4th Global Summit on
DIABETES AND ENDOCRINOLOGY

A novel cholesterol-lowering PCSK9 variant is associated with low blood glucose level and lower cardiovascular risk in type 2 diabetes

Edgard S.R. Tchéoubi,[1,2] Casimir D. Akpovi,[2] Frédérique Coppée[3], Anne-Emilie Declèves,[3] Gaétan J. Sègbo,[2,4] Clément Agbangla[4], Sophie Laurent[1] and Carmen Burtea[1]

[1]Laboratory of NMR and Molecular Imaging, General, Organic and Biomedical Chemistry Unit, University of Mons, Belgium
[2]Non-Communicable Diseases and Cancer Research Unit, Laboratory of Applied Biology Research, University of Abomey-Calavi, Benin
[3]Laboratory of Metabolic and Molecular Biochemistry, University of Mons, Belgium
[4]Laboratory of Molecular Genetics and Genome Analyzes, Faculty of Sciences and Technics, University of Abomey-Calavi, Benin

Introduction

- Diabetes mellitus is a major problem of public health (WHO, 2016)
- Type 2 Diabetes mellitus (T2DM): >50% of dyslipidemia; atherosclerotic cardiovascular diseases (ACVD)
- Use of cholesterol lowering drug

Statins

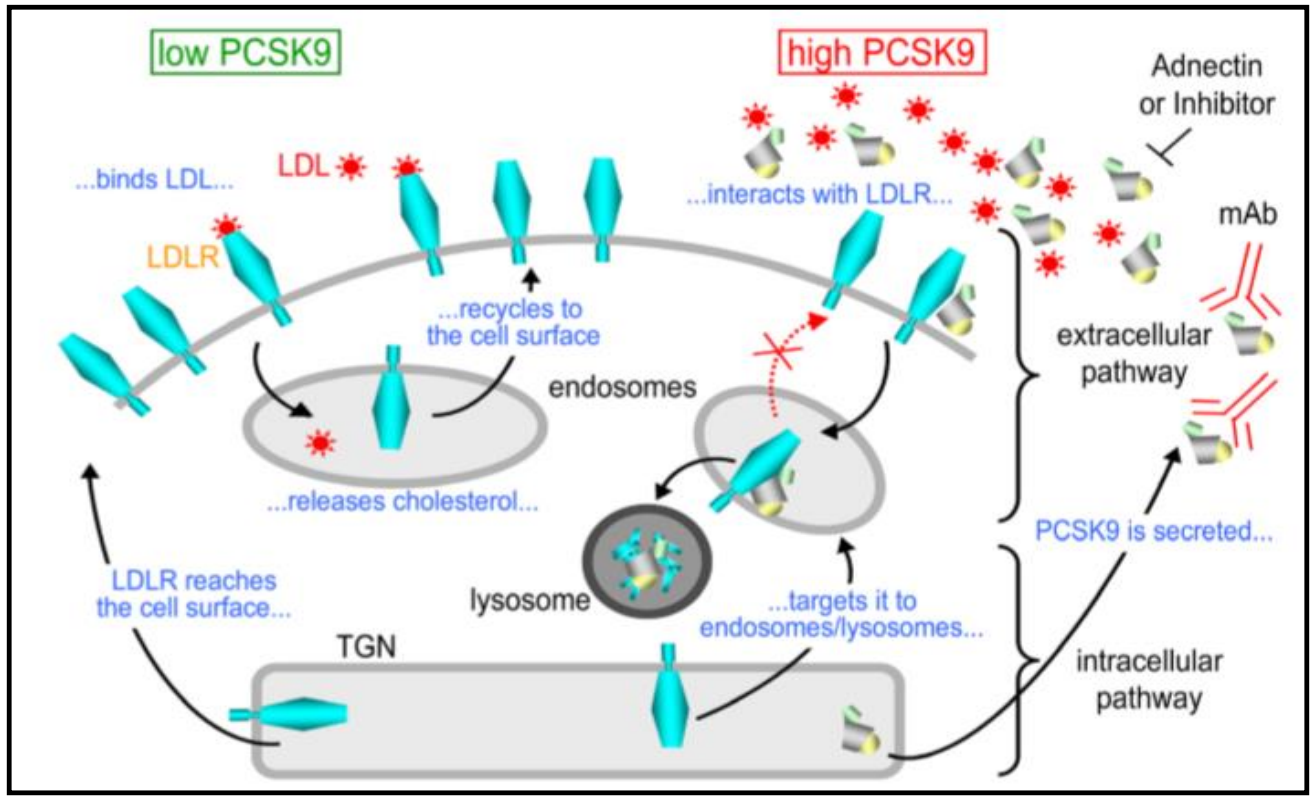
- Resistance
- New onset T2DM

→

Proprotein convertase subtilisin-kexin type 9 inhibitors (PSK9i)

mAb authorized by FDA and EMA since 2015

Introduction



PCSKi mAb binds to secreted PCSK9 and prevents its association with cell surface LDLR and subsequent lysosomal destruction

PCSK9i

- Decrease LDLc level by 50-60%
- Important reduction of ACVD
- **New onset T2DM?**

Objective

To assess the association of a PCSK9 variant to T2DM, precisely through

- lipid profile and
- glucose homeostasis parameters.

Results and Discussion

Socio-demographic and anthropometric characteristics of the study subjects (n=171)

Parameters	T2DM (n=132)	Control (n=39)	P-value
Age (ans)	57±11	46±12	**<0.001**
Female sex	61%	69%	0.823
WC (cm)	95.00 (88.25-103.00)	94.00 (83.00-107.00)	0.587
BMI (Kg/m²)	27.13 (23.18-30.09)	29.03 (22.68-35.57)	0.215
Physical activity	57.58%	89.74%	0.281
Alcohol	10.77%	0%	-
Tobacco	6.87%	0%	-
SBP (mmHg)	130 (120-150)	130 (120-140)	0.137
DBP (mmHg)	80 (70-90)	80 (70-90)	0.725
HTA	58.01%	51.28%	0.643

- 132 T2DM and 39 Ctrl (F>60%)
- 97.73% on metformin+Glibenclamide (22.73%)
- No significant difference between T2DM patients and controls according to gender, anthropometric and clinical characteristics

Results and Discussion

Genetic analysis

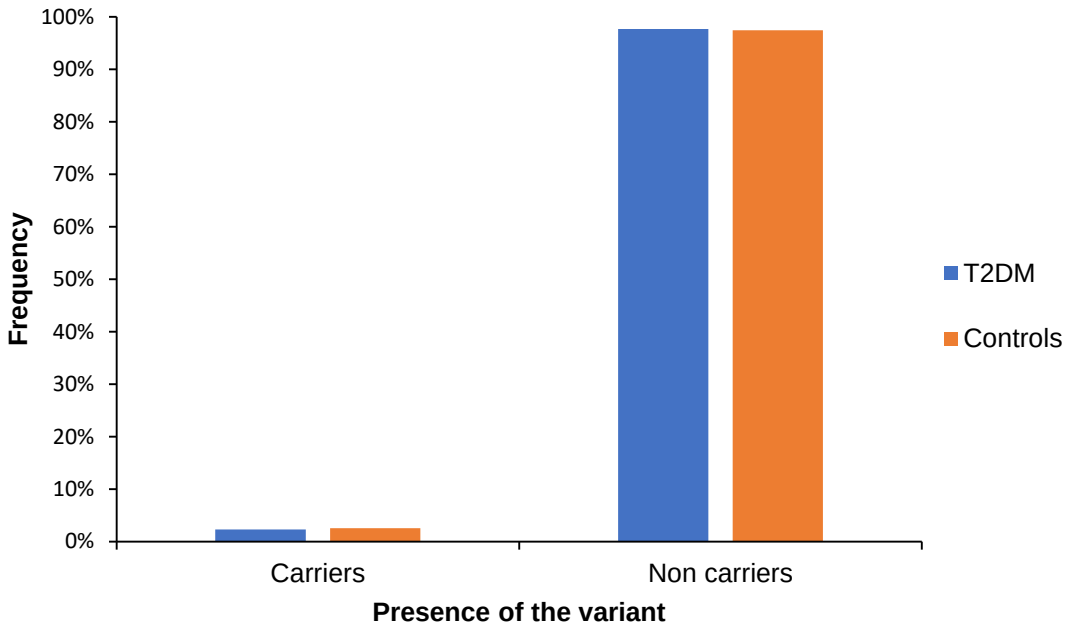
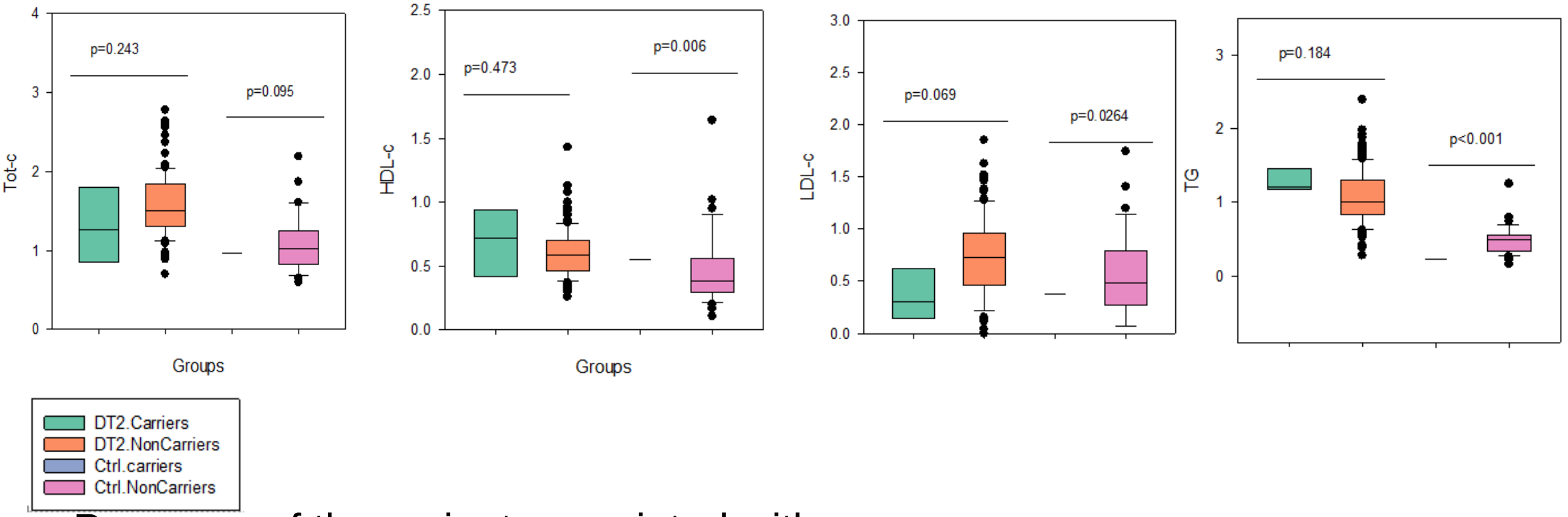


Figure : Distribution of the variant according to T2DM status

- The variant was detected in 2.34% (2.27% of T2DM patients and 2.56% of control subjects respectively).
- There was no statistical association of the variant with T2DM (p=0.621).

Results and Discussion

Lipid profile

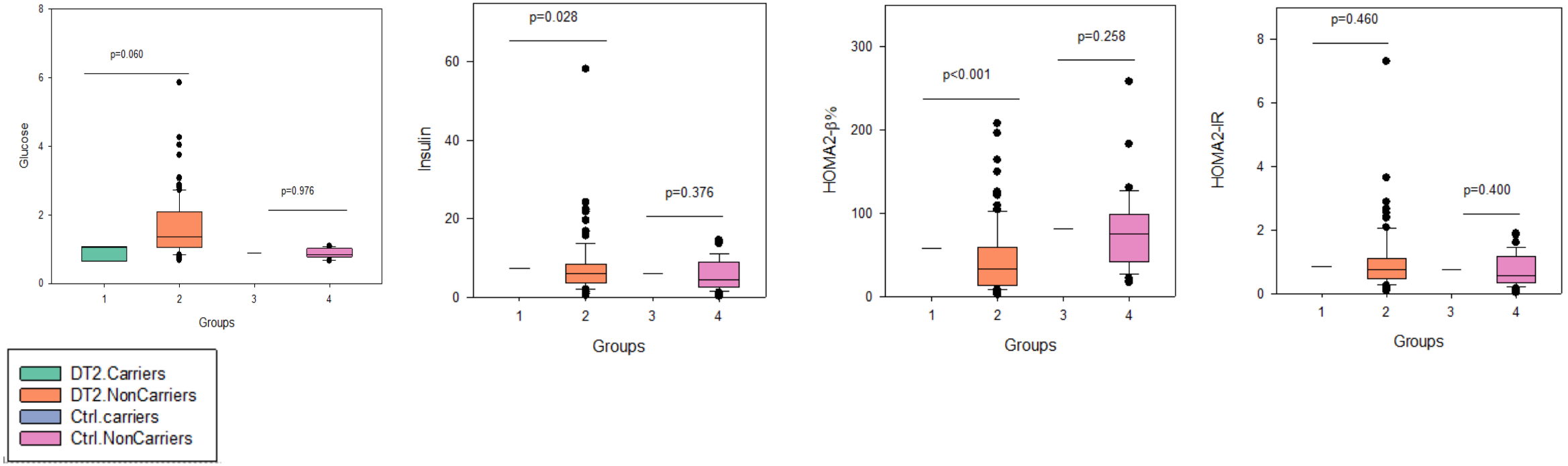


Presence of the variant associated with

- HDL-c ⬆ in non diabetic Control (p=0.006)
- LDL-c ⬇ in non diabetic Control (p=0.0264) and T2DM patients (0.069) (Cohen and *al.*, 2005)
- TG ⬇ in non diabetic Control (p<0.001)

Results and Discussion

Glucose homeostasis parameters

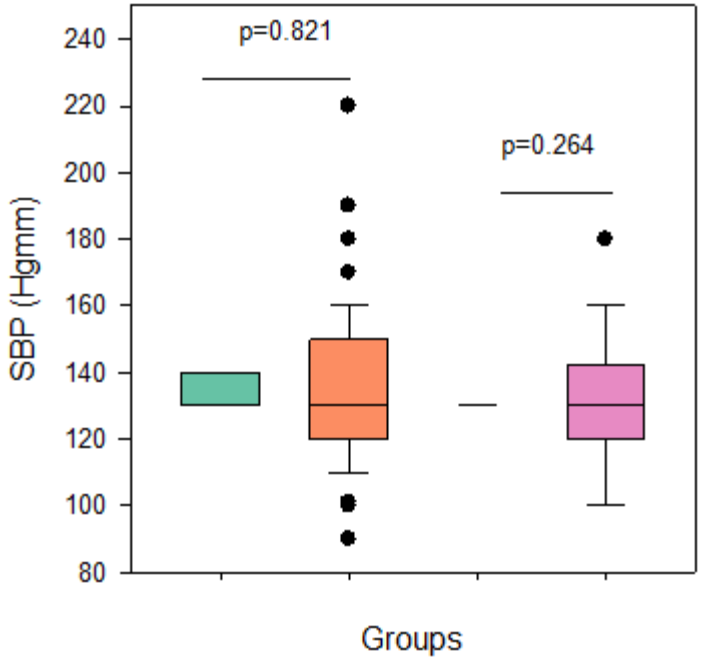


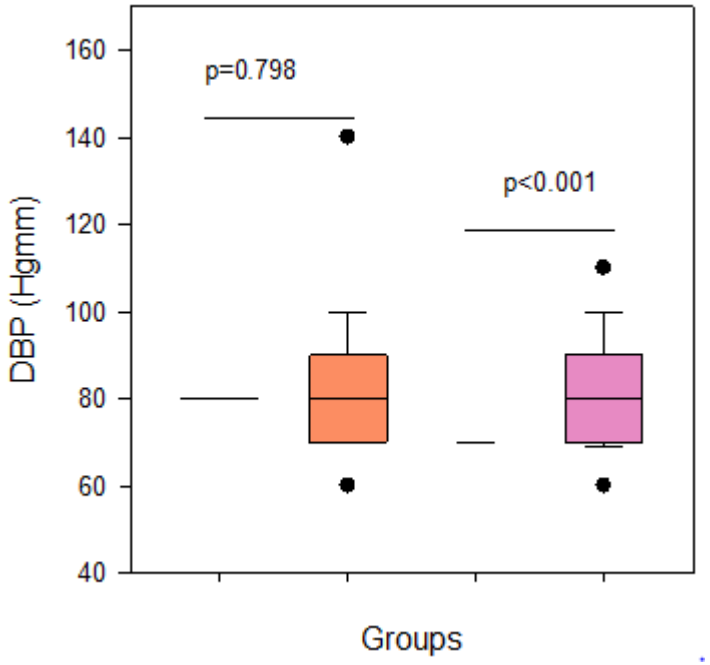
Presence of the variant associated with

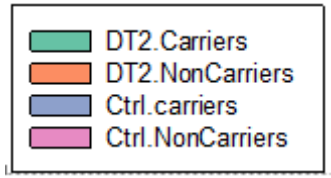
- Trend to low Glucose level in T2DM patients (p=0.06) (Chikowore et *al.*, 2018 vs Schmidt et *al.*, 2017)
- High insulin level and HOMA2 β% in T2DM (p=0.028), not HOMA2-IR (Da Dalt et al, 2019)
- Better response to glibenclamide (Reviewed in Aquilante, 2010)

Results and Discussion

Cardiovascular complications







Presence of the variant associated with

- Low %HTA: control (Carriers:0%; non carriers:52.63%); DT2M (carriers 33.33%; non carriers:58.59%)
- Low DBP in nondiabetic Control (p<0.001)
- SBP: No significant difference

Conclusion and Perspectives

- We identified a PCSK9 variant associated with
- low LDL-cholesterol level
- a better glucose homeostasis in T2DM patients on insulin secretagogue therapy and
- a lower cardiovascular risk.

- Next step:
- assess if the variant has a functional impact (mRNA and protein) and
- describe its mechanism of action

Aknowledgement

ACADÉMIE
DE RECHERCHE ET
D'ENSEIGNEMENT
SUPÉRIEUR

THANK YOU FOR YOUR ATTENTION