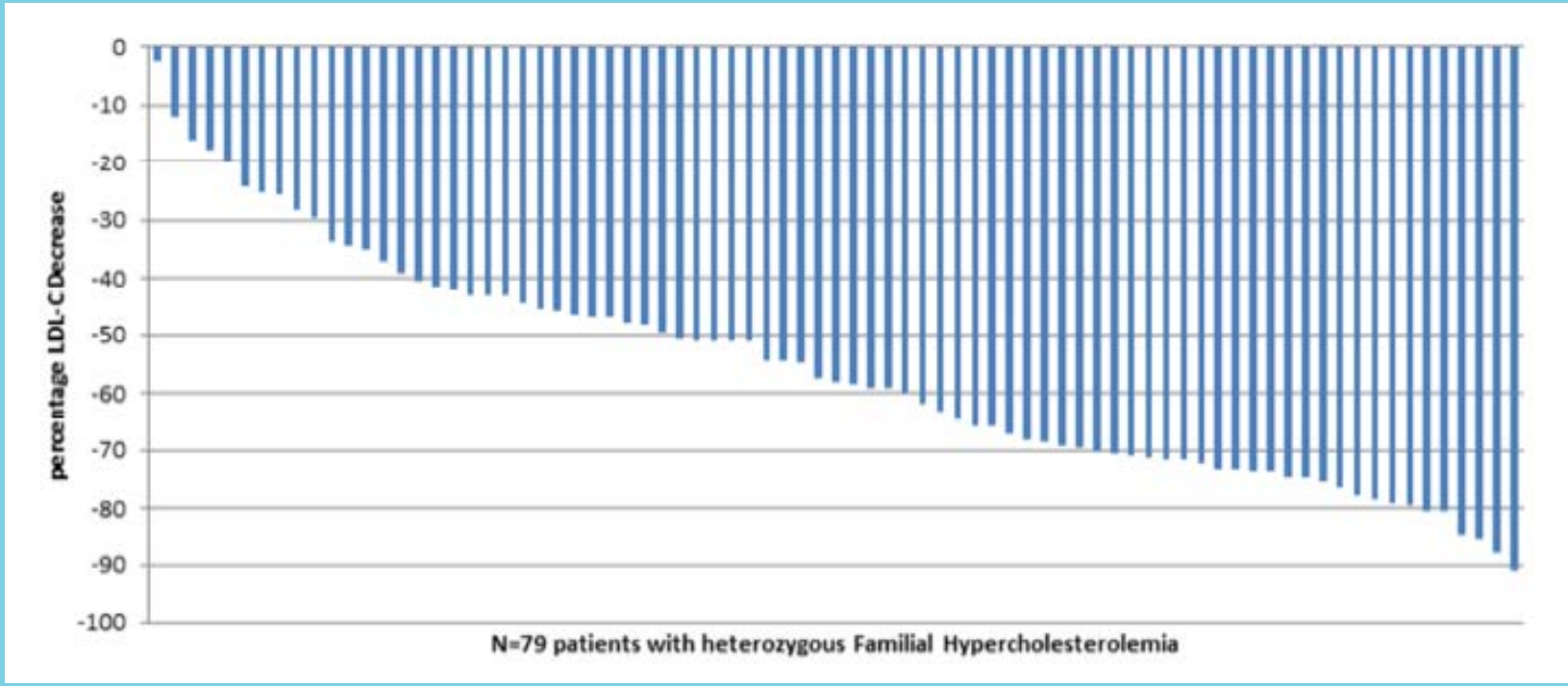
Resultaten na gemiddeld 42 dagen

- Gemiddelde daling LDL-c 55%±21%
- Vergelijkbaar met klinische trials
- Geen verschil in PCSK9 remmer
- Verschil in LDL-c daling per FH groep

N=79 patients with heterozygous FH



Variatie in LDL-c daling



Bijwerkingen

- Klinische trials niet meer bijwerkingen dan bij controlls

Deze studie 39% bijwerkingen

- Meer injectie spuit reacties;
  13% versus 6% trials
- Toedienen injectie; geen probleem
- 7 patiënten gestopt;
  5 vanwege bijwerkingen
  2 geen effect

Patient reported side effects of PCSK9 inhibitors	32 patients 39%
Any event, n(%)	52
Flu like symptoms	12 (14)
Neurological	8 (10)
Abdominal symptoms	6 (7)
Nasopharyngitis	4 (5)
Allergic skin reactions	4 (5)
Myalgia/jointpain	4 (5)
Headache	4 (5)
Eye irritation	3 (4)
Fatigue	3 (4)
Others	4 (5)

Met dank aan

Patiënten en het team van de CardioVasculair Genetica