

A golden balance scale is centered in the background of the slide. It has two pans hanging from a horizontal beam, and a central column with a decorative top. The scale is slightly tilted to the right.

Real world data PCSK9 remmers- Efficacy and side effects

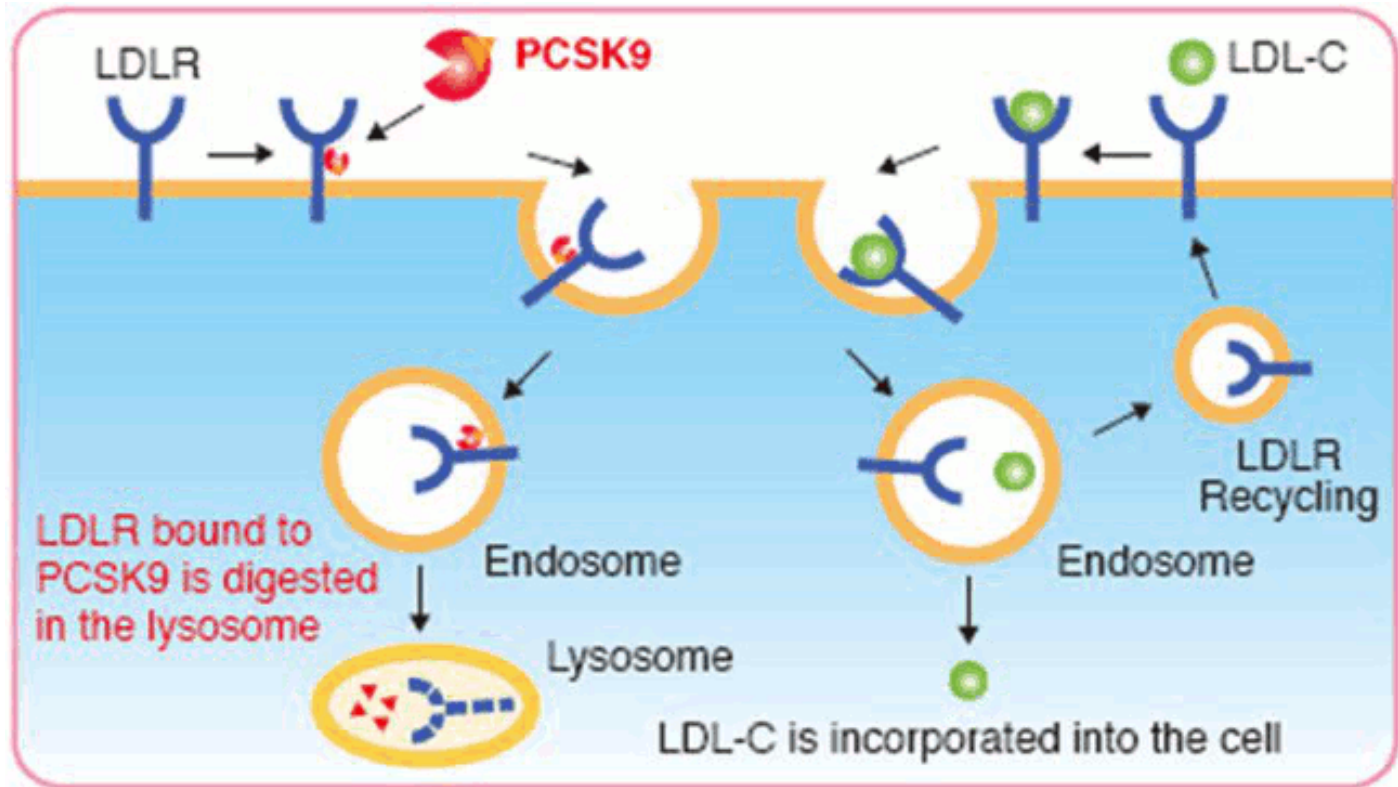
Jeanine Roeters van Lennep
Internist vasculaire geneeskunde
Erasmus MC, Rotterdam

Disclosure

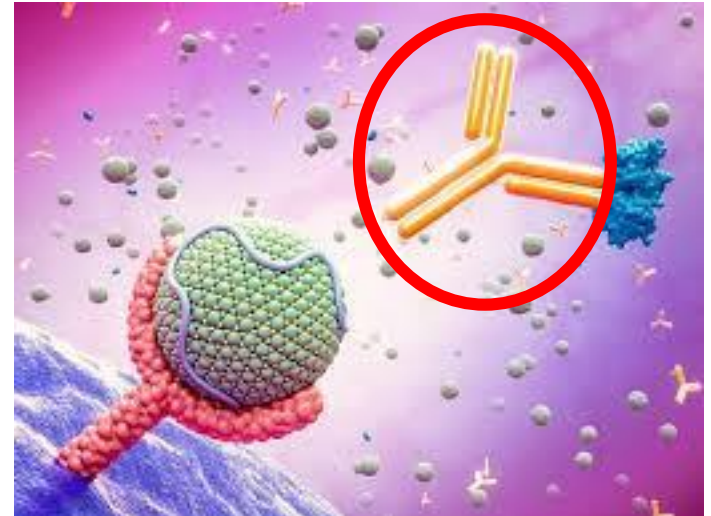
The institution receive honorary fees from

- Akcea
- Amryt

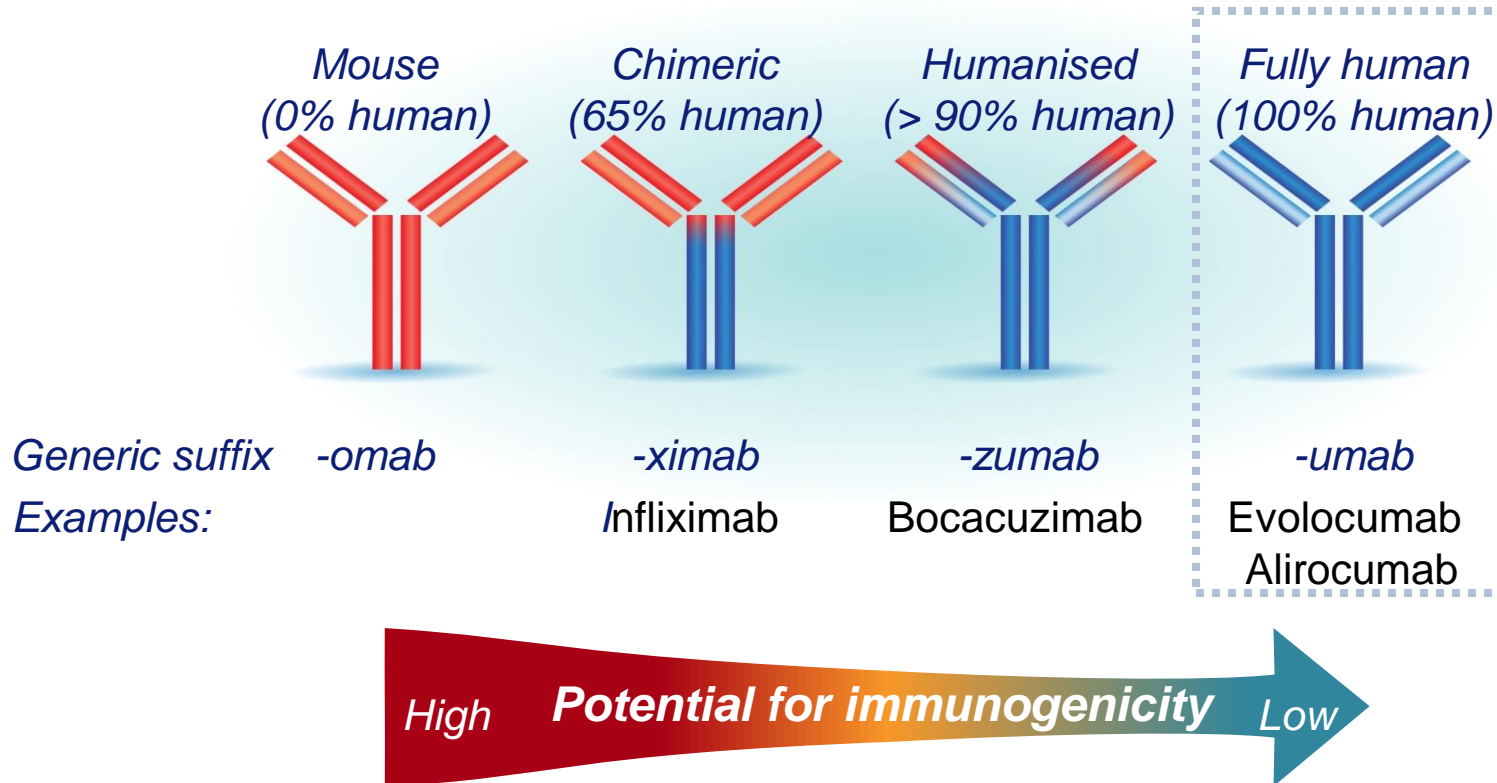
Mechanism of action PCSK9i



Mechanism of action PCSK9i



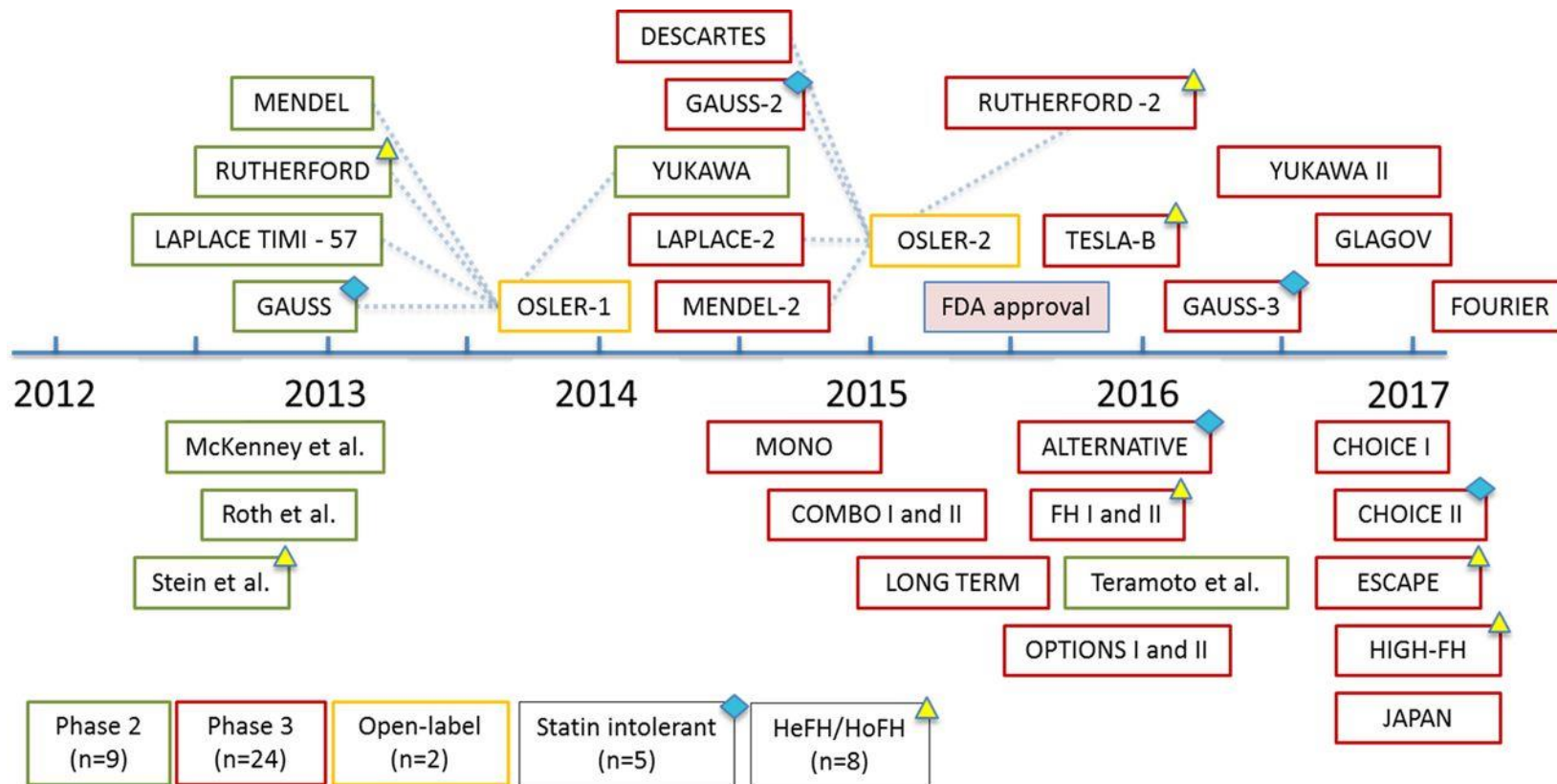
Antilichamen van muis naar mens



PCSK9 inhibitors (PCSK9i)¹

- Monoclonal antibodies
 - Alirocumab (Praluent)
 - Evolocumab (Repatha)
 - ~~Bococizumab~~
- FDA & EMA approved since 2015

Trial overview



Trial overview

HeFH	High CV Risk		
On top of max-tolerated statin	On top of max-tolerated statin	On top of typical statin doses	Not receiving statin
<i>FH I</i> (N=486)	COMBO I (N=316)	OPTIONS I (N=355)	MONO ² (N=103)
<i>FH II</i> (N= 249)	COMBO II (N=720)	OPTIONS II (n=305)	Statin intolerant
<i>HIGH FH</i> (N=107)	CHOICE I (N=700)		ALTERNATIVE (N=314)
LONG TERM (N=2341)			CHOICE II ³ (N=200)
<i>OLE</i> ¹ (N ≥1,000)	OUTCOMES (N=18,000)		

Overall conclusion

- Most common AEs in RCTs in ALI/EVO group¹⁻³:
 - Nasopharyngitis 5.9% - 12.2%
 - Upper respiratory tract infection 3.2% - 8.5%
 - Injection-site reactions 3.1% - 7.4%
 - Influenza like illness 2.1% - 7.3%
 - Myalgia 3.5% - 7.2%
 - Back pain 2.6% - 6.4%
 - Arthralgia 1.7% - 5.7%
 - Headache 3.2% - 5.0%
- Cochrane Review:
 - No significant difference of AEs compared to PBO⁴
- Alirocumab and evolocumab are generally well tolerated³

1. Jones. 2016. *Am J Cardiol.*

2. Toth. 2017. *Circulation.*

3. Zhang. 2015. *BMC Med.*

4. Schmidt. 2017. *Cochrane Database Syst. Rev.*

PCSK9 inhibitors (PCSK9i)¹

Evolcumab (Repatha)

1 april 2016

140 mg SC/2 weeks
420 mg SC/2 weeks (*hoFH*)



Alirocumab (Praluent)

1 juni 2016

75 mg SC/2 weeks
150 mg SC/2 weeks





ESC

European Society
of Cardiology

European Heart Journal (2018) **39**, 1131–1143
doi:10.1093/eurheartj/ehx549

CURRENT OPINION

Lipids

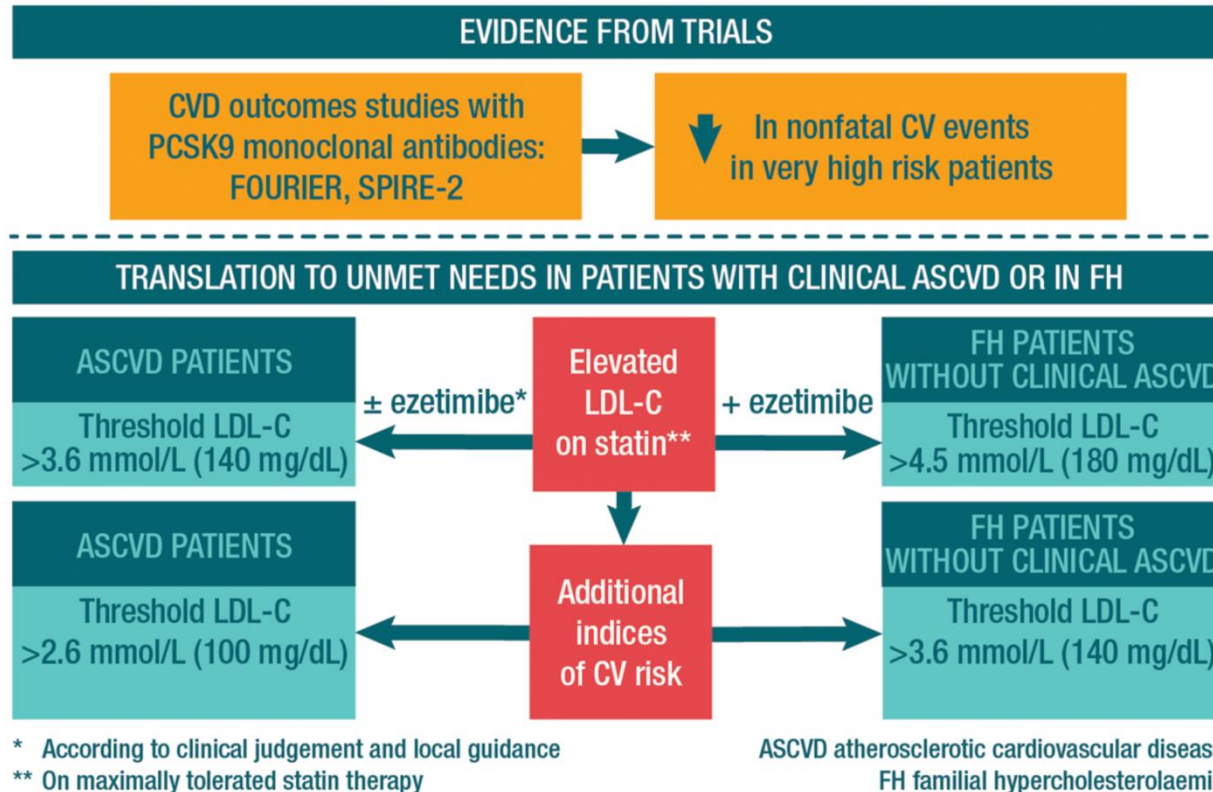
2017 Update of ESC/EAS Task Force on practical clinical guidance for proprotein convertase subtilisin/kexin type 9 inhibition in patients with atherosclerotic cardiovascular disease or in familial hypercholesterolaemia

Ulf Landmesser^{1*†}, M. John Chapman^{2†}, Jane K. Stock³, Pierre Amarenco⁴, Jill J.F. Belch⁵, Jan Borén⁶, Michel Farnier⁷, Brian A. Ference⁸, Stephan Gielen⁹, Ian Graham¹⁰, Diederick E. Grobbee¹¹, G. Kees Hovingh¹², Thomas F. Lüscher¹³, Massimo F. Piepoli¹⁴, Kausik K. Ray¹⁵, Erik S. Stroes¹², Olov Wiklund¹⁶, Stephan Windecker¹⁷, Jose Luis Zamorano¹⁸, Fausto Pinto¹⁹, Lale Tokgözoğlu²⁰, Jeroen J. Bax²¹, and Alberico L. Catapano²²

Overall conclusion

- A PCSK9 inhibitor should be considered in ASCVD patients with substantially elevated LDL-C levels despite maximally tolerated statin with or without ezetimibe therapy, or inability to tolerate appropriate doses of at least three statins, especially if there are additional indices of risk severity, i.e. familial hypercholesterolaemia, multivessel, or polyvascular disease or with rapidly progressive ASCVD (refer to *Figure 3*).

EAS/ESC guidelines for PCSK9i therapy



PCSK9 inhibitors vergoeding

Patiënten met hypercholesterolemie én voldoende hoog risico,
niet op streefwaarde* ondanks:

Maximaal verdraagbare statine én ezetimibe

Primaire
Preventie
(LDL-c \geq 2,5
mmol/l)

Secundaire Preventie
(LDL-c \geq 1,8 mmol/l)

HeFH / HoFH *

HeFH / HoFH *
&
CVE

Statine
Intolerantie**
&
CVE

CVE
&
recidief event

DM type II
&
CVE

- Alleen evolocumab

Overall conclusion

Box 4 Gaps in knowledge concerning proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor therapy

- Inter-individual variability in low-density lipoprotein cholesterol (LDL-C) lowering response to alirocumab and evolocumab
- Dedicated trials in patients with recent (<1 month) cardiovascular events
- Impact of PCSK9 inhibition in patients with chronic kidney disease (not requiring dialysis)
- Long-term efficacy and safety of PCSK9 inhibitors in clinical use
- Long-term safety of very low LDL-C levels
- Long-term impact of PCSK9 inhibition on disability and cardiovascular mortality
- Long-term evaluation of risk for type 2 diabetes
- Impact of sustained and marked LDL-C lowering to very low levels on plaque composition and stability
- Long-term impact of reduction in elevated lipoprotein(a) with PCSK9 inhibition
- Cost-effectiveness of PCSK9 inhibition added to maximally tolerated statin with or without ezetimibe therapy.

Real-world data

- Real-world data provides complimentary information to RCTs¹
- Data is scarce, only 5 studies²⁻⁷
- Relatively small study population (largest n=105)
- Any AE rate 15-39%
- Most common AEs:
 - Flu-like symptoms
 - Neurological symptoms
 - Abdominal symptoms
 - Myalgia
 - Injection-site reactions

1. Nallamotheu. 2008. *Circulation*.
2. Choi. 2017. *Lipids Health Dis*.
3. Galema-Boers. 2017. *J Clin Lipidol*.
4. Kohli. 2017. *Int J Clin Pract*.
5. Pandey. 2017. *Curr Opin Caridol*.
6. Saborowski. 2017. *Cardiol J*
7. Stoekenbroek 2018, *Atherosclerosis*.

Research questions

- Main question:
 - What are the main AEs associated with the use of PCSK9 inhibitor prescribed in the clinical setting?
- Subquestions:
 - Is there a difference in AE profile between alirocumab and evolocumab?
 - Is there a sex difference in AEs?
 - Are there predictors of AEs?
 - What is the time course of AEs?
 - Which AEs lead to drug discontinuation?

Methods (1)

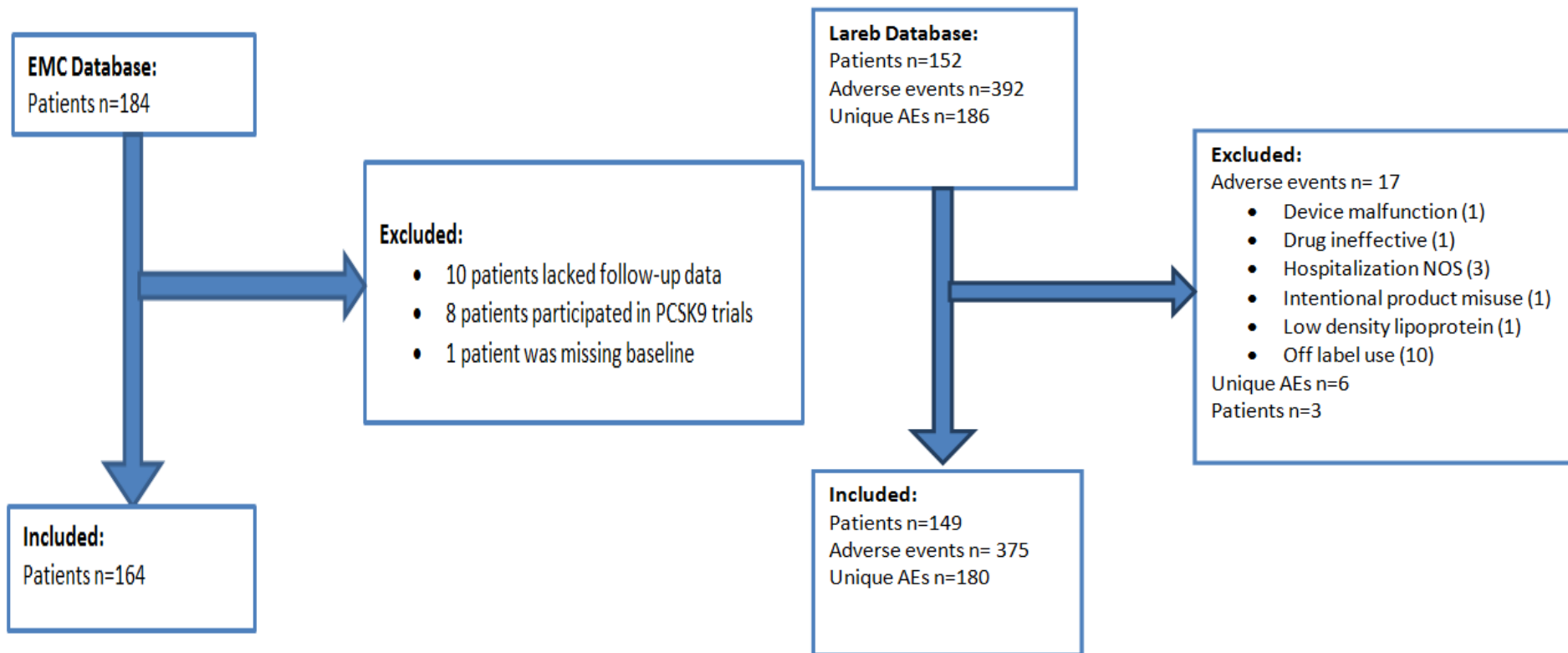
- 3 Databases: EMC, Lareb and VigiLyze
- Erasmus MC database PCSK9i:
 - Inclusion criteria:
 - All patients ≥ 18 years, who started on PCSK9i between 06-2015* and 11-2017
 - Exclusion criteria:
 - Patients who (had) participated in PCSK9i trials
 - Patients without follow-up data
- Data on age, gender, BMI, diabetes, history of CVD, FH, LLT from patients' files
- Baseline date: instructions and 1st administration
- Routine CV lab before/after start PCSK9i
- Follow-up at 6 – 18 – 42 weeks

* *Compassionate use program*

Methods (2)

- Lareb database:
 - Contains spontaneous adverse drug reaction reports in NL
 - Reports by health professionals, patients or pharmaceutical industry
 - All reports from all ages are included
 - One report may contain several adverse events
- VigiLyze database:
 - Contains spontaneous ADRs worldwide 110 countries
 - Same as above

Results – Flowcharts



Results – Patient characteristics

Characteristics	EMC, n=164*	Lareb, n=149	VigilLyze, n=15,554
Age (y), median (IQR)	58 (48-65)	63 (56-69)	
Age groups, n (%)			
0-27 days	0 (0)	0 (0.0)	1 (0.0)
2-11 years	0 (0)	0 (0.0)	1 (0.0)
12-17 years	0 (0)	0 (0.0)	6 (0.0)
18-44 years	24 (15)	5 (3.4)	289 (1.9)
45-64 years	91 (56)	71 (47.7)	4,210 (27.1)
65-74 years	46 (28)	56 (37.6)	4,835 (31.1)
≥ 75 years	3 (2)	8 (5.4)	2,670 (17.2)
Age unknown, n (%)	0 (0)	9 (6)***	3,542 (22.8)
Gender, n (%)			
Male	90 (55)	70 (47)	5,975 (38.4)
Female	74 (45)	78 (52)	8,772 (56.4)
Unknown	0 (0)	1 (1)	807 (5.2)
BMI (kg/m ²), median (IQR)	27.4 (24.4-30.2)		
Diabetes, n (%)	29 (18)		
Hypertension, n (%)	75 (46)		
Ever smoker, n (%)	78 (48)		
Current smoker, n (%)	24 (15)		
History of CVD, n (%)	108 (66)		
Familial hypercholesterolemia, n (%)	148 (90)		
Heterozygous	98 (60)		
Homozygous**	7 (4)		
Clinical	43 (26)		
Lipid lowering therapy, n (%)			
Statin use	100 (61)		
High Intensity	63 (38)		
Moderate Intensity	30 (18)		
Low Intensity	7 (4)		
Ezetimibe	164 (100)		
Ezetimibe monotherapy	64 (39)		
LDL cholesterol (mmol/L), median (IQR)	4.28 (3.34 -5.14)		

*Baseline characteristics before starting PCSK9 inhibitor

**Double heterozygous LDLR/APOB gene mutation (n=1), compound heterozygous LDLR gene mutation (n=6)

***One patient was reported to be 114 years old, which was put as missing value.

Results – Patient characteristics

- EMC
 - 49% ALI vs 51% EVO; no sign difference
- Lareb
 - 28% ALI vs 72% EVO; similar distr. age/sex
- VigilLyze
 - 30% ALI vs 70% EVO; similar distr. age/sex

Characteristics	EMC, n=164*	Lareb, n=149	VigilLyze, n=15,554
Age (y), median (IQR)	58 (48-65)	63 (56-69)	
Age groups, n (%)			
0-27 days	0 (0)	0 (0.0)	1 (0.0)
2-11 years	0 (0)	0 (0.0)	1 (0.0)
12-17 years	0 (0)	0 (0.0)	6 (0.0)
18-44 years	24 (15)	5 (3.4)	289 (1.9)
45-64 years	91 (56)	71 (47.7)	4,210 (27.1)
65-74 years	46 (28)	56 (37.6)	4,835 (31.1)
≥ 75 years	3 (2)	8 (5.4)	2,670 (17.2)
Age unknown, n (%)	0 (0)	9 (6)***	3,542 (22.8)
Gender, n (%)			
Male	90 (55)	70 (47)	5,975 (38.4)
Female	74 (45)	78 (52)	8,772 (56.4)
Unknown	0 (0)	1 (1)	807 (5.2)
BMI (kg/m ²), median (IQR)	27.4 (24.4-30.2)		
Diabetes, n (%)	29 (18)		
Hypertension, n (%)	75 (46)		
Ever smoker, n (%)	78 (48)		
Current smoker, n (%)	24 (15)		
History of CVD, n (%)	108 (66)		
Familial hypercholesterolemia, n (%)	148 (90)		
Heterozygous	98 (60)		
Homozygous**	7 (4)		
Clinical	43 (26)		
Lipid lowering therapy, n (%)			
Statin use	100 (61)		
High Intensity	63 (38)		
Moderate Intensity	30 (18)		
Low Intensity	7 (4)		
Ezetimibe	164 (100)		
Ezetimibe monotherapy	64 (39)		
LDL cholesterol (mmol/L), median (IQR)	4.28 (3.34 -5.14)		

*Baseline characteristics before starting PCSK9 inhibitor

**Double heterozygous LDLR/APOB gene mutation (n=1), compound heterozygous LDLR gene mutation (n=6)

***One patient was reported to be 114 years old, which was put as missing value.

Results – Adverse events: Erasmus MC

*41% report
Treatment emergent
adverse events*

ERASMUS MC	Total (n=68*)	OR (95% CI) Male vs Female
Any TEAE, n (%)	68 (100.0)	0.58 (0.31-1.09)**
1 event	37 (54.4)	
2 events	21 (30.9)	
≥3 events	10 (14.7)	
Events, median (IQR)	1.0 (1.0-2.0)	
Total no. of TEAEs reported	116	
TEAEs leading to discontinuation	11 (16.2)	
TEAEs leading to death	0 (0.0)	
Most common (≥4%) TEAEs, n (%)		
Influenza like illness	19 (27.9)	0.56 (0.19-1.66)
Injection-site haematoma	13 (19.1)	0.43 (0.12-1.56)
Nasopharyngitis	11 (16.2)	0.52 (0.16-2.25)
Abdominal discomfort	8 (11.8)	2.04 (0.45-9.31)
Myalgia	7 (10.3)	0.41 (0.07-2.30)
Cognitive disorder	6 (8.8)	2.43 (0.41-14.25)
Fatigue	6 (8.8)	2.43 (0.41-14.25)
Headache	6 (8.8)	0.53 (0.09-3.13)
Injection-site pain	6 (8.8)	1.14 (0.21-6.08)
Injection-site swelling	6 (8.8)	2.43 (0.41-14.25)
Rash	4 (5.9)	0.36 (0.04-3.60)
Injection-site reactions, n (%)	23(33.8)	0.62 (0.22-1.71)
Injection-site haematoma	13 (19.1)	0.43 (0.12-1.56)
Injection-site pain	6 (8.8)	1.14 (0.21-6.08)
Injection-site swelling	6 (8.8)	2.43 (0.41-14.25)
Injection-site erythema	2 (2.9)	1.13 (0.07-18.8)
Injection-site infection	1 (1.5)	

Results – Adverse events: Lareb

Lareb	Total (n=149)	OR (95% CI) Male vs Female
Any TEAE, n (%)	149 (100.0)	
1 event	51 (34.2)	
2 events	41 (27.5)	
≥3 events	61 (38.3)	
Events, median (IQR)	2.0 (1.0-3.0)	
Total no. of TEAEs reported	375	
TEAEs leading to discontinuation	60 (40.3)	
TEAEs leading to death	1 (0.7)	
Most common (≥4%) TEAEs, n (%)		
Myalgia	19 (12.8)	1.63 (0.62-4.32)
Influenza like illness	14 (9.4)	2.15 (0.69-6.77)
Fatigue	12 (8.1)	1.13 (0.35-3.67)
Headache	12 (8.1)	0.20 (0.04-0.95)
Arthralgia	10 (6.7)	1.73 (0.47-6.42)
Dyspnoea	9 (6.0)	0.13 (0.02-1.04)
Nausea	9 (6.0)	0.54 (0.13-2.24)
Malaise	8 (5.4)	0.35 (0.07-1.81)
Muscle spasms	8 (5.4)	0.65 (0.15-2.84)
Pain in extremity	8 (5.4)	0.35 (0.07-1.81)
Diarrhoea	6 (4.0)	0.54 (0.10-3.07)
Dizziness	6 (4.0)	0.54 (0.10-3.07)
Injection-site reactions, n (%)	3 (2.0)	2.27 (0.20-25.53)
Injection-site haematoma	1 (0.7)	
Injection-site haemorrhage	1 (0.7)	
Injection-site swelling	1 (0.7)	

Results – Adverse events: Vigilyze

Vigilyze	Total (n=15,554)	OR (95% CI) Male vs Female
Any TEAE, n (%)	15,554 (100.0)	

Total no. of TEAEs reported	29,956	
TEAEs leading to discontinuation	N/A	
TEAEs leading to death	N/A	
Most common (≥4%) TEAEs, n (%)		
Myalgia	1,287 (8.3)	1.11 (0.99-1.25)
Drug dose omission	1,151 (7.4)	0.87 (0.77-0.99)
Injection-site pain	959 (6.2)	0.55 (0.48-0.65)
Influenza like illness	818 (5.3)	1.06 (0.91-1.23)
Back pain	816 (5.2)	0.95 (0.82-1.09)
Arthralgia	789 (5.1)	1.01 (0.87-1.17)
Fatigue	764 (4.9)	0.92 (0.79-1.06)
Pain in extremity	755 (4.9)	0.77 (0.66-0.90)
Muscle spasms	719 (4.6)	0.81 (0.69-0.95)
Pain	703 (4.5)	0.66 (0.56-0.78)
Headache	651 (4.2)	0.72 (0.61-0.86)
Injection-site reactions (≥1.0%), n (%)	3291 (21.2)	0.55 (0.50-0.60)
Injection-site pain	959 (6.2)	0.55 (0.48-0.65)
Injection-site bruising	526 (3.4)	0.56 (0.46-0.67)
Injection-site haemorrhage	373 (2.4)	0.72 (0.58-0.89)
Injection-site erythema	268 (1.7)	0.49 (0.37-0.65)
Injection-site swelling	229 (1.5)	0.61 (0.45-0.81)
Injection-site pruritus	152 (1.0)	0.42 (0.29-0.62)

Results – Adverse events ALI vs EVO

- EMC:
 - 43% of ALI vs 40% of EVO with AEs
 - Influenza like illness (29% vs 27%)
 - ISRs (37% vs 30%)
 - No significant differences in AE profile
- Lareb
 - Myalgia (7% vs 15%)
 - ISRs (2% vs 2%)
 - Similar AE profile
- Vigilyze
 - Myalgia (9% vs 8%)
 - ISRs (22% vs 21%)
 - Back pain 3x more frequent in EVO

Results – Predictors

	OR (95% CI)	P-value
Age	0.98 (0.96-1.01)	0.202
Gender (Male)	0.58 (0.31-1.09)	0.091
BMI	0.99 (0.92-1.07)	0.740
Hypertension (Yes)	1.34 (0.72-2.50)	0.356
Current Smoker (Yes)	0.63 (0.25-1.57)	0.320
Diabetes (Yes)	1.00 (0.44-2.25)	0.992
History of CVD (Yes)	1.44 (0.74-2.80)	0.283
Familial hypercholesterolemia (FH) (Yes)	0.90 (0.32-2.56)	0.845
FH – Genetic mutation (Yes)	1.46 (0.70-3.04)	0.318
Statin use (Yes)	1.18 (0.62-2.23)	0.618
Statin intensity (High vs Low+Mod)	1.68 (0.73-3.88)	0.225
LDL-C at baseline	1.05 (0.88-1.24)	0.590
LDL-C at follow-up 1	1.14 (0.94-1.38)	0.187
LDL-C <0.5 mmol/L* at follow-up 1	1.83 (0.47-7.07)	0.383
PCSK9 inhibitor (EVO vs ALI)	0.87 (0.47-1.62)	0.654

*0.5 mmol/L = 19.3 mg/dl

Results – Follow-up

- 60% AEs at both
- 74% reported different AEs
- In 40% AEs resolved at FU2
- 23% developed new AEs at FU2
- in >70% AEs resolve at FU3

		Follow-up 2 (n=131)		Follow-up 3 (n=94)	
		AEs	No AEs	AEs	No AEs
Follow-up 1	AEs	31 59.6%	21 40.4%	11 28.9%	27 71.1%
	No AEs	18 22.8%	61 77.2%	7 12.5%	49 87.5%
Follow-up 2	AEs			11 33.3%	22 66.7%
	No AEs			7 11.5%	54 88.5%

FU1 vs. FU2: McNemar's $p=0.749$; FU2 vs. FU3: McNemar's $p=0.009$;

FU1 vs. FU3: McNemar's $p=0.001$

Results – Drug discontinuation

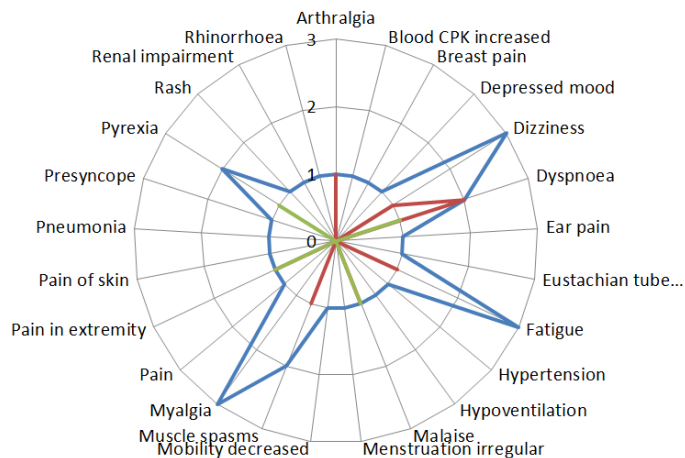
EMC	Drug Discontinued (n=12)	Lareb	Drug Discontinued (n=60)
TEAEs, n (%)	11 (90)*	TEAEs, n (%)	60 (100)
0 event	1 (8)	0 event	0 (0)
1 event	4 (33)	1 event	13 (22)
2 events	2 (17)	2 events	13 (22)
≥3 events	5 (42)	≥3 events	34 (57)
Events, median (IQR)	2.0 (1.0-3.0)	Events, median (IQR)	3.0 (2.0-4.0)
No. of reported AEs	25	No. of reported AEs	179
Gender, n (%)		Gender, n (%)	
Male	4 (33)	Male	29 (48)
Female	8 (67)	Female	31 (52)
PCSK9 inhibitor, n (%)		PCSK9 inhibitor, n (%)	
Alirocumab	5 (42)	Alirocumab	12 (20)
Evolocumab	7 (58)	Evolocumab	48 (80)
TEAEs leading to discontinuation (≥5%), n (%)		TEAEs leading to discontinuation (≥5%), n (%)	
Influenza like illness	6 (50)	Myalgia	11 (18)
Cognitive disorder	3 (25)	Headache	8 (13)
Abdominal discomfort	2 (17)	Nausea	7 (12)
Fatigue	2 (17)	Arthralgia	6 (10)
Malaise	2 (17)	Fatigue	6 (10)
Arthralgia	1 (8)	Influenza like illness	5 (8)
Dizziness	1 (8)	Back pain	4 (7)
Dyspnoea	1 (8)	Cough	3 (5)
Epistaxis	1 (8)	Dizziness	3 (5)
Eye infection	1 (8)	Dyspnoea	3 (5)
Myalgia	1 (8)	Fatigue	3 (5)
Pruritus	1 (8)	Malaise	3 (5)
Syncope	1 (8)	Myalgia	3 (5)
Visual impairment	1 (8)	Nasal congestion	3 (5)
Weight decreased	1 (8)	Pain in extremity	3 (5)

*One patient discontinued drug due to non-response.

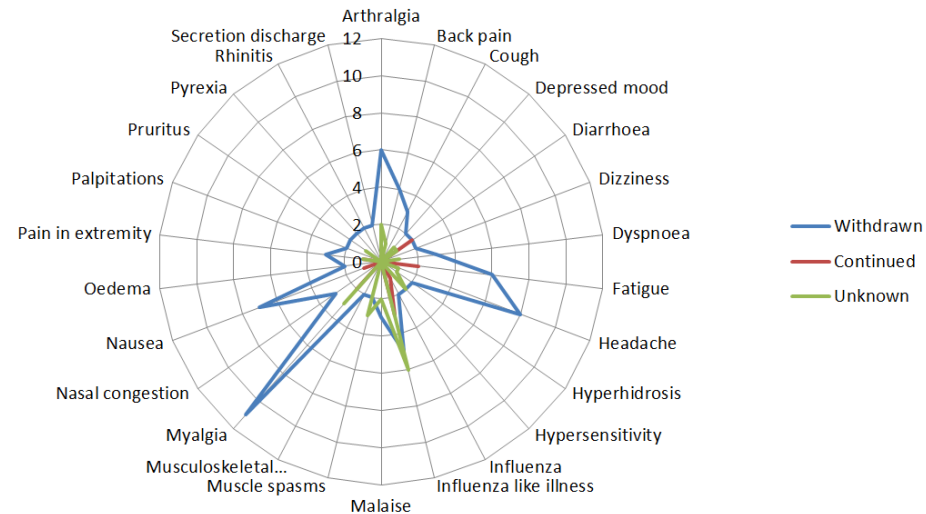
- EMC
 - 12 (7%) patients (1 non-response)
 - 2/3 Female
 - Most reported ≥ 3 events
 - Influenza like illness
- Lareb
 - 60 (39%) patients
 - 52% Female
 - Most reported ≥ 3 events
 - Myalgia

Results – Lareb Drug discontinuation

Alirocumab



Evolocumab



Discussion – Rates of AEs

- EMC
 - Higher AE rate in our study (41.5%), most transient
 - Nasopharyngitis and influenza occurred at similar rates
 - ISRs were reported frequently, similar to trials
 - Myalgia rate was comparable to RCTs
- Lareb + Vigilyze:
 - ISRs were reported more frequently in Vigilyze vs Lareb
 - High myalgia rate in Lareb + Vigilyze, maybe attributed to concomitant statin use

Other real world data

Table 2 Effect of PCSK9 inhibitors after 6-week follow-up

Characteristic	Total, n = 83
PCSK9 inhibitors, n (%)	
Evolocumab	52 (63)
Alirocumab	31 (37)
Lipid values, mean \pm SD	
Total cholesterol (mmol/L)*	4.3 \pm 2.4
LDL cholesterol (mmol/L)*	2.4 \pm 2.1
HDL cholesterol (mmol/L)*	1.4 \pm 0.4
Triglyceride (mmol/L) [†]	1.4 \pm 0.9
Apo B (g/L)	0.9 \pm 0.6
Glucose (mmol/L)	6.1 \pm 2.0
LDL-c decrease (% mean \pm SD)	54.9 \pm 20.6
LDL-c \leq 1.0 mmol/L*	14 (17)
LDL-c by treatment goal, n (%)	48 (58)
Primary prevention, LDL-c \leq 2.5 mmol/L*	18 (55)
Secondary prevention, LDL-c \leq 1.8 mmol/L*	30 (60)
Liver tests, mean \pm SD	
ASAT (U/L)	27.1 \pm 13.4
ALAT (U/L)	32.2 \pm 29.3
Gamma GT (U/L)	28.5 \pm 10.2

Quit PCSK9 inhibitors	7 (8)
Side effects	5 (6)
Nonresponders	2 (2)

Table 3 Patient-reported side effects of PCSK9 inhibitors

Event, n (%)	32 patients (39%)
Any	52
Flu-like symptoms	12 (14)
Neurological	8 (10)
Abdominal symptoms	6 (7)
Nasopharyngitis	4 (5)
Allergic skin reactions	4 (5)
Myalgia/joint pain	4 (5)
Headache	4 (5)
Fatigue	3 (4)
Eye irritation	3 (4)
Anxiety attacks	1 (1)
Dysarthria	1 (1)
Flushes	1 (1)
Hoarseness	1 (1)
Discontinuation	7 (8)
Injection site reactions, n (%)	11 patients (13%)
Any	16
Hematomas	4 (5)
Redness	2 (2)
Painful injection	6 (7)
Swelling	4 (5)

Other real world data

TABLE 1 Baseline characteristics and response to PCSK-9 therapy in a cohort of consecutive patients prescribed evolocumab or alirocumab

	DGH (n = 35)		UH (n = 70)		All (n = 105)	
	Pre	Post	Pre	Post	Pre	Post
Age (years)	62 ± 10		61 ± 14		62 ± 13	
Gender (% male)	67		44		52	
Smoking (%)	19		6		10	
T2DM (%)	16		10		12	
NICE- FH & LDL-C > 5 mmol/L (%)	89		69		75	
NICE- statin intolerant (%)	92		54		67	
NICE CHD & LDL-C > 4 mmol/L (%)	44		33		37	
NICE CVD & LDL-C > 3.5 mmol/L (%)	42		17		25	
Other (%)	6		21		16	
TC (mmol/L)	7.74 ± 1.31	5.57 ± 1.82	7.75 ± 2.63	5.33 ± 2.19	7.74 ± 2.26	5.43***±2.03
TG (mmol/L) (median & range)	1.67 0.50-4.9	1.51 0.59-5.21	1.95 0.50-34.8	1.80 0.39-7.7	1.89 0.5-35.8	1.63 0.39-7.7
HDL-C (mmol/L)	1.50 ± 0.36	1.49 ± 0.45	1.37 ± 0.41	1.39 ± 0.47	1.41 ± 0.40	1.44 ± 0.46
LDL-C (mmol/L)	5.41 ± 1.27	3.33 ± 1.65	5.17 ± 2.06	2.86 ± 1.77	5.25 ± 1.83	3.07***±1.72

Adverse events in 10 (9.5%) patients:

8 myalgia

1 nausea

1 transient ALT rise 2 xULN

Other real world data

Table 1
Baseline characteristics.

	N = 238
Age, years (SD)	58 (11)
Male, n (%)	139 (58.4)
White, n (%)	232 (97.5)
Previous CVD, n (%)	149 (62.6)
FH, n (%)	160 (67.2)
Statin intolerance ^a , n (%)	102 (42.9)
Smoking	
Current, n (%)	31 (16.5)
Former, n (%)	66 (35.1)
Never, n (%)	91 (48.4)
Unknown, n (%)	50
BMI, kg/m ² (SD)	27.6 (4.6)
Hypertension, n (%)	97 (40.8)
Type 2 diabetes, n (%)	40 (16.8)
Concomitant lipid-lowering therapy	
Statins, n (%)	133 (55.9)
Ezetimibe, n (%)	217 (91.2)
Fibrates, n (%)	8 (3.4)
Bile acid sequestrants, n (%)	8 (3.4)

Table 2
PCSK9 inhibitor treatment.

	N = 238
Prior study participation, n (%)	99 (41.6)
Initial treatment	
Evolocumab 140 mg/2 weeks, n (%)	118 (52.0)
Evolocumab 420 mg/months, n (%)	3 (1.3)
Alirocumab 75 mg/2 weeks, n (%)	42 (18.5)
Alirocumab 150 mg/2 weeks, n (%)	64 (28.2)
Unknown ^a	11 (4.6)
Change in PCSK9 inhibitor treatment, n (%)	8 (3.4)
Discontinued PCSK9 inhibitor treatment, n (%)	6 (2.5)

Other real world data

Table 4

Discontinuation rate and side effects.

Discontinuation total, n (%)	6 (2.5)
Discontinuation due to side effects, n (%)	6 (2.5)
Skipping doses, n (%)	11 (4.6)
Side effects	
Any, n (%)	37 (15.5)
Muscle symptoms, n (%)	9 (3.8)
Injection-site reactions, n (%)	8 (3.4)
Flu-like symptoms/nasopharyngitis, n (%)	6 (2.6)
Joint pain, n (%)	2 (0.8)
Fatigue, n (%)	2 (0.8)
Headache/neurological, n (%)	2 (0.8)
Other, n (%)	8 (3.4)
Non-response, n (%)	3 (1.3)
<25% LDL-cholesterol reduction, n (%)	15 (6.5)

Discussion – Mechanism AEs

- Cytokine-mediated type alpha immune response is main mechanism for common AEs such as flu-like symptoms and ISRs¹
- Pathogenic mechanism for myalgia is unclear
- Possible protective effect of PCSK9 on cognitive function^{2,3}
- Very low LDL-C not associated with an increase in overall AE rates^{4,5} or neurocognitive AEs^{6,7} and did not affect vitamin E, steroid or gonadal hormones⁸.

1. Scherer. 2010. *J Dtsch Dermatol Ges.*
2. Wu. 2014. *Biomed Rep.*
3. Swiger. 2015. *Drug Saf.*
4. Giugliano. 2017. *Lancet.*
5. Robinson. 2017. *J Am Coll Cardiol.*
6. Giugliano. 2017. *N Eng J Med.*
7. Harvey. 2017. *Eur Heart J*
8. Blom. 2015. *Circ Res.*

Spontaneous reports

- Pharmacovigilance databases have a higher threshold to report
- Women are at higher risk of developing and reporting AEs^{1,2}
- Women represented 52% of Lareb and 56% of VigiLyze reports
- GIP Database: 42% of all patients using PCSK9 were female³
- Report ratio 1.18 in hospital registry and 1.23 in pharmacovigilance

1. Martin. 1998. *Br J Clin Pharmacol*.
2. Montastruc. 2002. *Fundam Clin Pharmacol*.
3. Zorginstituut Nederland. 2017. *GIP Databank*.

Strengths & Limitations

- Strengths
 - Largest in-depth study of AEs of PCSK9i in clinical setting
 - Low reporting bias due to enquiry during visits in EMC registry
 - Follow-up up to 42 weeks for insight on how Aes develop
 - Different methods of AE monitoring for complete overview
- Limitations
 - Low power in EMC hospital registry
 - Multiple testing
 - Variable follow-up might have led to uncaptured AEs
 - Drug discontinuation rates were low to allow for extensive analysis
 - Lareb + Vigilyze: amount of available information varied between cases

Conclusion

- In real-world setting, PCSK9 inhibitors are well tolerated.
- AE profile comparable to trials
- Influenza like illness, nasopharyngitis, myalgia and ISRs most common
- No significant difference between ALI & EVO
- No significant difference between sexes
- No significant predictors of AEs
- Most AEs resolve over time and drug discontinuation was infrequent
- Myalgia main reason for discontinuation in pharmacovigilance database

Recommendations

- Monitoring of long-term safety of PCSK9 inhibitors indispensable
- Contribute to monitor AEs by reporting these to pharmacovigilance agencies
- Collect long-term data in a local, national and ultimately an international database.

Thanks to:



Erasmus MC

- Muhammed Gurguze
- Michelle Schreuder
- Eric Boersma
- Annette Galema-Boers
- Kim Steward

Lareb

- Annemarie Muller