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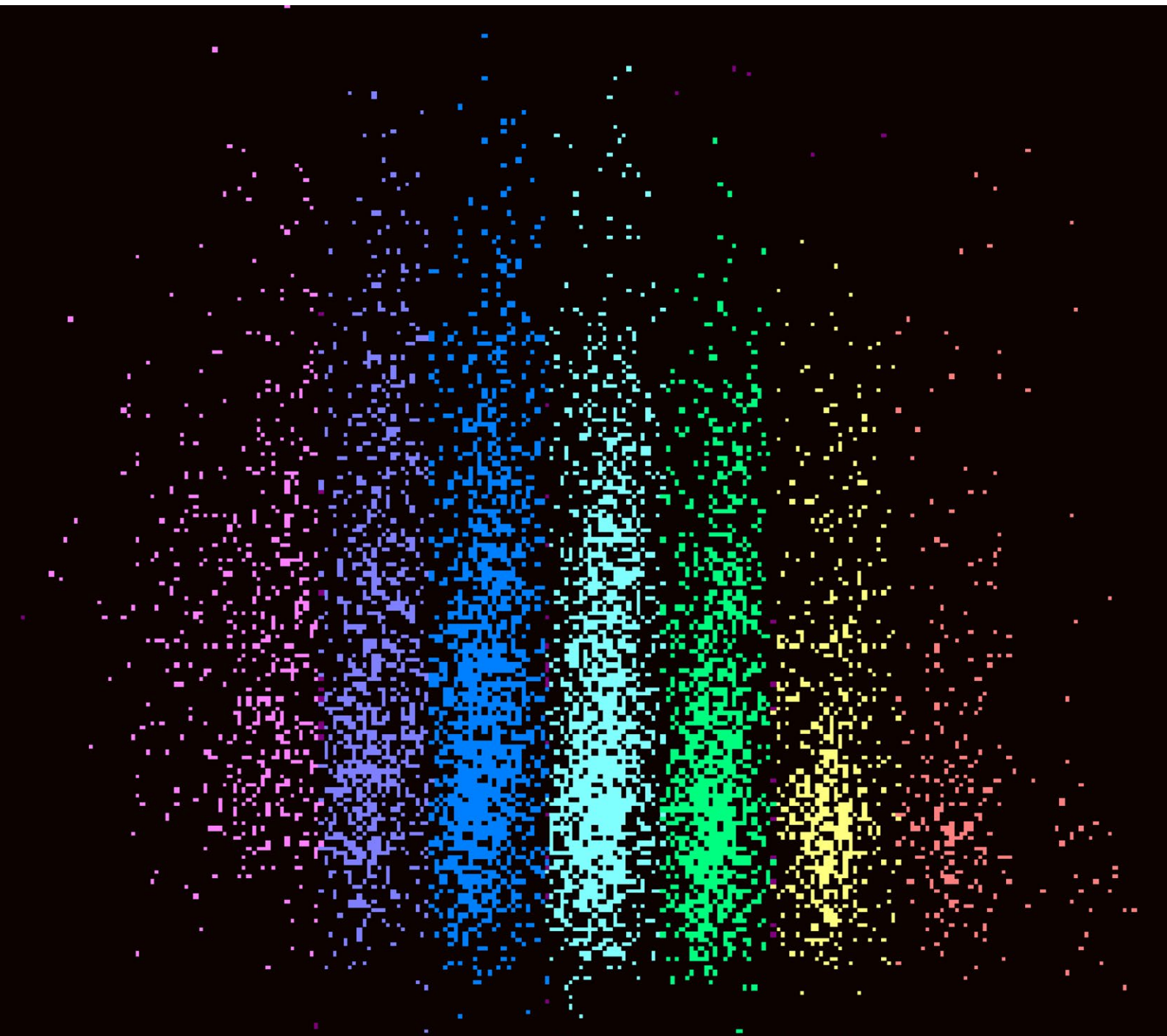

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Contents

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Parental coronary and peripheral artery disease and artery segments in patients and partners – The first and second generation in the Norwegian Stroke in the Young Study

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Keywords
Heredity; atherosclerosis; parental history of cardiovascular disease (CVD); young stroke; carotid intima-media thickness (cIMT) and femoral intima-media thickness (fIMT)

ABSTRACT

Introduction: Age, sex and family history of cardiovascular disease (CVD) are non-modifiable risk factors of CVD in offspring. Our aim was to relate parental CVD (pCVD) to artery vessel-wall measurements in offspring.
Patients and methods: Offspring consisted of acute ischaemic stroke patients (15-60 years) and their partners. Young offspring was defined as ≤45 years old. Arterial wall changes were assessed as intima-media thickness of carotid and femoral arteries (cIMT/fIMT), abdominal aortic plaques (AAP), and ankle-arm index (AAI). Any offspring reported parental coronary artery disease (pCAD) and parental peripheral artery disease (pPAD). In addition, pCAD and pPAD were also verified by standardized questionnaires for living parents, or by medical records for deceased parents.
Results: Reported vs. verified pCVD was present for around 90% vs. 50% of parents. Reported pCAD/pPAD was positive for 227/67 offspring and verified pCAD/pPAD was positive for 148/36 offspring, respectively.
Reported and verified pCAD and pPAD were related to higher cIMT and fIMT. Reported and verified pCAD was also related to AAP and reported pPAD to AAI. The effect attenuated after adjusting for age, hypertension, dyslipidemia, diabetes mellitus and smoking. Among young offspring, reported pCAD was associated with higher cIMT and fIMT, even though the total number of young offspring was 4-fold lower compared to middle-aged offspring.
Conclusions: Parental CVD is related to artery wall changes in offspring, particularly in young offspring. Regarding CVD risk assessment, extensive parental verification of CVD might not be necessary as many young patients and partners seem to be well-orientated about their parental CVD. Primary prevention from young age should get more attention.

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Introduction

Most diseases are now recognized as results of genetic aspects and environmental and lifestyle risk factors. Atherosclerosis is a generalized disease and a major risk factor for cardiovascular events (CVE), such as ischaemic stroke, coronary artery disease (CAD), and peripheral artery disease (PAD). Several studies demonstrated increased early mortality in young stroke patients, mainly as result from coronary death due to atherosclerosis [1-3].

Challenges in performing family studies of CVE include accuracy in documenting the different types of strokes. In addition, previous studies have also combined negative parental CVE with uncertain

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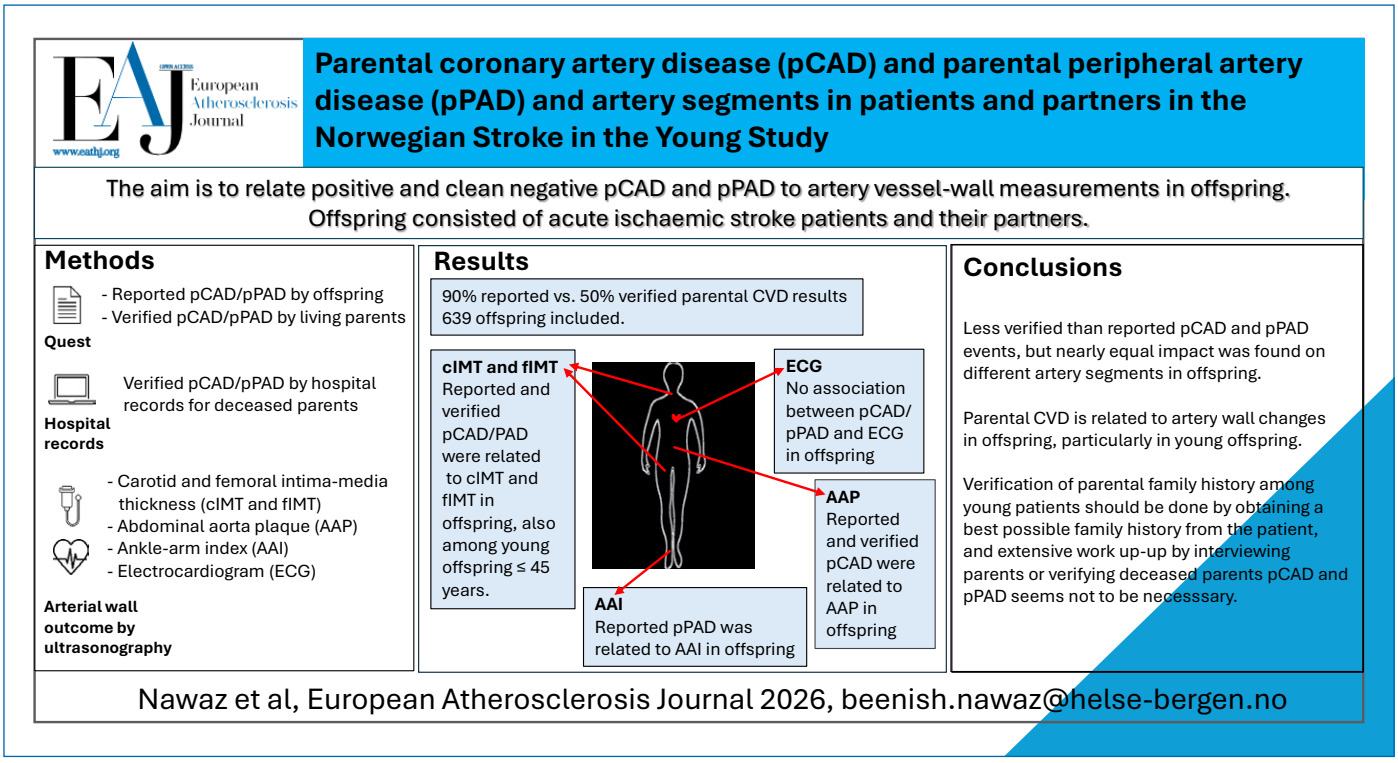


Graphical Abstract

parental CVE, grouping them altogether as negative to avoid exaggeration of the results [4, 5]. However, uncertainty may have led to blurred results, and premature parental CAD (pCAD) is widely accepted as a marker of increased CVE risk in offspring [6].

The aim of this study was to present data as accurate as possible by restricting parental CVD (pCVD) to CAD and PAD, both mainly caused by atherosclerosis. Comparing parental CAD (pCAD) and parental PAD (pPAD) information from offspring with verified information from living parents and verified information by medical records for deceased parents contributed to the accuracy of pCVD. Only either positive or pure negative pCVD data were then related to standardized artery segment measurements by a standardized ultrasound protocol in offspring, consisting of acute ischaemic stroke patients and their partners.

Patients and methods

First and second generation

Inclusion was conducted between 1st September 2010 to 31st December 2015. The first generation consisted of parents of young stroke patients and their partners. pCAD and pPAD were obtained either as reported by their offspring (r-pCAD and r-pPAD), who were

Abbreviations

AAI	Ankle arm index
AAP	Abdominal aorta plaque
CAD	Coronary artery disease
CVD	Cardiovascular disease
CVE	Cardiovascular events
CI	Confidence interval
cIMT	Carotid intima-media thickness
ECG	Electrocardiogram
fIMT	Femoral intima-media thickness
OR	Odds ratio
PAD	Peripheral artery disease
pCAD	Parental coronary artery disease
pCVD	Parental cardiovascular disease
pPAD	Parental peripheral artery disease

r-pCAD	Reported parental coronary artery disease
r-pCADneg	Negative reported parental coronary artery disease
r-pCADpos	Positive reported parental coronary artery disease
r-pCVD	Reported parental cardiovascular disease
r-pPAD	Reported parental peripheral artery disease
r-pPADneg	Negative reported parental peripheral artery disease
r-pPADpos	Positive reported parental peripheral artery disease
v-pCAD	Verified parental coronary artery disease
v-pCADneg	Negative verified parental coronary artery disease
v-pCADpos	Positive verified parental coronary artery disease
v-pCVD	Verified parental cardiovascular disease
v-pPAD	Verified parental peripheral artery disease
v-pPADneg	Negative verified parental peripheral artery disease
v-pPADpos	Positive verified parental peripheral artery disease

regarded as the second generation [7] or verified directly by participating parents by standardized questionnaires or by medical records for deceased parents (v-pCAD and v-pPAD) [8, 9].

Parental history was defined as positive if at least one parent had a positive history of CAD or PAD ($pCAD^{pos}$ and $pPAD^{pos}$). Parental history was defined as negative if none of the parents had a history of CAD or PAD ($pCAD^{neg}$ and $pPAD^{neg}$). Missing or uncertain parental history was excluded from analysis.

The second generation included ischaemic stroke patients at age 15-60 years and their partners or ex-partners, if the patients consented to invite them for inclusion. Partners were at least 18 years old. Inclusion criteria were young and middle-aged acute stroke patients at age 15-60 years, who were admitted to the Department of Neurology at Haukeland University Hospital. Young study participants were defined as 15-45 years old, and middle aged were defined as >45 years old. The diagnosis of ischaemic stroke was verified radiologically. Patients with post-traumatic stroke, stroke caused by sinus venous thrombosis, septicaemia, intracerebral haemorrhage, procedure-related cerebral infarction, serious co-morbidity (advanced cancer or multiple sclerosis) or otherwise limited co-operation (non-native language speakers or patients with severe psychiatric illness) were excluded from the study. Patients consented to contact their partners/ex-partners and parents, and partners/ex-partners consented to contact their parents. Living parents were invited to participate actively by returning a standardized questionnaire [10].

Outcome variables of artery wall measurements and vascular risk factors in the second generation

Patients and partners performed a standardized ultrasound protocol for staging of atherosclerosis by a) carotid and femoral intima-media thickness (cIMT and fIMT). Mean IMT measurements were obtained at 1 cm predefined segments of the common carotid artery, carotid bifurcation, internal carotid artery, common femoral artery and superficial femoral artery. We used the maximum of 12 mean cIMT segment values and 4 fIMT segment values for further analysis, and plaques were included into the IMT measurements at pre-defined standardized sites [11]; b) presence of abdominal aortic plaques (AAP); c) pathological ankle-arm index (AAI) ≤0.9 and d) presence of ischaemic electrocardiogram (ECG), evaluated by a cardiologist (SS). Detailed description of methods was published previously, including the ultrasound protocol, by which any including doctor was internationally certified [10].

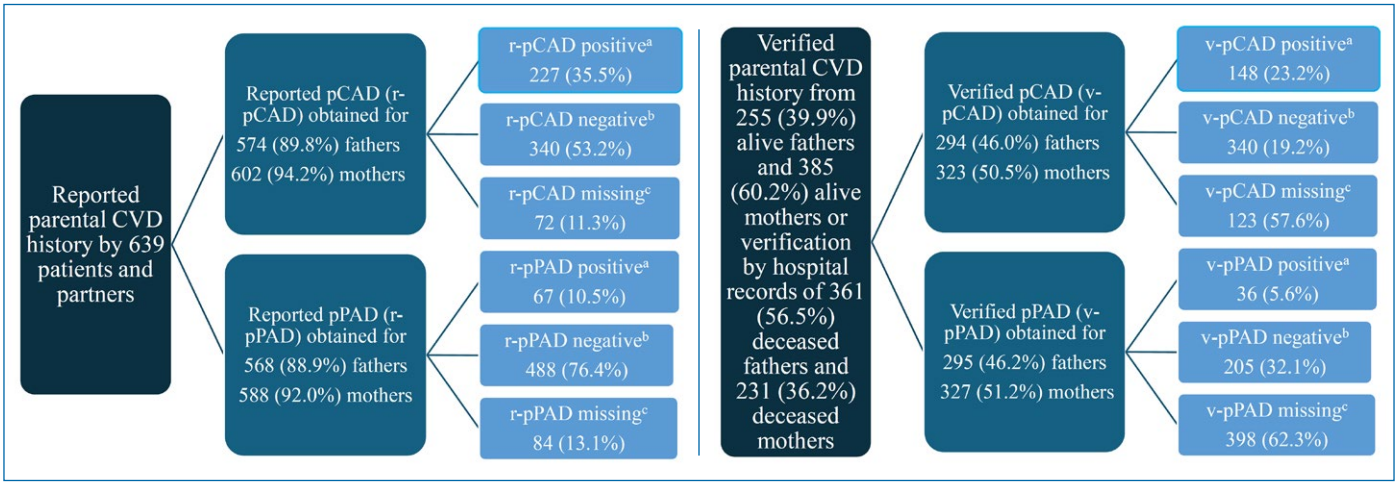
Hypertension and dyslipidaemia were defined as known when treated by lifestyle changes and/or by medications. Hypertension was newly diagnosed if blood pressure was >140/90 mmHg in two separate measurements in both arms after 15-30 minutes rest in supine position after performed ultrasound. Diabetes mellitus and dyslipidaemia was diagnosed by blood samples by HbA1c ≥ 6.5%, a total cholesterol >5.0 mmol/L, low-density lipoprotein >3.0 mmol/L, high density lipoprotein <1.0 mmol/L, and/or fasting triglycerides >2.5 mmol/L in stroke patients only. The history of smoking was considered present if an active study participant was a current (smoked within the past year before inclusion) or former smoker.

Ethical considerations

The study complies with the Declaration of Helsinki and is approved by the Regional Ethics Committee (REK-Vest 2010/74) and registered in ClinicalTrials.gov: NCT01597453. Written consent is present for all active study participants. Parents of patients and partners/ex-partners were invited to the study after patients' and partners' consent, respectively. Verification of pCAD and pPAD in hospital records of deceased parents was done after patients' or partners' consent.

Statistics

Descriptive statistics are presented as frequencies or mean values and 95% confidence intervals (CI). Comparisons between positive and negative pCAD and pPAD, and outcome variables of atherosclerosis in their offspring were done by performing t-test and linear regression for continuous variables (cIMT and fIMT), and chi-square test and logistic regression for dichotomous variables (ECG, AAP, AAI). The results for linear and logistic regression were given as coefficients and odds ratios (OR) with 95% CI, respectively. Multivariable linear and



Flowchart 1 | Participation rates of parents and results of parental coronary heart disease (pCAD) and peripheral artery disease (pPAD) in Norwegian Stroke in the Young Study.
Abbreviations: CVD = cardiovascular disease.
[a]At least one parental positive result.
[b]Both parents were negative.
[c]One or both parents with uncertain results.

logistic regression analyses were also adjusted for age, sex and vascular risk factors including hypertension, diabetes mellitus, dyslipidaemia and smoking. Data analyses were performed using Stata SE 18.0. A P-value <0.05 was considered significant.

Results

Participation rates of parents in the first generation

Reported pCVD history was obtained for around 90% of parents (**Flowchart 1**). For the purpose of verification of the pCVD, patients and partners consented to contact 255 (39.9%) living fathers and 385 (60.2%) living mothers, whereas hospital records were checked for 361 (56.5%) deceased fathers and 231 (36.2%) deceased mothers. In total, verified pCVD history was obtained for around 50% of parents (**Flowchart 1**).

Participation rates of offspring in the second generation

After exclusion of 6 adopted study participants, 381 ischaemic stroke patients (59.6%) and 258 partners (40.4%) were included. Of 639 study participants, 168 (26.3%) were at young age ≤45 years, and 340 (53.2%) were men. Patients were at age 15-60 years, and partners were at age 21-69 years. The mean age of offspring was 49.8 (SD ±9.3) years.

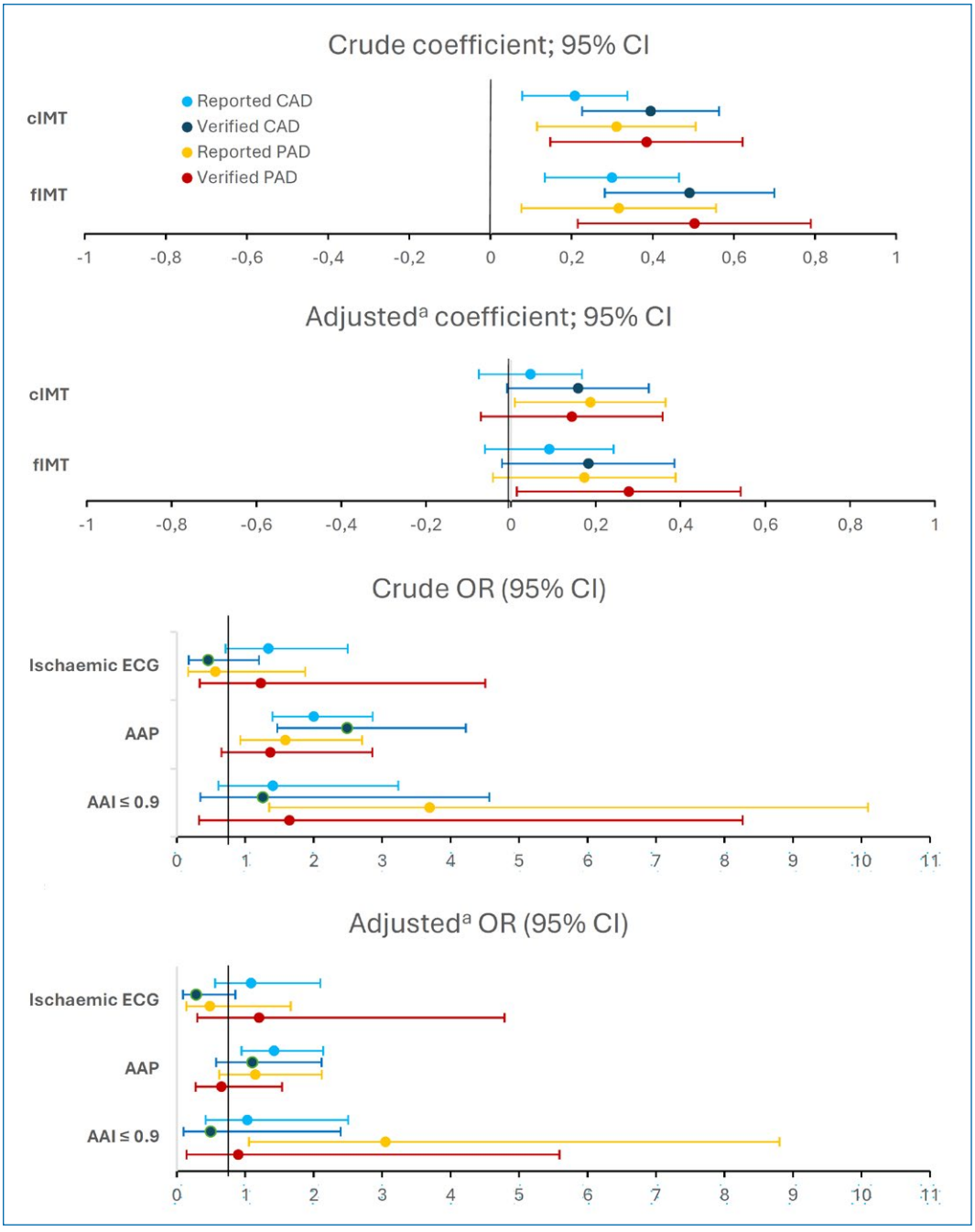


Figure 1A
Forest plot showing association between reported and verified parental coronary artery disease (CAD) and parental peripheral artery disease (PAD) to arterial outcome measurements among 639 offspring, consisting of acute ischaemic stroke patients and their partners in the Norwegian Stroke in the Young Study.

Parental cardiovascular events

There were more r-pCVD results than v-pCVD results (around 90% vs 50%, Flowchart 1). The missing data was much lower for the r-pCVD group than for the v-pCVD group (around 12% vs 60%, **Figure 1**).

After exclusion of missing data, the prevalence of r-pCAD vs. v-pCAD was 40.0% vs. 54.6%; r-pPAD vs. v-pPAD was 12.1% vs. 14.9%, respectively. Among young participants ≤45 years, the prevalence of r-pCAD vs. v-pCAD was 23.0% vs. 30.0%, and r-pPAD vs. v-pPAD was 7.1% vs. 6.8%, respectively.

Prevalent atherosclerosis among the second generation

Mean cIMT and fIMT among all study participants were 1.23 mm and 1.24 mm, respectively (**Table 1**). AAP had the highest prevalence with 42.1%.

Mean cIMT and fIMT among young study participants were 0.79 mm and 0.75 mm, respectively. Young study participants had significantly lower cIMT, fIMT, AAP and AAI compared to middle-aged participants (**Table 1**).

Association of parental CAD and PAD to artery segments in offspring in the second generation

r-pCAD and v-pCAD were associated with higher cIMT, fIMT and AAP. r-pPAD and v-pPAD were associated with higher cIMT and fIMT, and r-pPAD was also associated with AAI (**Table 2**, **Figure 1a** and **Supplementary Table 1a**). The effect was not affected by sex of study participants.

r-pCAD was associated with higher fIMT after adjustment for vascular risk factors (hypertension, diabetes mellitus, dyslipidaemia and smoking), and with AAP after adjustment for age. v-pCAD was associated with higher cIMT and fIMT after adjustment for age and vascular risk factors separately, and there was a trend towards higher cIMT and fIMT after adjustments for both age and vascular risk factors (p = 0.063 and p = 0.078, respectively). v-pCAD was inversely related to ischaemic ECG. (**Figure 1b** and **Supplementary table 1a**).

Table 1 | Prevalent atherosclerosis among offspring in the second generation, consisting of young and middle-aged ischaemic stroke patients and their partners in the Norwegian Stroke in the Young Study.

	Offspring, n = 639	NA	≤45 years, n = 168 (26.3%)	>45 years, n = 471 (73.7%)	P-value
Mean cIMT, mm (95% CI)	1.23 (1.17, 1.29)	3	0.79 (0.74, 0.83)	1.39 (1.31, 1.46)	**<0.001**[a]
Mean fIMT, mm (95% CI)	1.24 (1.16, 1.32)	8	0.75 (0.67, 0.83)	1.41 (1.32, 1.51)	**<0.001**[a]
Ischaemic ECG, n (%)	47 (7.4)	4	9 (5.3)	38 (8.1)	0.238[b]
AAP, n (%)	247 (42.1)	52	24 (15.4)	223 (51.7)	**<0.001**[b]
AAI ≤0.9, n (%)	24 (3.9)	28	1 (0.6)	23 (5.1)	**0.011**[b]

Abbreviations: n = number of offspring; NA = missing; cIMT = carotid intima-media thickness; mm = millimeter; CI = confidence interval; fIMT = femoral intima-media thickness; ECG = electrocardiogram; AAP = abdominal aorta plaques; AAI = ankle arm index.
[a] P-value is estimated by t-test.
[b] P-value is estimated by chi-square test.

Table 2 | Association between reported and verified parental coronary artery disease (CAD) and peripheral artery disease (PAD) and arterial outcome variables among offspring, consisting of acute ischaemic stroke patients and partners in the Norwegian Stroke in the Young Study.

	Reported parental CAD			Verified parental CAD		
Arterial outcome variables in offspring	**n**	**Value (95% CI)**	**P-value**	**n**	**Value (95% CI)**	**P-value**
Mean cIMT[a]	564	1.20 (1.14, 1.27)	**0.002**	270	1.15 (1.06, 1.24)	<0.001
Mean fIMT[a]	561	1.21 (1.14, 1.30)	**<0.001**	270	1.12 (1.01, 1.23)	<0.001
Ischaemic ECG[b]	563	1.34 (0.72, 2.49)	0.362	269	0.46 (0.17, 1.20)	0.106
AAP[b]	520	2.00 (1.40, 2.86)	**<0.001**	250	2.49 (1.47, 4.22)	0.001
AAI ≤0.9[b]	544	1.40 (0.61, 3.24)	0.631	260	1.26 (0.35, 4.56)	0.727
	Reported parental PAD			**Verified parental PAD**		
Mean cIMT[a]	552	1.21 (1.14, 1.27)	**0.018**	240	1.12 (1.04, 1.21)	0.045
Mean fIMT[a]	547	1.19 (1.11, 1.27)	**0.016**	240	1.06 (0.95, 1.16)	0.005
Ischaemic ECG[b]	553	0.56 (0.17, 1.88)	0.343	239	1.23 (0.33, 4.50)	0.757
AAP[b]	512	1.58 (0.93, 2.71)	0.090	225	1.36 (0.65, 2.86)	0.408
AAI ≤0.9[b]	532	3.69 (1.35, 10.09)	**0.007**	232	1.65 (0.33, 8.27)	0.542

Abbreviations: CAD = coronary artery disease; *n* = number of offspring; CI = confidence interval; cIMT = carotid intima-media thickness; fIMT = femoral intima-media thickness; ECG = electrocardiogram; AAP = abdominal aorta plaque; AAI = ankle-arm index; PAD = peripheral artery disease.
[a] Mean difference (95% CI), p-value estimated by t-test
[b] Odds ratio (95% CI), p-value estimated by chi-square test.

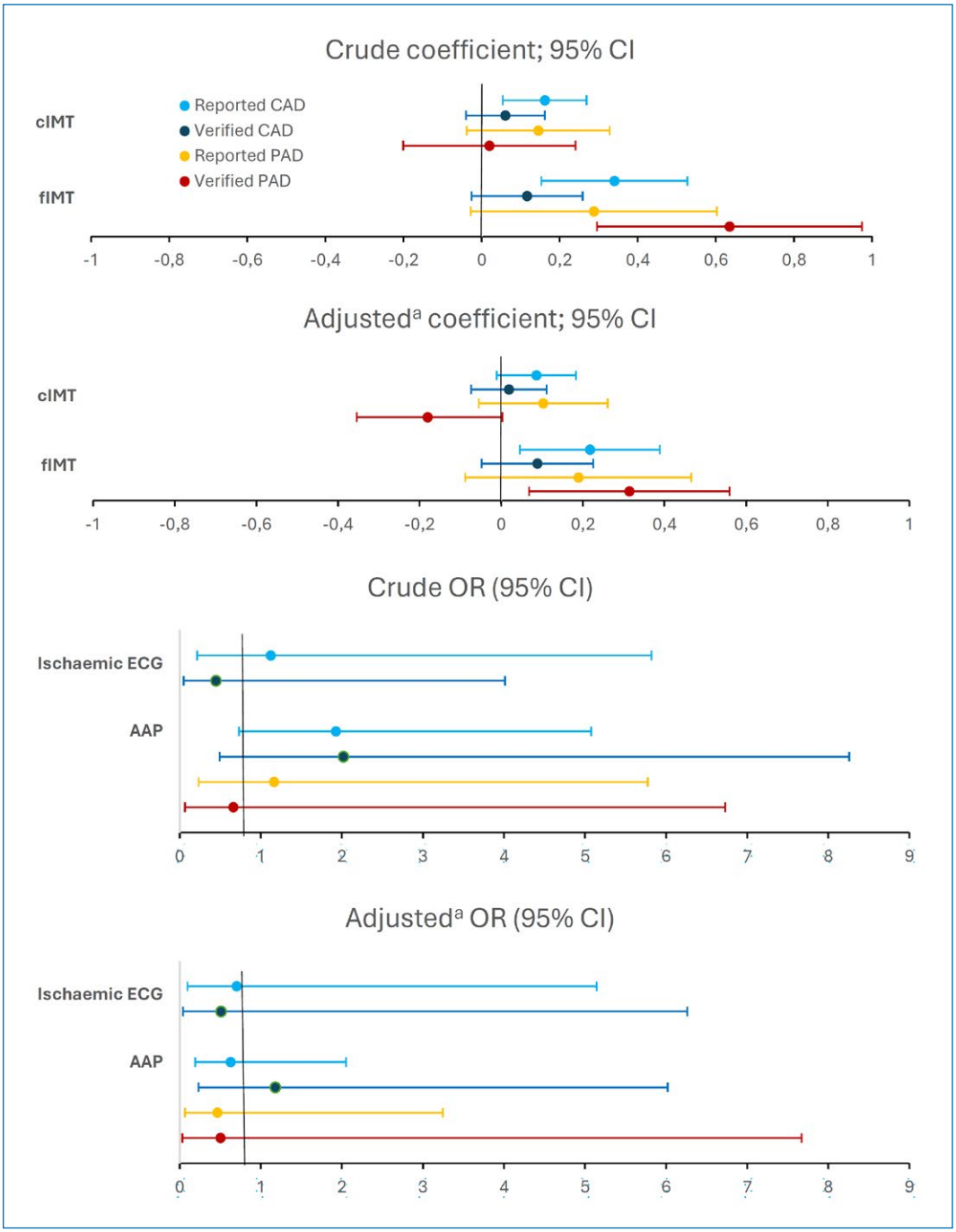


Figure 1B
Forest plot showing association between reported and verified parental coronary artery disease (CAD) and parental peripheral artery disease (PAD) to arterial outcome measurements among 168 offspring, consisting of acute ischaemic stroke patients and their partners aged ≤45 years in the Norwegian Stroke in the Young Study. Abbreviations: CI = confidence interval, cIMT = carotid intima-media thickness; fIMT = femoral intima-media thickness; OR = odds ratio; ECG = electrocardiogram; AAP = abdominal aorta plaques; AAI = ankle-arm index; a Adjusted for age and vascular risk factors (hypertension, diabetes mellitus, dyslipidaemia and smoking).

r-pPAD was related to higher cIMT and AAI after adjustments for age and risk factors. v-pPAD was related to higher cIMT after adjustment for risk factors, and to fIMT after adjustments for age and risk factors. (**Figure 1b** and **supplementary Table 1a**).

A sub-analysis for young study participants showed that r-pCAD was related to higher cIMT and fIMT (**Table 3b**, **Figure 1b** and **Supplementary Table 1b**). v-pPAD was related to higher fIMT. Sex had no impact on the results. After adjusting for age and vascular risk factors, r-pCAD and v-pPAD were related to higher fIMT. (**Supplementary Table 1b**).

Comparison of reported positive and negative parental family history to arterial wall changes in the second generation

Crude results of reported vs. verified pCVD were almost similar, however, there were more missing results in the verified group. Therefore, comparisons of positive and negative pCAD and pPAD to arterial wall changes among offspring were only performed for the reported group. Mean cIMT and fIMT were higher and AAP was more frequent among study participants with r-pCAD^{pos} compared with those with r-pCAD^{neg} (**Table 3A**). Mean cIMT and fIMT were higher and AAI more frequent

among study participants with r-pPAD^{pos} compared with those with r-pPAD^{neg}.

For young study participants ≤45 years, mean cIMT and fIMT were higher among study participants with r-pCAD^{pos} compared with those with r-pCAD^{neg} (**Table 3B**). For middle-aged study participants, AAP was more frequent among study participants with r-pCAD^{pos} compared with those with r-pCAD^{neg}, and AAI was more frequent among study participants with r-pPAD^{pos} compared to those with r-pPAD^{neg} (**Table 3C**).

Discussion

Positive pCAD and pPAD is along with age and sex a well-known non-modifiable marker of atherosclerosis, and is regarded as a

Table 3 | Arterial outcome variables among offspring, consisting of ischaemic stroke patients and their partners for reported positive and negative parental coronary artery disease (CAD) and peripheral artery disease (PAD) in the Norwegian Stroke of the Young Study.

Arterial outcome variables among all offspring	**Positive reported parental CAD**		**Negative reported parental CAD**		**P-value**
Mean cIMT, mm (95% CI)	*n* = 226	1.33 (1.22, 1.44)	*n* = 338	1.12 (1.04, 1.20)	0.002[a]
Mean fIMT, mm (95% CI)	*n* = 226	1.39 (1.26, 1.53)	*n* = 335	1.10 (0.99, 1.20)	<0.001[a]
Ischaemic ECG, n (%)	*n* = 225	20 (8.9)	*n* = 338	23 (6.80)	0.362[b]
AAP, *n* (%)	*n* = 209	107 (51.2)	*n* = 311	107 (34.4)	<0.001[b]
AAI ≤0.9, *n* (%)	*n* = 217	11 (5.1)	*n* = 327	12 (3.7)	0.631[b]
	Positive reported parental PAD		**Negative reported parental PAD**		**P-value**
Mean cIMT, mm (95% CI)	*n* = 67	1.48 (1.23, 1.73)	*n* = 485	1.17 (1.11, 1.24)	0.018[a]
Mean fIMT, mm (95% CI)	*n* = 66	1.47 (1.22, 1.71)	*n* = 481	1.15 (1.07, 1.23)	0.016[a]
Ischaemic ECG, *n* (%)	*n* = 66	3 (4.5)	*n* = 487	38 (7.8)	0.343[b]
AAP, *n* (%)	*n* = 61	31 (50.8)	*n* = 451	178 (39.47)	0.090[b]
AAI ≤0.9, *n* (%)	*n* = 63	6 (9.5)	*n* = 469	13 (2.8)	0.007[b]
Arterial outcome variables among offspring ≤45 years	**Positive reported parental CAD**		**Negative reported parental CAD**		**P-value**
Mean cIMT, mm (95% CI)	*n* = 35	0.90 (0.76, 1.03)	*n* = 115	0.73 (0.69, 0.78)	0.024[a]
Mean fIMT, mm (95% CI)	*n* = 35	0.99 (0.74, 1.23)	*n* = 114	0.64 (0.57, 0.71)	0.010[a]
Ischaemic ECG, n (%)	n = 35	2 (5.7)	*n* = 117	6 (5.1)	0.892[b]
AAP, *n* (%)	n = 35	8 (22.9)	*n* = 105	14 (13.3)	0.180[b]
AAI ≤0.9, *n* (%)	n = 35	0 (0.0)	*n* = 113	1 (0.9)	0.577[b]
	Positive reported parental PAD		**Negative reported parental PAD**		**P-value**
Mean cIMT, mm (95% CI)	*n* = 11	0.91 (0.69, 1.14)	*n* = 141	0.77 (0.72, 0.82)	0.192[a]
Mean fIMT, mm (95% CI)	*n* = 11	0.99 (0.55, 1.44)	*n* = 140	0.71 (0.62, 0.79)	0.189[a]
Ischaemic ECG, *n* (%)	*n* = 11	0 (0.0)	*n* = 143	8 (5.6)	0.649[b]
AAP, *n* (%)	*n* = 11	2 (18.2)	*n* = 131	21 (16.0)	0.852[b]
AAI ≤0.9, *n* (%)	*n* = 11	0 (0.0)	*n* = 140	1 (0.70)	0.779[b]
Arterial outcome variables among offspring >45 years	**Positive reported parental CAD**		**Negative reported parental CAD**		**P-value**
Mean cIMT, mm (95% CI)	*n* = 191	1.41 (1.29, 1.53)	*n* = 223	1.32 (1.22, 1.43)	0.291[a]
Mean fIMT, mm (95% CI)	*n* = 191	1.47 (1.32, 1.62)	*n* = 221	1.33 (1.19, 1.47)	0.174[a]
Ischaemic ECG, *n* (%)	*n* = 190	18 (9.5)	*n* = 221	17 (7.7)	0.519[b]
AAP, *n* (%)	*n* = 174	99 (56.9)	*n* = 206	93 (45.1)	0.022[b]
AAI ≤0.9, *n* (%)	*n* = 182	11 (6.0)	*n* = 214	11 (5.1)	0.696[b]
	Positive reported parental PAD		**Negative reported parental PAD**		**P-value**
Mean cIMT, mm (95% CI)	*n* = 56	1.59 (1.31, 1.88)	*n* = 344	1.34 (1.25, 1.42)	0.089[a]
Mean fIMT, mm (95% CI)	*n* = 55	1.56 (1.28, 1.84)	*n* = 341	1.33 (1.23, 1.44)	0.126[a]
Ischaemic ECG, n (%)	*n* = 55	3 (5.5)	*n* = 344	30 (8.7)	0.414[b]
AAP, n (%)	*n* = 50	29 (58.0)	*n* = 320	157 (49.1)	0.240[b]
AAI ≤0.9, n (%)	*n* = 52	6 (11.5)	*n* = 329	12 (3.6)	0.013[b]

Abbreviations: cIMT = carotid intima-media thickness; mm = millimeter; CI = confidence interval; n = number of offspring; fIMT = femoral intima-media thickness; ECG = electrocardiogram; AAP = abdominal aorta plaques; AAI = ankle arm index; PAD = peripheral artery disease.
[a] P-value is estimated by t-test.
[b] P-value is estimated by chi-square test.

surrogate marker for genetic predisposition [12]. Few studies have analyzed the sharing of familial susceptibility to atherosclerotic disease at several vascular areas. In a Swedish nationwide register study, risk of CAD, ischaemic stroke, PAD and aortic disease was increased among siblings and offspring [13]. To our knowledge, our study is unique as this is a prospective study where patients/partners as the second generation were thoroughly examined at standardized artery segments at different vascular areas by an extensive ultrasonographic protocol. Previous studies of pathology have shown that atherosclerosis is not equally distributed in the body [14]. A study of 212 patients without known CVD showed high presence of subclinical atherosclerosis in carotid, femoral and coronary areas, but only a weak concordance between different vascular territories, and suggested that all three vascular areas should be investigated [15].

Interestingly, most of our crude (unadjusted) results were not affected by the methods chosen to obtain the pCVD history. Our previous study showed that reported pCVD history by patients was in good concordance with parental reports [8]. Our results show that comprehensive verification work of parental history may give us slightly higher prevalence of CAD and PAD in the verified group, however, due to the large number of missing data among the verified group, it is not easy to draw a conclusion.

We found a positive association between pCAD and higher cIMT, fIMT and AAP, suggesting that parental CAD increases the risk of generalized atherosclerosis in the next generation, mainly in carotid and femoral arteries and aorta. A positive association of pCAD to cIMT in offspring has been well-documented in other studies, also in the younger population [16-21] However, data is scarce for the association of pCAD with fIMT and AAP. A study has shown that parental occurrence of premature CVD may predict abdominal aortic calcification in the second and third generation [22].

Our study showed a weak inverse relation of v-pCAD to ischaemic ECG changes in the offspring. This may be attributed to selection bias among partners who participated, and a low sample size with low prevalence of ischaemic ECG (7.4%). Another possible explanation could have been a trend towards a healthier lifestyle for young adults with known pCAD history. However, a cross sectional study from three large epidemiological studies reported positive association of pCAD with ECG changes in offspring after adjustment for age, smoking, BMI and sex, [23] so there may be a type 1 error in our study.

Overall, pPAD is less studied than pCAD. We found a positive association of pPAD to cIMT and pathological AAI, suggesting that pPAD increases the risk of generalized atherosclerosis. There is scarce literature on the association of pPAD to cIMT, which makes our study quite unique. The San Diego Population study of 2404 participants from an ethnically diverse population aged between 29-91 years, found that there was a strong association between pPAD to PAD prevalence (OR 1.83) and PAD-severity (OR 2.42) in the offspring. PAD was defined as AAI ≤0.90.(24) In another study, young individuals with occult PAD ≤49 years were three times more likely to have a family history of PAD (OR 2.76) [25]. In another study, pPAD and pCAD were independently associated with the presence of PAD, and the association was age-dependent, being stronger in younger individuals (<68 y vs ≥68 y) [26].

Another important observation in our study is that r-pCAD was strongly associated with higher cIMT and fIMT among the young study participants, even though the total number of participants in the young group was 4-fold lower (26.3%) compared to the middle-aged group, which may potentially have limited the statistical power. This demonstrates that positive history of r-pCVD shows the risk of arterial wall changes already early in life in the offspring. In the middle-aged group, positive history of r-pCAD was related to AAP and positive history of r-pPAD to AAI. However, there were a lot more participants in the middle-aged group (73.7%), and the prevalence of peripheral artery disease and abdominal aorta plaques increases with age [27-28].

Strengths of our study include a thorough investigation of pCAD and pPAD. We increased the accuracy of our study by excluding uncertain family history information and including only pure positive and negative pCAD and pPAD. The comparisons of reported and verified pCVD represents also a methodological strength and provides meaningful insight into the reliability of routine clinical assessment. The assessment of artery wall changes was done by objective and extensive ultrasound protocol to enhance the robustness of the findings.

There were also limitations. The offspring in this study consisted of ischaemic stroke patients and their partners rather than a general population sample due to the three-generation design of the Norwegian Stroke in the Young Study, which may restrict generalizability, and could lead to a possible selection bias. Another limitation was that only patients performed blood tests for blood-lipids and glucose, while partners provided information on dyslipidaemia and diabetes mellitus only by self-reported questionnaires, probably underestimating dyslipidaemia and diabetes mellitus among partners. Among the v-pCVD group, there was a substantial amount of missing information attributed due to either non-consent from study participants to contact their parents, or due to serious comorbidity among living parents. However, most of the crude results of reported and verified pCVD still were similar. Furthermore, as our study participants were young and middle-aged, it would be of great interest to know whether their pCVD was premature, but this information was not obtained as we did not ask about age at the time of the parental event.

This study explores the relationship between pCVD to presence of subclinical and clinical atherosclerosis in the offspring, and particularly among the young offspring. Our study highlights the value of using a clear parental history in CVD risk assessment. As the study showed almost similar crude results for reported and verified pCVD history, there might not be a need for an extensive verification of the parental history of young patients. It would also be time saving both in research and in clinical practice. Early arterial wall changes are associated with positive pCVD, particularly in young adults ≤45 years. This would be of great practical value in clinical practice with higher focus on screening and primary prevention of modifiable risk factors for cardiovascular disease.

Conflict of interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article

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Author contribution

UWA – conceived the study and was involved in protocol development and gaining ethical approval. Data collection was done by BN, HØ, AF and UWA. Data interpretation of parental family history was done by HØ, SB and BN. Data interpretation of electrocardiograms were done by SS. BN did the literature search and wrote the first draft of the manuscript. Statistical analysis was done by BN and JA. All authors reviewed and edited the manuscript and approved the final version.

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An Observational Longitudinal Multicenter Prospective Study to Evaluate Treatment Patterns in High, Very High, and Extreme Cardiovascular Risk Patients with Hypercholesterolemia, Including Familial Hypercholesterolemia, Over a 1-Year Follow-Up: Protocol of the TRAP-HC Study

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Keywords
Hypercholesterolemia; LDL cholesterol; Cardiovascular risk; LDL-C goal attainment; Real-world evidence

ABSTRACT

Background: Elevated low-density lipoprotein cholesterol (LDL-C) is a causal driver of atherosclerotic cardiovascular disease (ASCVD). Although current European guidelines recommend intensive LDL-C lowering strategies in high, very high, and extreme cardiovascular risk patients, real-world data consistently show suboptimal goal achievement.
Aim and Methods: The TRAP-HC study aims to evaluate real-world treatment patterns, LDL-C goal attainment, and adherence to lipid-lowering therapies (LLTs) in patients with hypercholesterolemia, including familial hypercholesterolemia (FH), at high, very high, and extreme cardiovascular risk over a 1-year follow-up.
TRAP-HC is a multicenter, prospective, longitudinal, observational study conducted across up to 15 lipid clinics within the Italian LIPIGEN network. Approximately 2,500 adult patients will be enrolled and followed for one year. The primary endpoint will be the change in LDL-C levels and achievement of guideline-recommended LDL-C goals. Secondary endpoints will include adherence, treatment intensification patterns, and patient-reported attitudes toward therapy.
Conclusion: TRAP-HC will provide contemporary real-world evidence on lipid management in high-risk populations and identify gaps between guideline recommendations and clinical practice.

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Introduction

Cardiovascular disease (CVD) remains the leading cause of mortality worldwide, with ischemic heart disease representing the principal contributor to global cardiovascular burden. Data from the Global Burden of Disease study have consistently demonstrated the magnitude of this challenge and its persistent impact on healthcare systems and populations [1]. Among modifiable cardiovascular risk factors, elevated low-density lipoprotein cholesterol (LDL-C) plays a central causal role in the initiation and progression of atherosclerotic cardiovascular disease (ASCVD).

Robust genetic, epidemiological, and interventional evidence supports the concept that LDL-C reduction translates into proportional reductions in cardiovascular events [2, 3]. Consequently, contemporary European guidelines from the European Society of Cardiology and the European Atherosclerosis Society advocate intensive

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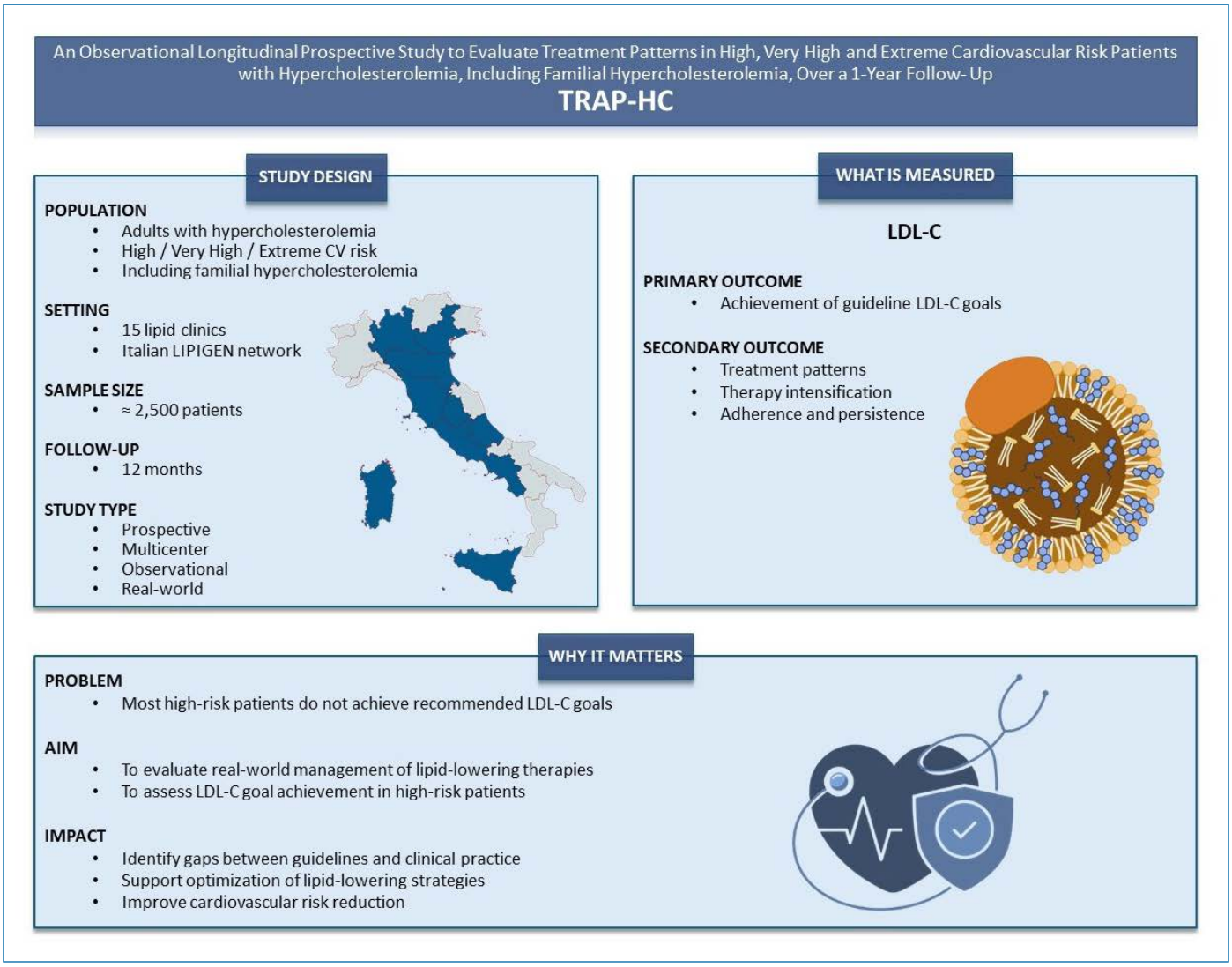

Graphical Abstract

LDL-C lowering strategies, particularly in patients at high, very high, and extreme cardiovascular risk [4]. Current recommendations include a ≥50% reduction in LDL-C from baseline and absolute LDL-C goals of <70 mg/dL in high-risk patients, <55 mg/dL in very high-risk patients, and <40 mg/dL in individuals categorized as extreme risk [5].

Several lipid-lowering therapies (LLTs) are currently available for the management of hypercholesterolemia. Contemporary strategies rely on a stepwise approach, with statins as first-line treatment, followed by the addition of non-statin agents when needed to achieve LDL-C targets. These include cholesterol absorption inhibitors (e.g., ezetimibe), PCSK9-targeting therapies, ATP-citrate lyase inhibitors, and other agents with complementary mechanisms of action [6-8].

Despite the availability of effective combination therapies, their use in clinical practice remains suboptimal. Several large real-world European studies have revealed substantial gaps between guideline recommendations and clinical practice. The EUROASPIRE V survey highlighted that a significant proportion of patients with established coronary disease fail to achieve LDL-C goals, even in specialized care settings [9]. Similarly, the DA VINCI study demonstrated that LDL-C goal attainment remains unsatisfactory across Europe, particularly among very high-risk individuals [10]. More recently, the SANTORINI study showed that approximately 80% of high and very high cardiovascular risk patients do not reach recommended LDL-C levels, with monotherapy still frequently employed despite the availability of effective combinations and advanced LLTs [11].

The gap between real-world practice and optimal cholesterol management is also evident in patients with familial hypercholesterolaemia (FH), a group characterized by markedly elevated LDL-C levels and particularly high cardiovascular risk. Even in specialized lipid clinics, achieving guideline-recommended LDL-C thresholds in FH patients remains challenging, underscoring the need for better understanding of real-world management strategies [10-13].

Despite the availability of effective therapies and well-defined guideline recommendations, LDL-C goal attainment remains suboptimal in real-world practice. However, there is still limited understanding of how LLTs are actually prescribed, combined, and intensified in routine clinical care, and how these patterns translate into LDL-C outcomes. This lack of granular real-world data is particularly evident in the Italian context.

In this scenario, comprehensive evaluation of treatment patterns, therapeutic intensification, adherence behaviors, and LDL-C outcomes in contemporary clinical practice is critically needed. The TRAP-HC (TReatment pAtterns in Patients with HyperCholesterolemia at high, very high and extreme cardiovascular risk) study has been designed to provide real-world evidence on LLT patterns and LDL-C goal attainment in Italy, with the aim of better characterizing and understanding the extent of the gap between guideline recommendations and routine clinical practice.

Methods

Study design and objectives

TRAP-HC is a multicenter, prospective, observational, longitudinal cohort study designed to evaluate real-world lipid management in patients at high, very high, and extreme cardiovascular risk.

The observational design reflects routine clinical practice. No investigational medicinal products will be administered and no therapeutic decisions will be dictated by the protocol. Patients will continue to receive LLTs according to the judgment of their treating physicians and current standards of care.

The primary objective of the TRAP-HC study is to assess real-world LDL-C control in patients with hypercholesterolemia at high, very high, and extreme cardiovascular risk over a 1-year follow-up. Secondary objectives include the characterization of LLT patterns over time, including treatment intensification, combination strategies, switching, and discontinuation. The study also examines adherence and persistence to LLTs and explores their association with LDL-C goal attainment.

Study population

The study will be conducted in 15 lipid clinics in Italy participating in the LIPIGEN network, a nationwide collaborative network of lipid clinics coordinated by the Italian Society for the Study of Atherosclerosis [14].

The participating centres will competitively enrol 2,500 adult subjects (≥18 years) with hypercholesterolemia, including individuals classified as high, very high, or extreme cardiovascular risk, according to curent European guidelines. Subjects with clinically or genetically diagnosed FH will also be included Patients with secondary dyslipidemia, as well as subjects with hypertriglyceridemia (HTG), will be excluded. . The study population is expected to consist predominantly of non-FH patients (approximately 85%), reflecting the real-world distribution within lipid clinics.

The sample size of 2,500 subjects was determined to ensure high precision in estimating LDL-C variations across the entire cohort and within key clinical subgroups. Based on an expected standard deviation of 25 mg/dL, this sample size provides 80% power to detect even minor mean longitudinal changes in LDL-C (down to 1.5 mg/dL) at a two-sided significance level of 0.05. Furthermore, this robust sample size guarantees adequate statistical power for analysis within the FH subpopulation (n≈375), allowing for the detection of clinically relevant differences of 4 mg/dL. The final target also accounts for potential data attrition, ensuring the study remains powered for all secondary and exploratory endpoints.

Study procedures and follow-up

All study procedures are conducted within the framework of routine clinical practice, without protocol-mandated therapeutic interventions. After verification of eligibility criteria, patients who provide written informed consent will be enrolled during a six-month recruitment window and followed for 1 year. Upon enrolment, each participant will be assigned a unique, centrally generated identification code to ensure pseudonymization and prevent duplication across participating centers. Only the treating physician will retain the link between the identification code and patient identity, in compliance with data protection regulations, including the European General Data Protection Regulation (GDPR; Regulation (EU) 2016/679).

Baseline period

At the baseline visit (T0), comprehensive clinical biochemical and therapeutic data will be collected. Demographic information includes age, sex, ethnicity, body weight, height, and body mass index (BMI). A detailed medical history will be obtained, with specific attention to prior major adverse cardiovascular events (MACE), including myocardial infarction, stroke, coronary, or peripheral revascularization procedures, and documented atherosclerotic cardiovascular disease. Relevant comorbidities such as diabetes mellitus, hypertension, and chronic kidney disease will be recorded.

The diagnosis of FH, whether clinical or genetically confirmed, will be documented. For newly referred patients without a prior confirmed diagnosis, the diagnosis will be documented during the follow-up, according to standard clinical practice.

A complete lipid profile will be collected at baseline, including total cholesterol, LDL-C, High-Density Lipoprotein Cholesterol (HDL-C), triglycerides, apolipoprotein B, and lipoprotein(a). When available, historical lipid data, particularly pre-treatment LDL-C levels, will be retrieved to allow estimation of baseline untreated cholesterol exposure. Laboratory assessments will also include liver function tests (alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase), renal function parameters (serum creatinine and estimated glomerular filtration rate), and creatine kinase levels.

Data regarding physical examination and assessment of vital signs, performed as part of routine care, will be also collected.

All prior and concomitant medications will be documented, with detailed recording of LLTs, including statins, ezetimibe, PCSK9 inhibitors, bempedoic acid, fibrates, lomitapide, evinacumab, and siRNA-based therapies, when applicable. Dosage and duration of therapy will be recorded.

Follow-up assessments

Participants will be followed for 1 year. Data collection at follow-up will include an assessment within 12 months from the baseline visit, in line with routine clinical practice, where at least one annual follow-up visit is recommended for these patients. Additionally, where available, a follow-up assessment within 6 months from baseline will also be collected. No additional visits beyond standard care are mandated by the protocol.

At each follow-up visit, an updated lipid profile will be recorded (if available), including total cholesterol, LDL-C, HDL-C, and triglycerides.

All modifications to LLTs will be systematically recorded, including treatment intensification, dose adjustments, switching between agents, initiation of combination therapy, or discontinuation. Reasons for therapeutic changes, such as inadequate LDL-C response, adverse effects, statin intolerance, patient preference, or reimbursement constraints, will be documented whenever available.

Adverse events (AEs) and serious adverse events (SAEs) occurring during the study period will be documented according to routine clinical practice and local regulatory requirements.

Data management

All collected data will be entered into a dedicated electronic Case Report Form (eCRF). Data entry will follow predefined quality con-

trol procedures to ensure accuracy, completeness and internal consistency. The database will undergo medical and scientific review prior to final analysis. Patient confidentiality will be maintained throughout the study and all analyses will be conducted on pseudonymized data.

Study endpoints

As for the primary objective of the TRAP-HC study (to assess real-world LDL-C control in patients with hypercholesterolemia), the primary endpoint is the proportion of patients achieving LDL-C goals at 12 months, according to contemporary recommendations from the European Society of Cardiology and the European Atherosclerosis Society. The secondary endpoints include i) the percentage of subjects who achieve the LDL-C goal at 6 months, and ii) the distance from the goal in subjects who do not achieve it, at 6 and 12 months

For the secondary objective related to the characterization of LLT patterns over time, primary endpoint is the proportion of patients receiving each class of LLT at baseline and at 12 months. Secondary endpoints include

i) proportion of patients undergoing treatment intensification (dose increase or addition of a new LLT) during follow-up;
ii) proportion of patients on combination therapy at each follow-up visit;
iii) rate of therapy switching (from one LLT to another) over 12 months; and
iv) rate of therapy discontinuation over 12 months.

For the secondary objective related to treatment adherence and persistence to LLTs primary endpoint is the proportion of patient's adherent to prescribed LLT at 12 months (based on self-reported patient data). Secondary endpoints include i) proportion of adherent patients at 6 months, ii) proportion of persistent patients with LLT at 6 and 12 months (no treatment discontinuation); iii) association between adherence/persistence and LDL-C goal attainment.

Statistical Analysis

All statistical analyses will be performed on the full study population with available data, considering a total observation period of 12 months from baseline.

The primary analysis will focus on the longitudinal change in LDL-C levels and the achievement of ESC/EAS cardiovascular risk-stratified goals within this one-year timeframe. Every enrolled subject is expected to have at least one follow-up assessment by the end of the study period to be included in the primary evaluation. For each patient, the percentage reduction in LDL-C will be calculated as (LDL-C minus pre-treatment LDL-C)/ pre-treatment LDL-C and compared both with the expected reduction of the prescribed lipid-lowering therapy (LLT) and the reduction required to reach individual guidelines targets. Subjects will be classified as 'at goal' or 'not at goal' based on their latest available assessment within the year, with further stratification according to their distance from the target.

A specific secondary analysis will be conducted on the subgroup of patients with a follow-up visit occurring within the first 6 months. Changes in the lipid profile (LDL-C, total cholesterol, HDL-C, and triglycerides) will be analysed using paired t-tests or Wilcoxon signed-rank tests, as appropriate, and further explored through linear mixed-effects models to account for the varying number and timing of follow-up visits while adjusting for baseline covariates. Cumulative lipid exposure, such as "cholesterol years," will be calculated where data allow.

The evolution of LLT regimens, including dose adjustments, treatment switches, or discontinuations, will be monitored and analysed alongside patient-reported adherence and persistence. Adherence will be defined as taking the therapy as directed, while persistence will track the continued use of LLT without interruption. Differences in adherence and goal attainment between subgroups – such as treatment-naïve versus previously treated patients, or different LLT types – will be assessed using Chi-square or Fisher's exact tests, and the association between these factors will be explored via logistic regression.

Final results will be stratified by age, sex, cardiovascular risk category, and FH status. Continuous variables will be summarized as mean ± standard deviation or median (interquartile range) according to their distribution, while categorical variables will be presented as counts and percentages. A two-sided p-value < 0.05 will be considered statistically significant, with adjustments for multiple comparisons where appropriate.

Ethical considerations

The study will be conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Informed consent will be obtained from all participants, and the study protocol will be reviewed and approved by an independent ethics committee.

Discussion

Current recommendations from EAS/ESC guidelines advocate intensive LDL-C reduction, particularly in patients at very high and extreme cardiovascular risk. However, large observational studies such as EUROASPIRE V, DA VINCI, and SANTORINI demonstrate that a substantial proportion of patients fail to achieve these goals, even in specialized settings. These findings suggest that therapeutic inertia, insufficient use of combination therapy, concerns about adverse effects, reimbursement constraints and suboptimal adherence contribute to residual lipid-related risk [16].

TRAP-HC aims at addressing these challenges by adopting a prospective longitudinal design that captures dynamic changes in therapy over time. Unlike cross-sectional registries, this approach allows evaluation of how clinicians respond to inadequate LDL-C control, whether intensification strategies are implemented and how patient adherence evolves during follow-up. By analysing treatment patterns at baseline, six months, and twelve months, the study will provide insight into the timing of therapeutic adjustments and their effectiveness in reducing LDL-C levels.

The inclusion of patients across high, very high, and extreme risk categories allows assessment of risk-stratified management. Patients at extreme risk, who are expected to achieve the most stringent LDL-C thresholds, represent a particularly vulnerable population in whom failure to reach goals may have substantial clinical consequences. The study also incorporates individuals with FH, a condition characterized by lifelong exposure to elevated LDL-C and markedly increased cardiovascular risk. Evaluating real-world LDL-C control in this subgroup is especially relevant given the complexity of their therapeutic management and frequent need for combination or advanced therapies.

Another important aspect of TRAP-HC is the integration of adherence and persistence analyses. Even highly effective lipid-lowering agents cannot reduce cardiovascular risk if not taken consistently [17]. By combining prescription data with patient-reported information, the study seeks to provide a comprehensive assessment of adherence patterns, including use of oral and injectable therapies. Understanding the relationship between adherence and LDL-C goal attainment may inform targeted strategies to improve long-term cardiovascular prevention.

The evaluation of treatment modification patterns is equally relevant. In an era of expanding therapeutic options, including high-intensity statins, ezetimibe, PCSK9 inhibitors, bempedoic acid, and siRNA-based agents, the real-world sequencing and combination of therapies remain heterogeneous. TRAP-HC offers an opportunity to describe contemporary prescribing behaviour within specialized lipid clinics and to determine whether intensification occurs appropriately in response to inadequate lipid control.

From a public health perspective, the findings of TRAP-HC may have implications beyond individual patient management. Identifying systematic barriers to LDL-C goal attainment, whether clinical, behavioural, or organizational, may support the development of structured care pathways and educational interventions. Moreover, the quantification of "distance from goal" provides a nuanced measure of residual risk, highlighting not only whether goals are achieved but also how far patients remain from recommended thresholds.

The observational nature of the study enhances external validity, as it reflects genuine clinical practice without protocol-driven interventions. Nevertheless, this design also entails limitations. Adherence measures based partly on self-report may be subject to reporting bias, as patients may overestimate their adherence or inaccurately recall medication use. Additionally, follow-up duration of one year, while sufficient to assess lipid dynamics and treatment adaptation, does not allow direct evaluation of long-term cardiovascular outcomes. Furthermore, participating centers are specialized clinics, many of which are already involved in studies evaluating LLTs. As a result, patient management and therapeutic optimization may not fully reflect patterns observed in general practice, where a substantial proportion of patients at cardiovascular risk are managed.

Despite these limitations, TRAP-HC is expected to generate clinically meaningful data in a large, characterized cohort managed within specialized centers. By providing detailed longitudinal evidence on LDL-C control, adherence and therapeutic evolution, the study contributes to bridging the gap between evidence-based recommendations and real-world implementation.

In conclusion, TRAP-HC addresses a critical unmet need in contemporary cardiovascular prevention: understanding how lipid-lowering strategies are applied in daily practice and which factors determine successful LDL-C goal achievement. The insights derived from this study may inform future optimization of lipid management strategies and ultimately contribute to reducing the burden of atherosclerotic cardiovascular disease.

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The XI Spring Meeting of Young Researchers of the Italian Society of Diabetology (SID), the Italian Society of Geriatrics and Gerontology, the Italian Society of Arterial Hypertension (SIIA), the Italian Society of Internal Medicine (SIMI), the Italian Society of Cardiovascular Prevention (SIPREC) and the Italian Society for the Study of Atherosclerosis (SISA)

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CONFERENCE REPORT

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The XI Spring Meeting of Young Researchers, jointly promoted by the Italian Society of Diabetology (SID), the Italian Society of Geriatrics and Gerontology (SIGG), the Italian Society of Arterial Hypertension (SIIA), the Italian Society of Internal Medicine (SIMI), the Italian Society of Cardiovascular Prevention (SIPREC), and the Italian Society for the Study of Atherosclerosis (SISA), was held in Rimini from April 19 to 21, 2026. Entitled *"Spring of Minds: from genetics to AI"*, this edition brought together young investigators from different scientific backgrounds to discuss how technological innovation, molecular medicine, artificial intelligence (AI), and a deeper understanding of biological complexity are reshaping research and clinical practice in the cardiometabolic field.

Consistent with the spirit of the Spring Meeting, the Congress was conceived as a meeting organized by young researchers for young researchers, providing a dynamic forum for scientific exchange, networking, and interdisciplinary discussion. The scientific programme included five thematic sessions and a dedicated workshop on AI in cardiometabolic medicine, covering a broad spectrum of topics ranging from digital technologies and wearable devices to precision medicine, organ protection, cardiovascular prevention, cardio-oncology, aging, frailty, and communication in the era of AI. The Meeting also offered young participants the opportunity to present their work through oral communications and poster sessions, fostering active discussion around emerging data and future research directions. In the following report, we summarize the main themes addressed during the scientific sessions and highlight the key messages emerging from the lectures and workshop activities. More than 120 young researchers actively participated in the oral and poster sessions, presenting their latest findings and engaging in multidisciplinary exchange. In the following report, we outline the core themes explored in the Meeting's lecture program.

The Meeting opened with a session entitled "*Technology and medicine: challenges and opportunities*", which addressed the increasingly central role of intelligent technologies and digital tools in the management of cardiometabolic diseases. The session framed technology not as a replacement for clinical reasoning, but as an opportunity to improve monitoring, decision-making, and personalization of care when critically integrated into clinical pathways.

Sara Coluzzi discussed the evolving role of diabetes technologies and AI in the management of type 1 diabetes, highlighting how technological innovation is progressively reducing the cognitive burden associated with daily glycaemic management. Particular emphasis was placed on continuous glucose monitoring (CGM), which has transformed glucose assessment from isolated measurements into a dynamic and integrated evaluation of glycaemic control, introducing metrics such as Time in Range (TIR) alongside HbA1c [1]. The presentation also focused on the increasing integration between CGM systems, smart insulin pens, and automated insulin delivery (AID) systems. Smart pens were described as improving treatment adherence and enabling more precise insulin titration through dose tracking and bolus calculation support. Advanced hybrid closed-loop systems were presented as the current standard of care in type 1 diabetes, allowing automated modulation of insulin delivery while still requiring meal announcement and carbohydrate estimation [2]. Finally, emerging perspectives toward fully closed-loop and bi-hormonal systems were discussed. AI-based carbohydrate counting, computer vision tools, and dual-hormone systems integrating insulin with glucagon or pramlintide were presented as promising strategies to further reduce patient workload, improve glycaemic stability, and move closer to physiological glucose regulation. Overall, the presentation emphasized that AI should not replace clinical judgement but rather enhance personalized diabetes care through greater automation and decision support.

Alessandro Croce then focused on the evolving role of wearable and cuffless technologies in blood pressure monitoring. Blood pressure assessment has progressively moved beyond traditional office-based measurements toward out-of-office strategies, reflecting the growing awareness that isolated clinical readings may not fully capture the complexity of blood pressure behaviour in daily life. Current ESH and ESC guidelines [3, 4] recommend that the diagnosis of hypertension should rely on repeated office blood pressure measurements, combined with out-of-office approaches such as home blood pressure monitoring and 24-hour ambulatory blood pressure monitoring, using validated upper-arm cuff devices. Ambulatory monitoring allows the evaluation of circadian blood pressure variability, whereas home monitoring improves reliability through repeated measurements over several days. This transition has significantly increased the quantity and quality of data available for clinical decision-making. In this context, cuffless and wearable devices represent a further step toward more frequent, unobtrusive, and potentially continuous blood pressure monitoring. Their limited interference with daily activities may improve long-term tracking, patient adherence, and the personalization of cardiovascular risk assessment. However, Croce also emphasized that the increasing amount of available data does not automatically translate into better clinical information. More frequent and less controlled measurements may introduce variability, reduce data quality, and raise new challenges regarding validation, interpretation, and integration into clinical decision-making. Overall, wearable technologies appear promising, but their clinical implementation requires careful evaluation to ensure that greater data availability is accompanied by adequate accuracy and reliability.

The following session, "*New therapeutic paradigms for organ protection and cardiovascular risk reduction*", explored how recent pharmacological innovations are reshaping the management of cardiometabolic diseases. The session highlighted a major conceptual shift: therapeutic success is no longer defined only by the control of individual risk factors, such as glucose or lipid levels, but also by the ability to reduce residual risk and protect target organs.

Martina Chiriacò presented new horizons in the pharmacotherapy of diabetes and obesity, emphasizing the shift from glucose-centric treatment toward integrated management of metabolic and cardio-renal disease.

A key question was why further enhance glucagon-like peptide-1 (GLP-1) receptor agonism. The addition of glucose-dependent insulinotropic polypeptide (GIP) agonism was described as exerting direct effects on adipose tissue. GIP signalling, acting on endothelial and immune cells within white adipose tissue, may enhance insulin sensitivity and increase lipid storage capacity, thereby limiting ectopic fat deposition [5]. In parallel, glucagon receptor co-agonism, beyond promoting weight loss, appears to exert hepatotropic effects, including reductions in hepatic steatosis and fibrosis, independently of GLP-1 pathways [6]. Amylin analogues, particularly long-acting compounds such as cagrilintide, were discussed as targeting central appetite regulation, with potential effects on caloric intake and eating behaviour [7]. These concepts converge in triple agonists (GLP-1/GIP/glucagon) such as retatrutide, where combined modulation of energy intake and expenditure may help sustain weight loss [8]. Overall, the presentation highlighted a shift toward integrated multi-target pharmacology, consistent with emerging trends in cardiometabolic research.

Andrea Baragetti focused on the persistent cardiovascular risk

that remains despite current evidence-based therapies [9]. A major theme is the rapid expansion of lipid-lowering biotechnology. Examples include oral Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) inhibitors, obicetrapib targeting cholesteryl ester transfer protein (CETP), muvalaplin for Lp(a), inclisiran, lerodalcibep as a PCSK9-targeting adnectin suitable for monthly self-administration, and VERVE-102, designed to achieve durable *PCSK9* gene inactivation. The presentation also discusses small-interfering RNA (siRNA) applications beyond cholesterol, including zilebesiran for resistant hypertension. Baragetti highlighted that the therapeutic landscape is moving toward a more integrated approach, in which different biological pathways are targeted through increasingly specific pharmacological and biotechnological strategies [10-12]. However, their clinical positioning will depend on trial evidence, appropriate biomarkers, guideline integration, patient accessibility, and healthcare-system affordability. Overall, the presentation argued that the growing burden of residual cardiovascular risk justifies the continued development of advanced pharmacological and biotechnological tools. The key challenge will be translating these innovations into practical, equitable, and sustainable care for patients at high cardiovascular risk.

The second day of the Meeting commenced with a session, entitled "*Genetics and epigenetics in metabolic diseases: from biological mechanisms to precision medicine*". This session provided a mechanistic and translational perspective on how genetic, epigenetic, and metabolic information may contribute to personalized risk stratification and treatment. **Luca Tagliafico** provided an overview of the relationship between metabolism, epigenetics, and biological aging, highlighting the translational relevance of aging biomarkers in clinical practice. Since Comprehensive Geriatric Assessment cannot reach a widespread application in routine practice, biomarkers may represent valuable complementary tools with predictive and prognostic purposes. Among these, epigenetic biomarkers and epigenetic clocks showed promising performances in estimating biological age and monitoring the effects of therapeutic interventions [13]. Nonetheless, they do not fully encompass all dimensions of aging. Also, as for their relevance throughout the cardiometabolic field, epigenetic age acceleration has been associated with obesity and worse cardiovascular outcomes, including heart failure [14]. Preliminary evidence further suggests that GLP-1 receptor agonists may contribute to reducing epigenetic age. The abovementioned epigenetic clocks still require further validation before routine clinical implementation. Currently, although they are not implemented in clinical care, they may provide a significant contribution to research, particularly in risk stratification and personalized care.

Alessia Di Costanzo discussed the role of genetics in lipid metabolism as a tool to predict the long-term effects of lipid targets and to support therapeutic development. She highlighted that plasma lipid levels are strongly influenced by genetic determinants and that Mendelian lipid disorders represent valuable in vivo models to clarify causal relationships between lipid traits and cardiovascular disease. A paradigmatic example is *PCSK9*: loss-of-function variants have been associated with lower LDL-C levels and reduced coronary heart disease risk, demonstrating how human genetics can identify causal pathways and druggable targets [15]. Di Costanzo then illustrated how Mendelian randomization can validate causal genotype–phenotype associations and prioritize therapeutic targets, as shown by *NPC1L1* variants, which predicted the clinical benefit of ezetimibe [16]. Importantly, lifelong genetically mediated LDL-C reduction appears to confer greater coronary protection than pharmacological LDL-C lowering initiated later in life, supporting the concept that "lower is better, earlier is better" [16]. The lecture also addressed the post-genomic view of lipid disorders, using severe hypertriglyceridaemia and data from the Italian LIPIGEN cohort were presented as examples of how genetic burden may influence triglyceride levels, pancreatitis risk, and treatment response [17]. Finally, rare loss-of-function variants in *APOB* and *ANGPTL3* were presented as tools to predict long-term safety issues of emerging lipid-lowering drugs, balancing cardiovascular benefit and potential hepatic adverse effects [18, 19]. Overall, lipid genetics emerged as a tool to guide target discovery, risk stratification, treatment personalization, and safety assessment.

The fourth session, "*Internistic complications in patients with cancer*", addressed cardio-oncology and geriatric oncology as a paradigmatic field in which translational research, clinical complexity, and multidisciplinary decision-making closely intersect.

The first lecture, delivered by **Mario Stabile**, focused on the mismatch between preclinical and clinical research in cardio-oncology. The speaker reviewed the mechanisms underlying cancer therapy-related cardiovascular toxicity, including targeted therapy-induced cardiac dysfunction and the central role of oxidative stress, as well as anthracycline cardiotoxicity, moving from classical paradigms to emerging mechanisms such as cellular senescence and genetic susceptibility [20, 21]. Particular attention was also devoted to immune checkpoint inhibitors (ICIs), whose cardiovascular toxicity extends beyond myocarditis to include arrhythmias, vasculopathy, heart failure, and accelerated atherosclerosis [22, 23]. A major limitation highlighted during the lecture was the difficulty of reproducing clinically relevant cardiotoxicity in validated preclinical models. This issue contributes to a significant translational gap: while preclinical cardio-oncology research remains disproportionately focused on anthracyclines, contemporary oncology trials increasingly involve tyrosine kinase inhibitors, alkylating agents, antimetabolites, and ICIs.

Fabrizio Vallelonga moved beyond this mismatch by presenting cardio-oncology as a rapidly expanding clinical discipline based on the integration of cardiovascular, oncological, and haematological expertise. Examples of cardiovascular risk stratification in patients receiving potentially cardiotoxic therapies were discussed, including blood pressure, blood pressure variability, pulse wave velocity, global longitudinal strain, and left atrial strain. These markers were presented as useful tools to identify high-risk patients and personalize surveillance, in line with contemporary guideline-based approaches [24]. The talk also emphasized that cardio-oncology practice often takes place in an area of uncertainty, where cardiovascular risk must be balanced against oncological benefit, prognosis, therapeutic alternatives, and patient preferences. Overall, the two lectures underscored cardio-oncology as both a translational research challenge and a patient-centred model of personalized care.

Closing the session, **Elena Page** shifted the focus from cardiovascular toxicity to the broader multidimensional assessment of older patients with cancer, highlighting how geriatric tools and predictive models may support safer and more personalized therapeutic decisions. She discussed predictive models of pharmacological toxicity in older patients with cancer, candidated for systemic therapy. The decision to initiate systemic treatment requires an assessment that goes beyond chronological age and considers the holistic complexity of the individual. Simple tools for clinical practice were illustrated to identify vulnerable older patients at increased risk of adverse events, deserving a comprehensive geriatric assessment. In particular, the G8 screening tool was described as an effective instrument for detecting vulnerability and performing multidisciplinary management [25]. Furthermore, predictive models of chemotherapy-related toxicity, including the CARG and CRASH scores, were also discussed as useful

tools for estimating the risk of severe adverse events and balancing the risks and benefits of treatment [26]. To sum up, the goal is to promote shared therapeutic decision-making based not only on tumor characteristics, but also on the patient's values and priorities. In this perspective, simultaneous care pathways may accompany active oncologic treatments to ensure symptom control, quality of life, and continuity of care.

The final day of the Meeting began with the session, entitled "*New and old challenges in cardiovascular prevention: between technological advancement and the rediscovery of biological complexity*". The session connected the technological focus of the Meeting with enduring clinical challenges in cardiovascular prevention, emphasizing that innovation must be interpreted within the broader complexity of patient biology and vulnerability.

Giulio Francesco Romiti discussed the role of AI in the diagnosis of cardiovascular diseases, focusing on its potential to support — rather than replace — clinical decision-making. He highlighted the rapidly increasing interest in AI in medicine and emphasized that AI-assisted diagnosis is among the applications closest to clinical implementation, provided that it addresses a clearly defined clinical problem. Romiti illustrated this concept through acute myocardial infarction diagnosis. Some patients without classical ST-elevation may still present a complete coronary occlusion, or occlusion myocardial infarction, and may experience delayed reperfusion and worse outcomes [27]. In this setting, AI-based electrocardiographic analysis may help identify patterns of coronary occlusion not captured by conventional ST-segment criteria. He presented evidence from convolutional neural networks trained on large ECG datasets with angiographic information, showing how AI may support the recognition of occlusive myocardial infarction and provide interpretable outputs [27]. The lecture then moved from opportunities to critical appraisal. Romiti stressed that AI is not a "perfect machine" and is not always justified when simpler prediction tools achieve comparable performance [28]. He also emphasized the importance of data quality, representative cohorts, and external validation, since many AI models in cardiovascular medicine still lack validation, making their performance uncertain [29].

Finally, he underlined that AI outputs should be interpreted like any other diagnostic test, within a Bayesian framework integrating pre-test probability, likelihood ratios, clinical context, and patient-specific factors [30]. The key message was that AI will not replace physicians but may become a collaborative tool to support better clinical decisions, provided that models are adequately validated and critically interpreted.

Pasquale Mone addressed the relationships between frailty and cardiometabolic diseases. Frailty was presented as a multidimensional geriatric syndrome characterized by reduced physiological reserve and increased vulnerability to stressors, leading to adverse outcomes such as disability, hospitalization, procedural complications, cognitive decline, and mortality [31]. In the context of population aging, frailty and cardiometabolic disorders frequently coexist and may amplify each other's negative effects, particularly in patients with multimorbidity [32, 33]. The presentation highlighted the importance of Comprehensive Geriatric Assessment in older adults with cardiometabolic diseases, while also discussing the Fried Frailty Phenotype, based on weight loss, exhaustion, weakness, slowness, and low physical activity, as a reference model for identifying physical frailty [31]. Mone also focused on cognitive frailty, defined by the coexistence of physical frailty and mild cognitive impairment, emphasizing the role of cognitive tests such as MMSE and MoCA in clinical evaluation. Finally, the lecture explored inflammation, oxidative stress, endothelial dysfunction, and sarcopenia as key mechanisms linking frailty and cardiometabolic disease, and discussed the potential role of preventive strategies during midlife in improving health trajectories in older age [34].

Within the Congress, a workshop entitled "*Understanding Artificial Intelligence in Cardiometabolic Medicine: Concepts, Practice, and Critical Evaluation*" was organized. The workshop offered participants both conceptual foundations and a practical framework for the critical appraisal of AI applications in medicine, with a specific focus on cardiometabolic research. The initial lecture by **Elena Olmastroni** and **Stefano Scotti** framed cardiovascular diseases as complex network disorders driven by the interaction of genetic, molecular, environmental, and behavioural factors, highlighting the limitations of traditional risk stratification based on a restricted set of clinical variables. In this context, omics sciences were presented as a key tool to improve the understanding of cardiovascular pathophysiology through the integration of multi-omics data, enabling the identification of molecular pathways, disease subtypes, and potential therapeutic targets within a network medicine approach. Building on this framework, AI and machine learning (ML) were introduced as enabling technologies for the analysis of high-dimensional biological data, supporting pattern recognition, risk stratification, and predictive modelling. The workshop then expanded on these concepts through a dedicated session conducted by **Monica Moroni** and **Marco Chierici** from Fondazione Bruno Kessler. They explored how AI works, with particular attention to its methodological and technical foundations and core analytical components. An introductory overview contextualised AI and ML within data-driven medicine, outlining key aspects related to model development, training, validation, and interpretation. This provided the basis for a gradual transition from theoretical principles to applied and critical perspectives. A substantial part of the workshop was dedicated to an interactive, practice-oriented component, in which participants analysed selected scientific articles to evaluate the clinical opportunities and limitations of AI in medicine. This activity promoted a structured and critical appraisal of real-world applications, with particular focus on ethical implications, methodological constraints, and implementation challenges. Within this session, the OMIGEN group was also presented as a young investigator initiative focused on the integration of omics and AI in cardiovascular research, with the aim of fostering interdisciplinary collaboration and methodological innovation in the field.

The Meeting concluded with an unconventional communication-focused lecture by Davide Gambardella, entitled "*You explained it very well. Too bad nobody understood you. Side effects of communication in the AI era*". The lecture offered a thought-provoking reflection on the challenges of scientific communication in an increasingly complex and technology-driven context, emphasizing that clarity, empathy, and the ability to adapt language to different audiences remain essential skills for researchers and clinicians.

Overall, the XI Spring Meeting offered an updated and multidisciplinary view of cardiometabolic research, highlighting how genetics, epigenetics, omics, artificial intelligence, digital tools, and clinical complexity are converging toward a more precise and integrated model of prevention and care.

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Ultrasound evaluation of carotid perivascular adipose tissue thickness as a potential marker of atherosclerosis and cardiovascular risk

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Aim: Perivascular adipose tissue (PVAT) is widely recongnized as a metabolically active organ that possibly play a role in the development of atherosclerotic cardiovascular (CV) disease. Accordingly, PVAT thickness at different arterial districts could serve as a marker of atherosclerosis and CV risk. The aims of our study were 1) to evaluate the feasibility a non-invasive, ultrasound-based approach for measuring carotid PVAT thickness (cPVATt), and 2) to evaluate the association between cPVATt, carotid atherosclerosis burden, and CV risk.
Methods: We conducted an observational, cross-sectional, pilot study. Carotid PVAT was evaluated bilaterally by ultrasonography using a 10-MHz multifrequency linear probe positioned at the base of the neck in contact with clavicle, perpendicular to the skin and in a transverse orientation. The mean distance between the common carotid adventitia and the sternocleidomastoid muscle anteriorly and the longus colli muscle posteriorly, measured on both the right and the left sides, was used as a cumulative measure of cPVATt.
Results: A total of 465 patients were included in the study. The median value of cPVATt was 0.68 (0.58-0.85) cm. Significant direct correlations emerged between cPVATt and body mass index (r=0.170, p<0.001), waist circumference (r=0.224, p<0.001), neck circumference (r=0.269, p<0.001), uric acid (r=0.106, p=0.031), triglycerides (r=0.095, p=0.048), and hs-CRP (r=0.202, p=0.019). A significant inverse correlation was observed between cPVATt and HDL cholesterol (r=-0.152, p=0.001). No correlation was observed between cPVATt and any measure of carotid atherosclerotic burden. There was a significant increase in cPVATt across CV risk categories (p for trend=0.043).
Conclusions: The present study preliminarly demonstrates the feasibility of an ultrasound approach for assessing cPVAT, the reliability of cPVATt as a measure of adiposity and its potential value as a marker of increased CV risk. However, it does not show any significant correlation between cPVATt and carotid atherosclerotic burden.

Extracellular vesicles isolated from patients with heart failure retain proinflammatory features

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Aim: Heart failure (HF) is a clinical syndrome involving structural and/or functional cardiac abnormalities, classified as reduced (HFrEF) or preserved (HFpEF) based on the ejection fraction percentage of the left ventricle. As extracellular vesicles (EVs) reflect onset and severity of cardiac diseases, they attract interest as potential liquid biopsies. Aim of the present project was to characterize EVs in HF patients, investigating their potential as biomarkers and tools to discriminate between HFrEF and HFpEF clinical phenotypes.
Methods: The study included 39 HF patients (13 HFpEF and 26 HFrEF) and 28 volunteers (CTR). EVs were isolated from plasma by size-exclusion chromatography and ultracentrifugation, then characterized using nanoparticles tracking analysis, transmission electron microscopy (TEM), Western blot (WB) and flow cytometry (FACS). Functional assays using patient-derived EVs were performed on cellular models of monocyte (THP-1) and cardiomyocyte (H9C2).
Results: Diagnosis of HF relied on echocardiographic (e.g. E/e' ratio) and biochemical parameters (e.g. NT-proBNP). Isolation of EV was confirmed by FACS and WB analyses (e.g. the presence of CD63, CD9, CD81, Alix and β1 integrin), while integrity by TEM. EV size was increased in HF (nm: 202 vs 181). Among different subpopulations of EVs, those from monocytes (CD14+), macrophages (CD206+), neutrophils (CD66b+), endothelial cells (CD202b+), activated endothelial cells (CD62E+), cardiomyocytes (CD172a+), platelets (CD41a+), were significantly reduced in HF. Conversely, EVs released by T helper lymphocytes (CD4+) were significantly increased in HF patients when compared to controls. Treatment of THP-1 and H9C2 cells with EVs derived from HF patients led to an increased expression of proinflammatory cytokines (i.e. IL-1α, IL-1β, IL-6), when compared to cells treated with EVs isolated from CTR subjects. This change was mostly driven by EVs derived from HFpEF patients.
Conclusions: EVs derived from HF patients exhibit a distinct profile that reflects the hemodynamic characteristics of the condition and possess proinflammatory properties.

Achievement of LDL cholesterol targets in HIV-positive patients

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Background and objectives: People living with HIV (PLWH) face an increased cardiovascular (CV) risk due to the interaction of traditional risk factors, chronic inflammation and cumulative antiretroviral therapy (ART) adverse metabolic effects. However, standard risk models often underestimate this burden, limiting effective prevention. This study evaluates LDL cholesterol target achievement in PLWH, based on European Society of Cardiology guidelines, and explores its association with clinical, immunological, and therapeutic HIV-related variables.
Methods: A retrospective analysis was conducted on 246 HIV-positive patients, aged ≥40, on ART at Niguarda Hospital. Clinical, laboratory, and therapeutic data were extracted from the hospital's electronic registries, while ten-year CV risk was assessed using SCORE2 from which each patients LDL cholesterol target was defined.
Results: Only 27.2% of the analyzed cohort achieved the recommended LDL cholesterol targets; a significantly higher prevalence of uncontrolled profiles was observed among patients belonging to the "high" or "very high" SCORE2 risk categories (29.3 and 14.6% of the population, respectively). 35.4% of the patients take statins, 12.2% ezetimibe while only the l'11.4% take their association. Univariate analysis showed that lower value of total cholesterol (r=-0.490, p<0.0001), triglycerides (r=-0.188, p=0.003), systolic blood pressure (r=-0.190, p=0.003), and SCORE2 risk class (r=0.270, p<0.0001) were significantly associated with an increased likelihood of achieving the LDL cholesterol target, whereas no significant relation was found with HIV-specific variables.
Conclusions: LDL cholesterol target achievement in PLWH remains suboptimal. A refined predictive model integrating HIV-specific variables, could be useful to enhance individualized risk stratification and to optimize therapeutic strategies tailored to PLWH.

Colonic (poly)phenol metabolites as promising tools to control inflammation and prevent cardiovascular disease

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Aim: Chronic inflammation underlies numerous diseases, including atherosclerosis. The identification of anti-inflammatory agents, particularly from dietary sources, is of great interest for the development of functional products targeting early stages of chronic inflammatory conditions. This study investigated the *in vitro* anti-inflammatory activity of chiral phenyl-γ-valerolactones, the main colonic metabolites of flavan-3-ols.

Methods: Human dermal fibroblasts were treated with 10 phenyl-γ-valerolactones (1 µM) for 48 hours. Compounds included pure enantiomers and methylated or sulfated derivatives, tested at concentrations representative of plasma levels following dietary intake. During the first 24 hours, cells were treated under basal conditions; during the second 24 hours, treatments were repeated in the presence or absence of lipopolysaccharide (LPS, 1 µg/mL). Cytotoxicity was assessed by MTT and lactate dehydrogenase assays (LDH). Anti-inflammatory activity was evaluated by measuring IL-6 and IL-8 secretion using ELISA, with data normalized to protein content (bicinchoninic acid assay). To investigate the underlying mechanism of action, NF-κB activation was assessed by western blot analysis of p65 expression, normalized to β-actin. A 24-hour pharmacokinetic study was conducted to evaluate compound biotransformation and to characterize metabolic products, monitoring 31 phenyl-γ-valerolactones.

Results: None of the tested compounds induced cytotoxicity. (4*R*)-5-(4′-hydroxyphenyl)-γ-valerolactone (R-CC01) reduced IL-6 and IL-8 secretion by 76% (p<0.001) and 70% (p<0.01), respectively, while its enantiomer (S-CC01) inhibited IL-6 by 89% (p<0.001) and IL-8 by 86% (p<0.01). (4*R*)-5-(3′,4′-dihydroxyphenyl)-γ-valerolactone (R-CC02) reduced both IL-6 and IL-8 by 83% (p<0.001). (4*S*)- and (4*R*)-5-(3′-hydroxy-4′-methoxyphenyl)-γ-valerolactones (CC03) reduced IL-6 by 90% and 78% (p<0.001), and IL-8 by 87% and 71% (p<0.01), respectively. Western blot analysis showed reduced NF-κB activation, with p65 levels decreased by 37% (R-CC01, p<0.05), 61% (R-CC02, p<0.01), and 73% (R-CC03, p<0.001). The analysis of cellular metabolism revealed that within 24 hours R-CC01 remained unmodified, whereas R-CC02 and R-CC03 formed sulfate metabolites in a time-dependent manner.

Conclusions: Phenyl-γ-valerolactones significantly reduced pro-inflammatory cytokine secretion in LPS-stimulated human fibroblasts, partly through NF-κB inhibition. These findings support their potential role in dietary or nutraceutical strategies targeting chronic inflammation.

Adipo-neuroinflammation, cognitive impairment and surrogate markers of cardiovascular risk in patients with MASLD

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Aim: The epidemiological burden MASLD have been slowly increasing in recent years. Starting from a background of metabolic dysfunction, we evaluated the associations between adipo-neuroinflammation markers (LCN2), indicators of cognitive impairment (MMSE score), surrogate cardiovascular risk indicators (RHI, IMT and MMEE), and MASLD.

Methods: In this cross-sectional study, we enrolled a group of 40 patients with a recent diagnosis of MASLD and a control group of 40 patients with no history of liver disease.

Results: Compared with the controls, patients with MASLD had higher serum levels of LCN2, lower RHI and MMEE values, and lower MMSE scores; univariate analysis also revealed that the differences between the groups in terms of heart rate, body weight, body mass index, body surface area, glycated haemoglobin, and echocardiographic variables (interventricular septal thickness, LVPWT, EF, LAVI, and E/A ratio) were statistically significant. Multinomial regression revealed that the presence of MASLD was significantly positively associated with LVPWT and LCN2, and significantly negatively associated with the RHI. With regards to assessments of cognitive impairment, the presence of MASLD was significantly negatively associated with the MMSE score. We also performed ROC curve analysis to explore the ability of RHI to predict MASLD; the results yielded an AUC of 0.826 (95% CI: 0.72–0.90; p<0.0005) at an optimal cut-off value of 1.87 (sensitivity=72.5%, specificity=90%), suggesting that the RHI can serve as a marker of endothelial dysfunction and thus as an indirect indicator of cardiovascular risk in patients with MASLD.

Conclusions: Patients with MASLD have greater cognitive impairment than controls; they also have higher serum levels of LCN-2 and greater endothelial dysfunction. These results imply that subjects with MASLD have a worse cardiovascular risk profile in addition to more pronounced cognitive impairment than controls do, thus suggesting that liver plays a greater role than simply serving as the metabolic centre.

Free fatty acids impair steroidogenesis and promote apoptosis in leydig cells: A new link between metabolic dysfunction and hypogonadism

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Excess circulating fatty acids contributes to the association between metabolic disorders and hormonal alterations. Indeed, obesity and diabetes mellitus are frequently associated with functional hypogonadism characterised by reduced testosterone levels. Although a high-fat-diet is known to negatively affect testicular function, its specific impact on steroidogenesis remains unclear. Therefore, the aim of this study has been to investigate the effects of different FFAs, with or without human chorionic gonadotropin (hCG) stimulation, on steroidogenesis and apoptosis in a murine Leydig cell line (mLTC1). mLTC1 cells were exposed with increasing concentrations of palmitate (PA) or oleate (OA), in the presence or absence of 0.2 IU/mL hCG. The expression of the Steroidogenic Acute Regulatory (STAR) protein, a key marker of steroidogenesis, was evaluated by immunoblotting. Testosterone secretion was measured by ELISA, while apoptosis was evaluated by cleaved caspase-3 (C3C) protein expression using immunoblotting.

Exposure to PA significantly reduced hCG-induced STAR protein expression in a dose-dependent manner after 6h and 15h, respectively, compared with PA-free conditions. Similarly, exposure to OA reduced STAR protein expression at all concentrations tested (0.4-1 mM). Prolonged treatment with PA (96 hours) further compromised steroidogenic capacity, leading to a reduction in testosterone production. Furthermore, PA significantly increased C3C levels. Notably, hCG stimulation during the last 6h of incubation significantly reduced PA-induced C3C levels at all concentrations.

In conclusion, both PA and OA impair hCG-induced steroidogenesis, while PA additionally promotes Leydig cell apoptosis. These findings suggest a direct detrimental role of excess FFAs on testicular function in obesity and indicate a potential protective role of hCG in preserving Leydig cell viability under conditions of metabolic stress.

Effect of elexacaftor/tezacaftor/ivacaftor therapy on serum lipoprotein functions in adults with cystic fibrosis

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Cystic fibrosis is a genetic and multisystemic disease associated with a very poor quality of life and life expectancy. The introduction of the combined treatment with elexacaftor/tezacaftor/ivacaftor (ETI, Kaftrio) has extended the life expectancy of adults with cystic fibrosis (awCF), which could have an impact on the prevalence of certain chronic diseases, such as cardiovascular (CV) diseases. In this regard, in a recent work, it was observed that treatment with Kaftrio has a heterogeneous effect on CV risk factors, ameliorating some of them, such as chronic inflammation, and worsening others. Among the relevant factors determining CV risk, the capacity of HDL to promote cholesterol efflux (HDL-CEC), one of the main functions of this class of lipoproteins, has proven to be a better predictor than plasma HDL concentrations. In addition, the serum capacity to load macrophages with cholesterol (cholesterol loading capacity, CLC) represents an index of serum lipoproteins' pro-atherogenic potential.

This work aimed to evaluate the effect of six months of therapy with Kaftrio on serum lipoprotein functions, namely HDL-CEC and serum CLC, in 16 awCF, and in 8 sex and age-matched healthy controls. HDL-CEC through the main pathways was evaluated with a radioisotopic cell-based assay in specific cell models, and serum CLC was assessed fluorimetrically in human monocyte-derived macrophages THP-1.

Concerning plasma lipid profile, after treatment with Kaftrio, total cholesterol, LDL-C, and HDL-C significantly increased as compared to baseline ($p<0.001$, $p<0.001$, and $p=0.023$, respectively), reaching values comparable to those of healthy controls. Regarding HDL function, HDL-CEC mediated by the transporter ABCA1 was significantly lower in awCF at baseline compared to healthy controls (-14%, $p=0.0142$). Treatment with Kaftrio increased ABCA1 HDL-CEC compared to awCF at baseline (+7%, $p=0.02499$). Similarly, ABCG1 HDL-CEC was significantly lower in awCF at baseline compared to healthy controls (-22%, $p=0.0218$) while significantly higher after treatment compared to not treated awCF (+18%, $p=0.0255$). In both cases, Kaftrio restored HDL-CEC levels to values comparable to those of healthy controls.

No significant differences were found for serum CLC in awCF compared to healthy controls. Kaftrio did not have any significant impact on this parameter, despite the increased LDL-C levels observed after treatment.

In conclusion, Kaftrio treatment had a positive impact on the functional lipid profile as it increased ABCA1 and ABCG1 HDL-CEC without negatively affecting serum CLC. All these effects may contribute to reducing the CV risk in awCF.

Lipoprotein(a) levels across histological severity in metabolic dysfunction–associated steatotic liver disease

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Background: Metabolic dysfunction–associated steatotic liver disease (MASLD) encompasses a spectrum ranging from simple steatosis to metabolic dysfunction–associated steatohepatitis (MASH) and cirrhosis. Lipoprotein(a) [Lp(a)] is a well-established atherogenic risk factor, but its relationship with MASLD and its histological severity has been poorly investigated. The aim of this study was to describe plasma Lp(a) levels across different histological stages and features of MASLD.

Methods: Eighty-eight patients enrolled in the PLINIO study (ClinicalTrials.gov Identifier: NCT04036357) who underwent liver biopsy were included. Plasma Lp(a) levels were measured using a specific ELISA kit. Patients were stratified according to histological diagnosis into simple steatosis (MASLD-SS), MASH, and cirrhosis. In a subgroup of 29 patients, immunohistochemical analysis was performed to assess hepatic Lp(a) expression on liver biopsy samples.

Results: Plasma Lp(a) levels increased progressively with histological severity (MASLD-SS: 22.1 [20.2–26.6] mg/dL; MASH: 28.7 [24.2–32.8] mg/dL; cirrhosis: 31.1 [29.4–33.1] mg/dL; p=0.001). Plasma Lp(a) correlated positively with fibrosis stage (rS=0.401, p<0.001), inflammation grade (rS=0.214, p=0.045), hepatocellular ballooning (rS=0.383, p<0.001), and NAFLD Activity Score (rS=0.410, p<0.001). In multivariable regression analysis including demographic and clinical variables, plasma Lp(a) was independently associated with LDL cholesterol (β=0.003, p=0.012) after adjustment for age, sex, ALT, and diabetes. At immunohistochemical analysis, no overall correlation was found between hepatic and plasma Lp(a) or histological features. However, after excluding cirrhotic patients, hepatic and plasma Lp(a) levels correlated significantly (rS=0.436, p=0.033). Among patients with MASH, hepatic Lp(a) expression was higher in those with more severe ballooning (p=0.043).

Conclusions: In this histologically characterized MASLD cohort, Lp(a) levels increased with disease severity and correlated with fibrosis and activity parameters. These findings suggest a potential role for Lp(a) in MASLD progression and warrant further studies to clarify its contribution to liver disease pathogenesis and cardiovascular risk in this population.

Age-Related Enhancement of COX-1–Mediated Thromboxane Production in Patients with Atrial Fibrillation

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Background: Enhanced platelet activation contributes to the increased cardiovascular risk of elderly patients with atrial fibrillation. The biological mechanisms underlying this phenomenon are not fully clarified. This study investigated whether age-related increases in serum thromboxane B_2 (TxB_2) are associated with platelet cyclooxygenase-1 (Cox-1) upregulation in older individuals.

Methods: Serum levels of Cox-1 and TxB_2 were assessed in patients with atrial fibrillation enrolled between 2022 and 2023. A subset of participants underwent in vitro analyses to evaluate the inhibitory effect of aspirin on platelet TxB_2 generation and to quantify platelet Cox-1 expression across different age groups (<65 vs. ≥65 years). The relationship between Cox-1 expression and aspirin-mediated inhibition of TxB_2 was also explored. Associations were analyzed using Spearman correlation, and mediation analysis was performed to assess indirect effects.

Results: The study included 134 patients. Age showed a positive correlation with both Cox-1 expression (R = 0.42, p <0.01) and TxB_2 levels (R = 0.44, p <0.01). Additionally, Cox-1 expression was positively associated with TxB_2 concentrations (R = 0.50, p <0.01). Mediation analysis demonstrated that Cox-1 partially mediated the relationship between age and TxB_2 levels (β = 5.23, 95% CI: 2.33–8.63). In vitro experiments revealed a reduced sensitivity to aspirin in older patients, as reflected by higher IC_{50} values for inhibition of platelet TxB_2 production (96.78 µM in ≥65 years vs. 48.92 µM in <65 years). This reduced response was accompanied by increased platelet Cox-1 expression in the elderly group. Moreover, higher Cox-1 levels were inversely correlated with aspirin-induced inhibition of platelet TxB_2 (R = –0.64, p <0.01).

Conclusions: Advancing age is associated with increased thromboxane production, driven in part by platelet Cox-1 upregulation. This alteration is accompanied by a reduced capacity of aspirin to suppress Cox-1 activity, potentially contributing to the heightened thrombotic risk observed in elderly patients.

Lipoprotein(a) does not correlate with hypertensive mediated organ damage and subsequent cardiovascular events in a primary prevention cohort

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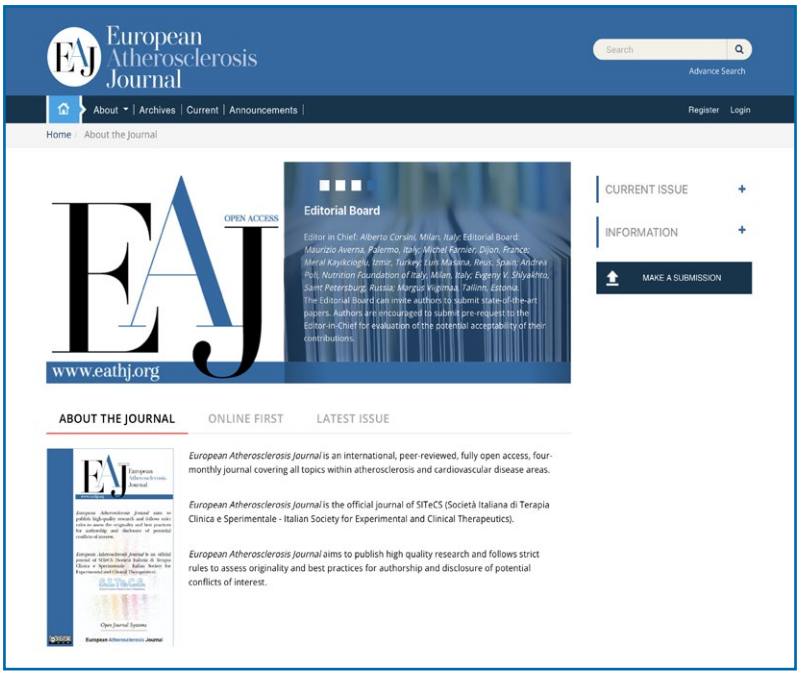
Aim: Elevated lipoprotein(a) [Lp(a)] levels have been strongly related to cardiovascular (CV) risk. However, its association with Hypertension Mediated Organ Damage (HMOD) and CV events in the primary prevention setting remains unclear. The aim of our study is to evaluate in these patients the correlation between Lp(a) levels and: (i) heart, vessels and kidney HMOD and; (ii) CV events and all-cause mortality in a primary prevention setting.

Methods: 747 low CV risk subjects were recruited between 2009 and 2014. HMOD was assessed through Pulse Wave Velocity (PWV), carotid Intima-Media Thickness (IMT), presence of carotid plaques, Left Ventricular Hypertrophy (LVH), Ejection Fraction (EF) and glomerular filtration rate (GFR). All-cause mortality and CV events up to 2021 were retrieved by electronic health records, for a median follow-up time of 10 years (I-III quartiles 9.6-11.1).

Results: Mean age was 50.8 ± 13.0 years and 63.5% of the subjects were men. The prevalence of hypertension was 37.9%, dyslipidemia 67.2%, smoking 17.8%, and diabetes mellitus 8.7%. Median Lp(a) value was 17 mg/dL (5.9–56.0), and 26.5% of patients had values above 50 mg/dL. Regarding HMOD, 10.3% subjects had arterial stiffness, 7.2% increased IMT, 19.8% carotid plaques while only 0.7% had LVH. No significant correlation was found between Lp(a) levels and indices of subclinical HMOD. Furthermore, no relationship was found between CV events and all-cause mortality and Lp(a) levels.

Conclusions: In this primary prevention cohort, elevated Lp(a) levels were not associated with significant structural damage to the heart, carotid arteries, or increased aortic stiffness and were not associated with CV events and all-cause mortality.



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