UNIVERSITY OF IOANNINA
SCHOOL OF HEALTH SCIENCES
FACULTY OF MEDICINE

SECTOR OF INTERNAL MEDICINE
2nd DEPARTMENT OF INTERNAL MEDICINE

ASSOCIATION OF ESTABLISHED AND NOVEL RISK FACTORS WITH CARDIOVASCULAR DISEASE IN PATIENTS WITH DYSLIPIDEMIA

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MEDICAL DOCTOR

PhD THESIS

IOANNINA 2020

ΠΑΝΕΠΙΣΤΗΜΙΟ ΙΩΑΝΝΙΝΩΝ
ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ
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ΠΑΘΟΛΟΓΙΚΟΣ ΤΟΜΕΑΣ
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ΔΙΔΑΚΤΟΡΙΚΗ ΔΙΑΤΡΙΒΗ

ΙΩΑΝΝΙΝΑ 2020

«Η έγκριση της διδακτορικής διατριβής από την Ιατρική Σχολή του Πανεπιστημίου Ιωαννίνων δεν υποδηλώνει αποδοχή των γνωμών του συγγραφέα Ν. 5343/32, άρθρο 202, παράγραφος 2 (νομική καταχώρηση του Ιατρικού Τμήματος)».

Ημερομηνία αίτησης του κ. Μπάρκα Φώτιου: 16-12-2011

Ημερομηνία ορισμού Τριμελούς Συμβουλευτικής Επιτροπής: 733ᵅ/3-4-2012

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Ημερομηνία ορισμού θέματος: 20-4-2012
«Συσχέτιση κλασικών και νεότερων παραγόντων κινδύνου με την εμφάνιση καρδιαγγειακής νόσου σε ασθενείς με δυσλιπιδαιμία»

Ημερομηνία ανασυγκρότησης της Τριμελούς Συμβουλευτικής Επιτροπής: 737ᵅ/12-6-2012
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Έγκριση Διδακτορικής Διατριβής με βαθμό **«ΑΡΙΣΤΑ»** στις **15-1-2020**

Ιωάννινα 21-1-2020

ΠΡΟΕΔΡΟΣ ΤΟΥ ΤΜΗΜΑΤΟΣ ΙΑΤΡΙΚΗΣ

Άννα Μπατιστάτου

Καθηγήτρια Παθολογικής Ανατομίας

Η Γραμματέας του Τμήματος

ΜΑΡΙΑ ΚΑΠΙΤΟΠΟΥΛΟΥ

Στους γονείς μου,

Στην Κωνσταντίνα και στη Δέσποινα

ΠΡΟΛΟΓΟΣ

Η παρούσα διδακτορική διατριβή εκπονήθηκε στο Ιατρείο Μελέτης των Διαταραχών του Μεταβολισμού, των Λιπιδίων και Παχυσαρκίας του Πανεπιστημιακού Γενικού Νοσοκομείου Ιωαννίνων.

Η πραγματοποίηση της παρούσας μελέτης δεν θα ήταν δυνατή χωρίς τη διαρκή καθοδήγηση του επιβλέποντα της διδακτορικής διατριβής κ. Ευάγγελου Λυμπερόπουλου, Αναπληρωτή Καθηγητή Παθολογίας της Ιατρικής Σχολής του Πανεπιστημίου Ιωαννίνων και του κ. Μωυσή Ελισάφ, Καθηγητή Παθολογίας της Ιατρικής Σχολής του Πανεπιστημίου Ιωαννίνων, τις χρήσιμες υποδείξεις τους, τις πρωτότυπες ιδέες τους, καθώς και την εμπιστοσύνη και ηθική υποστήριξή τους. Η μακρόχρονη συνεργασία μας αποτελεί εξαιρετική τιμή για μένα και τους ευχαριστώ θερμά. Ιδιαίτερα ευχαριστώ το μέλος της τριμελούς επιτροπής κ. Γεώργιο Λιάμη, Αναπληρωτή Καθηγητή Παθολογίας της Ιατρικής Σχολής του Πανεπιστημίου Ιωαννίνων, για τον πολύτιμο χρόνο που διέθεσε για την παρούσα διδακτορική διατριβή. Η συνεργασία μας ήταν για μένα μία πολύτιμη εμπειρία.

Ευχαριστώ επίσης θερμά τα μέλη της επταμελούς επιτροπής κ. Χαράλαμπο Μηλιώνη, κ. Λεωνίδα Χρήστου, κα. Σταυρούλα Τσιάρα, και κ. Παναγιώτη Κοραντζόπουλο. Θα ήθελα να ευχαριστήσω θερμά τους φίλους και συνεργάτες μου κκ. Ευάγγελο Ρίζο, Παθολόγο, Μιχάλη Κωσταπάνο, Παθολόγο, Θεοδόσιο Φιλιππάτο, Παθολόγο και Χρήστο Ρίζο, Παθολόγο, για τις πολύτιμες γνώσεις τους που μοιράστηκαν μαζί μου και την καθοριστική συμβολή τους στη συγγραφή των επιστημονικών εργασιών.

Ιδιαίτερα επίσης ευχαριστώ τους κκ. Ελευθέριο Κλούρα, Αναστάζια Κεή, Άγγελο Λιόντο, Θ. Παναγιωτοπούλου, Σεμπάστιαν Φίλιππα-Ντεκουάν, Ελίζα Χριστοπούλου και Θεοδώρα Δημητρίου για την πολύτιμη συμβολή τους στη συλλογή των δεδομένων.

Τέλος, θα ήθελα να ευχαριστήσω ιδιαίτερα τη σύζυγό μου Κωνσταντίνα Κυριλή για τη διαρκή και πολύτιμη υποστήριξή της για την διεκπεραίωση της διατριβής μου και να εκφράσω την ευγνωμοσύνη μου στους γονείς μου Αλέκα και Λάμπρο και την αδερφή μου Γεωργία για τη συνεχή και αδιάκοπη υποστήριξη, ηθική και οικονομική, και τη συμπαράστασή τους.

Ιωάννινα, Ιανουάριος 2020

Φώτιος Μπάρκας

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ABBREVIATIONS

95% CI, 95% Confidence Interval

AACE/ACE, American Association of Clinical Endocrinologists and American College of Endocrinology

ABI, Ankle-Brachial Index

ABPM, Ambulatory Blood Pressure Measurement

ACC/AHA, American College of Cardiology/American Heart Association

ACE, Angiotensin-Converting Enzyme

ADA, American Diabetes Association

AF, Atrial Fibrillation

ALT, Alanine aminotransferase

ANOVA, Analysis of variance

Apo, Apolipoprotein

ARB, Angiotensin Receptor Blockers

ASCVD, Atherosclerotic Cardiovascular Disease

BMI, Body Mass Index

BP, Blood Pressure

CABG, Coronary Artery Bypass Grafting

CAC, Coronary Artery Calcification

CCB, Calcium Channel Blockers

CHD, Coronary Heart Disease

CK, Creatine Kinase

CKD, Chronic Kidney Disease

CRP, C-Reactive Protein

CTT, Cholesterol Treatment Trialists

CV, Cardiovascular

CVD, Cardiovascular Disease

DASH, Dietary Approaches to Stop Hypertension

DBP, Diastolic Blood Pressure

DLCN, Dutch Lipid Clinic Network

DM, Diabetes Mellitus

DPP-4, Dipeptidyl Peptidase-4

EAS, European Atherosclerosis Society

EASD, European Association for the Study of Diabetes

ECG, Electrocardiogram

eGFR, estimated Glomerular Filtration Rate

ESC, European Society of Cardiology

FH, Familial Hypercholesterolemia

FOURIER, Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk

FPG, Fasting Plasma Glucose

FRS, Framingham Risk Score

GI, Gastrointestinal

GLP-1 RAs, Glucagon-Like Peptide-1 Receptor Agonists

HbA1c, Glycated hemoglobin

HBPM, Home Blood Pressure Measurement

HDL-C, High-Density Lipoprotein Cholesterol

HeFH, Heterozygous Familial Hypercholesterolemia

HF, Heart failure

HMOD, Hypertension-Mediated Organ Damage

HoFH, Homozygous Familial Hypercholesterolemia

HR, Hazard Ratio

IFG, Impaired Fasting Glucose

IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial

INR, International Normalized Ratio

IQR, Interquartile Range

IR, Insulin Resistance

LDL, Low-Density Lipoprotein

LDL-C, Low-Density Lipoprotein Cholesterol

LDLR, Receptor of Low-Density Lipoprotein

Lp(a), Lipoprotein (a)

LVH, Left Ventricular Hypertrophy

MANCOVA, Multivariate Analysis of Covariance

MetS, Metabolic Syndrome

MHNO, Metabolically Healthy Non-Obese

MHO, Metabolically Healthy Obese

MI, Myocardial Infarction

MixDys, Mixed Dyslipidemia

MTP, Microsomal Triglyceride transfer Protein

MUFAs, Monounsaturated Fatty Acids

MUNO, Metabolically Unhealthy Non-Obese

MUO, Metabolically Unhealthy Obese

NAFLD, Non-Alcoholic Fatty Liver Disease

NCEP-ATP III, National Cholesterol Education Program Adult Treatment Panel III

NHANES, National Health and Nutrition Examination Survey

NOAC, Non-vitamin K antagonist Oral Anticoagulant

non-HDL-C, non-High-Density Lipoprotein Cholesterol

ODYSSEY Outcomes, Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab

OR, Odds Ratio

PAD, Peripheral Artery Disease

PCE, Pooled Cohort Risk assessment Equation

PCI, Percutaneous Coronary Intervention

PCSK9, Proprotein Convertase Subtilisin/Kexin type 9

PPIs, Proton Pump Inhibitors

PreDM, Prediabetes

PUFAs, Polyunsaturated Fatty Acids

RAS, Renin-Angiotensin System

RCT, Randomized Controlled Trial

REDUCE-IT, Reduction of Cardiovascular Events with EPA-Intervention Trial

ROC, Receiver Operation Characteristic

RR, Relative Risk

SAMS, Statin-Associated Muscle Symptoms

SBP, Systolic Blood Pressure

SCORE, Systematic Coronary Risk Estimation

SD, Standard Deviation

SGLT2, Sodium-Glucose Transport protein 2

SPC, Single-Pill Combination

SU, Sulfonylureas

T1DM, Type 1 Diabetes Mellitus

T2DM, Type 2 Diabetes Mellitus

TC, Total Cholesterol

TGs, Triglycerides

TRLs, Triglyceride-Rich Lipoproteins

TZD, Thiazolidinedione

ULN, Upper Limit of Normal values

US, United States of America

VLDL, Very-Low Density Lipoproteins

WHO, World Health Organization

CHAPTER I. BACKGROUND

1.1 Epidemiology of Cardiovascular Disease

Cardiovascular disease (CVD) is common in the general population, affecting the majority of adults aged ≥60 years old.(1) According to the most recent report of the World Health Organization (WHO), 30% of 56.9 million deaths worldwide in 2016 were caused by coronary heart disease (CHD) and stroke (15.2 million deaths).(1) In Europe and United States of America (US), CVD is the leading cause of mortality.(2, 3) In Europe, CVD accounts for over 3.9 million annual deaths, corresponding to a proportion of 45% of all deaths.(2) In men, CVD is responsible for 40% of all deaths (1.8 million deaths), whereas the corresponding mortality rate is 49% (2.1 million deaths) in women.(2) On the contrary, cancer, the second cause of death in Europe, accounts for under 1.1 million deaths (24%) in men and under 900,000 deaths (20%) in women respectively (Figure 1A and Figure 1B).(2)

The burden of CVD mortality varies across European countries.(2) CVD prevalence is higher in Central and Eastern European countries compared with Northern, Southern and Western countries.(2) Within the European Union, the CVD mortality rate ranges from 23% in France to 60% in Bulgaria among men, while in women, the burden ranges from 25% in Denmark to 70% in Bulgaria.(2) Greece is among the European countries with intermediate CVD burden. Of the 116,669 registered deaths in 2012, CVD accounted for 43% of those (49,716 deaths).(2)

1.1.1 Atherosclerotic Cardiovascular Disease

Atherosclerotic cardiovascular disease (ASCVD) is comprised of coronary heart disease (CHD), stroke and peripheral artery disease (PAD).(2) The former is the leading cause of mortality in Europe, accounting for 862,000 deaths annually (19% of all deaths) among men and 877,000 deaths (20%) among women each year.(2) Stroke is the second most common cause of death in Europe, accounting for 405,000 deaths (9%) in men and 583,000 (13%) deaths in women annually (Figures 1A and 1B).(2) Similarly, CHD and stroke were the leading causes of ASCVD mortality in Greece accounting for 11,803 and 15,868 deaths in 2012, respectively.(2)

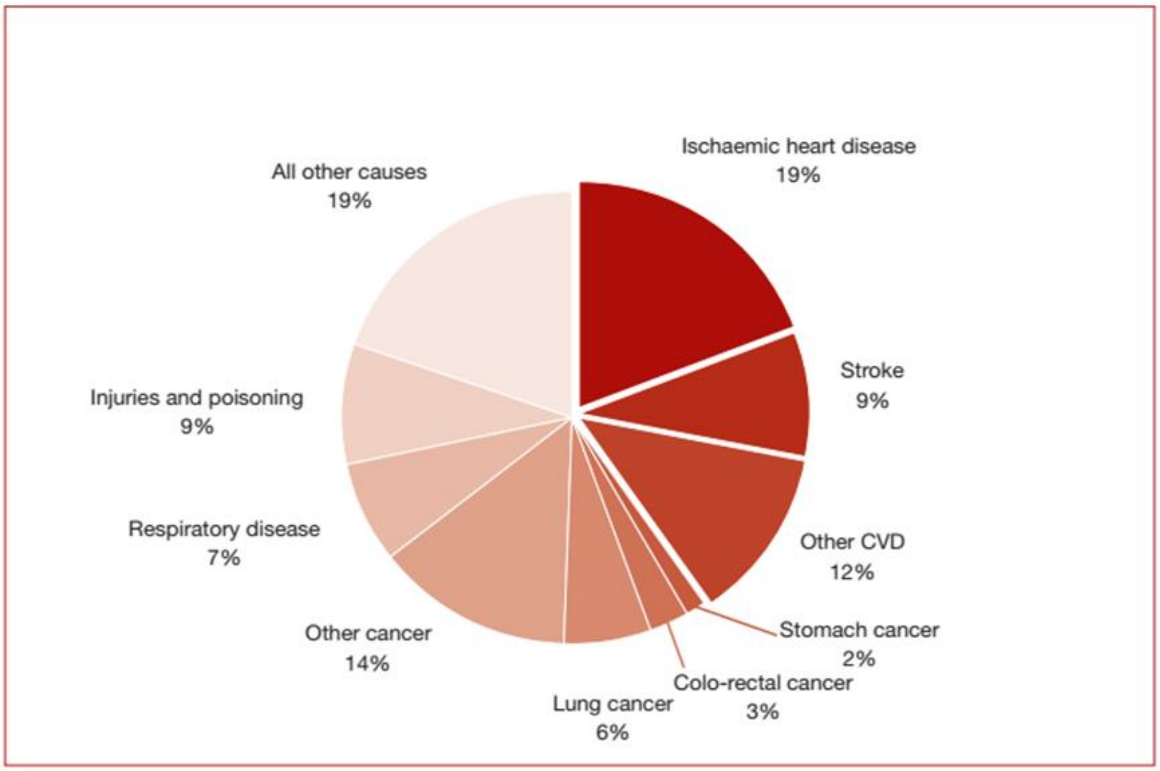


Figure 1A Mortality causes in men, latest available year, Europe

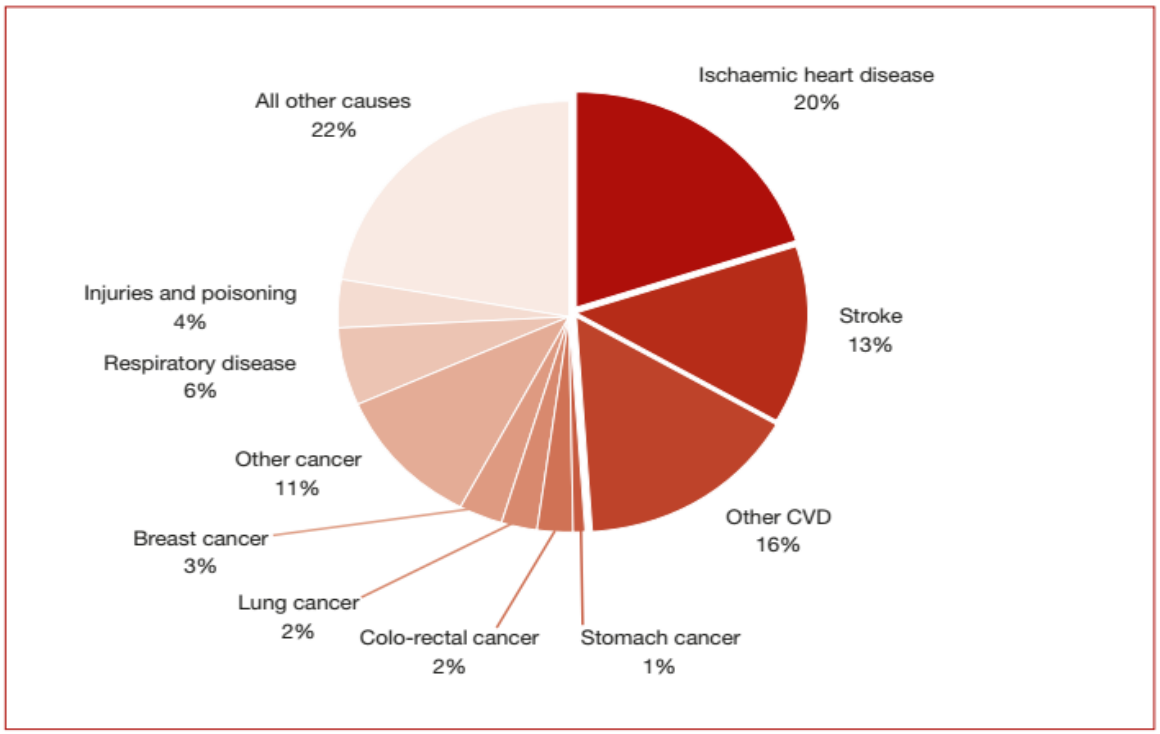


Figure 1B Mortality causes in women, latest available year, Europe

1.1.2 Atrial Fibrillation

Atrial fibrillation (AF) is an abnormal heart rhythm characterized by rapid and irregular beating of the atria.(4) In 2010, the estimated numbers of men and women diagnosed with AF worldwide were 20.9 million and 12.6 million, respectively, with higher incidence and prevalence rates noticed in developed countries.(4) There are only scarce data about its prevalence in Greece. In an epidemiological cross-sectional study (Arcadia Rural Study on AF-ARSAF) conducted between 2002-2003 in 5 rural villages of the Arcadia province in Greece and including 1,312 subjects, the overall prevalence of AF was 3.9% with an increasing trend across older ages ranging from 0.4% in patients <55 years to 10.7% in patients > 84 years.(5)

AF is independently associated with a 2-fold increased risk of all-cause mortality in women and a 1.5-fold increase in men.(6) Stroke-related death can be adequately mitigated by anticoagulation, but other cardiovascular (CV) deaths [i.e. death related with heart failure (HF) or sudden death] remain common even in properly treated patients.(7, 8) AF is also associated with increased morbidity, such as HF and stroke.(7, 8) Indeed, 20-30% of patients with ischemic stroke have been diagnosed with AF before, during or after the initial event.(9)

1.2 Risk factors for atherosclerotic cardiovascular disease

1.2.1 Prevalence of risk factors for atherosclerotic cardiovascular disease

Many individuals in the general population have one or more CV risk factors and over 90% of ASCVD events occur in individuals with at least one risk factor.(10-12) The 5 leading modifiable risk factors [hypercholesterolemia, diabetes mellitus (DM), hypertension, obesity, and smoking] account for more than half of CV mortality.(13) In this regard, the absence of major risk factors predicts a much lower risk of ASCVD.(12)

1.2.2 Established cardiovascular risk factors

Atherosclerosis is the underlying cause for ASCVD events.(14, 15) This insidious process begins with fatty streaks that are first seen in adolescence, which progress into plaques in early adulthood and culminate in thrombotic occlusions and CV events in middle age and later life.(14, 15) A variety of factors, often acting in concert, are associated with an increased risk for atherosclerotic plaques in coronary arteries and

other arterial beds.(16) The classic CV risk factors which have been associated with CVD include gender, age, cholesterol, hypertension, DM and family history of premature CHD.(16)

i) Gender and age

Age has been established as an independent CV risk factor. A cohort including 3.6 million individuals aged ≥40 years-old and screened for CVD demonstrated that the prevalence of CVD increased significantly with each decade of life.(17) The following rates of prevalent CVD were recorded: 2% in those aged 40-50 years old, 3.5% in 51-60 years old, 7.1% in 61-70 years old, 13% in 71-80 years old, 22.3% in 81-90 years old and 32.5% in 91-100 years old.(17)

Male sex has been long considered as a factor predisposing for CHD, although the potential mechanisms are not well understood. Several observational studies have demonstrated that the incidence and mortality related with CHD are higher in males.(18, 19)

ii) Family history of premature cardiovascular disease

Family history of CVD is a well-established CV risk factor, particularly among younger individuals.(20, 21) History of ASCVD or CVD death in a first-degree relative aged ≤55 years old for males and ≤65 years old for females is defined as positive family history of premature CVD.(22) However, it has been recently proposed that a less strict definition of premature CVD could include CVD in a first-degree relative of any age or other manifestations of atherosclerosis beyond myocardial infarction (MI) or CVD death, such as stroke or transient ischemic attack, CHD requiring revascularization in the absence of MI, PAD, and abdominal aortic aneurysm.(23) The importance of a family history of premature CVD death appears to be magnified in families with multiple premature deaths.(24) The Danish Family Relations Database included 3,985,301 persons born from 1950 to 2008 and followed for nearly 90 million person-years.(24) This study demonstrated that persons derived from families with 2 or more premature CV deaths among first-degree relatives had a 3-fold greater risk of incident CVD before the age of 50 [incidence Relative Risk (RR): 3.30, 95% confidence intervals (95% CI): 2.77-3.94].(24) Nevertheless, family history of CVD is

not intergreated in the available tools estimating CV risk.(25-27) Rather, it is considered as a risk-enhancing factor by the most recent European and American lipid guidelines.(27, 28)

iii) Hypertension

Hypertension has been long considered as an independent factor for CHD and stroke.(29, 30) A cohort including over 1.25 million subjects aged ≥30 years old without baseline CVD showed that those with hypertension experienced a higher risk of incident CVD compared with those having normal blood pressure (BP) levels (63.3 vs. 46.1%).(31)

iv) Cholesterol

Evidence for the pathogenic role of serum cholesterol has largely come from randomized controlled trials (RCTs) showing that reductions in total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels reduce coronary events and mortality in the setting of both primary and secondary prevention.(32-35) The determination of which cholesterol levels are 'normal' has long been the subject of debate among professional societies.(16, 22, 27, 36, 37) TC and high-density lipoprotein cholesterol (HDL-C) levels are considered by the available tools for CV risk estimation.(25-27)

v) Diabetes Mellitus

Insulin resistance (IR), hyperinsulinemia and elevated blood glucose are associated with a 3-fold increase in the risk of incident CVD.(10, 38) Traditionally, all-cause mortality risk associated with DM is thought to be similar to that of a prior MI,(39) and DM has been considered as a CHD equivalent.(27) Nowadays, DM patients are categorized as very-high, high or medium risk depending on the presence of ASCVD, target organ damage or multiple risk factors and duration of the disease.(40) Diabetic patients have a greater burden of other atherogenic risk factors, such as hypertension, obesity, atherogenic dyslipidemia as well as elevated plasma fibrinogen and other thrombotic risk factors.(27, 40) CVD risk in diabetics varies widely with the intensity of these risk factors and current guidelines suggest aggressive management and treatment.(27, 40)

vi) Smoking

Undoubtedly, cigarette smoking is an important CVD risk factor. Several cohorts have demonstrated that cigarette smoking dramatically increases the risk of incident MI up to 600%.(10, 41, 42) An observational cohort study of 8,770 participants has recently shown that former heavy smoker CVD risk was significantly lower within 5 years of smoking cessation relative to current smokers [hazard ratio (HR): 0.61].(43) Nevertheless, CVD risk remained significantly elevated for at least 5 to 10 years and possibly for 25 years after cessation relative to never smokers.(43)

1.2.3 Novel cardiovascular risk factors

i) Lipids and lipoproteins

Apart from LDL-C and HDL-C, the following lipid and lipoprotein abnormalities are associated with increased CHD risk: hypertriglyceridemia,(44) increased non-high-density lipoprotein cholesterol (non-HDL-C),(45) increased lipoprotein (a) [Lp(a)],(46) increased apolipoprotein (apo) C-III,(47) small-dense LDL particles (48) and different genotypes of apoE.(49)

Available evidence suggests that triglyceride-rich lipoproteins (TRLs), marked by high triglycerides (TGs), are strong and independent predictors of ASCVD and all-cause mortality, and that their cholesterol content (remnant cholesterol) are strong predictors of ASCVD.(50) Also, genetic studies using the Mendelian randomization design have demonstrated that TRLs are causally associated with ASCVD and all-cause mortality.(50)

LDL-C is a measure of cholesterol contained in the major atherogenic lipoprotein, whereas non-HDL-C represents the sum of the mass of cholesterol and cholesterol ester in all atherogenic lipoproteins [chylomicrons, very-low-density lipoprotein (VLDL) and their remnants, low-density lipoprotein (LDL) and Lp(a)] with apoB being their major apolipoprotein constituent.(27) Based on published epidemiological studies containing estimates of the relative risks of non-HDL-C and apoB for fatal or non-fatal ischemic cardiovascular events, a meta-analysis of 12 independent reports, including 233,455 subjects and 22,950 events, showed that apoB and non-HDL-C were more potent markers of CVD risk when compared with LDL-C.(51)

Lp(a) is an LDL particle with an apo(a) moiety covalently bound to its apoB component.(27) It is <70 nm in diameter and can freely flux across the endothelial

barrier, where it can become -similarly to LDL- retained within the arterial wall and thus increase the risk of ASCVD.(27) A recent Mendelian randomization study showed that the causal effect of Lp(a) on the risk of ASCVD is proportional to the absolute increase in plasma Lp(a) levels.(52) Importantly, this study also suggested that people with extremely high Lp(a) levels >180 mg/dL (>430 nmol/L) may have an increased lifetime risk of ASCVD similar to that of people with heterozygous FH (HeFH).(52) Because about 90% of a person's Lp(a) level is inherited, extremely elevated Lp(a) represent an inherited lipid disorder that is associated with extremely high lifetime risk of ASCVD and is 2-fold more prevalent than HeFH.(52)

ApoC-III is an atherogenic protein found on HDL, VLDL and LDL.(53) A meta-analysis of 11 studies including 2,832 cases with CV events showed significantly higher levels of apoC-III in the non-HDL fraction of plasma in CVD subjects compared with controls.(53) No difference was noticed for apoC-III levels in HDL and a trend toward higher total plasma apoC-III in those with CVD.(53)

LDL consists of several subclasses with distinct sizes, densities, and physicochemical compositions.(54) Accumulating evidence has shown that a predominance of small dense LDL is closely associated with CHD.(54) Small dense LDL-C concentrations are elevated in groups at a high risk for CHD, such as patients with type 2 diabetes mellitus (T2DM) and metabolic syndrome (MetS).(54)

ApoE gene, which affects the clearance of lipoproteins, has 3 major alleles: ε2, ε3, and ε4, coding for 3 isoforms: apoE2 (Cys112/Cys158), the most common apoE3 (Cys112/Arg158) and apoE4 (Arg112/Arg158).(55) ApoE isoforms have different effects on lipoprotein metabolism and certain polymorphisms (especially apoE4) have been associated with increased CVD risk.(55)

ii) Chronic Kidney Disease

The increased CHD risk in patients with end-stage renal disease has been well-described.(56) Mild to moderate renal dysfunction is also associated with a substantial increase in CHD risk.(56) In this context, recent guidelines consider chronic kidney disease (CKD) of stage 3-4 [estimated Glomerular Filtration Rate (eGFR) <30 ml/min/1.73 m^2] as very high-risk status, whereas patients with eGFR 30-60 ml/min/1.73 m^2 are considered to be at high CV risk.(27)

iii) Inflammatory markers

Strong evidence suggests that C-reactive protein (CRP),(57) interleukin-6,(58) and myeloperoxidase (59) are associated with increased CVD risk. Furthermore, CVD has also been associated with a variety of other markers of inflammation, such as elevated levels of white blood cells, erythrocyte sedimentation rates, interleukin-18, tumor necrosis factor alpha, transforming growth factor beta, soluble intercellular adhesion molecule-1, P-selectin, cathepsin S and lipoprotein-associated phospholipase A2.(60-69)

iv) Metabolic syndrome

Patients with the constellation of abdominal obesity, hypertension, dysglycemia, and dyslipidemia are considered to have the co-called MetS.(70) Such individuals have a 2-fold increased risk of CHD and all-cause mortality.(71)

1.2.4 Other cardiovascular risk factors

Several other factors, such as carotid artery intima-media thickness,(72) arterial stiffness (measured as the aortic pulse wave velocity between the carotid and femoral arteries),(73) calcium deposits in extracoronary arteries, particularly in the aortic arch and abdominal aorta (74) and coronary artery calcification (CAC) are prognostic markers of CVD.(75) Likewise, resting electrocardiogram (ECG) abnormalities, such as ST depression, T-wave inversion, left ventricular hypertrophy (LVH) or strain, and premature ventricular contractions are associated with increased CVD risk.(75) In addition, LVH,(76) endothelial dysfunction induced by dyslipidemia and oxidative stress,(77) along with resting and peak exercise heart rate are related with CVD and CV mortality.(78)

Moreover, other systemic conditions, such as androgen deficiency,(79) premature menopause,(80) systemic autoimmune diseases, especially rheumatoid arthritis, psoriatic arthritis and systemic lupus erythematosus,(81, 82) acute infectious illnesses,(83) non-alcoholic fatty liver disease (NAFLD),(84) abnormal sleep or sleep apnea (85) and small for gestational age (86) have been associated with increased incidence of CVD.

1.2.5 Lifestyle factors

i) Dietary factors

Various aspects of diet have been evaluated regarding their effect on CVD, such as, fruits and vegetables, meat, trans-fatty acids, fiber, coffee, low-glycemic index and low-cholesterol diets. Higher intake of dietary fiber, cereal fiber, and whole grains has been associated with lower risk of incident CVD,(87) whereas controversial data exists regarding the effect of glycemic index.(88-90) The beneficial effect of higher intake of fruit and vegetables might be attributed to their high content of fiber.(91, 92) On the other hand, consumption of red meat and processed meat has been associated with increased all-cause and CVD mortality, whereas consumption of white meat has been shown to decrease mortality.(93) Of note, the association between red meat and increased mortality has been attributed to processed red meat consumption rather than unprocessed.(94) A few studies have evaluated the effect of fat quality on CVD incidence.(95, 96) Higher intake of trans-fatty acids and saturated fat has been associated with higher CVD risk, whereas their replacement by monounsaturated (MUFAs) and polyunsaturated fatty acids (PUFAs) reduces this risk.(95, 96) As far as dietary pattern is concerned, Mediterranean Diet and Dietary Approaches to Stop Hypertension (DASH)-style diet have been demonstrated to protect against CVD.(97-99) Furthermore, moderate alcohol consumption has been shown to reduce CV mortality.(100, 101) On the contrary, heavy alcohol consumption (6 or more drinks per day) or binge drinking have been associated with increased all-cause and CV mortality.(102)

ii) Exercise

Aerobic exercise, even at moderate degree, protects against CVD and reduces all-cause mortality.(103, 104) In addition to the amount of exercise, the degree of CV fitness, a measure of physical activity determined by the duration of exercise and maximal oxygen uptake on a treadmill, is also associated with CV risk reduction and overall mortality.(105, 106) Although there is no data regarding the impact of anaerobic exercise on CVD development, a few studies have demonstrated a beneficial effect on several CV risk factors, such as BP and glucose reduction, improvement of insulin sensitivity and dyslipidemia, waist circumference decrease, and body composition improvement.(107, 108)

iii) Obesity

Obesity, defined as a body mass index (BMI) greater than 30 kg/m^2, is a highly prevalent condition, mostly in developed countries, reaching up to 35%.(109) Obesity, which is related with numerous risk factors for atherosclerosis, such as hypertension, dyslipidemia, IR and low levels of adiponectin, remains an independent CVD factor.(110) Indeed, a large prospective cohort demonstrated a continuous linear relationship between higher BMI and greater CVD risk.(111) Apart from the risk associated with obesity, large fluctuations in body weight (i.e, cycles of weight gain and weight loss) appear to also increase the risk of future CVD events.(112)

iv) Psychosocial factors

Psychosocial factors, such as depression, anger and stress have been correlated with CV outcomes.(113, 114) The link between psychologic stress and atherosclerosis may be either direct via the endothelium damage, or indirect via the aggravation of traditional CV risk factors, such as smoking, hypertension, and lipid metabolism.(115) Furthermore, socioeconomic deprivation has been recently demonstrated to increase all-cause and CVD mortality.(116)

1.3 Risk factors for atrial fibrillation

Hypertensive heart disease and CHD are the most common predisposing factors for AF.(117, 118) Additionally, almost any valvular lesion leading to significant stenosis or regurgitation, HF, hypertrophic cardiomyopathy, congenital heart disease and venous thromboembolism have been associated with AF.(119-122) Metabolic diseases, such as obesity, MetS and DM, along with CKD are also associated with AF.(123-126)

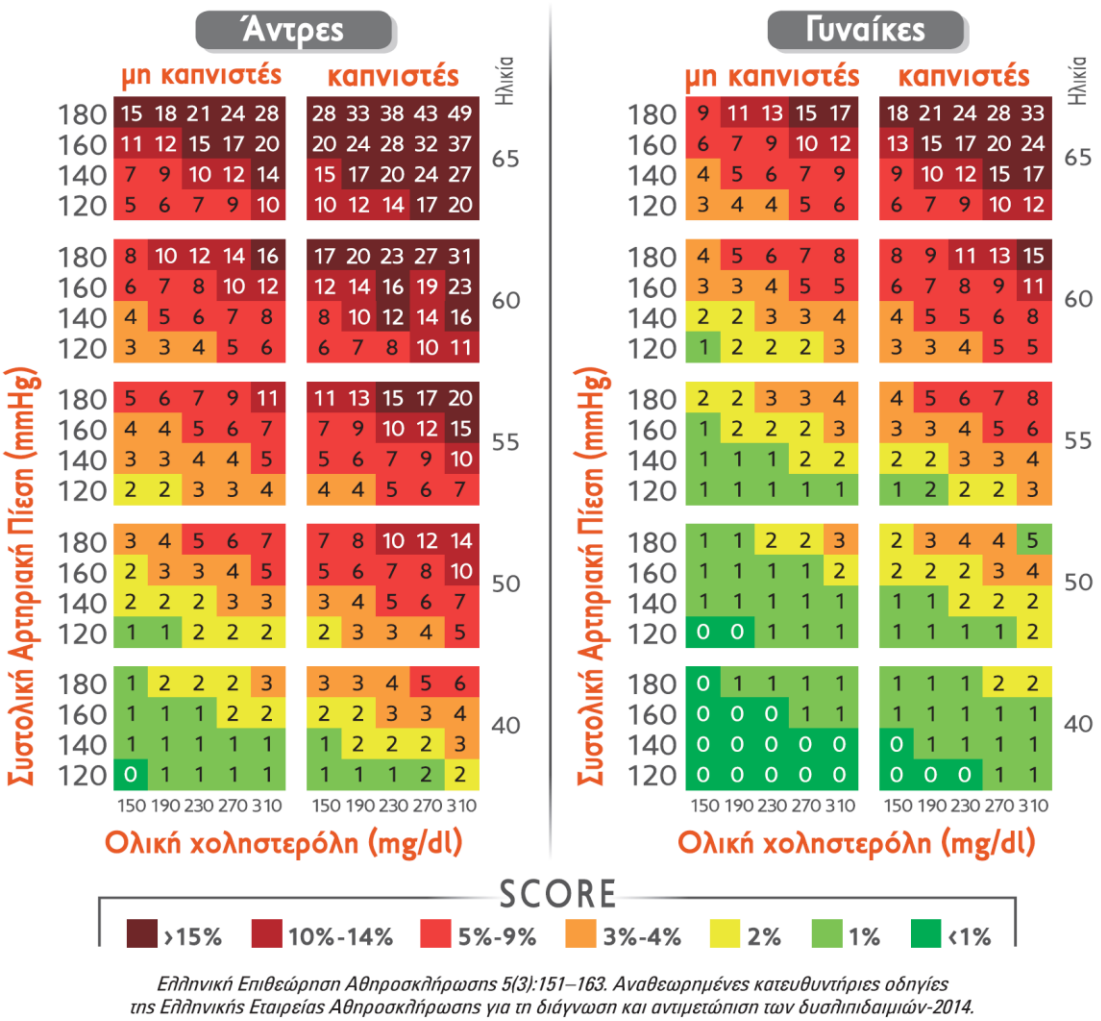
1.4 Prevention and treatment of atherosclerotic cardiovascular disease

1.4.1 Management of dyslipidemias

1.4.1.1 Total cardiovascular risk estimation

Updated guidelines for the management of dyslipidemias were recently published by the European Society of Cardiology and European Atherosclerosis Society (ESC/EAS).(27) ESC/EAS guidelines recommend the use of SCORE (Systematic Coronary Risk Estimation) in clinical practice to assess CV mortality risk because it is based on large, representative European cohort data sets and is relatively straightforward to recalibrate for

individual countries.(27) The SCORE equations have been calibrated to the Greek population and Hellenic SCORE has been proposed for improved estimation of 10-year fatal CVD risk in Greece (Figure 2).(25) SCORE is recommended for asymptomatic adults >40 years of age without evidence of CVD, DM, CKD, familial hypercholesterolemia (FH), or LDL-C >190 mg/dL (4.9 mmol/L). Persons with documented ASCVD, type 1 or type 2 diabetes mellitus (T1DM and T2DM, respectively), very high levels of individual risk factors, or CKD are generally considered to be at very high or high CV risk and therefore no risk estimation models are needed for such individuals.(27) For other, apparently healthy people, the use of a risk estimation system, such as SCORE, is recommended to estimate total CV risk, since many people have several risk factors that in combination may result in high total CV risk.(27)



Ελληνική Επιθεώρηση Αθηροσκλήρωσης 5(3):151–163. Αναθεωρημένες κατευθυντήριες οδηγίες της Ελληνικής Εταιρείας Αθηροσκλήρωσης για τη διάγνωση και αντιμετώπιση των δυσλιπιδαιμιών-2014.

Figure 2 HELLENIC SCORE Cardiovascular Risk Chart

The following factors could modify SCORE risk: social deprivation, obesity and central obesity, physical inactivity, psychosocial stress, family history of premature CVD, chronic immune-mediated inflammatory disorder, major psychiatric disorders, treatment of human virus infection, AF, LVH, CKD, obstructive sleep apnea syndrome and NAFLD.(27) Furthermore, for those at moderate risk, other factors, such as increased apoB, Lp(a), TGs, or CRP, the presence of albuminuria or atherosclerotic plaque in the carotid or femoral arteries, along with the CAC score may improve risk classification.(27) Total CV risk will also be higher than indicated in the SCORE charts in asymptomatic persons with abnormal markers of subclinical atherosclerotic vascular damage.(27) Reclassification should be reconsidered in people identified as being at moderate CV risk by using markers such as CAC score >100 Agatston units, ankle-brachial index (ABI) <0.9 or >1.40, carotid femoral pulse wave velocity >10 m/s, or the presence of plaques at carotid or femoral ultrasonography.(27) Some factors such as a high HDL-C up to 90 mg/dL (2.3 mmol/L) or a family history of longevity can be associated with lower CV risk.(27)

ESC/EAS 2019 guidelines for the management of dyslipidemias recommend the following levels of total CV risk: very high, high, moderate and low.(27)

As **very high risk** individuals are considered those with any of the following:

- Documented ASCVD, either clinical or unequivocal on imaging. Documented ASCVD includes previous acute coronary syndrome (MI or unstable angina), stable angina, coronary revascularization [percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), and other arterial revascularization procedures], stroke and transient ischemic attack, and PAD. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or computerized tomography scan (multivessel coronary disease with two major epicardial arteries having >50% stenosis), or on carotid ultrasound,
- DM with target organ damage or at least 3 major risk factors, or early onset of T1DM of long duration (>20 years),
- Severe CKD (eGFR) <30 mL/min/1.73 m^2,
- A calculated SCORE ≥10% for 10-year risk of fatal CVD,
- FH with ASCVD or with another major risk factor

As **high risk** individuals are considered those with:

- Markedly elevated single risk factors, in particular TC >310 mg/dL (>8 mmol/L), LDL-C >190 mg/dL (>4.9 mmol/L) or BP ≥180/110 mmHg,
- Patients with FH without other major risk factors,
- Patients with DM without target organ damage, with DM duration ≥10 years or another additional risk factor,
- Moderate CKD (eGFR 30-59 mL/min/1.73 m^2),
- A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD

As **moderate risk** persons are considered those:

- Young patients (T1DM <35 years; T2DM <50 years), with DM duration <10 years, without other risk factors,
- Calculated SCORE ≥1% and <5% for 10-year risk of fatal CVD

As **low risk** individuals are considered those with calculated SCORE <1% for 10-year risk of fatal CVD and without any of the above conditions.(27)

Non-invasive CV imaging techniques, such as arterial (carotid and/or femoral) plaque burden on arterial ultrasonography or CAC score assessment with computerized tomography, should be considered as a risk modifier in individuals at low or moderate risk.(27)

According to previous ESC/EAS guidelines published in 2016 and 2011, patients with FH without ASCVD were considered to be at high CV risk (36, 37), whereas patients with eGFR <60 ml/min/1.73 m^2 were considered to be at very-high CV risk.(37)

American College/American Heart Association (ACC/AHA) guidelines published in 2013 and 2018 proposed the following CV risk groups (22, 28):

- Patients with established ASCVD, aged ≤75 or >75 years
- Patients without established ASCVD, but baseline LDL-C levels ≥190 mg/dL (4.9 mmol/L),
- Patients with T2DM without clinical ASCVD, aged 40-75 years with LDL-C levels 70-190 mg/dL (1.8-4.9 mmol/L) and a 10-year ASCVD risk ≥7.5% or <7.5%,
- Patients with a 10-year ASCVD risk ≥7.5% not classified as above.

According to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) patients with established vascular disease as well as those with type 2

diabetes were considered as high CV risk.(16) Moderate risk patients were defined by the presence of 2 CV risk factors [increased age (>45 and 55 years for men and women, respectively), hypertension, smoking, family history of premature CHD, and low levels of HDL-C (<40 and 50 mg/dL, 1.0 and 1.3 mmol/L, for men and women, respectively)] and patients with 0-1 CV risk factors were considered as low-risk.(16)

1.4.1.2 Targets of lipid-lowering therapy

TC is used for the estimation of total CV risk by means of the SCORE system, whereas HDL-C is recommended to further refine risk estimation using the online SCORE system or special charts.(27) LDL-C is recommended as the primary lipid target for screening, diagnosis, and management, whereas TG measurement is recommended as part of the routine lipid analysis.(27) Plasma LDL-C can be measured directly using enzymatic techniques or preparative ultracentrifugation, but in clinical practice is usually calculated based on the Friedewald formula: LDL-C=TC-(HDL-C + TG/5) in mg/dL.(27) In case of high TG values >400 mg/dL (4.5 mmol/L) this formula cannot be used.(27) As an alternative to LDL-C, non-HDL-C can be calculated as (TC minus HDL-C) and is a measure of the cholesterol carried by all atherogenic apoB-containing lipoproteins, including TG-rich particles in very-low density lipoproteins and their remnants as well as Lp(a).(27) Non-HDL-C evaluation is recommended for risk assessment, particularly in individuals with high TG levels, DM, obesity, or very low LDL-C levels.(27) ApoB measurement is recommended for risk assessment, particularly in people with high TG levels, DM, obesity, MetS, or very low LDL-C levels.(27) If available, it can be used as an alternative to LDL-C, as the primary measurement for screening, diagnosis, and management, and may be preferred over non-HDL-C in people with high TG levels, DM, obesity, or very low LDL-C levels.(27) Additionally, Lp(a) measurement should be considered i) at least once in each adult person's lifetime to identify those with very high inherited Lp(a) levels >180 mg/dL (>430 nmol/L) who may have a lifetime risk of ASCVD equivalent to the risk associated with HeFH and ii) in selected patients with a family history of premature CVD, and iii) for reclassification in people who are borderline between moderate and high-risk.(27)

The targeted approach to lipid management is primarily aimed at reducing atherosclerotic risk by substantially lowering LDL-C. Table 1 summarizes the proposed

LDL-C targets by the most recent ESC/EAS guidelines.(27) Secondary goals have also been defined by inference for non-HDL-C and for apoB.(27) The specific goal for non-HDL-C should be 30 mg/dL (0.8 mmol/L) higher than the corresponding LDL-C target.(27) Adjustment of lipid-lowering therapy in accordance with these secondary goals may be considered in patients at very high CV risk after achievement of LDL-C goal.(27)

Table 1 *Recommendations for treatment goals for low-density lipoprotein cholesterol by European Society of Cardiology/European Atherosclerosis Society 2019*

LDL-C targets	Patient groups
LDL-C reduction ≥50% from baseline + LDL-C <55 mg/dL (1.4 mmol/L)	-In secondary prevention for patients at very high risk -In primary prevention for individuals at very high risk but without FH -In primary prevention for individuals with FH at very high risk
LDL-C <40 mg/dL (1.0 mmol/)	-For patients with ASCVD who experience a second vascular event within 2 years (not necessarily of the same type as the first event) while taking maximally tolerated statin-based therapy
LDL-C reduction ≥50% from baseline + LDL-C <70 mg/dL (<1.8 mmol/L)	-In patients at high risk
LDL-C <100 mg/dL (<2.6 mmol/L)	-In individuals at moderate risk
LDL-C <115 mg/dL (<3.0 mmol/L)	-In individuals at low risk

ASCVD, Atherosclerotic Cardiovascular Disease; FH, Familial Hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol

The recommended secondary targets are the following: i) non-HDL-C <85 mg/dL (2.2 mmol/L), <100 mg/dL (2.6 mmol/L), and <130 mg/dL (3.4 mmol/L) in people at very high, high, and moderate CV risk, respectively, and ii) apoB <65 mg/dL, <80 mg/dL, and <100 mg/dL in very high, high, and moderate CV risk, respectively.(27) To date, no specific goals for HDL-C or TG levels have been determined.(27) Clinicians should use clinical judgment when considering further treatment intensification in patients at high or very high CV risk.(27)

Table 2 shows proposed LDL-C targets in previous and current guidelines. (16, 36, 37)

Table 2 *Cardiovascular risk groups and proposed low-density lipoprotein cholesterol targets*

Cardiovascular risk	NCEP ATPIII	ESC/EAS 2011	ESC/EAS 2016	ESC/EAS 2019
Very high risk	<100 mg/dL (2.6 mmol/L)	<70 mg/dL (1.8 mmol/L)	<70 mg/dL (1.8 mmol/L) + LDL-C reduction ≥50% from baseline	LDL-C <55 mg/dL (1.4 mmol/L) or <40 mg/dL (1 mmol/)* + LDL-C reduction ≥50% from baseline
High risk	<130 mg/dL (3.4 mmol/L)	<100 mg/dL (2.6 mmol/L)	<100 mg/dL (2.6 mmol/L) + LDL-C reduction ≥50% from baseline	<70 mg/dL (1.8 mmol/L) + LDL-C reduction ≥50% from baseline
Moderate risk	<160 mg/dL (4.1 mmol/L)	<115 mg/dL (3 mmol/L)	<115 mg/dL (3 mmol/L)	<100 mg/dL (2.6 mmol/L)
Low risk	<190 mg/dL (4.9 mmol/L)	<190 mg/dL (4.9 mmol/L)	<190 mg/dL (4.9 mmol/L)	<115 mg/dL (3 mmol/L)

* For patients with atherosclerotic cardiovascular disease who experience a second vascular event within 2 years (not necessarily of the same type as the first event) while taking maximally tolerated statin-based therapy

ESC/EAS, European Society of Cardiology/European Atherosclerosis Society; NCEP ATPII, National Cholesterol Education Program's; LDL-C, low-density lipoprotein cholesterol

According to the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) the following groups of patients are defined as 'extreme' CV risk: i) patients with established CVD and DM, CKD stages 3-4 or FH, ii) patients with premature CVD and iii) patients with recurrent CVD event despite LDL-C <70 mg/dL.(127) The proposed LDL-C target in such patients is <55 mg/dL.(127)

1.4.1.3 Lifestyle modifications to improve plasma lipid profile

In general, no exposure to tobacco in any form is proposed, whereas healthy diet low in saturated fat with a focus on wholegrain products, vegetables, fruit, and fish is recommended.(27) Moreover, 3.5-7.0 h moderately vigorous physical activity per week or 30-60 min most days is beneficial.(27) Table 3 summarizes the currently available evidence on the influences of lifestyle changes and functional foods on lipoproteins.(27)

Table 3 *Impact of specific lifestyle changes on lipid levels*

	Magnitude of the effect
I. Lifestyle interventions to reduce TC and LDL-C levels	
Avoid dietary trans fats	5-10%
Reduce dietary saturated fats	5-10%
Increase dietary fibre	5-10%
Use functional foods enriched with phytosterols	5-10%
Use red yeast rice nutraceuticals	5-10%
Reduce excessive body weight	5-10%
Reduce dietary cholesterol	≤5%
Increase habitual physical activity	≤5%
II. Lifestyle interventions to reduce TG-rich lipoprotein levels	
Reduce excessive body weight	≤5%
Reduce alcohol intake	≥10%
Increase habitual physical activity	5-10%
Reduce total amount of dietary carbohydrates	5-10%
Use supplements of n-3 polyunsaturated fats	5-10%
Reduce intake of mono- and disaccharides	5-10%
Replace saturated fats with mono- or polyunsaturated fats	≤5%
III. Lifestyle interventions to increase HDL-C levels	
Avoid dietary trans fats	5-10%
Increase habitual physical activity	≥10%
Reduce excessive body weight	5-10%
Reduce dietary carbohydrates and replace them with unsaturated fats	5-10%
Modest consumption in those who take alcohol may be continued	5-10%
Quit smoking	≤5%

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides

1.4.1.4 Lipid-lowering drugs

i) Statins

Statins remain the cornerstone therapy for the management of dyslipidemia and CV prevention.(27) Statins reduce the hepatic synthesis of cholesterol by competively inhibiting the enzyme HMG-CoA reductase.(27) The reduced levels of intracellular cholesterol lead to increased LDL receptor (LDLR) expression at the surface of

hepatocytes, thus resulting in increased uptake of bloodstream LDL-C and decreased plasma concentrations of LDL and other apoB-containing lipoproteins, including TG-rich particles.(27)

Effects of statins on lipids

LDL-C reduction induced by statins is dose-dependent and varies across different statins.(27) A high-intensity regimen is defined as the dose of a statin that reduces LDL-C approximately by ≥50% (rosuvastatin 20-40 mg, atorvastatin 40-80 mg); moderate-intensity therapy is defined as the dose expected to reduce LDL-C by 30-50% (rosuvastatin 5-10 mg, atorvastatin 10-20 mg, pitavastatin 2-4 mg, simvastatin 20-40 mg, fluvastatin 80 mg, lovastatin 40 mg, pravastatin 40-80 mg) and low-intensity therapy is defined as the dose expected to reduce LDL-C by <30% (pitavastatin 1 mg, simvastatin 10 mg, fluvastatin 20-40 mg, lovastatin 20 mg, pravastatin 10-20 mg).(27) However, there is considerable interindividual variation in LDL-C reduction with the same dose of a drug.(27) This could be attributed to poor compliance, but also to different genetic background.(27) Statins reduce TG levels by 10-20% from baseline.(27) The more potent statins (atorvastatin, rosuvastatin and pitavastatin) are associated with robust TG reduction, especially at high doses and in patients with elevated TGs.(27) HDL-C may be increased by 1-10% with statin therapy, whereas no effect on or an increase of Lp(a) levels has been reported after statin treatment.(27) Although LDL-C reduction is the major mechanism of action of statins, a number of pleiotropic effects have been suggested.(128) Among such effects potentially relevant for CVD prevention are the anti-inflammatory and antioxidant effects of statin treatment.(128)

Effect of statins on cardiovascular morbidity and mortality

Undoubtedly, statins remain the cornerstone therapy in CV prevention, since they have been associated with a reduction in the incidence of CVD and CVD-related mortality.(129-131) The Cholesterol Treatment Trialists (CTT) meta-analysis including 26 RCTs with >170,000 participants and comparing statin vs control or a more vs less intensive statin regimen, demonstrated that each 1 mmol/L (38.6 mg/dL) reduction in LDL-C by statins reduced major vascular events (MI, CHD death, or any stroke or coronary revascularization) by ~22%, major coronary events by 23%, CHD-related

death by 20%, total stroke by 17%, and total mortality by 10% over 5 years.(129) Of note, the reduction in CV mortality has been demonstrated to be dose-dependent.(132) Although the benefit seems greater in patients with previous CVD, a lower but still significant benefit remains in the setting of primary CV prevention.(129, 133, 134)

Adverse effects of statins

Although statins are generally well tolerated, they do have some specific adverse effects on muscles, glucose hemostasis, and may be on hemorrhagic stroke.(27) Myopathy is the most clinically relevant adverse efffect of statin treatment, with drug interactions being a common cause.(27) Rhabdomyolysis is the most severe form of statin-induced muscle damage, characterized by severe muscular pain, muscle necrosis, and myoglobinuria, which potentially can lead to renal failure and death.(27) In rhabdomyolysis, elevation of creatine kinase (CK) levels by ≥10 times or even ≥40 times can be noticed.(27) Its prevalence has been estimated to 13 cases/100,000 patient-years.(27) Other muscle symptoms, such as muscular pain and tenderness (myalgia) without CK elevation or functional loss, have been described by the term 'statin-associated muscle symptoms' (SAMS) and their frequency varies between 10-15% among statin-treated individuals.(27) It has to be noticed though that blinded RCTs of statins vs placebo have demonstrated no or only a slightly increased frequency of muscle symptoms in statin allocated groups.(27)

Mild elevation of alanine aminotransferase (ALT) occurs in 0.5-2.0% of statin-treated patients, more commonly with potent statins or high doses.(27) A 3-fold increase of the upper limit of normal values (ULN) on 2 consecutive occasions has been commonly defined as clinically relevant ALT elevation.(27) After taking into consideration the fact that mild ALT elevation is not associated with true hepatotoxicity or changes in liver function, along with the exceedingly rare progression to liver failure, routine ALT monitoring during statin treatment is no longer recommended.(27)

Statin therapy has been associated with new DM onset in a dose-related manner.(135) Predisposing factors are treatment with potent statins at high doses, older age and other risk factors for DM, such as overweight and IR.(136) The number needed to treat to cause one case of DM has been estimated as 255 over 4 years.(137) However, the absolute reduction in CVD risk in high-risk patients clearly outweighs the possible DM

risk.(138) This effect could be attributed to the mechanism of action of statins, since mendelian randomization studies have confirmed increased DM risk in individuals with HMG-CoA reductase polymorphisms that reduce cholesterol synthesis.(139)

Although statin-induced LDL-C reductions has been associated with increased risk of hemorrhagic stroke, meta-analyses have shown conflicting results, thus underlying the need for further exploration.(27, 130) Nevertheless, the overall benefit on other stroke subtypes greatly outweighs this small and uncertain hazard.(130)

Although there is no clear evidence that statins have either a beneficial or an adverse effect on renal function, an increased risk of incident proteinuria has been reported for all statins and mostly with rosuvastatin at the highest dose of 80 mg.(27) However, with approved lower doses of <40 mg, the prevalence of proteinuria is much lower and in line with that noticed with the rest of statins.(27)

Interactions of statins

A number of important drug interactions with statins have been described that may increase the risk of adverse effects.(27) Mostly, inhibitors and inducers of enzymatic pathways involved in statin metabolism, such as cytochrome P450 3A4, interact with statins and could lead to increased risk of myopathy and rhabdomyolysis.(27) The drugs potentially interacting with statins include the following: i) anti-infective agents, such as itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin and protease inhibitors of human immunodeficiency virus, ii) calcium antagonists, such as verapamil, diltiazem and amlodipine and iii) ciclosporin, danazol, amiodarone, ranolazine, grapefruit juice and nefazodone.(27) Combination of statins with gemfibrozil must be avoided due to increased risk of myopathy.(27) No or very little increased risk for myopathy has been reported in combination therapies of statins with other fibrates, such as fenofibrate, bezafibrate, or ciprofibrate.(27)

ii) Cholesterol absorption inhibitors

Ezetimibe inhibits intestinal absorption of dietary and biliary cholesterol at the level of the brush border of intestine by interacting with the Niemann-Pick C1-like protein 1.(27) The inhibition of intestinal cholesterol absorption reduces the amount of cholesterol available to liver, leading to up-regulation of LDLR expression, which in turn increases LDL-C clearance from the blood.(27)

Effects of ezetimibe on lipids

Monotherapy with ezetimibe at the daily dose of 10 mg has been associated with a 15-22% reduction in LDL-C, ~13% reduction in TC, ~8% reduction in TGs and a significant ~3% increase in HDL-C levels.(27) The addition of ezetimibe on ongoing statin therapy reduces LDL-C by 21-27%.(27) Co-administration of ezetimibe and bile acid sequestrants (colesevelam, colestipol, or cholestyramine) has also been reported to reduce LDL-C levels by 10-20% when compared with the stable bile acid sequestrant regimen alone.(27)

Effect of ezetimibe on cardiovascular morbidity and mortality

Available RCTs have clearly demonstrated a benefit of ezetimibe on CV prevention in patients with previous CVD, CKD or stenosis of aortic valve.(140-142) In the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), ezetimibe was added to simvastatin (40 mg) in patients after acute coronary syndrome and a total of 18,144 patients were followed-up up to 7 years.(140) Treatment with ezetimibe decreased the risk of incident CVD by 6% (HR: 0.936, 95% CI: 0.89 to 0.99, p=0.016).(140) Although the absolute CV benefit from added ezetimibe was small, it remained significant and consistent with the CTT curve.(140) Therefore, IMPROVE-IT provided evidence that ezetimibe should be used as second-line therapy in association with statins when the therapeutic goal is not achieved at the maximal tolerated statin dose, or in cases where a statin cannot be prescribed.(27)

Adverse effects and interactions of ezetimibe

Ezetimibe is rapidly absorbed and extensively metabolized to pharmacologically active ezetimibe glucuronide.(27) The recommended daily dose of ezetimibe of 10 mg can be administered irrespective of food intake.(27) There are no clinically significant effects of age, sex, or race on ezetimibe pharmacokinetics, and there is no need for dosage adjustment in patients with mild hepatic impairment or CKD.(27) Reports for severe liver failure with ezetimibe as monotherapy or in combination with statins are extremely rare.(27) The addition of ezetimibe to statin therapy does not appear to increase the incidence of elevated CK levels beyond what is noted with statin treatment alone.(27) Also, no significant interactions with other drugs have been described.(27)

iii) Bile acid sequestrants

Bile acid sequestrants, such as cholestyramine, colestipol and colesevelam, prevent the intestinal absorption of cholesterol into the blood by binding bile acids, thereby removing a large portion of them from the enterohepatic circulation.(27) Due to bile acid depletion, the liver synthesizes more hepatic cholesterol, therefore increasing the hepatic demand for cholesterol and increasing LDLR expression, which results in a decrease of circulating LDL-C.(27)

Effects of bile acid sequestrants on lipids

Daily dose of 24 g of cholestyramine, 20 g of colestipol, or 4.5 g of colesevelam, reduce LDL-C by 18-25%.(27) No major effect on HDL-C has been reported, whereas TGs may increase.(27) A reduction in glucose levels by colesevelam has also been noticed in hyperglycemic patients.(27)

Effect of bile acid sequestrants on cardiovascular morbidity and mortality

In clinical trials, bile acid sequestrants have contributed greatly to the demonstration of the efficacy of LDL-C lowering in reducing CV events in hypercholesterolemic people, with a benefit proportional to the degree of LDL-C lowering.(27) However, there has been no clear evidence supporting that bile acid sequestrants reduce CV mortality.(143)

Adverse effects and interactions of bile acid sequestrants

Gastrointestinal (GI) adverse effects, such as flatulence, constipation, dyspepsia, and nausea, are often present with these drugs and limit their practical use.(27) These adverse effects can be attenuated with low starting doses and ingesting ample fluid.(27) Reduced absorption of fat-soluble vitamins and increase in TG levels have also been reported.(27) Due to the fact that several drugs interactions have been described with bile acid sequestrants, they must be administered either 4 h before or 1 h after other drugs.(27) Compared with the other 2 bile acid sequestrants, fewer adverse effects and interactions have been described with colesevelam, which can be taken together with statins and several other drugs.(27)

iv) Proprotein convertase subtilisin/kexin type 9 inhibitors

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors target PCSK9, which is involved in LDLR control.(27) Elevated concentration of PCSK9 has been demonstrated to reduce LDLR expression by promoting, upon binding, LDLR lysosomal catabolism, subsequently increasing plasma LDL-C.(27) Currently available therapeutic strategies include monoclonal antibodies, which bind plasma PCSK9, which in turn is not available to bind to LDLR.(27) The reduction in circulating PCSK9 levels leads to increased LDLRs expression at the hepatocyte surface and therefore to enhanced LDL-C reduction.(27) Currently, the only available approved PCSK9 inhibitors are 2 fully human monoclonal antibodies, alirocumab and evolocumab.(27)

Effects of proprotein convertase subtilisin/kexin type 9 inhibitors on lipids

Alirocumab and evolocumab, either alone or in combination with other lipid-lowering drugs, have been demonstrated to reduce LDL-C by ~60%.(27) PCSK9 inhibitors are effective in the vast majority of hypercholesterolemic patients, except for patients with homozygous FH (HoFH) who are LDLR-deficient and respond poorly to therapy.(27) These drugs have also been associated with a ~26% reduction in TG levels, along with a ~9% and ~4% increase in HDL-C and apoA-I, respectively.(27) In contrast to statins, treatment with PCSK9 inhibitors has been shown to reduce Lp(a) by 20-30%.(27)

Effect of proprotein convertase subtilisin/kexin type 9 inhibitors on cardiovascular morbidity and mortality

Two major trials, the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) and the Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab (ODYSSEY Outcomes), have investigated the impact of evolocumab and alirocumab on the risk of incident CVD and CVD-related mortality in patients with either previous CVD or recent MI/unstable angina.(144-146) The relative benefit ranged from 15-20% reductions in the risk of the primary endpoints in these trials (composite of CV death, MI, stroke, hospitalization for unstable angina or coronary revascularization).(144-146)

Adverse effects and interactions of proprotein convertase subtilisin/kexin type 9 inhibitors

PCSK9 inhibitors are specific monoclonal antibidies that do not interact with other drugs.(27) Itching at the injection site and rare flu-like symptoms are the most commonly described side effects.(27) The EBBINHAUS trial, which was specifically designed to detect neurocognitive function changes, along with the safety reports of the FOURIER and ODYSSEY trials showed no evidence of adverse neurocognitive effects.(144, 145, 147) Also, no evidence of increased new-onset DM or neutralizing antibodies was provided by these large studies.(27)

v) Lopitamide

The microsomal transfer protein (MTP) transfers TGs and phospholipids from the endoplasmic reticulum to apoB, as a necessary step in the formation of VLDL.(27) MTP inhibition thus prevents the formation of VLDL in the liver and chylomicrons in the intestine.(27) Lomitapide, an MTP inhibitor designed for oral treatment in patients with HoFH, has been associated with a up to ~50% LDL-C reduction, but no data exists yet regarding CV outcomes.(27) Lopitamide has been associated with increased aminotransferase levels, reflecting the increased fat in the liver as well as GI disturbances.(27) Therefore, prescription of lomitapide requires careful patient education and liver function monitoring during therapy.(27)

vi) Mipomersen

Mipomersen is an antisense oligonucleotide able to bind to the mRNA of apoB100, which triggers the selective degradation of mRNA.(27) After being subcutaneously injected, mipomersen is preferentially transported to the liver, where it binds to an apoB mRNA.(27) This results in prevention of apoB translation and consequently, reduction of atherogenic lipoproteins, like LDL and Lp(a).(27) Mipomersen is currently approved by the US Food and Drug Administration, but not by the European Medicines Agency, to reduce LDL-C in patients with HoFH.(27) Reactions at the injection site are the most common adverse effects, whereas liver toxicity remains the major concern regarding safety, since it has been associated with the development of steatosis.(27)

vii) Fibrates

Fibrates, which are agonists of peroxisome proliferator-activated receptor-a, act via transcription factors regulating, among others, various steps in lipid and lipoprotein metabolism.(27) As a consequence, fibrates have good efficacy in lowering fasting TGs as well as post-prandial TG and TG-rich lipoprotein remnant particles.(27)

Effect of fibrates on lipids

Fibrates reduce TGs by ~50%, LDL-C by 20% and increase HDL-C levels by 20%.(27)

Effect of fibrates on cardiovascular morbidity and mortality

Available evidence suggests that fibrates might have a favorable on CVD major outcomes, but not on mortality, in patients with atherogenic dyslipidemia.(148, 149) Thus, the overall efficacy of fibrates on CVD outcomes is much less robust than that of statins.

Adverse effects and interactions of fibrates

Fibrates are generally well tolerated with mild adverse effects, GI disturbances being reported in <5% of patients, and skin rashes in 2%.(27) In general, myopathy, liver enzyme elevations, cholelithiasis and pancreatitis represent the most well-known adverse effects associated with fibrate therapy.(27) The risk of myopathy has been reported to be 5.5-fold greater with gemfibrozil especially with combination with statins.(27) On the other hand, myopathy risk is less in the case of fenofibrate, since it does not share the metabolism of statins via the glucuronidation pathway.(27) Fenofibrate has been associated with an increase in serum creatinine and homocysteine levels, but no adverse effects on renal function are seen.(27) However, an increase in venous thromboembolic events has been reported.(27)

viii) n-3 fatty acids

The n-3 (or omega-3) fatty acids, such as eicosapentaenoic acid and docosahexaenoic acid, affect serum lipids and lipoproteins, in particular VLDL concentration at the daily dose of 2-4 g.(27) Although the exact mechanism remains unknown, TG reduction could be attributed to their ability to interact with peroxisome proliferator-activated receptors and decrease apoB secretion.(27)

Effects of n-3 fatty acids on lipids

Daily treatment with 2-4 g n-3 fatty acids has been shown to significantly reduce serum TGs up to 45% in a dose-dependent manner, but their effects on other lipoproteins are trivial.(27)

Effect of n-3 fatty acids on cardiovascular morbidity and mortality

Previous meta-analyses have reported that omega-3 PUFAs had no overall effect on total and CVD-related mortality,(150, 151) with only a suggestion of CHD event reduction (RR: 0.93; 95% Cl: 0.88-0.97).(151) Nevertheless, The Reduction of Cardiovascular Events with EPA-Intervention Trial (REDUCE-IT) evaluating the potential benefits of eicosapentaenoic acid on CVD outcomes in individuals with elevated serum TGs, has recently demonstrated that use of high doses (2 g b.i.d.) of eicosapentaenoic acid as compared with placebo (mineral oil) resulted in a ~25% relative risk reduction ($p < 0.001$) in major adverse CV events and CV mortality.(152) In this context, eicosapentaenoic acid has been very recently indicated by the FDA for CVD event reduction in high risk individuals with TGs >150 mg/dL.(153)

Adverse effects and interactions of n-3 fatty acids

The administration of n-3 fatty acids appears to be safe and devoid of clinically significant interactions, with GI disturbance being the most common side effect.(27) Only a few reports have associated their use with bleeding, especially when given in addition to aspirin or clopidogrel and a risk for prostate cancer.(27) In REDUCE-IT an increase in new AF was noticed.(152)

ix) Nicotinic acid

In the liver, nicotinic acid inhibits diacylglycerol acyltransferase-2 resulting in decreased secretion of VLDL particles.(27) Furthermore, nicotinic acid primarily raises HDL-C and apoA-I by stimulating apoA-I production in the liver.(27) Nevertheless, nicotinic acid has not been approved by European Medicines Agency because of 2 large RCTs demonstrating lack of benefit and increased frequency of serious adverse effects.(154, 155)

1.4.1.5 Strategies to control plasma cholesterol

Figure 3 demonstrates the proposed treatment algorithm for pharmacological LDL-C lowering by ESC/EAS 2019.(27) Briefly, high-intensity statins at the highest tolerated dose are recommended first.(27) If the goals are not achieved with the maximum tolerated dose of a statin, combination therapy of a statin with ezetimibe should be used.(27) PCSK9 inhibitors are recommended in patients at very high risk who do not achieve optimal LDL-C levels, despite maximum tolerated dose of a statin and ezetimibe.(27) If a statin-based regimen is not tolerated at any dosage (even after rechallenge), ezetimibe ± PCSK9 inhibitors should be considered.(27)

According to the Hellenic Expert Consensus, eligible patients for administration of monoclonal antibodies against PCSK9 include:(156)

- Adult patients with established ASCVD or diabetic patients with known CVD or CKD (eGFR ≤60 mL/min/1.73 m^2 and/or albuminuria for at least 3 months) or other target organ damage who have LDL-C ≥100 mg/dL despite being under appropriate healthy diet and maximum tolerated dose of a high-intensity statin (atorvastatin 40/80 mg or rosuvastatin 20/40 mg) + ezetimibe 10 mg,
- Adult patients with FH without known ASCVD and LDL-C ≥130 mg/dL despite being under appropriate healthy diet and maximum tolerated dose of a high-intensity statin (atorvastatin 40/80 mg or rosuvastatin 20/40 mg) + ezetimibe 10 mg,
- High or very high risk patients (HELLENIC SCORE >5% or >10%, respectively) who are intolerant to statins and have LDL-C ≥130 or ≥100 mg/dL, respectively, under any tolerated lipid-lowering treatment.

According to the ACC/AHA 2013 guidelines patients with clinical ASCVD and age ≤75 years should be treated with high-intensity statin therapy, while those aged >75 years with high or moderate-intensity statin treatment.(22) Those with primary elevations of LDL-C ≥190 mg/dL (4.9 mmol/L) should take high-intensity statin. High-intensity statin should also be prescribed to patients with DM and an ASCVD risk ≥7.5%.(22) A response to treatment of at least 50% LDL-C reduction is required in these groups; otherwise addition of ezetimibe could be considered.(22) Patients with DM exhibiting an ASCVD risk <7.5% could be treated with a moderate to high-intensity statin.(22) The same was relevant for those with an ASCVD risk ≥7.5% not classified as above.(22)

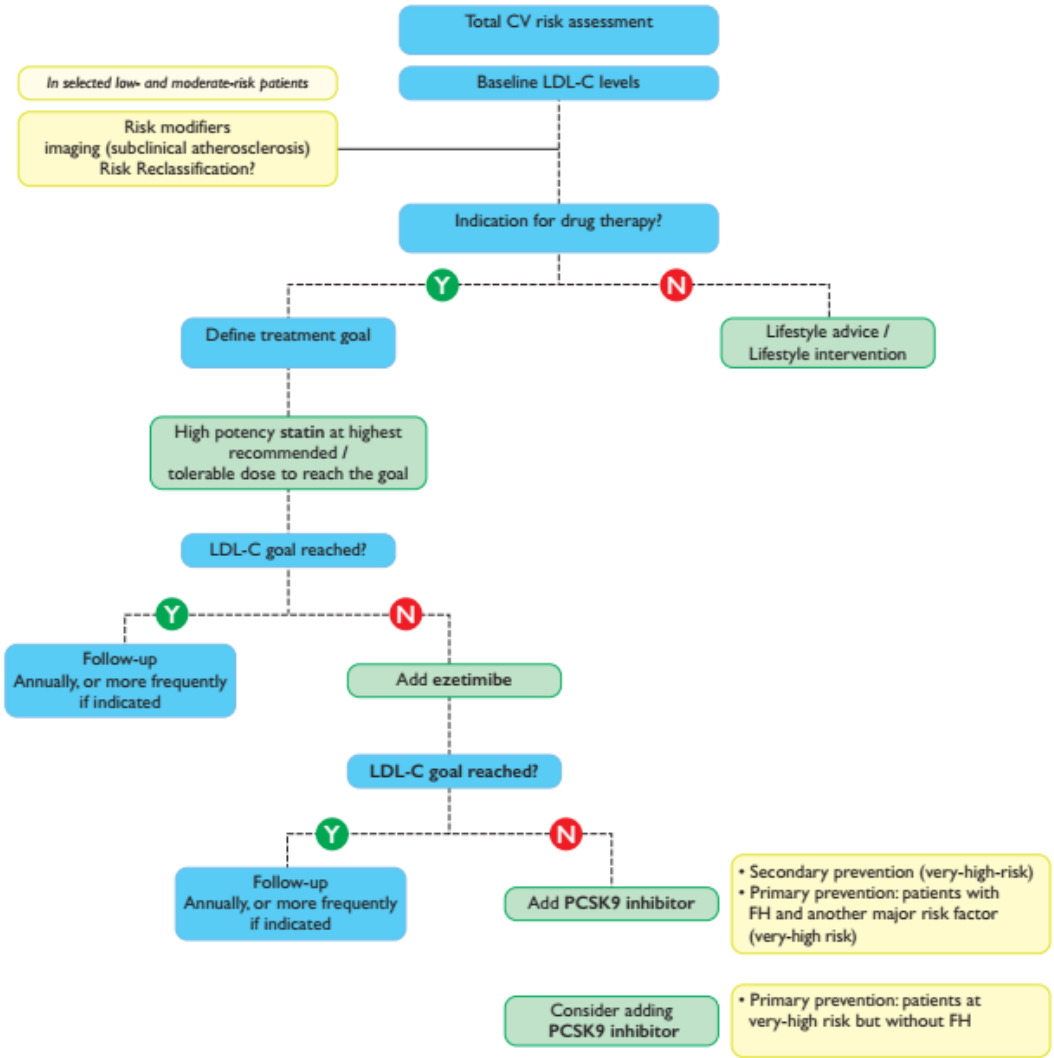


Figure 3 Treatment algorithm for pharmacological low-density lipoprotein cholesterol lowering by by European Society of Cardiology/European Atherosclerosis Society 2019

CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9

The most recent ACC/AHA guidelines published in 2018 recommend that patients with ASCVD and LDL-C >70 mg/dL or non-HDL-C >100 mg/dL, the addition of ezetimibe and subsequently PCSK9 inhibitors (if still above target) may be reasonable options.(28) In patients 20 to 75 years of age with LDL-C ≥190 mg/dL who achieve less than 50% reduction in LDL-C while receiving maximally tolerated statin therapy and/or have an LDL-C level of 100 mg/dL or higher, ezetimibe therapy is reasonable.(28) In patients 30 to 75 years of age with HeFH and with an LDL-C level of 100 mg/dL or higher while taking maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered.(28) Additionally, in patients 40 to 75 years of age

with a baseline LDL-C level of 220 mg/dL or higher (≥5.7 mmol/L) who achieve an on-treatment LDL-C level of 130 mg/dL or higher (≥3.4 mmol/L) while receiving maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered.(28)

ACC/AHA have recently proposed the use of a 70 mg/dL (1.8 mmol/L) LDL-C threshold in very high-risk ASCVD patients in order to consider addition of non-statin to statin therapy.(28)

1.4.1.6 Strategies to control plasma triglycerides

The use of TG-lowering drugs may be considered in high risk patients when TGs are >200 mg/dL (2.3 mmol/L) and cannot be lowered by lifestyle measures.(27) The available pharmacological interventions include statins, fibrates, n-3 PUFAs and PCSK9 inhibitors.(27) More specifically, statin treatment is recommended as the first drug of choice to reduce CVD risk in high risk individuals with hypertriglyceridemia [TGs >200 mg/dL (>2.3 mmol/L)].(27) In high risk (or above) patients with TG levels between 135-499 mg/dL (1.5-5.6 mmol/L) despite statin treatment, n-3 PUFAs (icosapentethyl 2 x 2 g/day) should be considered in combination with a statin.(27) In high risk patients with LDL-C at target but TGs >200 mg/dL (>2.3 mmol/L), fenofibrate and bezafibrate may be considered in combination with statins.(27)

1.4.1.7 Management of dyslipidemias in different clinical settings

i) Familial hypercholesterolemia

Heterozygous familial hypercholesterolemia

FH is a common metabolic disease related with premature CHD.(157-159) The prevalence of HeFH is ~1/200-300).(27) In Greece, it is estimated that 1 in 250 people have HeFH.(160) FH is caused mostly by mutations in genes encoding LDLR, apoB, PCSK9 and LDLR adaptor protein.(157) These mutations result in markedly reduced hepatic capacity to clear LDLs from the circulation, with consequent LDL-C accumulation.(157) If left untreated, males and females with HeFH typically develop CHD before age 55 and 60, respectively, while homozygotes (HoFH) develop CHD very early in life and if untreated many will die before age of 20.(161, 162) FH diagnosis is usually based on clinical presentation according to the most commonly used criteria of Dutch Lipid Clinic Network (DLCN).(27) FH should especially be

considered in patients with CHD aged <55 years for men and <60 years for women, in those with relatives with premature CVD, tendon xanthomas or severely elevated LDL-C [in adults >190 mg/dL (>4.9 mmol/L), in children >150 mg/dL (>3.9 mmol/L)], and in first-degree relatives of patients with FH.(27) In children, testing for FH is recommended from the age of 5 years, or earlier in case that HoFH is suspected.(27)
Lipid-lowering treatment should be initiated as soon as possible after a diagnosis has been made.(27) To improve risk assessment, the use of imaging techniques to detect asymptomatic atherosclerosis is recommended.(27) Treatment should be initiated with high-intensity statin therapy, usually combined with ezetimibe.(27) In very high risk FH patients (those with a prior history of ASCVD or another major risk factor), proposed LDL-C targets are an ≥50% LDL-C reduction from baseline and an LDL-C <55 mg/dL (<1.4 mmol/L).(27) In the absence of ASCVD or another major risk factor, patients with FH are categorized as high risk, and LDL-C goals are an ≥50% LDL-C reduction from baseline and an LDL-C <70 mg/dL (<1.8 mmol/L).(27) PCSK9 inhibitors are recommended in FH patients if treatment goal is not achieved by the combination of maximal tolerated statin and ezetimibe.(27) PCSK9 inhibitors are also recommended in FH patients who cannot tolerate statins.(27) Children with FH should be educated to adopt a proper diet and treated with a statin from 8-10 years of age.(27) Goals for treatment should be LDL-C <135 mg/dL (<3.5 mmol/L) at >10 years of age or ≥50% LDL-C reduction in younger age.(27)

Homozygous familial hypercholesterolemia

HoFH is a rare but life-threatening disease.(163) Its clinical picture is characterized by extensive xanthomas, premature and progressive CVD and TC >500 mg/dL (>13 mmol/L).(163) Most patients develop CHD and aortic stenosis before the age of 20 years and die before the age of 30.(163) The frequency of HoFH is estimated to be 1/160,000-1/320,000.(163) The early identification of these children and prompt referral to a specialized clinic is crucial.(163) Lifestyle intervention and maximal statin therapy are the mainstays of treatment, ideally started in the first year of life or at initial diagnosis, often with ezetimibe and other lipid-modifying therapy.(163) As patients rarely achieve LDL-C targets, adjunctive lipoprotein apheresis is recommended where available, preferably started by age 5 and no later than 8 years.(163) This treatment (every 12 weeks) can decrease plasma LDL-C levels by 55-70%.(163) The procedure

frequency may be adjusted for each patient as lipid levels and other disease-related parameters change.(163) The number of therapeutic approaches has recently increased after the approval of evolocumab (above 12 years), lomitapide (adults) and mipomersen (adults) for HoFH.(27, 163)

ii) Elderly

The proportion of older people (>65 years) is increasing and >80% of individuals who die from CVD are >65 years of age.(27) The proportion of patients with MI and >85 years of age has increased several-fold.(27) Considering the lack of data on the role of cholesterol reduction in primary CV prevention in such patients, along with the high frequency of adverse effects in the elderly, special attention should be paid.(27) Elderly with previous ASCVD should be treated similarly to younger ones.(27) In primary prevention treatment with statins is recommended for older people aged ≤75 years, according to their level of risk.(27) Those aged >75 years may be treated with statins if they are at high or very high risk.(27) In all cases though, the statin therapy should be initiated at a moderate dose and then titrated to achieve LDL-C treatment goals.(27)

iii) Chronic kidney disease

CKD is associated with CVD and statins have been reported to delay the progression of renal disease in patients with previous CKD.(27, 164) In this context, CKD stages 3-5 have been recently proposed as high or very high risk of ASCVD and the use of statins or combination therapy of statin with ezetimibe is highly recommended in non-dialysis-dependent patients.(27) In case of patients on statin therapy, ezetimibe, or a statin/ezetimibe combination at the time of dialysis, continuation of these drugs should be considered, particularly in those with ASCVD.(27) On the other hand, initiation of statin therapy is not generally recommended in patients with dialysis-dependent CKD.(27)

1.4.2 Management of hypertension

1.4.2.1 Definition and prevalence of hypertension

Systolic blood pressure (SBP) levels ≥140 mmHg and/or dystolic blood pressure (DBP) ≥90 mmHg is defined as hypertension according to the European Society of Cardiology/European Society of Hypertension (ESC/ESH) 2018 guidelines.(165) BP is classified in the following categories:

- Optimal: SBP <120 mmHg and DBP <80 mmHg
- Normal: 120-129 mmHg and/or DBP 80-84 mmHg
- High normal: 130-139 mmHg and/or DBP 85-89 mmHg
- Grade 1 Hypertension: 140-159 mmHg and/or DBP 90-99 mmHg
- Grade 2 Hypertension: 160-179 mmHg and/or DBP 100-109 mmHg
- Grade 3 Hypertension: ≥180 mmHg and/or DBP ≥110 mmHg
- Isolated Systolic Hypertension: ≥140 mmHg and DBP <90 mmHg

Based on office BP measurements, the global hypertension burden was estimated to be 1.13 billion in 2015, with a prevalence of over 150 million in central and eastern Europe.(165) The overall prevalence of hypertension in adults is around 30-45% and higher in the elderly (>60%).(165)

1.4.2.2 Blood pressure and cardiovascular risk

Elevated BP is among the leading causes of premature death and accounts for almost 10 million deaths and over 200 million disability-adjusted life years.(165) Both office and out-of-office BP are correlated with the incidence of CV events, such as CHD, stroke, MI, PAD, sudden death, AF and HF, as well as CKD.(165) The quantification of total CV risk is an important part of risk stratification and the SCORE system is therein recommended.(165) Estimation should be complemented by assessment of hypertension-mediated organ damage (HMOD), which can also increase CV risk to a higher level, even when asymptomatic.(165) Asymptomatic HMOD includes: i) arterial stiffening, ii) electrocardiographic or echocardiographic findings of LVH, iii) microalbuminuria, iv) eGFR <60 mL/min/1.73 m^2, v) ABI <0.9 and vi) advanced retinopathy.(165) Therefore, CV risk assessment with the SCORE system is recommended for hypertensive patients who are not already at high or very high risk due to established CVD, renal disease, or DM, a markedly elevated single risk factor (e.g. cholesterol), or hypertensive LVH.(165)

1.4.2.3 Blood pressure measurement

Oscillometric semiautomatic or automatic sphygmomanometers are the preferred method for measuring office BP.(165) Out-of-office BP measurements include home blood pressure measurement (HBPM) and ambulatory blood pressure measurement

(ABPM).(165) HBPM is the average of all BP readings performed with a semiautomatic, validated BP monitor, for at least 3 days (preferably 6-7) consecutive days, with morning and evening readings, taken in a quiet room after 5 min of rest, with the patient seated and arm supported.(165) Two measurements should be taken performed 1-2 min apart.(165) The diagnostic threshold for hypertension diagnosis in HBPM is ≥135/85 mmHg.(165) ABPM provides the average of BP readings over a defined period, usually 24 h.(165) The device is typically programmed to record BP at 15-30 min intervals, and average BP values are usually provided for daytime, night-time, and 24 h.(165) A diary of the patient activities and sleep time should be recorded.(165) The diagnostic threshold for hypertension is ≥130/80 mmHg over 24 h, ≥135/85 mmHg for daytime average, and ≥120/70 mmHg for nighttime average.(165)

1.4.2.4 General principles of antihypertensive treatment

BP-lowering strategies include lifestyle intervention and drug treatment.(165) Although lifestyle interventions are effective in lowering BP, the vast majority of the hypertensive patients need medications to have their BP controlled.(165) A 10-mmHg SBP or a 5-mmHg DBP reduction has been associated with significant reductions in major CV events by ~20%, all-cause mortality by 10-15%, stroke by ~35%, coronary events by ~20%, and HF by ~40%.(165) Likewise, antihypertensive therapy slows the rate of decline in renal function, especially in those with T2DM or CKD.(165) Initiation of antihypertensive therapy along with lifestyle intervention is strongly recommended in patients with grade 2-3 hypertension or those with grade 1 hypertension and high CV risk or HMOD.(165) In low or moderate risk patients without CVD, renal disease or HMOD and grade 1 hypertension, antihypertensive pharmacotherapy is recommended after 3-6 months of unsuccessful lifestyle intervention.(165) Of note, BP-lowering therapy might be considered in very high risk patients with CVD, especially with CHD, who have BP 130-139/85-89 mmHg.(165) In fit older patients aged over 80 years, BP-lowering drug treatment and lifestyle intervention are recommended when SBP is ≥160 mmHg.(165)

1.4.2.5 Blood pressure treatment targets

In patients <65 years SBP should ideally range between 120 and 129 mmHg and in the elderly SBP should be targeted to 130-139 mmHg.(165) Regarding DBP, it should be targeted 70-80 mmHg for all hypertensive patients.(165)

ESC/ESH guidelines previously published in 2013 recommended reducing SBP <140 mmHg in adult hypertensives and to between 150 and 140 mmHg in the elderly with SBP ≥160 mmHg.(166) The corresponding DBP target was <90 and <85 mmHg for the non-diabetics and diabetics, respectively.(166)

1.4.2.6 Treatment of hypertension

i) Lifestyle intervention

The recommended lifestyle measures for BP lowering include salt restriction (5 g per day), moderate alcohol consumption (<14 and 8 units per week, for men and women, respectively), high consumption of vegetables and fruits, weight reduction and maintaining an ideal body weight, regular physical activity (at least 30 min of moderate dynamic exercise on 5-7 days per week) and smoking cessation.(165)

ii) Antihypertensive drugs

Blockers of the renin-angiotensin system

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are among the most commonly prescribed BP-lowering drugs.(165) Their combination is not permitted.(165) Both ACE inhibitors and ARBs are more effective in reducing albuminuria compared with other drugs.(165) Their adverse effects include cough, angioedema (for ACE inhibitors) and hyperkalemia (for both).(165) ACE inhibitors are contraindicated in case of previous angioedema, whereas pregnancy, hyperkalemia and bilateral renal artery stenosis are contraindications against treatment with ACE inhibitors and ARBs.(165)

Calcium channel blockers

Calcium channel blockers (CCBs) are widely used for the treatment of hypertension.(165) CCBs are classified in dihydropyridines and nondihydropyridines (verapamil and diltiazem).(165) The most common adverse effects of dihydropyridines are pedal edema, headache, flushing and tachycardia, whereas bradycardia, heart block,

constipation and decreased cardiac contractility are the main side effect of nondihydropyridines.(165) Any high-grade sinoatrial or atrioventricular block, severe LV dysfunction (LV ejection fraction <40%) and bradycardia (heart rate <60 bpm) are compelling contraindications against treatment with verapamil and diltiazem.(165)

Thiazide/Thiazide-like diuretics

Diuretics appear to be more effective in preventing HF compared with other drug classes.(165) Hypokalemia, hyponatremia, alkalosis, hyperuricemia, dehydration and hypercalcemia are possible side effects of thiazide/thiazide-like diuretics.(165) Patients with gout must not be treated with this drug class, whereas MetS, glucose intolerance, pregnancy, hypercalcemia and hyponatremia are considered as possible contraindications.(165) Thiazides are not effective if eGFR <30 mL/min/1.73 m^2. In this case a loop diuretic (i.e. furosemide, torasemide) should be used.(165)

Beta-blockers

Beta-blockers are useful for the treatment of hypertension in specific conditions, such as symptomatic angina, heart rate control, post-MI, HF with reduced ejection fraction and in younger hypertensive women planning pregnancy or of child-bearing potential.(165) Their potential adverse effects include bradycardia, fatigue, insomnia, erectile dysfunction and bronchospasm in patients with asthma or chronic obstructive pulmonary disease.(165) Patients with asthma, any high-grade sinoatrial or atrioventricular block and bradycardia (heart rate <60 bpm) should not take any beta-blockers.(165)

Other antihypertensive drugs

Spironolactone and eplerenone, which are potassium-sparing diuretics, are preferred as third-line agents in case of resistant hypertension.(165) Their most common side effects include hypekalemia and hyponatremia.(165) Treatment with spironolactone is associated with the development of painful gynecomastia.(165)

Centrally active drugs and direct vasodilators were widely used in the past, but are not frequently used now.(165) Alpha-adrenergic antagonists might be preferred in hypertensive patients with symptomatic prostatic hypertrophy.(165)

1.4.2.7 Strategies to control blood pressure

Figure 4 demonstrates the proposed core drug treatment strategy for uncomplicated hypertension proposed by ESC/ESH 2018.(165)

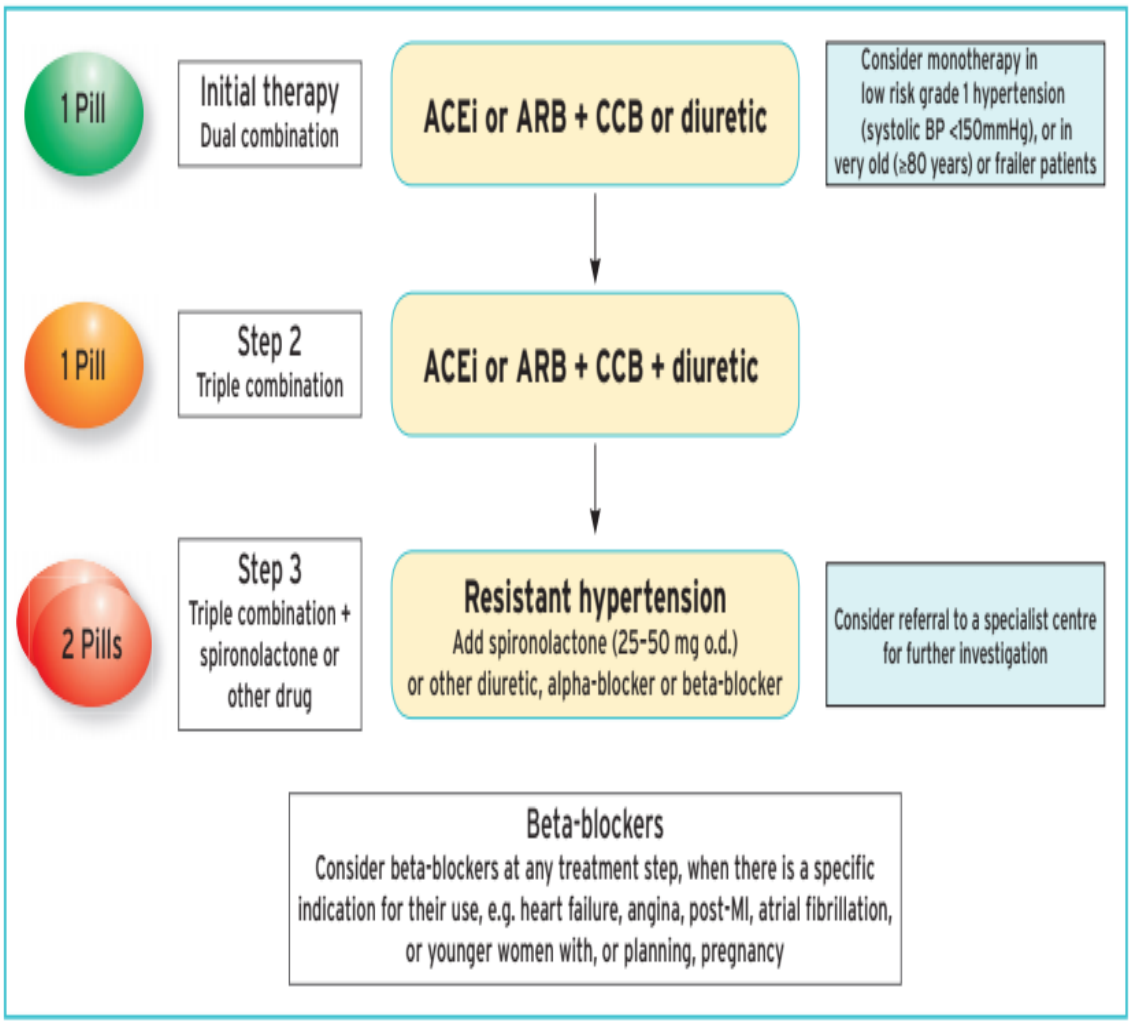


Figure 4 Core drug treatment strategy for uncomplicated hypertension

Angiotensin-converting enzyme inhibitor, ACE-I; ARB, angiotensin II receptor blockers, ARB; BP, bloode pressure; CCB, calcium channel blocker; MI, myocardial infarction

Briefly, considering the factors contributing to poor BP control in treated hypertensive patients, the following are recommended for the treatment of hypertension:

- The initiation of treatment in most patients with a single pill combination (SPC) comprising 2 drugs is recommended.

- Renin angiotensin system (RAS) blocker with a CCB or a diuretic is the preferred 2-drug combination. A beta-blocker in combination with a diuretic or any drug from the other major classes is an alternative in case of angina, post-MI, HF, or need for heart rate control.
- Low-risk patients with stage 1 hypertension whose SBP is <150 mmHg, very high-risk patients with high-normal BP, or frail older patients can be treated with monotherapy.
- If BP is not controlled by a 2-drug SPC, a 3-drug SPC (RAS blocker + CCB + diuretic) should be used.

In case of resistant hypertension, treatment with spironolactone should be initiated.

The use of other classes of antihypertensive drugs are recommended in the case in which BP is not controlled by the above treatments.(165)

1.4.2.8 Hypertension in specific circumstances

i) Resistant hypertension

Hypertension is defined as resistant when the recommended treatment strategy, comprised of best-tolerated doses of an appropriate therapeutic strategy including a diuretic, fails to lower office BP <140/90 mmHg, the inadequate BP control is confirmed by ABPM or HBPM and adherence to therapy has been confirmed.(165)

Various causes of pseudo-resistant hypertension (especially poor medication adherence) and secondary hypertension should have been previously excluded.(165) Treatment of resistant hypertension includes i) reinforcement of lifestyle measures and especially sodium restriction, ii) addition of low-dose spironolactone to existing treatment, iii) the addition of further diuretic therapy in case of intolerance to spironolactone, with either eplerenone, amiloride, a higher dose of thiazide/thiazide-like diuretic, or a loop diuretic and iv) addition of bisoprolol or doxazosin.(165)

ii) Secondary hypertension

Patient characteristics that should raise the suspicion of secondary hypertension include: i) younger patients (<40 years) with grade 2 hypertension or onset of any grade of hypertension in childhood, ii) acute worsening hypertension in patients with previously documented controlled BP, iii) resistant hypertension, iv) severe hypertension or a hypertension emergency, v) presence of extensive HMOD, vi) clinical or biochemical

features suggestive of endocrine causes of hypertension or CKD, vii) clinical features suggestive of obstructive sleep apnea and viii) symptoms suggestive or family history of pheochromocytoma.(165)

Obstructive sleep apnea, renal parenchymal disease, renovascular disease (atherosclerotic renovascular disease and fibromuscular dysplasia), endocrine causes, such as primary aldosteronism, pheochromocytoma, Cushing's syndrome, thyroid disease and hyperparathyroidism, along with coarctation of the aorta are the most common causes of secondary hypertension.(165)

Oral contraceptive pills, diet pills (i.e. phenylpropanolamine and sibutramine), nasal decongestants, stimulant drugs (amphetamine, cocaine and ecstacy), liquorice, immunosuppressive medications (cyclosporin A and steroids), antiangiogenic cancer therapies, anabolic steroids, erythropoietin, non-steroidal anti-inflammatory drugs and herbal remedies (e.g. ephedra and ma huang) may increase BP.(165)

Furthermore, Liddle syndrome, apparent mineralocorticoid excess, Gordon syndrome, Geller syndrome and glucocorticoid remediable hypertension are rare genetic causes of secondary hypertension.(165)

1.4.3 Management of diabetes mellitus

1.4.3.1 Definition and prevalence of diabetes mellitus

There are about 60 million people with DM in the European Region.(40) Prevalence of DM is increasing among all ages, mostly due to increases in overweight and obesity, unhealthy diet and physical inactivity.(40) Worldwide, high blood glucose kills about 3.4 million people annually.(40) Almost 80% of these deaths occur in low- and middle-income countries, and almost half are people aged less than 70 years.(40) These massive numbers have led to the prediction that >600 million individuals would develop T2DM worldwide by 2045, with around the same number developing prediabetes (preDM).(40) Screening for potential T2DM in patients with CVD should be initiated with glycated hemoglobin (HbA1c) and fasting plasma glucose (FPG) measurement, and an oral glucose tolerance test should be added if HbA1c and FPG are inconclusive.(40) The diagnosis of DM is made upon: i) HbA1c ≥6.5% (48 mmol/mol), ii) FPG levels ≥126 mg/dL (7 mmol/L) in 2 separate measurements in different visits or iii) when glucose levels are ≥200 mg/dL (11 mmol/L) 2 hours following 75 g of oral glucose or d) symptoms plus FPG ≥200 mg/dL (11 mmol/L).(40, 167)

1.4.3.2 Diabetes mellitus and cardiovascular risk

DM is undoubtedly a considerable risk factor predisposing to CVD, as it has been associated with a 2-fold excess risk of CV outcomes.(40) As far as CV risk classification is concerned, patients with DM and established CVD or other target organ damage or 3 or more CV major risk factors or early onset T1DM of long duration (>20 years) are considered to be at very high CV risk.(40) Patients with DM duration ≥10 years without target organ damage but with any other additional major risk factors are considered as high risk.(40) Young patients (T1DM aged <35 years or T2DM aged <50 years) with DM duration <10 years and without major risk factors are considered as moderate risk.(40)

1.4.3.3 Glycemic targets

There is a debate whether HbA1c reduction is associated with a reduction in CV outcomes and CVD-related mortality.(40) It has been assumed that long follow-up (≤20 years) might be necessary to demonstrate a beneficial effect on macrovascular complications, and that early glycemic control is associated with long-term CV benefits.(40) Nevertheless, an HbA1c target of <7% (<53 mmol/mol) has been proposed to reduce microvascular complications.(40, 168) However, more-stringent goals [6-6.5% (42-48 mmol/mol)] are recommended in younger patients with a short DM duration and no evidence of CVD, if achieved without significant hypoglycemia.(40, 168) Less-stringent HbA1c goals [<8% (64 mmol/mol) or ≤9% (75 mmol/mol)] may be adequate for elderly patients with longstanding DM and limited life expectancy, or frailty with multiple comorbidities, including hypoglycemic episodes.(40, 168)

1.4.3.4 General principles of glucose-lowering treatment

i) Lifestyle intervention

Lifestyle changes are the cornerstone for DM prevention and management.(40) Reduced calorie intake is recommended to lower excessive body weight in patients with DM and a Mediterranean diet supplemented with olive oil and/or nuts is recommended in such patients due its relation with reduction in CVD incidence.(40) Low-carbohydrate diets in patients with DM could be beneficial, but there is a debate regarding their long-term impact.(40) As far as physical activity is concerned, moderate to vigorous exercise of ≥150 min/week is recommended for DM prevention and control.(40) Smoking cessation is strongly recommended due to its association with CVD and premature death.(40)

ii) Glucose-lowering drugs

Therapeutic agents that manage hyperglycemia can be broadly categorized in the following groups: i) insulin sensitizers (metformin and pioglitazone), ii) insulin providers [insulin, sulfonylureas (SU) and meglitinides], iii) incretin-based therapies [glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and dipeptidyl peptidase 4 (DPP-4) inhibitors], iv) GI glucose absorption inhibitor (acarbose) and v) renal glucose reuptake inhibitors [sodium-glucose transport protein 2 (SGLT2) inhibitors].(40) Table 4 summarizes all the available glucose-lowering drugs, along with their efficacy, risk of hypoglycemia, impact on weight change, CV outcomes and their potential adverse effects.(40, 169)

1.4.3.5 Strategies to control hyperglycemia

Figure 5 shows the proposed treatment algorithm in patients with T2DM by European Society of Cardiology [in collaboration with European Association for the Study of Diabetes (ESC/EASD)].(40) Briefly, SGLT2 inhibitors or GLP-1 RAs are recommended in patients with ASCVD or high/very high CV risk either as monotherapy or in combination with metformin.(40) If HbA1c is above target, the addition of the other class (GLP-1 RAs or SGLT2 inhibitors) with proven CVD benefit should be considered.(40) If HbA1c remains above target, the addition of a DPP-4 inhibitor (if not on GLP-1 RA), basal insulin, thiazolidinedione (TZD) or SU should be considered.(40)

Metformin monotherapy is the first-line therapy in moderate CV risk patients without ASCVD. In case of poor glycemic control, the following glucose-lowering drugs can be used: DPP-4 inhibitors, GLP-1 RAs, SGLT2 inhibitors or TZD. If HbA1c remains above target after the combination of all the previously outlined agents (DPP-4 inhibitors and GLP-1 RAs cannot be combined), the addition of SU or basal insulin should be considered.(40, 169)

In case of compelling need to minimize weight gain or promote weight loss, treatment with a GLP-1 RA with good efficacy for weight loss or a SGLT2 inhibitor is proposed.(169)

In case that HbA1c levels are above target despite dual/triple therapy or in case of HbA1c >10% (86 mmol/mol), initial injectable combination can be considered.(169) GLP-1 RAs should be considered in most patients prior to insulin.(169) In case of poor

glycemic control or HbA1c >11%, or presence of catabolic symptoms, or probalility of T1DM, initiation and titration of basal insulin is proposed.(169) Thereafter, stepwise additional injections of prandial insulin are recommended. (169)

SGLT2 inibitors and GLP1-RAs have been recently proposed in individuals with HF or CKD.(169)

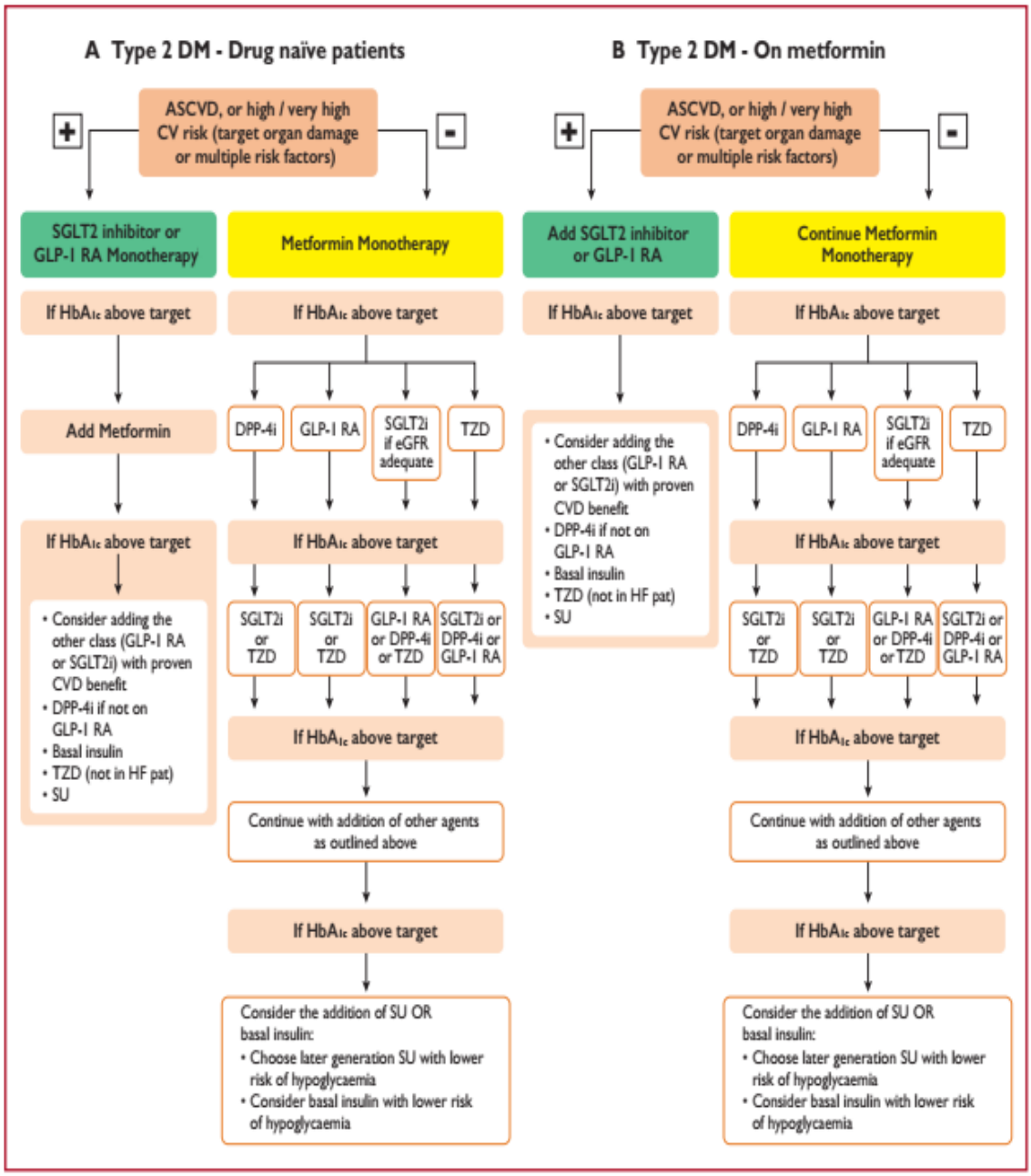


Figure 5 Treatment algorithm in patients with type 2 diabetes mellitus

ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; CVD, cardiovascular disease; DM, diabetes mellitus; DPP-4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; HF, heart failure; SGLT2i, sodium-glucose transport protein 2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione

Table 4 *Drug-specific factors to consider for the selection of antihyperglycemic treatment in patients with type 2 diabetes*

Drug (route)	Efficacy	Hypoglycemia	Weight change	Cardiovascular effects		Additional considerations
				ASCVD	**CHF**	
Metformin (oral)	High	No	Potential modest loss	Potential benefit	Neutral	GI side effects (diarrhea, nausea), potential B12 deficiency
SGLT2 inhibitors (oral)	Intermediate	No	Loss	Benefit (empagliflozin, canagliflozin, dapagliflozin)	Benefit (empagliflozin, canagliflozin, dapagliflozin)	Risk of amputation and bone fractures (canagliflozin), diabetic ketoacidosis, genitourinary infections, risk of volume depletion, hypotension, increase in LDL-C, risk of Fournier's gangrene
GLP-1 RAs (subcutaneous)	High	No	Loss	Benefit (liraglutide, semaglutide, exenatide LAR, dulaglutide)	Neutral	Risk of thyroid C-cell tumors, GI side effects (nausea, vomiting, diarrhea), injection site reactions, risk of acute pancreatitis
DPP-4 inhibitors (oral)	Intermediate	No	Neutral	Neutral	Potential risk (saxagliptin, alogliptin)	Potential risk of acute pancreatitis, joint pain
Thiazolidinediones (oral)	High	No	Gain	Potential benefit (pioglitazone)	Increased risk	Congestive heart failure, fluid retention, risk of pone fractures, bladder cancer (piogliazone), increase in LDL-C (rosiglitazone), benefit in NASH
Sulfonylureas (2nd generation) (oral)	High	Yes	Gain	Neutral	Neutral	Increased risk of cardiovascular mortality (based on studies of older sulfonylureas)
Insulin (human or analogs) (subcutaneous)	Highest	Yes	Gain	Neutral	Neutral	Injection site reactions

ASCVD, atherosclerotic cardiovascular disease; CHF, congestive heart failure; DPP-4, dipeptidyl peptidase 4; GLP-1 RA, agonists of glucagone-like peptide 1 receptor; LDL-C, low-density lipoprotein cholesterol; NASH, non-alcoholic steatohepatitis

1.4.4 Antiplatelet treatment

1.4.4.1 Primary prevention

In patients with DM at high/very high risk, aspirin (75-100 mg/day) may be considered in primary prevention in the absence of clear contraindications.(40)

1.4.4.2 Secondary prevention

In secondary prevention, low-dose (75-160 mg) aspirin remains the recommended drug.(40) Clopidogrel provides an alternative for aspirin-intolerant patients, and is combined with low-dose aspirin as dual antiplatelet therapy (clopidogrel 75 mg and aspirin 75-160 mg) in patients with acute coronary syndrome and those undergoing PCI or CABG.(40, 165) Of note, treatment with ticagrelor or prasugrel (P2Y12 receptor blockers) is recommended in patients with DM and acute coronary syndrome for 1 year with aspirin, and in those who undergo PCI or CABG.(40) Dual antiplatelet therapy lasts up to 12 months, but its prolongation beyond 12 months should be considered, for up to 3 years, in patients at very high CV risk who have tolerated dual antiplatelet therapy without major bleeding complication.(40)

1.5 Management of atrial fibrillation

1.5.1 Prevention of thromboembolism

1.5.1.1 Clinical risk scores for stroke and systemic embolism

CHA_2DS_2-VASc score [Congestive Heart failure, Hypertension, Age ≥75 (doubled), DM, Stroke (doubled), Vascular disease, Age 65-74, and Sex (female)] is recommended for estimating the risk of stroke in patients with AF (except for those with moderate-to-severe mitral stenosis or mechanical heart valve).(170) In case of a score of 1 or greater in men or 2 or greater in women, oral anticoagulants are indicated for the prevention of thromboembolism.(170) There are available bleeding risk scores which could be used in patients with AF taking oral anticoagulation to identify and treat modifiable risk factors for major bleeding.(170)

1.5.1.2 Anticoagulation treatment

Anticoagulant regiments include vitamin K agonists (warfarin and acenocoumarol) and the following classes of non-vitamin K antagonist oral anticoagulants (NOACs): i) the direct thrombin inhibitor dabigatran and ii) the factor Xa inhibitors apixaban, edoxaban, and rivaroxaban.(170) NOACs are recommended over warfarin in patients with AF

(except for those with moderate-to-severe mitral stenosis or mechanical heart valve).(170) On the other hand, warfarin is recommended in patients with AF and moderate-to-severe mitral stenosis or a mechanical heart valve and in those with contraindications against NOACs.(170) Treatment with warfarin or apixaban might be reasonable for oral anticoagulation in patients with end-stage CKD or on dialysis.(170) In case of treatment with warfarin, the international normalized ratio (INR) should be determined at least weekly during initiation of anticoagulant therapy and at least monthly when anticoagulation (INR in range) is stable (2-3).(170)

1.5.2 Rate control therapy

In the setting of acute new-onset AF heart rate needs to be controlled.(170) In this context, beta-blockers (metoprolol, esmolol) and diltiazem/verapamil are preferred over digoxin because of their rapid onset of action and effectiveness at high sympathetic tone.(170) Such therapy aims initially at a resting heart rate <110 bpm.(170) Amiodarone can be used in patients with hemodynamic instability or severely reduced left ventricular ejection fraction.(170) Urgent cardioversion should be also considered in unstable patients.(170)

Therapies for long-term rate control include beta-blockers (bisoprolol, carvedilol, metoprolol and nebivolol), non-dihydropyridines (verapamil and diltiazem), cardiac glycosides (digoxin and digitoxin) and amiodarone at last resort.(170) Atrioventricular node ablation and pacing are the last therapeutic options when medications fail to control rate symptoms.(170)

1.5.3 Rhythm control therapy

Acute restoration of sinus rhythm can be achieved with either antiarrhythmic drugs (flecainide, propafenone, ibutilide, vernakalant and amiodarone) or synchronized direct current electrical cardioversion.(170) The latter is the method of choice in hemodynamically compromised patients with new-onset AF.(170) Anticoagulation must be initiated immediately in all patients scheduled for cardioversion.(170) Patients who have been diagnosed with AF for longer than 48 h should be treated with anticoagulants 3 weeks before cardioversion and for 4 weeks afterwards.(170) In case of patients at risk of stroke, anticoagulation therapy should be continued indefinitely.(170) Therapeutic option for long term rhythm control include amiodarone, dronedarone, flecainide, propafenone, sotalol and catheter ablation.(170)

CHAPTER II. AIMS & OUTLINE

During the last decade, a revolution has evolved in the setting of CV prevention. A plethora of therapeutic options confronting CV risk factors is available. Statins remain the cornerstone of CV prevention, since their use has been long associated with a reduction in major vascular events and CHD-related mortality.(129) Ezetimibe and PCSK9 inhibitors also reduce the risk of incident CVD.(140, 144, 145) Likewise, drug-mediated BP reduction has been associated with significant decline in all major CV events and all-cause mortality.(171, 172) Although older glucose-lowering drugs seemed to protect only against microvascular T2DM complications, pioglitazone and novel antidiabetic therapies, such as GLP-1 RAs and SGLT2 inhibitors have been associated with a significant reduction in CVD risk and CV mortality.(173-177) Interestingly, the prescription rates of antihypertensive, hypoglycemic and lipid-lowering therapies have been raised during the last decade and the age-adjusted death rate attributable to CVD has declined.(3) Nevertheless, 840,678 individuals died from CVD in 2016 in United States of America (USA) and CVD currently claims more lives each year than cancer and chronic lung disease together.(3)

There are several factors accounting for the so-called residual CV risk. First, a considerable proportion of patients remains sub-optimally treated in everyday clinical practice. Indeed, EUROASPIRE V, a cross-sectional study conducted in 27 European countries, demonstrated that 42% of CHD patients (n=8,261) had BP $\geq$ 140/90 mmHg and 71% had not optimal LDL-C levels.(178) Similar poor target attainment was noticed in high risk patients (n=4,579), with less than half (42.8%) of the those taking BP-lowering drugs reaching the target of <140/90 mmHg.(179) Among treated dyslipidemic patients, only 32.7% attained the LDL-C target of <100 mg/dL, whereas 58.5% of those with T2DM achieved the HbA1c target of <7.0%.(179) Likewise, an analysis of the Dyslipidemia International Study II demonstrated that only 1 of 4 patients with CHD achieved optimal LDL-C levels in Greece.(180) Even FH, which is associated with high risk of premature death if left untreated, remains underdiagnosed and undertreated.(160) According to the Hellenic FH (HELLAS-FH) Registry, 63.1% of patients with FH were taking lipid-lowering therapy on inclusion in the registry, and the majority of them (87.9%) did not achieve the proposed LDL-C targets.(181)

Multifactorial target attainment is much more difficult to be achieved in clinical practice. The International ChoLesterol management Practice Study, demonstrated that only 12.2% of the study participants (n=2,377) achieved simultaneous control of LDL-

C, DM and BP.(182) Poor patient compliance is a major factor accounting for suboptimal control of CV risk factors in clinical practice.(183) Indeed, ~60% of patients have good adherence to CV medications, whereas a considerable proportion of all CVD events (~9%) could be attributed to poor adherence to vascular medications alone.(184, 185) Physician awareness and adherence to CVD prevention guidelines also play a major role.(186, 187)

Another assumption justifying residual CVD risk could be that either the existing tools underestimate CV risk or the proposed targets are not appropriate. Indeed, the available CV risk-estimation systems have been questioned and compared with each-other,(188) whereas the proposed LDL-C and BP targets have repeatedly been changed during the last decade.(27, 36, 37, 165, 166) Additional targets have been proposed in certain

Patient groups, such as apoB in patients with high TG levels, DM, obesity, MetS, or very low LDL-C levels.(27) Furthermore, additional therapies are needed to confront novel risk factors for CVD, such inflammation and Lp(a).(27)

In this context, we conducted the present doctorate thesis in order to:

- Evaluate the association of established and novel risk factors with CVD in patients with dyslipidemia
- Compare the effectiveness of the available tools estimating CVD risk
- Assess target attainment in clinical practice
- Assess adverse effects of CV therapies and possible risk factors, with a particular emphasis on lipid-lowering treatment

CHAPTER III. METHODS

3.1 Study design

This was a retrospective study including consecutive adult patients with dyslipidemia who attended the Outpatient Lipid Clinic of the University Hospital of Ioannina in Greece for ≥3 years (from 1999 to 2015). Initially, a total of 1,000 consecutive patients were enrolled and finally study sample reached 1,334 participants. The majority of performed analyses were based on the initial study sample. Our study protocol was approved by the Local Institutional Ethics Committee and informed consent was obtained from each patient.

3.2 Subjects and methods

All study participants were Caucasians of Hellenic origin. A complete assessment of their clinical and laboratory profile was performed at the baseline visit, after 6 months and at the most recent visit.

3.2.1 Subjects' demographic, clinical and laboratory data

Patient demographic and clinical characteristics included: i) sex, ii) age, iii) smoking, iv) alcohol consumption, v) family history of premature CVD, DM, dyslipidemia and hypertension, vi) follow-up duration and vii) concomitant diseases, with a particular emphasis on CVD and CV risk factors.

Clinical and laboratory data included: i) BMI and waist, ii) BP, iii) FPG, HbA1c and iv) a complete lipid profile, including TC, TG, HDL-C, LDL-C, non-HDL-C, apoA-I, apoB, apoE and Lp(a). Office BP measurements were based on ESC/ESH guidelines and performed with a validated upper-arm cuff BP measurement device and an appropriate cuff size.(165) The corresponding instruments measuring subjects' waist, height and weight were validated and calibrated, whereas BMI was calculated as: (weight, kg) / (height, m)^2.

Blood samples were collected in the morning into sterile Vacutainer-SST II advance tubes (Becton-Dickinson, Plymouth, UK) after overnight fasting for at least 8-12 h. Tubes were refrigerated immediately after collection, were centrifuged at 4^{o}C within 40 min of blood sampling, and then were analyzed within 2 h. Serum concentrations of TC were determined enzymatically on an Olympus AU600 Clinical Chemistry Analyzer (Olympus Diagnostica, Hamburg, Germany). HDL-C was determined by a direct assay (Olympus Diagnostica, Hamburg, Germany). LDL-C was calculated using the

Friedewald formula, provided that TG levels were <400 mg/dL (4.5 mmol/L). Serum apoA-I, apoB, apoE and Lp(a) levels were measured with a Behring Nephelometer BN100 and with reagents from Dade Behring GmbH analyzer (Liederbach, Germany). Furthermore, a complete blood count, creatinine, urea, electrolytes, liver enzymes, CK, thyroid function and urine analysis were assessed. Renal function was estimated by eGFR with CKD-EPI (CKD Epidemiology Collaboration) formula using creatinine results from a method that had calibration traceable to isotope dilution mass spectrometry.(189) Sodium levels below the lowest quintile (<138 mEq/L) were defined as hyponatremia.(190)

ECG indexes were assessed at baseline in the supine position. Apart for the assessment of rhythm and abnormal findings, we performed a specific analysis of the QT and the QT peak intervals manually on ECG recordings at a paper speed of 50 mm/sec. QT interval was assessed as the time between the first deflection of QRS and the point of return of the T wave to the isoelectric line. The Tpe interval was calculated as QT – QT peak. The QT interval was measured in as many of the 12 leads as possible, while the Tpe interval was assessed in leads II, V2, V5.(191-193) The Tpe interval and the Tpe/QT ratio were calculated using the corresponding values from each lead. The measurements were obtained in 3 consecutive complexes of each lead and the resulting average value was accepted. In order to avoid diurnal variations, all procedures were performed during the same time interval (from 9:00 to 13:00 h). QT interval corrected for heart rate (QTc) was calculated using the Bazett's formula ($QTc=QT/RR^{-2}$).(194) The Tpe and QTc reported values were the maximum obtained. All measurements were performed by one experienced investigator unaware of the clinical characteristics of study participants. To identify intra-observer variability, the ECG tracings of 20 randomly selected patients were reexamined 10 days after the initial evaluation. Intra-observer variation was less than 5%.(191-194)

3.2.2 Concomitant diseases

ASCVD comprised of CHD (MI, stable angina, unstable angina, PCI, CABG), stroke (ischemic stroke, hemorrhagic stroke, transient ischemic attack), PAD (history of claudication plus ABI <0.9, or previous revascularization or amputation) and carotid stenosis >50%.(27) Incident ASCVD events were self-reported during their follow-up visits. HF diagnosis was based on the presence of clinical symptoms plus findings from

ECG andechocardiography.(195) The diagnosis of AF was i) based on irregular pulse during auscultation and confirmed by ECG or 24h Holter monitor of heart rhythm, ii) self-reported by patients and confirmed by ECG or iii) based on new treatment with anticoagulants and confirmed by ECG. In the case of paroxysmal AF detected by Holter monitoring, at least 30 seconds of AF duration was required.(170, 196)

Study participants were diagnosed with hypertension according to ESC/ESH guidelines or in case they were already on antihypertensive treatment.(165)

The diagnosis of T2DM was based on ESC/EASD guidelines.(40) HbA1c was rarely measured before DM diagnosis, since Hellenic guidelines do not recommend HbA1c as a diagnostic criterion. The diagnosis of impaired fasting glucose (IFG) was defined by a baseline FPG concentration 100-125 mg/dL (5.5-7 mmol/L).(40)

MetS was defined in case of the presence of ≥3 metabolic abnormalities: i) FPG ≥100 mg/dL (5.6 mmol/L), ii) TGs ≥150 mg/dL (1.7 mmol/L), iii) HDL-C <40 mg/dL (1 mmol/L) or 50 mg/dL (1.3 mmol/L), in males and females, respectively, iv) BP ≥130/85 mmHg or diagnosed hypertension and v) BMI ≥30 kg/m^2 or waist ≥102 cm, for males and BMI ≥27 kg/m^2 or waist ≥88 cm for females.(70)

Diagnosis of atherogenic dyslipidemia was made in case of baseline TGs ≥200 mg/dL (2.3 mmol/L) and HDL-C <40 mg/dL (1 mmol/L) or <50 mg/dL (1.3 mmol/L) in male and female subjects, respectively.(197)

BMI <25 kg/m^2 was considered as normal weight, whereas overweight and obesity were defined as BMI 25-30 kg/m^2 and BMI ≥30 kg/m^2, respectively.(198) As metabolically healthy individuals were considered those having ≤2 of the following: i) BP >135/85 mmHg or antihypertensive therapy, ii) TGs >150 mg/dL, iii) HDL-C <40 and <50 mg/dL for men and women, respectively, and iv) FPG >100 mg/dL or antidiabetic treatment.(199-201)

FH was defined according to the diagnostic criteria of DLCN.(157) Hyperlipidemic individuals fulfilling the criteria of ‘definite’ or ‘probable’ FH were considered as heterozygous FH patients in the present study.(157)

Study participants were diagnosed with CKD in case of a decline in eGFR <60 ml/min/1.73 m^2 in 2 periodical examinations performed in a timeline of at least 3 months.(202)

Data regarding alcohol consumption were self-reported and collected during visits by asking whether the subject consumes alcohol. In case of a positive answer, the number

of drinks/weeks of each type of favorite beverage (beer, wine or spirits) was recorded. Ethanol consumption was estimated, assuming that concentrations of alcohol were 5% for beer, 12% for wine, and 40% for liquor. Patients were classified as ‘non-drinkers’, ‘occasional drinkers’ (drinking on a monthly basis), ‘mild drinkers’ (consuming a mean of 1-19 g ethanol/day), ‘moderate drinkers’ (consuming a mean of 20-45 g ethanol/day) and ‘heavy drinkers’ (consuming a mean of 45 g ethanol/day).(203)

3.2.3 Concomitant therapies

Concomitant therapy was additionally recorded, with a particular emphasis on lipid-lowering drugs (i.e. statins, ezetimibe, PCSK9 inhibitors, fibrates, colesevelam and n-3 fatty acids). The intensity of statin therapy was classified as ‘high’, ‘moderate’ and ‘low’ on the basis of the average expected LDL-C lowering of ≥50, 30-50 and <30%, respectively. Compliance with treatment was assessed by questionnaires and pill count. Patients were classified according to their compliance to treatment as ‘good’ and ‘poor’ compliers if they took ≥ or <80% of the prescribed tablets, respectively. Statin escape phenomenon was defined as an increase in subject LDL-C levels at the most recent visit by >10% compared with the value at 6 months following initiation of statin therapy.(204) Rates of adverse events were recorded: increase of liver enzymes >3 times the ULN and increase of the CK >10 times the ULN, myalgias, hypotension, GI disorders and hypoglycemia.

3.2.4 Cardiovascular risk and proposed treatment targets

We recorded the attainment of lipid-lowering treatment targets as proposed by i) NCEP ATP III (16), ii) ESC/EAS guidelines published in 2011 (37), 2016 (36) and 2019 (27) and iii) ACC/AHA guidelines published in 2013 (22). We recorded the attainment of BP goals recommended by ESC/ESH in 2013.(166) We recorded the achievement of HbA1c goals proposed by ESC/EASD.(40) Moreover, we recorded the rates of eligibility for therapy with PCSK9 inhibitors in regard to the Hellenic Expert Consensus and ACC/AHA 2018 guidelines.(28, 156)

3.2.5 Tools estimating risk of cardiovascular disease and atrial fibrillation

Ten-year CV death risk was estimated by the Hellenic SCORE,(25) whereas Pooled Cohort Risk Assessment Equation (PCE) proposed by ACC/AHA was used to estimate

the 10-year risk of incident ASCVD.(22) Of note, a risk of ASCVD event of 7.5% has been suggested that it corresponds to a 2.5% risk for CV disease death in 10 years according to the SCORE model.(205)

$CHADS_2$ score was calculated for all patients by assigning 1 point for each of the following criteria: congestive heart failure (C), hypertension (H), age ≥75 years (A), and DM (D).(206) A further 2 points was added for the criterion of previous stroke or transient ischemic attack (S_2).(206) In contrast, the is based on a point system in which 2 points each are assigned for age ≥75 years (A_2) and for history of stroke, TIA, or thromboembolism (S_2) and 1 point is assigned for each of the following criteria: congestive heart failure (C), hypertension (H), DM (D), age 65 to 75 years (A), vascular disease (VASc) (defined as previous MI, complex aortic plaque, carotid stenosis, and PAD) and female sex category (Sc).(206) Low levels of HDL-C were defined those <40 and <50 mg/dL for male and female subjects, respectively. For the incorporation of HDL-C into the $CHADS_2$ and CHA_2DS_2-VASc score, 1 point was additionally assigned in case of low HDL-C levels. After excluding individuals with AF at baseline visit, we identified which factors are associated with incident AF.

3.2.6 Statistical analysis

Continuous variables were tested for normality by the Kolmogorov-Smirnov test and logarithmic transformations were performed if necessary. Data are presented as mean ± standard deviation (SD) and median [interquartile range (IQR)] for parametric and non-parametric data, respectively. For categorical values, frequency counts and percentages were applied. Chi-square test was performed for interactions between categorical values. Independent sample t-test (parametric and non-parametric) was used for the comparison of continuous numeric values between 2 groups. One-way analysis of variance (one-way ANOVA) was performed to assess the difference of the variables of interest between ≥2 groups. Multivariate analysis of covariance (MANCOVA) was performed to compare the variables of interest among 2 or more groups, after controlling for the predefined confounding factors. Paired sample t-test (parametric and non-parametric) was performed to investigate the change of the numeric variables of interest during follow-up within each group. Pearson's and Spearman's correlation coefficients were used to investigate the relationships between variables. Linear regression analysis was performed to assess the relationship between a scalar dependent

variable and one (univariate) or more independent variables (multivariate; backward conditional method was used). Univariate binary logistic regression analysis was performed to investigate the association of a factor with the investigated outcomes of interest. Multivariate logistic regression analysis was conducted using the variables that were statistically significant in the univariate analyses (backward conditional method was used). Associations with the outcomes of interest are expressed as odds ratios (OR) with accompanying 95% CI. Cox regression analysis was used for the investigation of the association between 1 or more variables and the outcomes of interest in a period of time. Risk of the primary endpoint are expressed as HR with accompanying 95% CI. Receiver operating characteristics (ROC) curve analysis was used to analyze the prognostic value of the investigated variables for the corresponding outcomes of interest. C-statistic (area under the curve) is presented as a unified estimate of sensitivity and specificity. Kaplan-Meier analysis was performed to study the differences in event-free survival from the investigated outcomes of interest. Two-tailed significance was defined as $p < 0.05$. Analyses were performed with the Statistical Package for Social Sciences (SPSS) v21.0 software (SPSS IBM Corporation, Armonk, New York, USA).

CHAPTER IV. RESULTS

4.1 Baseline characteristics of study participants

A total of 1,334 subjects [46% males, age 49 (57-65) years] were included in the present study and followed-up for a median of 6 years (4-10). Table 5 demonstrates baseline characteristics of study participants.

Table 5 *Baseline characteristics of study participants*

Variables	
N	1,334
Sex (male), %	46
Age, years	49 (57-65)
Follow-up, years	6 (4-10)
Atherosclerotic cardiovascular disease, %	16
Coronary heart disease, %	6
Stroke, %	8
Peripheral artery disease, %	2
Aortic abdominal aneurysm, %	1
Atrial fibrillation, %	1
Heart failure, %	1
Familial hypercholesterolemia, %	12
Type 2 diabetes mellitus, %	11
Weight status	
Normal weight, %	25
Overweight, %	49
Obesity, %	26
Chronic kidney disease, %	9
Hypertension, %	60
Metabolic syndrome, %	44
Family history of premature cardiovascular disease, %	21
Family history of diabetes mellitus, %	21
Family history of hypertension, %	44
Family history of dyslipidemia, %	37
Smoking	
Non-smokers, %	67
Former smokers, %	16
Smokers, %	17
Fasting plasma glucose, mg/dL	88 (95-106)
Body mass index, kg/m^2	25.1 (27.4-30.1)
Waist, cm	91 (99-106)

Systolic blood pressure, mmHg	125 (140-150)
Diastolic blood pressure, mmHg	80 (85-94)
Estimated glomerular filtration rate, mL/min/1.73 m^2	71 (81-92)
Total cholesterol, mg/dL	212 (250-287)
Triglycerides, mg/dL	94 (131-188)
High-density lipoprotein cholesterol, mg/dL	44 (52-62)
Low-density lipoprotein cholesterol, mg/dL	132 (166-197)
Non-high-density lipoprotein cholesterol, mg/dL	160 (195-225)
White blood cells, per μL	5200 (6140-7350)
Uric acid, mg/dL	4.1 (5.1-6.1)
Concomitant treatment	
Lipid lowering therapy, %	22
Blood pressure lowering therapy, %	45
Glucose lowering therapy, %	8
Antiplatelet therapy, %	14

Values are expressed as median (interquartile range), respectively, unless percentages are shown. To convert from mg/dL to mmol/L multiply by 0.02586 for cholesterol indices, by 0.01129 for triglycerides and by 0.06 for fasting plasma glucose.

Hypertension was the leading concomitant disease (60%), followed by MetS (44%), FH (12%) and T2DM (11%). Baseline prevalence of ASCVD was 16%, with stroke and CHD being leading categories (8% and 6%). Almost half of subjects were taking antihypertensive therapy (45%) and 22% were on lipid-lowering treatment at baseline visit (Table 5).

Cardiovascular drug therapy at the most recent visit is demonstrated in Table 6. During follow-up, lipid-lowering therapy was prescribed to the majority of the study participants (94%) with statins being the main treatment (91%). Atorvastatin and rosuvastatin were the most commonly prescribed statins at a median dose of 20 mg. Almost 1 of 4 patients was also treated with ezetimibe. The vast majority of the subjects was on antihypertensive therapy at the most recent visit (70%), with ARBs, CCBs, thiazides and beta-blockers being the most commonly prescribed BP lowering drugs (Table 6). As far as antidiabetic therapy is concerned, metformin and DPP-4 inhibitors were the most common medications for T2DM management (Table 6).

Table 6 *Cardiovascular drug treatment of study participants at the most recent visit*

Variables	
Lipid-lowering therapy, %	94
Statins	91
Class of statin therapy	
Rosuvastatin, % (median dose)	29 (20 mg)
Atorvastatin, % (median dose)	41 (20 mg)
Simvastatin, % (median dose)	20 (40 mg)
Fluvastatin, % (median dose)	3 (80 mg)
Pravastatin, % (median dose)	1 (40 mg)
Fibrates, %	6
Ezetimibe, %	24
N-3 fatty acids, %	4
Colesevelam, %	1
Blood pressure lowering therapy, %	70
Angiotensin receptor blockers, %	53
Angiotensin converting enzyme inhibitors, %	9
Calcium channel blockers, %	37
Thiazide/thiazide-like diuretics, %	38
Loop diuretics, %	2
Potassium sparing diuretics, %	4
Beta blockers, %	26
Centrally acting antihypertensive drugs, %	2
Glucose lowering therapy, %	20
Metformin, %	18
Dipeptidyl peptidase 4 inhibitors, %	7
Sulfonylureas, %	4
Pioglitazone, %	2
Insulin, %	3
Antiplatelet therapy, %	31

4.2 Incidence of cardiovascular disease and risk factors

During 6-year of follow-up, a total of 95 subjects (7%) were diagnosed with incident ASCVD. The rate of incident ASCVD was 10.4/1,000 patient-years. A total of 39 subjects (3% of the total study participants) were diagnosed with CHD during their follow-up; of those 20 (51%) experienced an acute coronary syndrome, 12 (31%) had unequivocally documented CHD on imaging, 4 subjects (10%) underwent coronary revascularization (PCI or CABG) and 3 subjects (8%) were diagnosed with stable angina. A total of 39 subjects (3%) were diagnosed with stroke during follow-up; of those 21 (54%) experienced an ischemic stroke, while the rest were diagnosed with transient ischemic attack. Moreover, 29 (2%) and 13 (1%) subjects were diagnosed with PAD and carotid stenosis, respectively, during follow-up.

Univariate Cox regression analysis showed that male sex, age, smoking, history of ASCVD, DM, CKD and hypertension were significant predictors of incident ASCVD (Table 7). Multivariate Cox regression analysis showed that DM, history of ASCVD, smoking and age were significantly and independently associated with new ASCVD during follow-up.

Table 7 *Risk factors associated with incident atherosclerotic cardiovascular disease in study participants during 6-year follow-up*

Variables	Univariate analysis	Multivariate analysis
Sex (male)	1.59 (1.05-2.40), p <0.05	-
Age, per 1 year increase	1.07 (1.05-1.09), p <0.001	1.07 (1.04-1.09), p <0.001
Atherosclerotic cardiovascular disease	2.74 (1.67-4.49), p <0.001	2.04 (1.21-3.43), p <0.001
Familial hypercholesterolemia	0.83 (0.39-1.72), p >0.05	-
Diabetes mellitus	3.05 (1.77-5.28), p <0.001	2.09 (1.18-3.70), p=0.01
Chronic kidney disease	2.06 (1.14-3.72), p <0.05	-
Hypertension	1.48 (1.10-1.98), p <0.01	-
Metabolic dyndrome	1.23 (0.82-1.85), p >0.05	-
Family history of premature cardiovascular disease	1.21 (0.76-1.93), p >0.05	-
Smoking	1.51 (0.99-2.29), p=0.05	1.82 (1.17-2.84), p <0.001
Fasting plasma glucose, per 1 mg/dL increase	1.006 (0.999-1.013), p >0.05	-
Body mass index, per 1 kg/m^2 increase	1.03 (0.97-1.08), p>0.05	-
Waist circumfernce, per 1 cm increase	1.02 (0.99-1.04), p >0.05	-
Systolic blood pressure, per 1 mmHg increase	1.001 (0.995-1.008), p >0.05	-
Diastolic blood pressure, per 1 mmHg increase	0.986 (0.971-1.003), p >0.05	-
Estimated glomerular filtration rate, per 1 mL/min/1.73 m^2 increase	0.98 (0.97-0.99), p=0.001	-
Total cholesterol, per 1 mg/dL increase	0.997 (0.993-1.000), p >0.05	-
Triglycerides, per 1 mg/dL increase	0.999 (0.997-1.001), p >0.05	-

High-density lipoprotein cholesterol, per 1 mg/dL increase	1.002 (0.987-1.017), p >0.05	-
Low-density lipoprotein cholesterol, per 1 mg/dL increase	0.998 (0.993-1.002), p >0.05	-
Apolipoprotein A-I, per 1 mg/dL increase	0.997 (0.980-1.015), p >0.05	
Apolipoprotein B, per 1 mg/dL increase	0.998 (0.984-1.011), p >0.05	
Apolipoprotein E, per 1 mg/L increase	1.014 (0.996-1.033), p >0.05	
Lipoprotein (a), per 1 mg/L increase	0.993 (0.967-1.020), p >0.05	
Non-high-density lipoprotein cholesterol, per 1 mg/dL increase	0.997 (0.993-1.000), p >0.05	-
White blood cells, per 1 µL increase	1.00 (1.00-1.00), p >0.05	-
Uric acid, per 1 mg/dL increase	1.11 (0.98-1.26), p >0.05	-
Reduction of low-density lipoprotein cholesterol, per 1 mg/dL	0.898 (0.997-1.004), p >0.05	-
Reduction of systolic blood pressure, per 1 mmHg	0.999 (0.991-1.007), p >0.05	-
Reduction of diastolic blood pressure, per 1 mmHg	0.994 (0.981-1.007), p >0.05	-
Reduction of fasting plasma glucose, per 1 mg/dL	1.000 (0.997-1.004), p >0.05	-

Values are expressed as Hazard Ratio (95% Confidence Intervals).

4.3 Prognostic value of tools estimating cardiovascular disease

4.3.1 Prognostic value of tools estimating the risk of atherosclerotic cardiovascular disease

After excluding those already diagnosed with AF (n=10), a total of 990 consecutive subjects were included in the present analysis. Of those, 10% developed ASCVD during 6-year follow-up (4-10 years). $CHADS_2$ and CHA_2DS_2-VASc scores were correlated with ASCVD incidence (r=0.105, p=0.001 and r=0.077, p <0.05, respectively). Subjects with $CHADS_2$ score ≥2 (n=268) exhibited a higher rate of incident ASCVD when compared with $CHADS_2$ score 1 (n=531) or 0 (n=191) (15% vs 10% vs 6%, respectively, p <0.05 for the comparison, after adjusting for smoking and LDL-C levels). Likewise, higher rates of incident ASCVD were noticed in those having CHA_2DS_2-VASc score ≥2 (n=586) and 1 (n=286) when compared with those having CHA_2DS_2-VASc score 0 (n=118) (11% vs 9% vs 4%, p<0.05 for the comparison, after adjusting for smoking and LDL-C levels). Higher $CHADS_2$ and CHA_2DS_2-VASC scores were correlated with decreased survival (log-rank=32.2, p <0.001 and log-rank=32.4, p <0.001, respectively). ROC curve analysis indicated that $CHADS_2$ and CHA_2DS_2-VASc scores have a strong predictive value for incident ASCVD (C-statistic: $CHADS_2$ 0.592, p <0.01; CHA_2DS_2-VASc 0.568, p <0.05). Nevertheless, they were not superior to SCORE and ASCVD risk, which both predicted the development of ASCVD in our population after the exclusion of patients with baseline ASCVD, FH, DM, CKD or those taking lipid-lowering therapy (n=451) (C-statistic: 0.612, p <0.001 and 0.717, p <0.001, respectively).

4.3.2 Prognostic value of $CHADS_2$ and CHA_2DS_2-VASc scores estimating the risk of atrial fibrillation in dyslipidemic individuals: role of incorporating low high-density lipoprotein cholesterol levels

After excluding 18 patients with AF at baseline and 93 subjects with no data on their heart rythm, 1,223 individuals were included in the present analysis. During a median follow-up of 6 years (IQR: 4-10), 34 patients (2.8%) developed AF. As shown in Table 8, patients with incident AF were older and had higher levels of SBP and lower levels of TC, LDL-C and HDL-C compared with no AF. $CHADS_2$ and CHA_2DS_2-VASc scores were higher in new AF compared with no AF subjects (Table 8). Also, a higher proportion of new AF patients were taking ACE inhibitors or antiplatelet treatment at baseline visit in comparison with no AF (Table 8).

Table 8 *Baseline characteristics of study participants with and without incident atrial fibrillation*

	No atrial fibrillation	New atrial fibrillation
N (%)	1189 (96.8 %)	34 (2.8 %)
Sex (male), %	47	35
Age, years	56 (48-65)	67 (62-71)*
Follow-up, years	6 (4-10)	6 (4-12)
Smoking, %	17	18
Heart failure, %	1	3
Hypertension, %	60	91*
Metabolic syndrome, %	44	59
Diabetes mellitus, %	12	24
Cardiovascular disease, %	15	24
Coronary heart disease, %	5	12
Stroke, %	7	12
Peripheral artery disease, %	2	0
Carotid stenosis, %	3	0
Estimated glomerular filtration rate, mL/min/1.73 m^2	79 (69-89)	76 (60-89)
Fasting plasma glucose, mg/dL	95 (88-106)	100 (91-108)
Glycated hemoglobin, %	6.6 (5.9-7.8)	6.6 (6.7-7.6)
Body mass index, kg/m^2	27.4 (25.0-30.1)	27.8 (26.1-30.1)
Systolic blood pressure, mmHg	140 (125-150)	150 (135-160)*
Diastolic blood pressure, mmHg	85 (80-95)	89 (80-90)
Total cholesterol, mg/dL	251 (214-289)	225 (199-260)*
Triglycerides, mg/dL	131 (94-189)	146 (102-208)
High-density lipoprotein cholesterol, mg/dL	52 (44-62)	45 (39-52)*
Low-density lipoprotein cholesterol, mg/dL	168 (132-198)	144 (123-167)*
Thyroid stimulating hormone, mIU/L	1.22 (0.80-1.87)	1.03 (0.67-1.10)
$CHADS_2$ score	1.0 (0.0-1.0)	1.0 (1.0-2.0)*
0-2, n (%)	93	82*
≥3, n (%)	7	18*
CHA_2DS_2-VASc score	2.0 (1.0-2.0)	2.5 (2.0-4.0)*
0-2, n (%)	78	50*
≥3, n (%)	22	50*
Concomitant therapy		
Beta blockers, %	14	21
Angiotensin converting enzyme inhibitors, %	14	29*
Angiotensin receptors inhibitors, %	19	24
Calcium channel blockers, %	16	21
Antiplatelet treatment, %	14	29*
Statin, %	18	21

Values are expressed as median (interquartile range), unless percentages are shown. Conversion factors for units: fasting plasma glucose in mg/dL to mmol/L, ×0.05551; cholesterol indices in mg/dL to mmol/L, ×0.02586; triglycerides in mg/dL to mmol/L ×0.01129. * p <0.05 for the comparison between subjects with and without atrial fibrillation

Binary logistic regression for incident AF

Univariate analysis showed that age, hypertension, CKD, ACE inhibitors use and antiplatelets were significantly associated with higher risk of incident AF (Table 9). A marginally non-significant trend towards increased risk of new-onset AF was noticed for DM (OR: 2.23, 95% CI: 0.991-5.02, p=0.053). On the other hand, LDL-C and HDL-C were inversely associated with the risk of incident AF (Table 9).

Multivariate binary logistic regression analysis including all characteristics associated with new-onset AF in univariate analysis showed that age (adjusted OR: 1.07, 95% CI: 1.03-1.11, p=0.001), hypertension (adjusted OR: 5.07, 95% CI: 1.15-22.3, p <0.01) and HDL-C levels (adjusted OR: 0.96, 95% CI: 0.93-0.98, p <0.01) remained independent factors for incident AF. Furthermore, individuals with low levels of HDL-C (<40 mg/dL men/<50 mg/dL women) exhibited higher risk of incident AF compared with those having normal levels (adjusted OR: 3.79, 95% CI: 1.85-7.75, p <0.001).

Prediction of incident AF

ROC curve analysis showed that both $CHADS_2$ (C-Statistic: 0.679, 95% CI: 0.599-0.758, p <0.001) and CHA_2DS_2-VASc (C-Statistic: 0.697, 95% CI: 0.612-0.782, p <0.001) were significant predictors for incident AF (Figure 6).

Higher $CHADS_2$ score predicted higher risk of incident AF (adjusted OR: 1.71, 95% CI: 1.28-2.29, p <0.001), with up to 190% increase in patients with $CHADS_2$ ≥3 when compared with those having 0-2 (adjusted OR: 2.89, 95% CI: 1.16-7.24, p <0.05). Similarly, CHA_2DS_2-VASc score was associated with an increased risk of new-onset AF (adjusted OR: 1.56, 95% CI: 1.26-1.92, p <0.001), with up to 260% increase in patients with CHA_2DS_2-VASc ≥3 when compared with those with 0-2 (adjusted OR: 3.58, 95% CI: 1.79-7.16, p <0.001).

Kaplan-Meier analysis demonstrated that patients with higher $CHADS_2$ score had significantly reduced event-free survival from AF (log-rank=10.62, p=0.001; Figure 7a). An even larger difference in event-free survival was noticed when stratified by CHA_2DS_2-VASc score (log-rank=22.29, p <0.001; Figure 7b)

CHA_2DS_2-VASc-HDL achieved the highest C-Statistic for AF prediction (0.728, 95% CI: 0.645-0.811, p <0.001; Figure 6). Using Kaplan-Meier analyses, the incorporation

of low HDL-C levels strengthened the predictive performance of both $CHADS_2$ (Figure 7c) and CHA_2DS_2-VASc score (Figure 7d) ($CHADS_2$-HDL: log-rank=17.35, p <0.001; CHA_2DS_2-VASc-HDL: log-rank=28.17, p<0.001).

Table 9 *Risk factors for incident atrial fibrillation (univariate analysis)*

	OR (95% CI)	p
Sex (male)	0.69 (0.42-1.17)	NS
Age, per 1 year increase	1.08 (1.04-1.12)	<0.001
Follow-up, per 1 year increase	1.05 (0.97-1.14)	NS
Smoking	1.05 (0.68-1.62)	NS
Heart failure	3.97 (0.49-32.28)	NS
Hypertension	6.85 (2.08-22.54)	<0.001
Metabolic syndrome	1.84 (0.92-3.67)	NS
Diabetes mellitus	2.23 (0.991-5.02)	0.053
Cardiovascular disease	1.77 (0.79-3.98)	NS
Chronic kidney disease	3.24 (1.43-7.34)	<0.01
Estimated glomerular filtration rate, per 1 mL/min/1.73 m^2 increase	0.98 (0.96-1.004)	NS
Fasting plasma glucose, per 1 mg/dL increase	1.007 (0.997-1.017)	NS
Glycated hemoglobin, per 1% increase	1.07 (0.57-2.007)	NS
Body mass index, per 1 kg/m^2 increase	1.00	NS
Systolic blood pressure, per 1 mmHg increase	1.002 (0.998-1.006)	NS
Diastolic blood pressure, per 1 mmHg increase	1.003 (0.975-1.031)	NS
Total cholesterol, per 1 mg/dL increase	0.994 (0.987-1.00)	NS
Triglycerides, per 1 mg/dL increase	1.001 (0.998-1.003)	NS
High-density lipoprotein cholesterol, per 1 mg/dL increase	0.966 (0.939-0.993)	<0.05
Low-density lipoprotein cholesterol, per 1 mg/dL increase	0.991 (0.984-0.999)	<0.05
Thyroid stimulating hormone, per 1 mIU/L	0.89 (0.63-1.28)	NS
Concomitant therapy		
Beta blockers	1.59 (0.68-3.72)	NS
Angiotensin-converting enzyme inhibitors	3.42 (1.78-6.58)	<0.001
Angiotensin receptors inhibitors	0.99 (0.87-1.13)	NS
Calcium channel blockers	1.37 (0.59-3.19)	NS
Antiplatelet treatment	3.32 (1.52-7.29)	<0.01
Statin treatment	1.16 (0.49-2.69)	NS

95% CI, 95% confidence intervals; NS, non-significant; OR, odds ratio

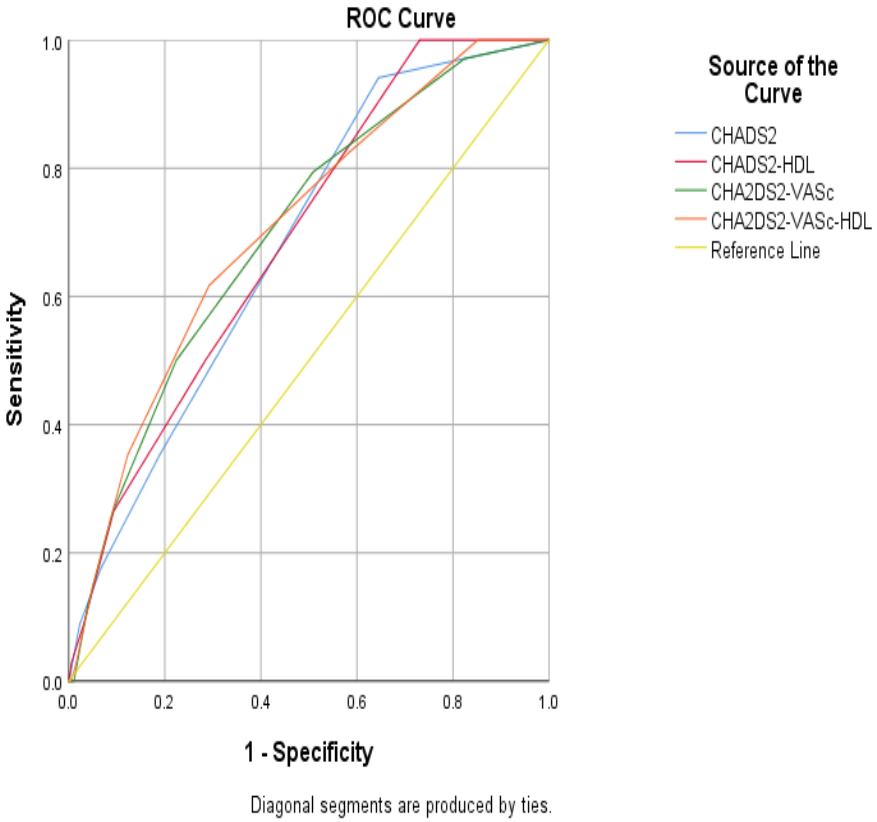
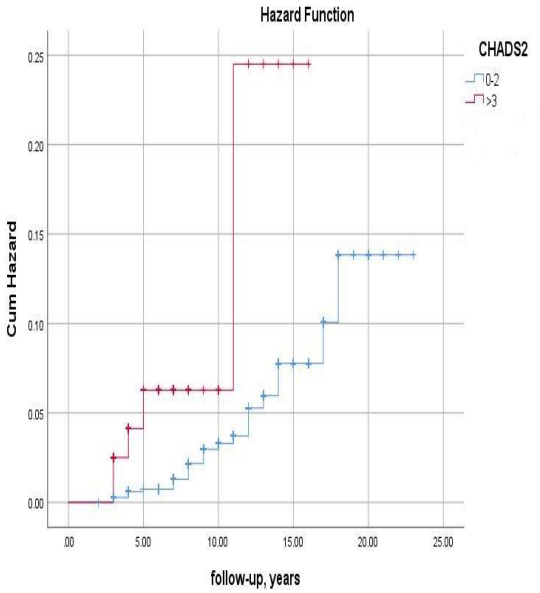


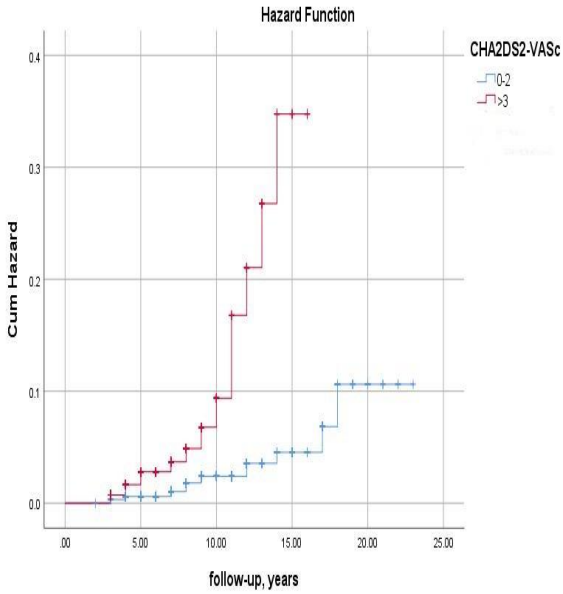
Figure 6 Receiver-operating characteristic curves of $CHADS_2$ and CHA_2DS_2-VASc scores before and after the incorporation of low high-density lipoprotein cholesterol levels for new atrial fibrillation

C-Statistic (area under the curve) - 95% confidence interval (95% CI): $CHADS_2$: 0.679 (0.599-0.758), p <0.001; $CHADS_2$-HDL: 0.704 (0.627-0.782), p <0.001; CHA_2DS_2-VASc: 0.697 (0.612-0.782), p <0.001; CHA_2DS_2-VASc-HDL: 0.728 (0.645-0.811), p <0.001. HDL-C, high-density lipoprotein cholesterol; ROC, receiver operating characteristic

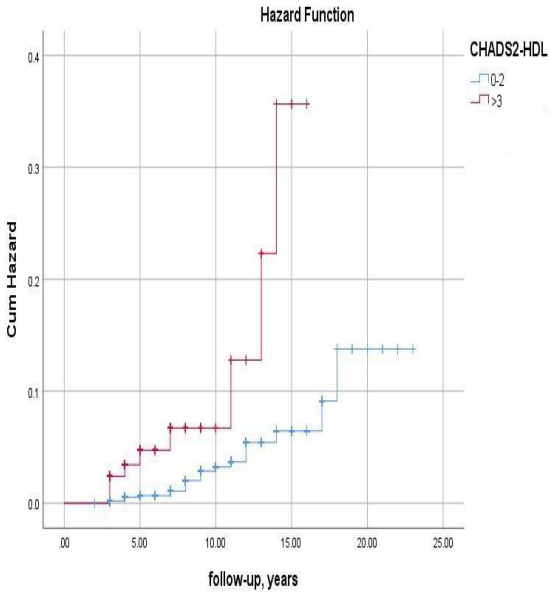
(a) CHADS2 score



(b) CHA_2DS_2-VASc score



(c) **CHADS2-HDL score**



(d) CHA_2DS_2-VASc-HDL score

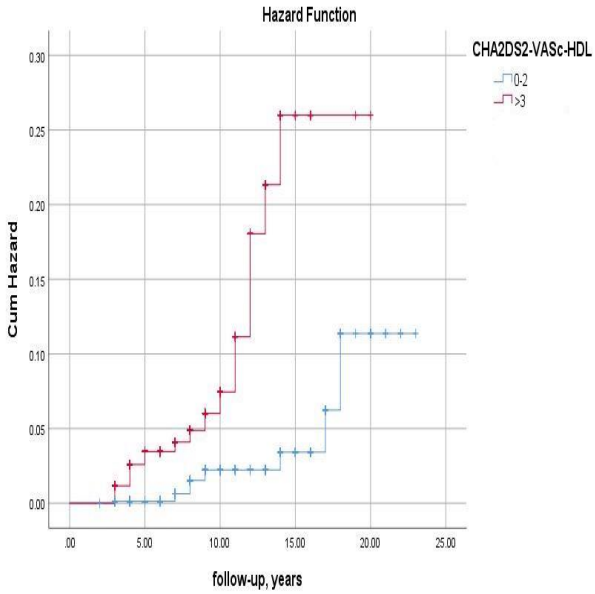


Figure 7 Kaplan-Meier survival curves as stratified by baseline CHADS2 and CHA2DS2-VASc scores before and after the incorporation of low high-density lipoprotein cholesterol

Higher $CHADS_2$ score (a) was associated with significantly reduced event-free survival from AF (log-rank=10.62, p=0.001). A similar but a larger difference in survival was noticed when stratified by CHA_2DS_2-VASc score (b) (log-rank=22.29, p <0.001). After incorporating low HDL-C levels the predictive performance of both $CHADS_2$ and CHA_2DS_2-VASc score were improved: (c) $CHADS_2$-HDL: log-rank=17.35, p <0.001; (d) CHA_2DS_2-VASc-HDL: log-rank=28.17, p <0.001. HDL-C, high-density lipoprotein cholesterol

4.4 Association between high-density lipoprotein cholesterol levels and ventricular repolarization indexes

Subjects with TGs >500 mg/dL, CKD, hypothyroidism and liver disease were excluded from the present analysis. Other exclusion criteria were recent acute coronary syndrome within the past 6 months, recent PCI or CABG, CHF, history of channelopathies, presence of bundle brunch block, QRS duration >120 ms, presence of second or third degree atrioventricular block, persistent or permanent AF, previous implantation of a pacemaker or an implantable defibrillator, administration of antiarrhythmic drugs, administration of drugs that prolong the QT interval, acute and chronic infections or inflammatory diseases as well as use of lipid-lowering drugs.

The final sample for the present analysis consisted of 440 patients (199 men) with a median age of 56 (48-65) years. The baseline demographic, clinical, laboratory and electrocardiographic characteristics of participants are listed in Table 10.

Correlation analysis (Spearman's) failed to show any association between HDL-C and studied electrocardiographic parameters (P duration, PR duration, QRS duration, QTc interval, Tpe interval in leads II, V5, V6, and Tpe/QT ratio in II, V2, V5). Moreover, no correlation between other lipid parameters (TC, LDL-C, TGs) and electrocardiographic indexes was evident. Study population was divided in quartiles according to the HDL-C values: HDL-Q1 (≤43 mg/dL), HDL-Q2 (44-50 mg/dL), HDL-Q3 (51-59 mg/dL), HDL-Q4 (≥60 mg/dL). Comparison of ventricular repolarization parameters across groups failed to show any significant difference (Table 11, Figures 9 and 10).

Table 10 *Baseline clinical, laboratory and electrocardiographic characteristics of patients included in the analysis investigating the association between high-density lipoprotein cholesterol levels and ventricular repolarization indexes*

Number of patients	**440**
Sex (male), %	45.2
Age, years	56 (48-65)
Body mass index, kg/m ^{2}	27.7 (25.4-30.5)
Smoking, %	25.6
Hypertension, %	58.5
Diabetes mellitus, %	11.4
Coronary artery disease, %	5.7
Systolic blood pressure, mmHg	138 (127-150)
Diastolic blood pressure, mmHg	85 (80-92)
Baseline heart rate, bpm	70 (64-80)
Beta-blockers, %	15
Angiotensin converting enzyme inhibitors, %	16
Angiotensin receptor blockers, %	19
Calcium channel blockers, %	16
Diuretics, %	21
Centrally acting antihypertensives, %	2
Aspirin, %	12
Clopidogrel, %	5
Total cholesterol, mg/dL	246 (214-287)
Triglycerides, mg/dL	129 (94-190)
High-density lipoprotein cholesterol, mg/dL	52 (44-60)
Low-density lipoprotein cholesterol, mg/dL	162 (136-193)
P wave, ms	80 (74-120)
PR interval, ms	160 (142-206)
QRS interval ms	90 (76-120)
QTc interval, ms	432 (410-462)

Values are expressed as median (interquartile range), respectively, unless percentages are shown. To convert from mmol/L to mg/dL multiply by 39 for cholesterol indices and by 89 for triglycerides.

Table 11 *Electrocardiographic parameters in different quartiles of high-density lipoprotein cholesterol.*

	HDL-C (Q1)	HDL-C (Q2)	HDL-C (Q3)	HDL-C (Q4)	P value
QTc (ms)	427 (410-457)	438 (412-461)	432 (398-463)	440 (414-472)	0.372
Tpe II (ms)	80 (60-88)	80 (62-84)	81 (65-85)	79 (58-83)	0.356
TpeV2 (ms)	80 (78-84)	80 (60-84)	82 (62-85)	82 (60-84)	0.372
TpeV5 (ms)	80 (60-82)	82 (73-84)	81 (62-84)	81 (63-83)	0.112
Tpe/QT II	19 (15-22)	20 (15-25)	20 (16-22)	20 (15-23)	0.348
Tpe/QT V2	20 (18-23)	19 (15-22)	20 (15-22)	18 (14-22)	0.162
Tpe/QT V5	19 (15-23)	20 (16-22)	18 (14-21)	18 (15-20)	0.122

HDL-C, high density lipoprotein cholesterol; QTc, QT corrected; Tpe, T peak-to-end interval

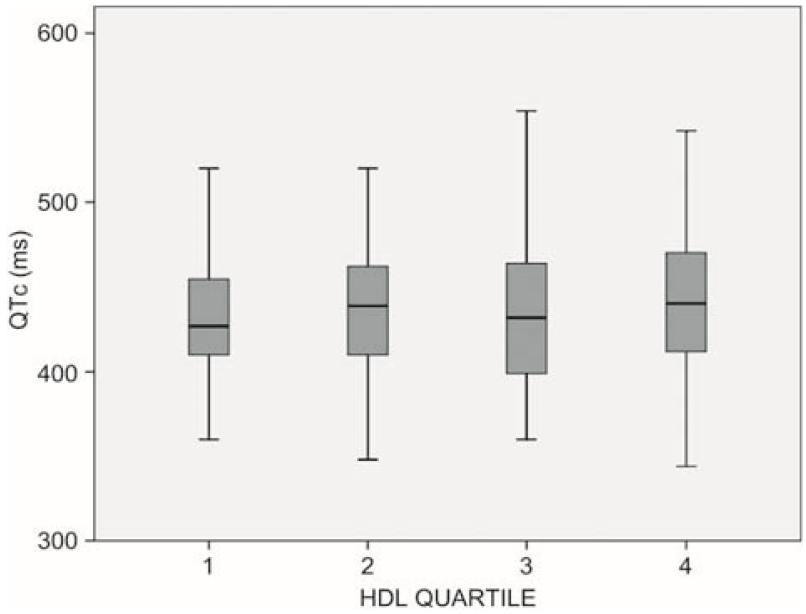


Figure 8 QTc interval in different quartiles of high-density lipoprotein cholesterol

HDL, high-density lipoprotein cholesterol; QTc, corrected QT

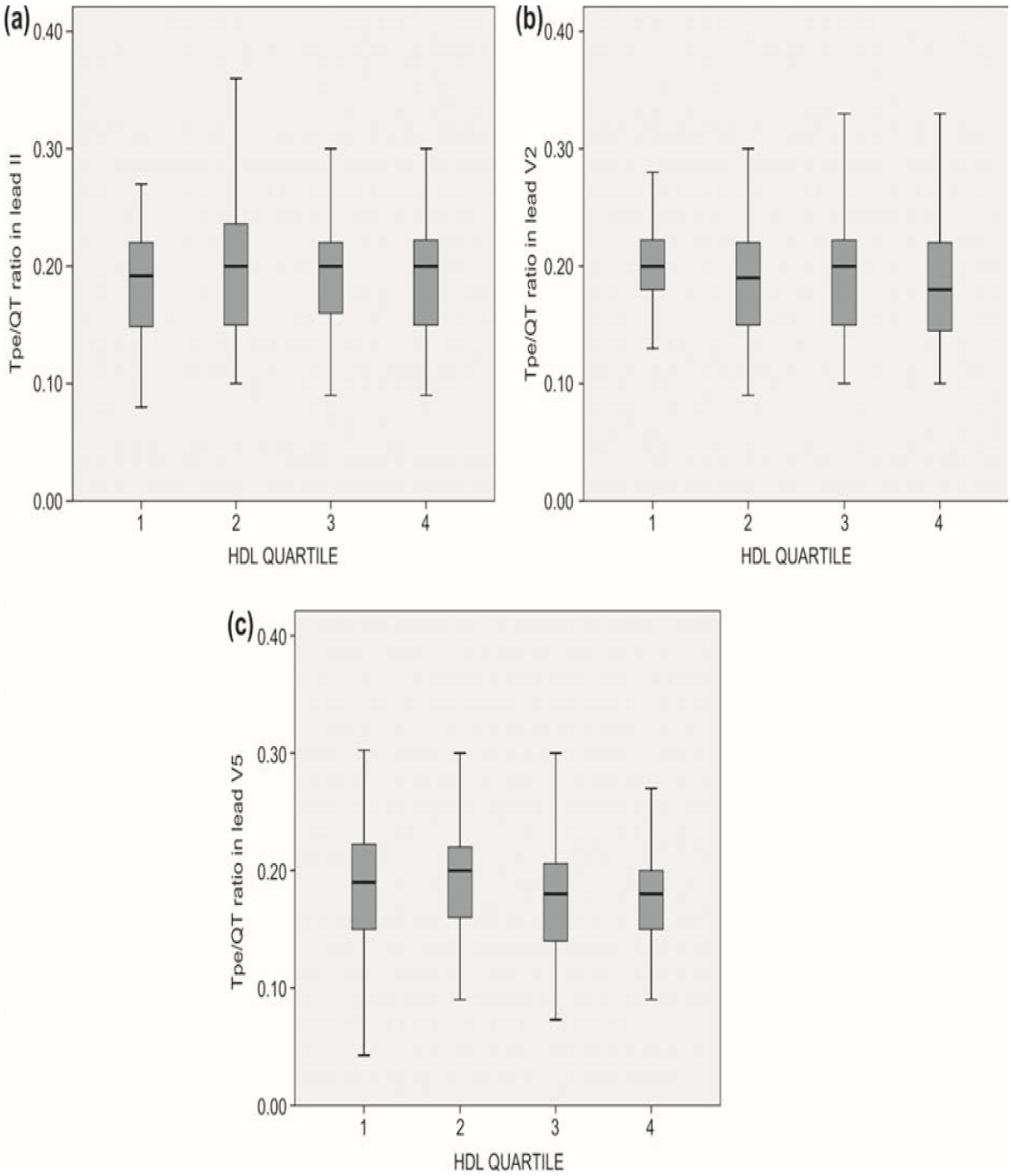


Figure 9 (A-C) Tpe/QT ratio in different quartiles of high-density lipoprotein cholesterol measured in leads II, V2, V5

HDL, high-density lipoprotein cholesterol

4.5 Target attainment of cardiovascular therapy

4.5.1 Lipid target attainment among patients at very high and high cardiovascular risk according to National Cholesterol Education Program Adult Treatment Panel III and European Society of Cardiology/European Atherosclerosis Society 2011 guidelines

We assessed rates of LDL-C target attainment defined by NCEP ATP III and ESC/EAS 2011 guidelines. A total of 885 consecutive subjects at very high and high CV risk were included in the present analysis. These subjects were followed for 8 years (mean). Of these, 477 patients (48%) had very high and 408 (41%) high CV risk according to the ESC/EAS 2011 guidelines. Demographic, clinical and laboratory characteristics of subjects at the most recent visit are shown in Table 12. Among very high CV risk patients, DM (44%) was the most prevalent disease state, followed by CKD (37%), stroke (23%) and CHD (21%). Of note, 12% of all patients were diagnosed with FH.

Lipid-lowering treatment

Ninety five percent of patients were on active lipid-lowering treatment at the most recent visit: 92% were on statins [67% on statin monotherapy and 33% statin therapy in combination with ezetimibe (25%), omega-3 fatty acids (5%), fibrates (4%) or colesevelam (2%)]; some patients were receiving more than one drug, eg. statin + ezetimibe +/- colesevelam. Atorvastatin (mean daily dose 26 mg), rosuvastatin (mean daily dose 22 mg), simvastatin (mean daily dose 30 mg) and fluvastatin (mean daily dose 80 mg) were used in 43, 32, 21 and 3% of treated patients, respectively; the remaining 1% was receiving pravastatin and lovastatin.

One hundred percent of patients with CHD or abdominal aortic aneurysm were treated with lipid-lowering drugs. Corresponding rates were 97% for stroke, 96% for PAD, 95% for DM, 95% for carotid stenosis, and 94% for CKD patients.

Of patients not on statins (8% of the whole population), 66% were not on any hypolipidemic medication, 29% were on fibrates, 10% on ezetimibe and 5% on omega-3 fatty acids. Three percent of all patients were unable to tolerate even low-dose statin treatment.

Changes in serum lipid profile as well as kidney and liver function parameters during follow-up are shown in Table 13. Briefly, significant reductions in TC, TGs, LDL-C and non-HDL-C levels by 30, 23, 43 and 39%, respectively, were noted. Also, a small though significant increase in HDL-C levels by 4% was found. No change in transaminase activities was noticed except for alkaline phosphatase, which significantly

declined by 29%. eGFR significantly declined by 7.5% during follow-up, while no significant change in serum uric acid levels was noted.

Table 12 *Demographic, clinical and laboratory* ***c****haracteristics of subjects at very high and high cardiovascular risk at the most recent visit*

	All subjects	Cardiovascular risk groups	
		Very high	High
Age, years	64 ± 13	69 ± 10	58 ± 14*
Sex (male/female), %	46/54	52/48	44/56
Smoking, %	16	13	20*
Body mass index, kg/m^2	28.8 ± 4.4	29.2 ± 4.4	28.4 ± 4.2*
Metabolic syndrome, %	59	68	48*
Hypertension, %	80	90	68*
Systolic blood pressure, mmHg	128 ±14	132 ± 14	128 ± 12*
Diastolic blood pressure, mmHg	78 ± 10	76 ± 10	78 ± 8*
Low-density lipoprotein cholesterol, mg/dL	99 ± 33	90 ± 30	109 ± 33*
Non-high density lipoprotein cholesterol, mg/dL	123 ± 36	115 ± 34	133 ± 36*
Lipid-lowering treatment, %	95	96	93
Statin treatment, %	92	94	89*
Disease group, %			
Diabetes mellitus	24		
Chronic kidney disease	20		
Stroke	12		
Coronary heart disease	11		
Peripheral artery disease	6		
Carotid stenosis	5		
Abdominal aortic aneurysm	2		
Familial hypercholesterolemia	12		

Values are expressed as mean ± standard deviation, unless percentages are shown. To convert cholesterol indices from mg/dL to mmol/L multiply by 0.02586; for triglycerides multiply by 0.01129; *p <0.05 for comparison with very high risk subjects

Sixty percent of subjects had baseline TG levels <150 mg/dL (1.69 mmol/L), while 17, 21 and 1% exhibited TG levels of 151-199, 200-499 and >500 mg/dL (1.7-2.25, 2.26-5.63 and >5.64 mmol/L), respectively. Those with higher baseline TG levels were more likely to be on a fibrate at last visit compared with those with lower baseline levels. The respective rates of treatment with fibrate for patients with baseline TG levels of <150, 151-199, 200-499 and >500 mg/dL (<1.69, 1.7-2.25, 2.26-5.63 and >5.64 mmol/L) were 1, 4, 17 and 82%.

Table 13 *Baseline and last visit metabolic profile of very high and high risk subjects*

	Baseline visit	Last visit
Total cholesterol, mg/dL	256 ± 61	178 ± 38*
Triglycerides, mg/dL	132 (33-1750)	112 (11-668)*
High-density lipoprotein cholesterol, mg/dL	52 ± 14	54 ± 13*
Low-density lipoprotein cholesterol, mg/dL	172 ± 54	99 ± 33*
Non-high-density lipoprotein cholesterol, mg/dL	203 ± 58	123 ± 36*
Aspartate aminotransferase, U/L	23 ± 15	24 ± 8
Alanine aminotransferase, U/L	25 ± 16	25 ± 14
Gamma glutamyltranspetidase, U/L	18 (5-245)	19 (5-333)
Alkaline phosphatase, U/L	90 ± 50	64 ± 29*
Estimated glomerular filtration rate, mL/min/1.73m^2	79 ± 18	73 ± 16*
Serum uric acid, mg/dL	5.3 ± 3.0	5.4 ± 1.5

Values are expressed as means ± standard deviations, except for triglycerides and gamma-glutamyltranspetidase which are expressed as median (range). To convert from mg/dL to mmol/L multiply by 0.02586 for cholesterol indices and by 0.01129 for triglycerides. *p <0.05 for paired comparison

Lipid target attainment

LDL-C levels in very high and high CV risk patients are shown in Table 12. Respective levels were 80 ± 27 mg/dL (2.1 ± 0.7 mmol/L) in patients with DM, 89 ± 35 mg/dL (2.3 ± 0.9 mmol/L) in those with CHD, 89 ± 35 mg/dL (2.3 ± 0.9 mmol/L) in those with stroke, 87 ± 32 mg/dL (2.2 ± 0.8 mmol/L) in those with PAD, 85 ± 26 mg/dL (2.2 ± 0.7 mmol/L) in those with carotid stenosis, 86 ± 30 mg/dL (2.2 ± 0.8 mmol/L) in those with aortic aneurysm, and 94 ± 31 mg/dL (2.4 ± 0.8 mmol/L) in those with CKD. FH patients had higher LDL-C levels (i.e. 114 ± 42 mg/dL; 2.9 ± 1.1 mmol/L).

According to NCEP ATP III goals, the respective rates of LDL-C and non-HDL-C target attainment were 66 and 72% in very high CV risk patients. The corresponding rates were 86 and 87% in high CV risk ones. Interestingly, among very high CV risk patients only 25% achieved LDL-C levels <70 mg/dL (1.8 mmol/L), while 34% achieved non-HDL-C levels <100 mg/dL (2.6 mmol/L), as recommended by ESC/EAS 2011. Rates of achievement of ESC/EAS 2011 LDL-C and non-HDL-C targets were higher among high CV risk patients (42 and 53%, respectively). Among very high CV risk patients those with diabetes were more likely to achieve LDL-C goals (Table 14). The respective proportions of LDL-C and non-HDL-C goal achievement according to

NCEP ATP III and ESC/EAS 2011 in patients with different disease states are shown in Table 14. Among patients with FH, 42% achieved the recommended LDL-C target (<100 mg/dL; 2.6 mmol/L).

Table 14 *Rates of lipid target attainment at the most recent visit among very high and high cardiovascular risk patients*

		LDL-C at goal (%)		Non-HDL-C at goal (%)	
		NCEP ATP III guidelines	ESC/EAS 2011 guidelines	NCEP ATP III guidelines	ESC/EAS 2011 guidelines
Total		75	33	78	42
Sex	Male	76	36	78	44
	Female	74	30*	79	41
CV risk	Very high	66	25	72	34
	High	86‡	42‡	87‡	53‡
Disease group	Diabetes mellitus	83	35	82	43
	Chronic kidney Disease	75	22	77	26
	Stroke	72	35	77	49
	Coronary heart disease	71	24	78	30
	Peripheral artery disease	69	35	73	40
	Carotid stenosis >50%	77	28	84	35
	Abdominal aortic aneurysm	73	40	80	60

CV, cardiovascular; (ESC/EAS), European Society of Cardiology/European Atherosclerosis Society, NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol. *p <0.05 for comparison with males. ‡p <0.05 for comparison with very high risk patients.

Patients treated with combination therapy were more likely to achieve the LDL-C goals: 41% of those on combination treatment vs 31% on statin monotherapy had optimal LDL-C levels according to ESC/EAS 2011 guidelines, respectively (p <0.05 for the comparison between 2 groups).

As expected, compliance with lipid-lowering treatment was positively associated with lipid target attainment. According to NCEP ATP III, respective rates of LDL-C and non-HDL-C target achievement were 81% and 85% for 'good' compliers. In contrast, these rates were much lower in 'poor' compliers (38% for both targets). A similar difference was noticed for lipid goals according to the ESC/EAS 2011 guidelines: the rates of LDL-C/non-HDL-C target achievement were 37/48% and 10/11% for 'good' and 'poor' compliers, respectively.

Smoking and alcohol consumption had no association with LDL-C goal achievement. Rates of LDL-C goal achievement were 32% and 36% in smokers and non-smokers, respectively ($p > 0.05$ for interaction). Also, no difference in LDL-C goal attainment was noted between patients classified as 'never', 'occasional', 'mild', 'moderate', or 'heavy' drinkers (the respective rates were 35, 42, 30 and 28%, $p > 0.5$ for interaction).

BMI showed no significant association with LDL-C target attainment. Respective rates of LDL-C target attainment were 27, 31 and 36% in the 'normal-weight', 'overweight' and 'obese' patients ($p > 0.05$ for interaction). The corresponding rates for non-HDL-C goal achievement were 47, 42 and 39%, respectively ($p > 0.05$ for interaction).

4.5.2 Lipid target attainment according to the European Society of Cardiology/European Atherosclerosis Society 2011 guidelines and American College of Cardiology/American Heart Association 2013 guidelines

A total of 1,000 consecutive subjects were included in the present analysis and followed-up for 8 years (mean). Demographic and clinical characteristics of study population are shown in Table 15. Mean age at last visit was 63 years; 45% of participants were males.

Ninety four percent of subjects were on lipid-lowering therapy at last visit and 91% on statins (68% on statin monotherapy and 32% on combined therapy). In 25% of subjects, statins were combined with ezetimibe, 5% with n-3 fatty acids, 4% with fibrates, and 1% with colesevelam. Some patients were on triple combinations (e.g. statin + ezetimibe + fibrate). Among non-statin treated patients (9% of entire population), 69% were not on any lipid-lowering medication, 24% were on fibrates, 9% on ezetimibe and 7% on n-3 fatty acids. Four percent of all patients were unable to tolerate even low-dose statin treatment.

Table 15 *Demographic and clinical characteristics of 1,000 consecutive study participants at baseline and last visit*

Variable	Baseline visit	Last visit
Age, years	55 ± 13	63 ± 13*
Sex (male), %	45	
Smoking, %	17	15
Family history of premature coronary heart disease, %	23	
Metabolic syndrome*, %	44	55
Hypertension, %	62	73
Body mass index, kg/m^2	27.8 ± 4.3	28.6 ± 4.3*
Systolic blood pressure, mmHg	145 ± 25	129 ± 13*
Diastolic blood pressure, mmHg	89 ± 13	78 ± 8*
Total cholesterol, mg/dL	257 ± 59	180 ± 38*
Triglycerides, mg/dL	131 (33-1750)	112 (11-668)*
High-density lipoprotein cholesterol, mg/dL	53 ± 14	55 ± 14*
Low-density lipoprotein cholesterol, mg/dL	172 ± 54	101 ± 3*
Non-high density lipoprotein cholesterol, mg/dL	203 ± 57	125 ± 36*
Lipid-lowering treatment, %	18	94
Statin treatment, %	16	91
Morbidities, %		
Diabetes mellitus	10	21
Chronic kidney disease	8	18
Stroke	8	11
Coronary heart disease	6	10
Peripheral artery disease	2	5
Carotid stenosis	3	4
Abdominal aortic aneurysm	1	2

Values are expressed as mean ± standard deviation. Triglycerides levels are expressed as median (range). To convert from mg/dL to mmol/L multiply by 0.02586 for cholesterol indices, and by 0.01129 for triglycerides. * p <0.05 for paired comparison between baseline and last visit

Lipid-lowering treatment and LDL-C goal achievement according to the ESC/EAS 2011 guidelines

Almost half patients (48%) were at very high, 41% at high and 11% at moderate CV risk according to the ESC/EAS 2011 guidelines. Mean LDL-C levels (at the first and last visit), LDL-C reduction, selected lipid-lowering treatment and rates of LDL-C target achievement across CV risk groups defined by ESC/EAS 2011 are shown in Table 16. Patients at very high CV risk were more likely to receive high-intensity statin treatment compared with those at high and moderate CV risk, while approximately half of patients in each CV risk group were treated with a moderate-intensity statin therapy (Table 16).

A non-significant trend towards a higher rate of a statin + ezetimibe combination treatment was noted in subjects at very high and high CV risk compared with those at moderate CV risk (Table 16). Patients at very high CV risk had the lowest rate of LDL-C target attainment compared with the other 2 groups (25 vs 42 vs 57%, p <0.05) (Table 16).

Table 16 *Changes in low-density lipoprotein cholesterol levels and intensity of statin treatment classified according to the European Society of Cardiology/European Atherosclerosis Society 2011 guidelines*

Variable	Cardiovascular risk classification according to ESC/EAS 2011 guidelines		
	Moderate risk	High risk	Very high risk
N	115	408	477
Baseline LDL-C, mg/dL	175 ± 48‡	185 ± 55	161 ± 54‡
LDL-C at last visit, mg/dL	116 ± 33‡	109 ± 33	90 ± 30‡
Mean LDL-C reduction, %	28‡	37	39
LDL-C goal achievement, %	57*	42*	25
Intensity of statin treatment			
High-intensity, %	17*	27*	40
Moderate-intensity, %	55	57	53
Low-intensity, %	7*	4*	1
No statin treatment	21*	12*	6
Statin plus ezetimibe, %	19	24	24

Values are expressed as mean ± standard deviation, unless percentages are shown. To convert from mg/dL to mmol/L multiply by 0.02586 for LDL-C. ESC/EAS, European Society of Cardiology/European Atherosclerosis Society; LDL-C, low density lipoprotein cholesterol. ‡ p <0.05 for the comparison with individuals at very high cardiovascular risk. * p <0.05 for the comparison with individuals at very high cardiovascular risk.

The impact of 'intensity' of statin treatment as suggested by ACC/AHA 2013 on LDL-C goal achievement was analyzed across risk groups classified according to ESC/EAS. There was no significant difference between moderate and high-intensity statins regarding LDL-C goal achievement in each CV risk group.

Individuals on statin + ezetimibe were more likely to achieve LDL-C targets compared with those on statin monotherapy (46% vs 35%, p <0.01). Across CV risk groups, the favorable impact of combination therapy on LDL-C target attainment was most evident in subjects at very high CV risk. Indeed, 37% of very high CV risk patients on statin + ezetimibe achieved LDL-C targets, while the corresponding rate for statin monotherapy was 21% (p=0.001). A similar albeit non-significant trend was demonstrated in patients at high and moderate CV risk.

'Appropriate-intensity' statin treatment ± ezetimibe and LDL-C reduction in CV risk groups according to the ACC/AHA 2013 guidelines

By applying the ACC/AHA 2013 guidelines, 21% of subjects were diagnosed with clinical ASCVD, 28% had baseline LDL-C levels ≥190 mg/dL (4.9 mmol/L), 6% had DM (aged 40-75 years) with LDL-C levels 70-189 mg/dL (1.8-4.9 mmol/L) and 14% were not classified as above and had an ASCVD risk ≥7.5%.

Changes in LDL-C levels, intensity of statin treatment or statin combination with ezetimibe as well as LDL-C response across all subgroups according to ACC/AHA 2013 guidelines are shown in Table 17.

In the total population, 33, 55 and 3% of subjects were receiving high, moderate and low-intensity statin treatment, respectively. The corresponding median LDL-C reduction (range) was 49% (40-58%), 41% (30-51%) and 29% (26-32%), respectively.

The achievement of LDL-C reduction ≥50% was compared between patients on moderate- or high-intensity statin treatment. A similar comparison was performed between subjects on high-intensity statin monotherapy or on high-intensity statin + ezetimibe combination (Figure 10).

Overall, more patients on high-intensity statin achieved an LDL-C reduction ≥50% compared with those on moderate-intensity statin (47% vs 29%, p <0.001). A significantly greater rate of LDL-C reduction ≥50% was noted in subjects receiving high-intensity statin plus ezetimibe compared with those on high-intensity statin monotherapy (76% vs 47%, p <0.001) (Figure 10).

The ACC/AHA risk calculation and underestimation of the cardiovascular risk

A significant proportion of individuals without established clinical ASCVD with baseline LDL-C levels 70-189 mg/dL (1.8-4.9 mmol/L) and an ASCVD risk ≥7.5% were at very high CV risk according to the ESC/EAS 2011 guidelines: 24% had CKD, 2% abdominal aortic aneurysm, 1% carotid stenosis and 14% DM aged <40 or >75 years old.

Among those having a lower ASCVD risk (<7.5%), 9% had CKD, 1% abdominal aortic aneurysm and 1% DM. Furthermore, 45% had MetS, 7% NAFLD, 5% an autoimmune disease and 23% high TG levels (≥200 mg/dL; 2.3 mmol/L).

Table 17 *Changes in low-density lipoprotein cholesterol levels and intensity of statin treatment in the study population classified according to the Americal College of Cardiology/American Heart Association 2013 guidelines*

	Cardiovascular risk classification according to the ACC/AHA guidelines					
Variable	**ASCVD ≤75 years old**	**ASCVD >75 years old**	**LDL-C levels ≥190 mg/dL**	**Diabetes and ASCVD risk ≥7.5%**	**Diabetes and ASCVD risk <7.5%**	**ASCVD risk ≥7.5%**
N	142	73	276	34	25	144
Baseline LDL-C, mg/dL	159 ± 55ǂ	151 ± 47ǂ	223 ± 47	139 ± 35ǂ	135 ± 35ǂ	153 ± 27ǂ
LDL-C at last visit, mg/dL	88 ± 32ǂ	87 ± 29ǂ	110 ± 33	89 ± 30ǂ	77 ± 29ǂ	97 ± 25ǂ
Mean LDL-C reduction, %	40ǂ	37ǂ	48	31ǂ	40	36ǂ
LDL-C reduction ≥50%, %	40ǂ	38ǂ	57	40ǂ	35	27*
LDL-C goal achievement, %	26	34	33	26	40	42*
Intensity of statin treatment						
High-intensity, %	55	30*	44*	24*	20*	12*
Moderate-intensity, %	42	58*	46	68*	64*	74*
Low-intensity, %	0	1	4*	3	0	3
No statin treatment	3	11	6	5	16*	11*
Statin plus ezetimibe, %	36	26	32	3	18*	12*

Values are expressed as mean ± standard deviation, unless percentages are shown. To convert from mg/dL to mmol/L multiply by 0.02586 for LDL-C. ACC/AHA, American College of Cardiology/American Heart Association; ASCVD, atherosclerotic clinical cardiovascular disease; LDL-C, low-density lipoprotein cholesterol. ǂ $p < 0.05$ for comparison with patients having baseline LDL-C levels ≥190 mg/dL. * $p < 0.05$ for the comparison with patients with ASCVD ≤75 years old.

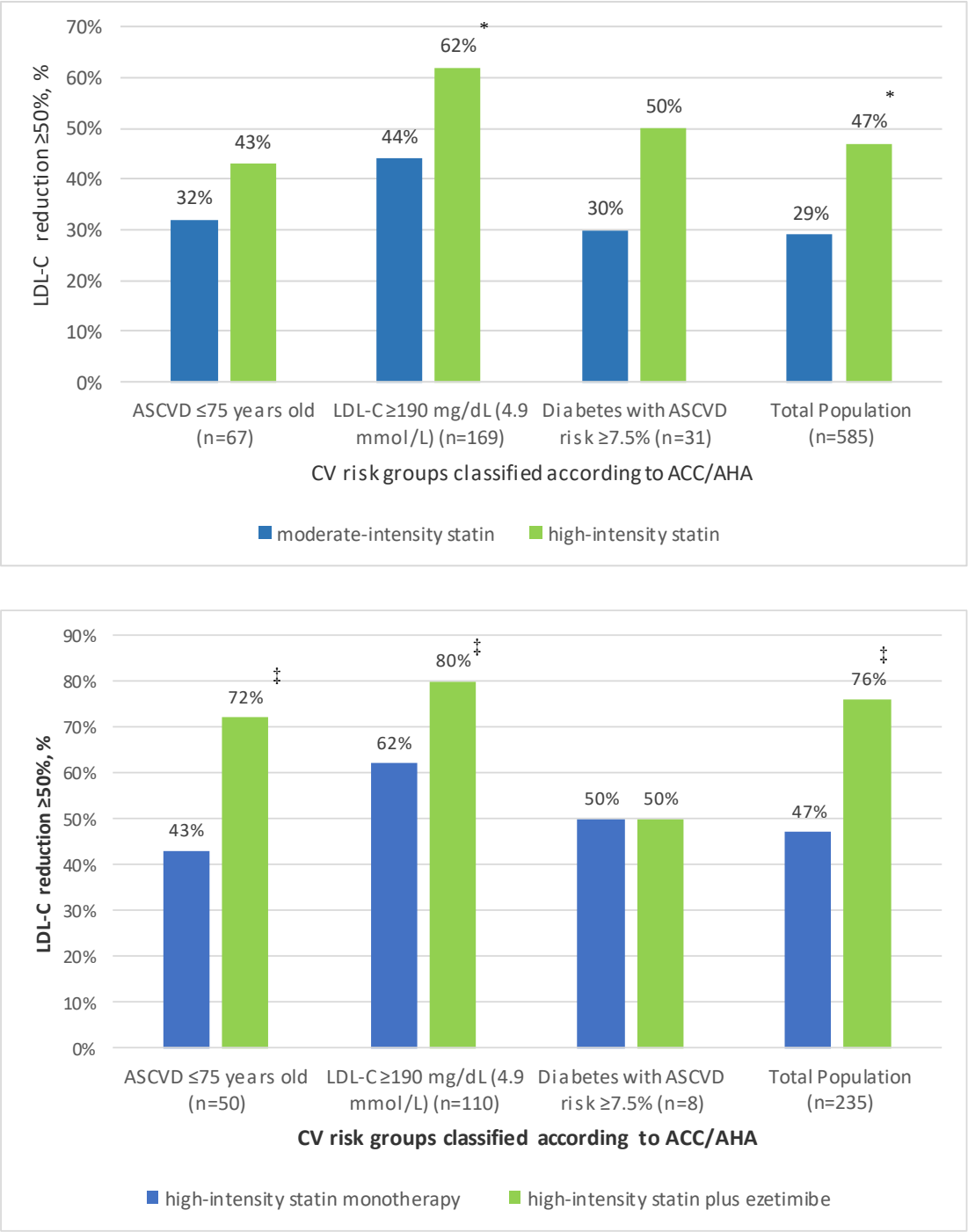


Figure 10 Impact of intensity of statin and statin + ezetimibe treatment on LDL-C reduction ≥50% in risk groups classified according to the American College of Cardiology/American Heart Association

ACC/AHA, American College of Cardiology/American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; LDL-C, low density lipoprotein cholesterol. *p <0.05 for the comparison with moderate-intensity statin therapy. ‡p <0.001 for the comparison with high-intensity statin monotherapy.

4.5.3 Cholesterol target attainment in patients with familial hypercholesterolemia

After screening 1,000 consecutive subjects, 120 fulfilled the criteria of 'probable' or 'definite' HeFH. Median age of participants was 56 years; 45% were males and were follow-up for 6 (4-10) years. Baseline and clinical characteristics are shown in Table 18. Briefly, FH individuals had higher levels of atherogenic lipoproteins [ie. such as LDL-C, apoB and Lp(a)] in comparison with the non-FH subjects (Table 18). FH group exhibited better profile regarding MetS markers and glucose homeostasis and exhibited a lower DM prevalence (Table 18).

Prevalence and incidence of CVD in FH and non-FH individuals

As shown in Figure 11A, a non-significant trend towards a higher prevalence of overall CVD was noticed in FH individuals compared with those not fulfilling the criteria of FH (OR: 1.45, 95% CI: 0.68-3.05, p >0.05, after adjusting for sex, age, smoking, hypertension, DM and family history of premature CVD). Importantly, FH was associated with a higher prevalence of CHD compared with non-FH individuals (adjusted OR: 2.89, 95% CI: 1.12-7.45, p <0.05), while no differences were noticed regarding the prevalence of stroke, PAD and carotid stenosis (Figure 11A).

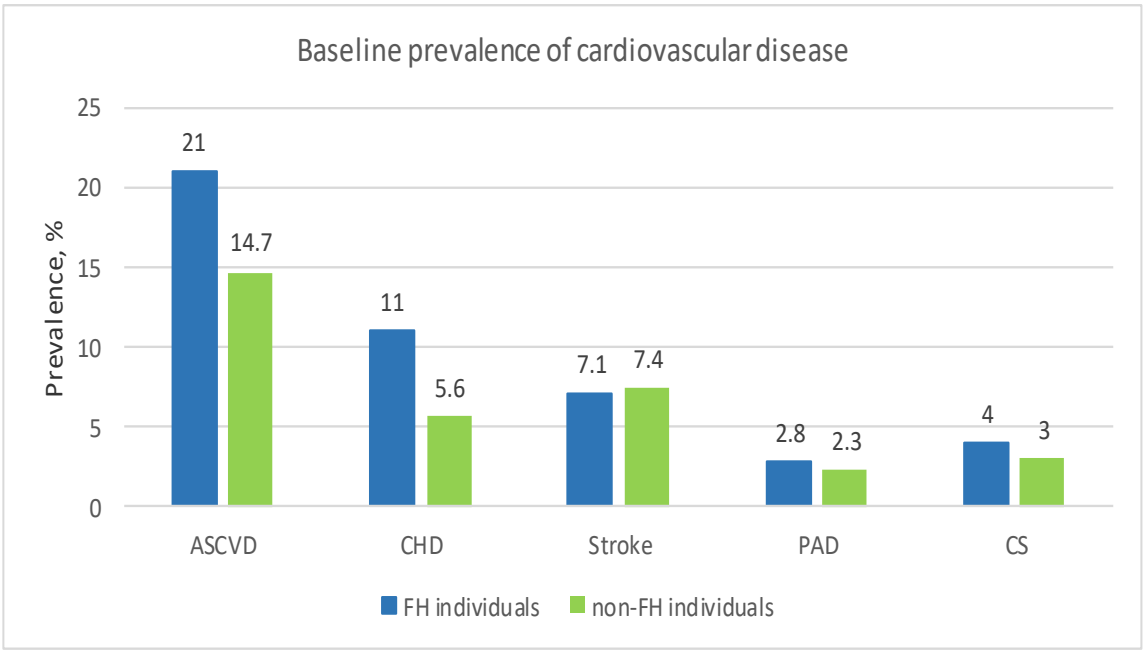
After a median follow-up of 6 years, a non-significant trend towards a higher risk of incident overall CVD was noticed in FH patients (HR: 1.14, 95% CI: 0.51-2.54, p >0.05, after adjusting for sex, age, smoking, hypertension, DM, family history of premature CVD, baseline CVD and untreated LDL-C levels at the most recent visit). Incident CHD (adjusted HR: 1.59, 95% CI: 0.49-5.08, p >0.05) tended to occur more frequently in FH individuals compared with the non-FH ones (Figure 11B). Similarly increased, albeit non-significant, was the risk of incident PAD (adjusted HR: 2.08, 95% CI: 0.48-8.97, p >0.05) and carotid stenosis (adjusted HR: 1.98, 95% CI: 0.26-15.03, p >0.05), whereas no difference was noticed regarding the risk of stroke (Figure 11B).

Table 18 *Baseline characteristics of subjects with and without familial hypercholesterolemia*

	FH individuals	non-FH individuals
N	120	880
Sex, (male), %	48	45
Age, years	43 (31-54)	57 (50-65)*
Follow-up duration, years	6 (5-11)	6 (4-10)
Smoking, %	15	17
Hypertension, %	13	68*
Diabetes mellitus, %	0	12*
Metabolic syndrome, %	10	48*
Fasting plasma glucose, mg/dL	91 (83-97)	97 (89-108)*
Fasting insulin, µU/mL	6.2 (3.6-9.2)	7.7 (5.0-11.7)
HOMA-IR	1.26 (0.85-2.26)	1.88 (1.11-11.70)*
Body mass index, kg/m^2	24.7 (22.9-26.9)	27.5 (25.4-30.1)*
Waist, cm	90 (85-100)	99 (92-106)*
Systolic blood pressure, mmHg	120 (110-135)	140 (130-155)*
Diastolic blood pressure, mmHg	80 (70-87)	88 (80-95)*
Total cholesterol, mg/dL	308 (276-350)	247 (212-281)*
Triglycerides, mg/dL	105 (75-149)	135 (99-195)*
High-density lipoprotein cholesterol, mg/dL	55 (47-64)	51 (44-61)*
Low-density lipoprotein cholesterol, mg/dL	227 (195-261)	164 (132-191)*
Apolipoprotein A-I, mg/dL	143 (127-164)	146 (129-172)
Apolipoprotein B, mg/dL	144 (128-169)	120 (101-137)*
Apolipoprotein E, mg/L	47 (40-56)	45 (36-56)
Lipoprotein (a), mg/dL	17.7 (10.0-38.3)	10.5 (4.9-22.2)*
Lipid-lowering treatment		
Statins, %	19	16
Ezetimibe, %	1	1
Fibrates, %	1	2
Omega-3 fatty acids, %	0	1
Colesevelam, %	1	1

Values are expressed as median (interquartile range), unless percentages are shown. To convert from mg/dL to mmol/L multiply by 0.02586 for cholesterol, by 0.01129 for triglycerides and by 0.06 for fasting plasma glucose. FH, familial hypercholesterolemia; HOMA-IR, homeostatic model assessment of IR. * $p < 0.05$ for the comparison with FH individuals.

A.



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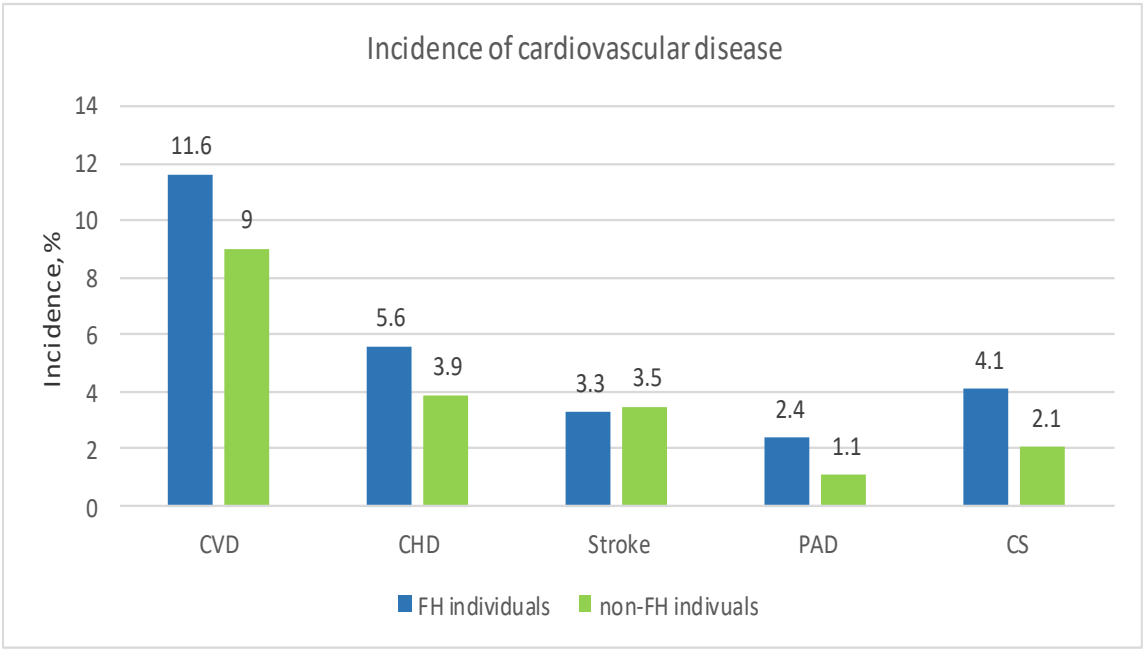


Figure 11 Prevalence (A) and incidence (B) of cardiovascular disease in subjects with and without familial hypercholesterolemia

ANCOVA was performed across 2 groups after adjusting for gender, age, smoking, hypertension, diabetes, family history of premature cardiovascular disease, previous cardiovascular disease, follow-up duration and untreated LDL-C levels at the most recent visit. p >0.05 for all comparisons with FH individuals.

ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; CS, carotid stenosis; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; PAD, peripheral arterial disease

Lipid-lowering therapy and LDL-C target attainment

A low proportion (15%) of both FH and non-FH groups were on statin therapy at the baseline visit (Table 18). This number increased to 94% at the most recent visit. As shown in Table 19, FH individuals were more likely to receive high-intensity statin or statin/ezetimibe combination treatment compared with non-FH (64 vs 28%, p <0.05 and 63 vs 25%, p <0.05, respectively).

Table 19 *Prescribed lipid-lowering treatment to subjects with and without familial hypercholesterolemia at the most recent visit*

	FH individuals	non-FH individuals
Statins, %	98	90
Specific statin, % (median dose, mg)		
Atorvastatin	26 (40)	40* (20)
Rosuvastatin	66 (40)	24* (20)
Simvastatin	6 (40)	22* (40)
Fluvastatin	0	4* (80)
Intensity of statin treatment		
High-intensity statin, %	64	28*
Moderate-intensity statin, %	33	59*
Low-intensity statin, %	1	3
Ezetimibe, %	61	18*
Colesevelam, %	8	0
Fibrates, %	1	6
Omega-3 fatty acids, %	2	5
Statin plus ezetimibe, %	63	25*

FH, Familial hypercholesterolemia. * p <0.05 for the comparison with FH individuals.

Regarding target attainment, only 1 of 3 study participants had optimal LDL-C levels as proposed by ESC/EAS 2011 guidelines. As shown in Figure 12, among those being at high cardiovascular risk, both FH and non-FH individuals exhibited similarly low rates of LDL-C target attainment. On the other hand, FH individuals at very high cardiovascular risk were less likely to achieve optimal LDL-C levels <70 mg/dL compared with non-FH subjects (Figure 12).

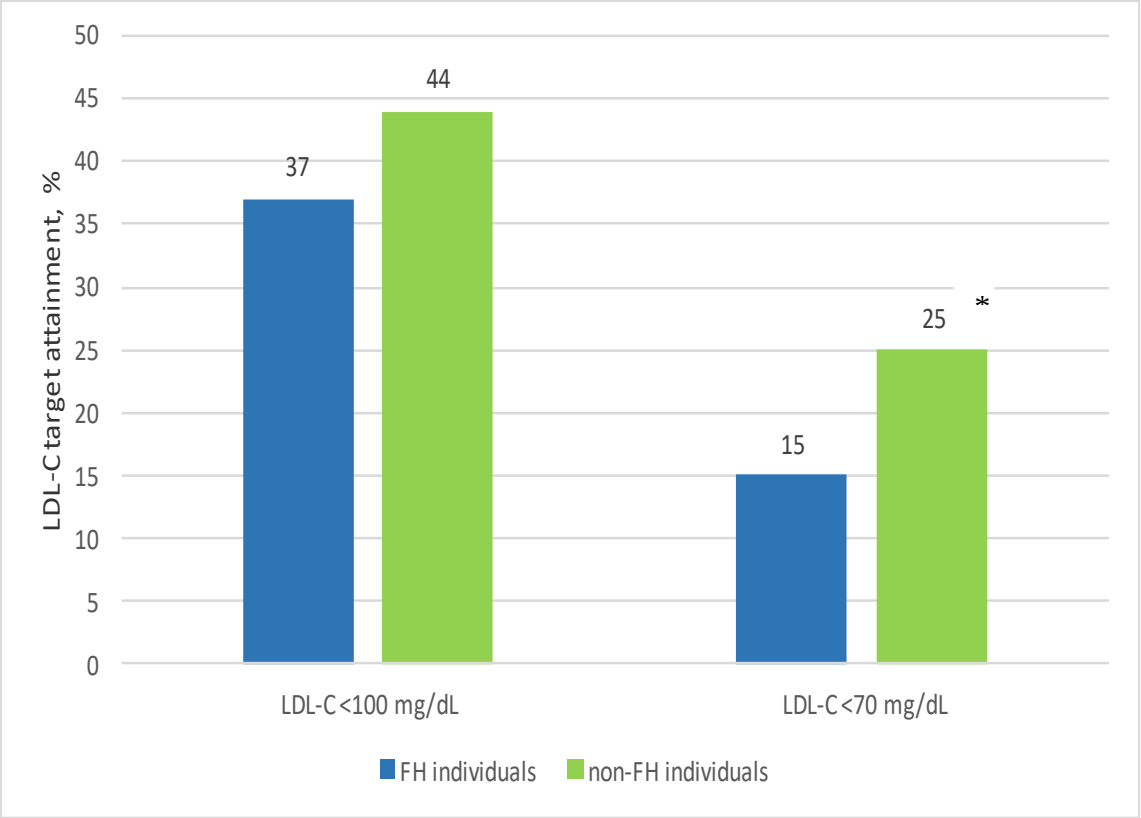


Figure 12 Low-density lipoprotein cholesterol target attainment among individuals with and without familial hypercholesterolemia

LDL-C target were defined according to the Hellenic and the European Atherosclerosis Society guidelines (2011). FH, Familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol, CV, cardiovascular. * p <0.05 for the comparison with FH individuals.

4.5.4 LDL-C target attainment in patients at 'extreme' cardiovascular risk according to American Association of Clinical Endocrinologists/American College of Endocrinology 2017 guidelines

Patients at 'extreme' CVD risk as proposed by AACE/ACE 2017 were eligible for the present analysis. Specifically, 244 patients (18.1%) had CVD with 48.4% of them (n=118) having features of 'extreme' CVD risk. Their characteristics are depicted in Table 20.

Table 20 *Characteristics of study participants at 'extreme' cardiovascular risk*

	Patients at 'extreme' cardiovascular risk (n=118)
Sex (male), %	37
Age, years	74 (65-79)
Follow-up, years	7 (4-11)
Diabetes mellitus, %	60
Chronic kidney disease stage 3 or 4, %	52
Familial hypercholesterolemia, %	15
Premature coronary artery disease, %	40
Recurrent cardiovascular event despite low-density lipoprotein cholesterol <70 mg/dL, %	8
Coronary artery disease, %	49
Stroke, %	40
Peripheral artery disease, %	39
Carotid stenosis, %	13
Total cholesterol, mg/dL	152 (135-175)
Triglycerides, mg/dL	117 (87-146)
High-density lipoprotein cholesterol, mg/dL	48 (41-56)
Low-density lipoprotein cholesterol, mg/dL	78 (62-99)
Statin therapy, %	96
High-intensity statins, %	34
Moderate-intensity statins, %	60
Low-intensity statins, %	2
Combination therapy of a statin plus ezetimibe, %	33

Variables are presented as median (interquartile range), unless percentages are shown.

Notably, the majority of these patients were diagnosed with DM or CKD and 1 out of 3 were receiving high-intensity statin treatment, while one third were also receiving ezetimibe (Table 20). Figure 13 shows the distribution of LDL-C levels in relevance to targets. Of the 'extreme' CVD risk patients, 37% achieved LDL-C <70 mg/dL, while 16% achieved the most stringent goal of <55 mg/dL. Among those on high-intensity statin monotherapy (n=30), the rates of target attainment were 48% for LDL-C <70 mg/dL and 19% for LDL-C <55 mg/dL. The corresponding rates were lower (30% and 10%, respectively) among those taking a combination therapy of a high-intensity statin with ezetimibe (n=10). However, the latter group was more likely to have FH (33% vs 7%) and therefore having higher baseline LDL-C levels compared with those on statin monotherapy [224 (187-269) vs 165 (136-181) mg/dL, p <0.05].

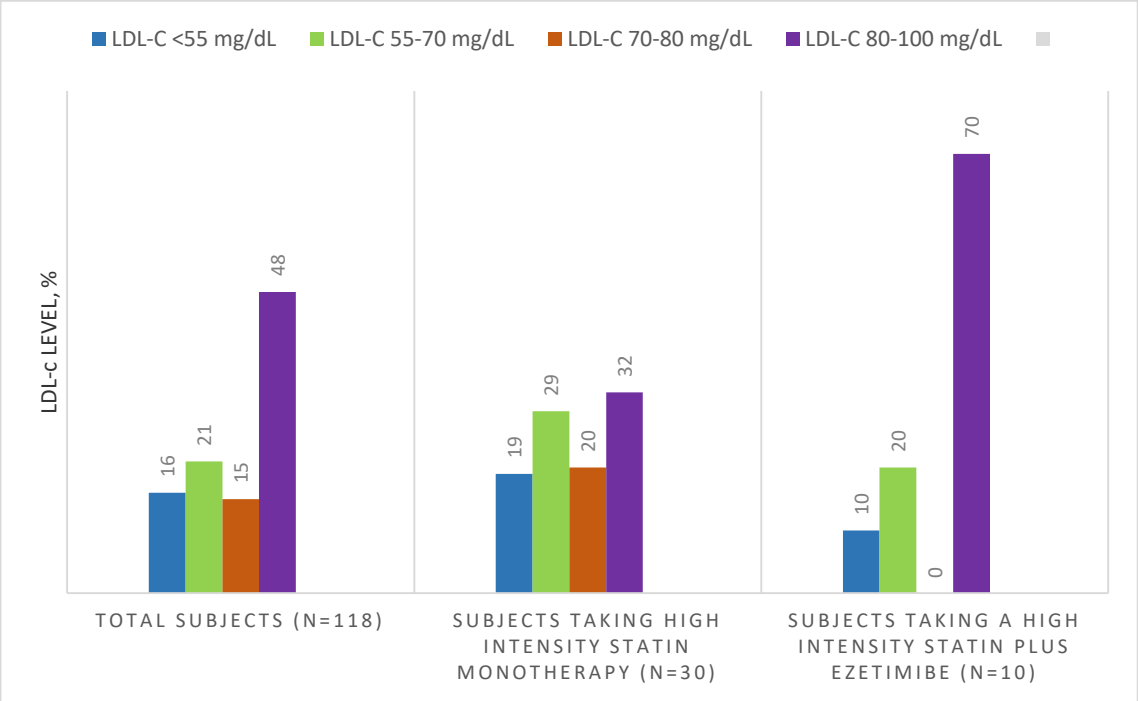


Figure 13 Distribution of low-density lipoprotein cholesterol levels across subjects at 'extreme' cardiovascular risk

LDL-C, low-density lipoprotein cholesterol

4.5.5 Eligibility for treatment with proprotein convertase subtilisin/kexin type 9 inhibitors according to the statement of Greek experts

A total of 1,000 consecutive subjects were included in the present analysis. Tables 15 and 16 demonstrate clinical characteristics, prescribed therapy and rates of LDL-C goal achievement according to the ESC/EAS 2011 guidelines. Of patients, 17% had ASCVD, 6% T2DM with target organ damage, 11% FH and 4% statin intolerance. LDL-C levels for the first 3 groups of patients receiving high-intensity statin treatment plus ezetimibe were 97 mg/dL (46-305), 69 mg/dL (54-159) and 107 mg/dL (45-242), respectively. Patients with statin intolerance receiving any hypolipidemic treatment at any tolerable dose had LDL-C levels of 104 mg/dL (32-230). Of patients receiving intense lipid-lowering treatment, 11 out of 34 CVD patients and 1 of 9 diabetic patients with target organ damage had LDL-C ≥100 mg/dL, whereas 8 of 37 FH patients had LDL-C ≥130 mg/dL. Furthermore, 1 out of the 16 statin-intolerant patients were also candidates for PCSK9 inhibitors. In total, 22% of patients at high CV risk taking maximally tolerated lipid-lowering therapy were eligible for taking PCSK9 inhibitors.

4.5.6 Distance to targets of low-density lipoprotein cholesterol and eligibility for treatment with proprotein convertase subtilisin/kexin type 9 inhibitors in patients at high cardiovascular risk as proposed by the American College of Cardiology/American Heart Association 2018

For the present analysis, 642 subjects were included (244 very high risk ASCVD patients and 398 individuals with LDL-C ≥190 mg/dL). Of those, 112 and 188 were on high-intensity statin monotherapy ± ezetimibe, respectively. Figure 14 demonstrates LDL-C levels of subjects taking high-intensity statin monotherapy and those on combination therapy of a high-intensity statin plus ezetimibe. After considering the additional LDL-C reduction by ~20% by the addition of ezetimibe on those taking high-intensity statin monotherapy, 51/112 (46%) patients with very high risk ASCVD and 58/188 (31%) individuals with LDL-C ≥190 mg/dL would be eligible for treatment with PCSK9 inhibitors according to ACC/AHA 2018 guidelines.

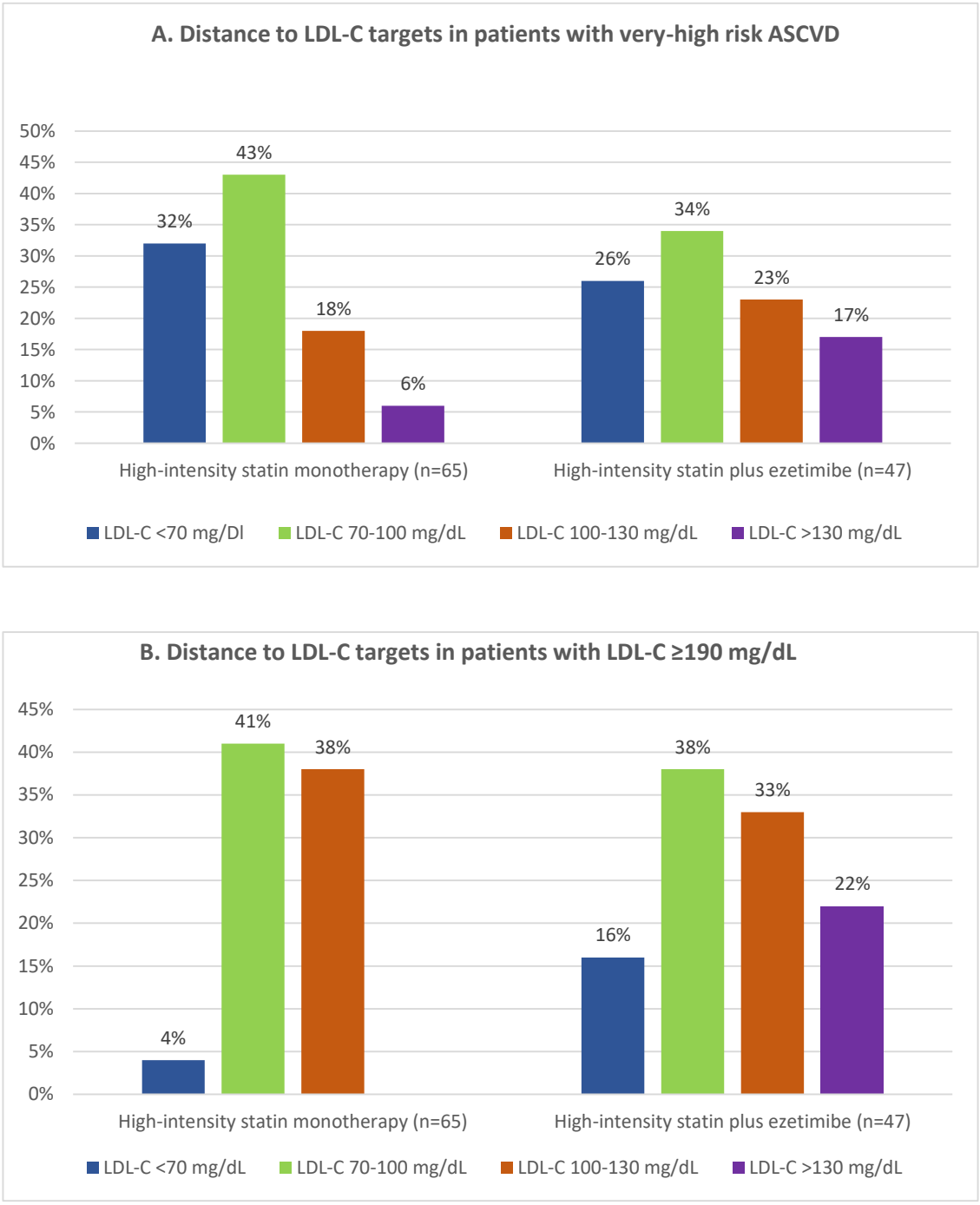


Figure 14 Distance to targets of low-density liporpotein cholesterol in patients with very high risk atherosclerotic cardiovascular disease (A) and those with low-density liporpotein cholesterol ≥190 mg/dL (B).

ASCVD, Atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol

4.5.7 Cholesterol target attainment according to European Society of Cardiology/European Atherosclerosis Society 2019 guidelines

A total of 1,000 consecutive subjects were included in the present analysis. Of those, 39% were at very high CV risk, 46% at high risk, 10% at moderate risk and 5% at low risk according to the ESC/EAS 2019 guidelines. Figure 15 demonstrates the actual rates of LDL-C target attainment, along with the hypothetical rates of LDL-C goal achievement supposing that all patients were treated with i) a high-intensity statin plus ezetimibe and ii) a high-intensity statin plus ezetimibe plus PCSK9 inhibitor.

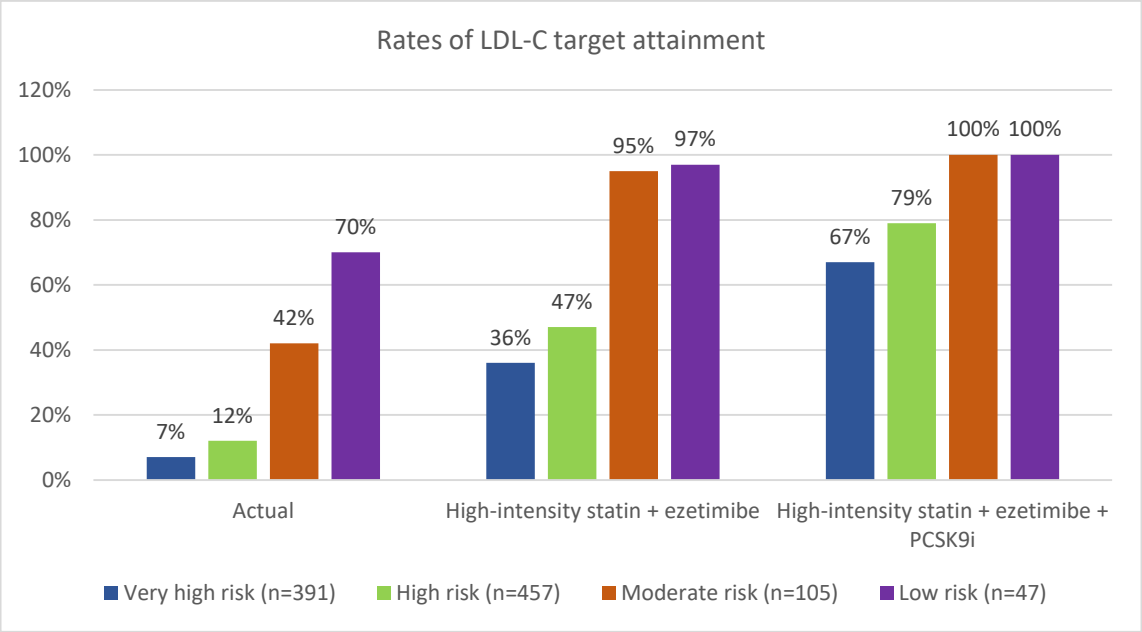


Figure 15 Rates of low-density liporpotein cholesterol target attainment in line with European Society of Cardiology/European Atherosclerosis Society guidelines published in 2019

ESC/EAS, European Society of Cardiology/European Atherosclerosis Society; LDL-C, low-density lipoprotein cholesterol; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitors

4.5.8 Attainment of multifactorial treatment targets in the elderly patients

For the present analysis, 465 subjects aged ≥65 years old were included and followed for mean of 8 years. Demographic, clinical and laboratory characteristics are shown in Table 21. Briefly, the majority of subjects (68%) were at very high CV risk according to the ESC/EAS 2011 guidelines. DM was the most prevalent comorbidity (31%), followed by CKD (23%), stroke (15%) and CHD (15%).

Table 21 *Demographic, clinical, and laboratory characteristics of the elderly at the most recent visit*

	Elderly patients
N	465
Age, years	73 ± 6
Sex (male), %	41
Smoking, %	8
Body mass index, kg/m^2	28.8 ± 4.3
Waist, cm	103 ± 10
Metabolic syndrome, %	62
Diabetes mellitus, %	31
Fasting plasma glucose, mg/dL	107 ± 24
Glycated hemoglobulin, % [a]	7.1 ± 1.0
Estimated glomerular filtration rate, mL/min/1.73 m^2	69 ± 16
Systolic blood pressure, mmHg	133 ± 13
Diastolic blood pressure, mmHg	76 ± 8
Total cholesterol, mg/dL	173 ± 33
Triglycerides, mg/dL	112 (22-405)
High-density lipoprotein cholesterol, mg/dL	56 ± 14
Low-density lipoprotein cholesterol, mg/dL	93 ± 27
Non-high density lipoprotein cholesterol, mg/dL	117 ± 30
Lipid-lowering treatment, %	95
Antihypertensive treatment, %	89
Antidiabetic treatment, %	29
Cardiovascular risk, % [b]	
Very high	68
High	28
Moderate	4
Disease group, %	
Diabetes mellitus	31
Chronic kidney disease	23
Stroke	15
Coronary heart disease	15
Peripheral artery disease	8
Carotid stenosis	6
Abdominal aortic aneurysm	3

Values are expressed as mean ± standard deviation except for triglycerides which are expressed as median (range). To convert from mg/dL to mmol/L multiply by 0.02586 for cholesterol indices, by 0.01129 for triglycerides and by 0.05549 for fasting plasma glucose. [a] For diabetic patients. [b] Cardiovascular risk was defined according to the European Society of Cardiology/ European Atherosclerosis Society (2011) guidelines for the management of dyslipidemias.

Treatment

Lipid-lowering treatment is depicted in Table 22. Of patients 98% were receiving statins (80% statin monotherapy and 20% combination of statin + ezetimibe), 5% omega-3 fatty acids, 4% fibrates and 1% colesevelam; some patients were receiving more than 2 drugs, for example statin + ezetimibe +/- fibrate. The most commonly used statin was atorvastatin, followed by rosuvastatin and simvastatin (Table 22).

ARBs were the most commnonly used BP lowering drugs, followed by CCBs, thiazides and beta blockers. The majority of hypertensive participants were receiving double or triple combination of BP lowering agents (Table 22).

In diabetic subjects, metformin was the most common medication, followed by DDP-4 inhibitors and SU (Table 22). The majority DM patients were receiving metformin plus another oral antihyperglycemic drug (46%).

Changes in study participant metabolic profile and adverse events

Multifactorial treatment improved overall patient metabolic profile, as shown in Table 23. Significant reductions in TC, TGs, LDL-C and non-HDL-C were noted, along with a small though significant increase in HDL-C. SBP and DBP were significantly declined by 15 and 10 mmHg, respectively. Also, HbA1c significantly declined by 0.7% in DM patients (Table 23).

No significant changes were noticed in liver enzymes, except for a decrease in ALP by 21%. Of note, renal function declined by 5 mL/min/1.73 m^2 during the 8-year follow-up period (Table 23).

Low rates of adverse events were demonstrated in elderly individuals receiving lipid-lowering treatment: 2.3% exhibited myalgias, while 1.6% and 0.2% had increased liver enzymes >3 times and CK >10 times the ULN, respectively. The rates of adverse events for those receiving antihypertensive treatment were 4.8% for leg swelling, 0.7% for hypotension and 0.5% for cough. Moreover, 2.2% and 1.0% of those taking antidiabetic therapy experienced hypoglycemia and GI disorders, respectively.

Table 22 *Prescribed therapy to the elderly at the most recent visit*

10	Total
I. Lipid lowering treatment	
Statins, %	98
Atorvastatin, % (median dose)	46 (20 mg)
Rosuvastatin, % (median dose)	26 (20 mg)
Simvastatin, % (median dose)	24 (40 mg)
Fluvastatin, % (median dose)	3 (80 mg)
Pravastatin, % (median dose)	1 (40 mg)
Ezetimibe, %	21
Fibrates, %	4
Colesevelam, %	1
Omega-3 fatty acids, %	5
Statin + ezetimibe, %	20
II. Antihypertensive treatment	
Angiotensin receptor blockers, %	79
Calcium channel blockers, %	61
Thiazides, %	58
Beta blockers, %	40
Angiotensin converting enzyme inhibitors, %	9
Aldosterone receptor antagonists, %	8
Centrally acting drugs, %	3
Combinations of antihypertensive drugs	
≥4 drugs, %	15
3 drugs, %	34
2 drugs, %	35
Monotherapy, %	16
III. Antidiabetic treatment	
Metformin, %	89
Dipeptidyl peptidase 4 inhibitors, %	32
Sulfonylureas, %	21
Pioglitazone, %	13
Insulin, %	13
Combinations of antidiabetic drugs	
Metfromin + oral antidiabetics, %	46
Metformin monotherapy, %	35
Insulin ± oral antidiabetics, %	13
Oral antidiabetics without metformin, %	6

Table 23 *Metabolic profile of the elderly patients followed-up for a mean of 8 years*

	Baseline visit	Last Visit
Fasting plasma glucose, mg/dL	134 ± 43	126 ± 32
Glycated hemoglobin, % [a]	7.8 ± 1.4	7.1 ± 1*
Estimated glomerular filtration rate, mL/kg/1.73 m^2	74 ± 15	69 ± 16*
Aspartate aminotransferase, U/L	21 (11-344)	22 (9-144)
Alanine aminotransferase, U/L	20 (3-201)	20 (6-240)
Gamma-glutamyltranspetidase, U/L	17 (5-142)	17 (5-333)
Alkaline phosphatase, U/L	73 (23-210)	58 (23-210)*
Creatine phosphokinase, U/L	91 (16-485)	95 (20-645)
Total cholesterol, mg/dL	251 ± 57	173 ± 33*
Triglycerides, mg/dL	132 (41-750)	112 (22-405)*
High-density lipoprotein cholesterol, mg/dL	54 ± 13	56 ± 14*
Low-density lipoprotein cholesterol, mg/dL	165 ± 49	93 ± 27*
Non-high-density lipoprotein cholesterol, mg/dL	196 ± 55	117 ± 30*
Systolic blood pressure, mmHg	148 ± 19	133 ± 13*
Diastolic blood pressure, mmHg	86 ± 13	76 ± 8*

Values are expressed as mean ± standard deviation except for non-parametric data which are as median (range). To convert from mg/dL to mmol/L multiply by 0.02586 for cholesterol, by 0.01129 for triglycerides and by 0.05549 for fasting plasma glucose. [a] For diabetic patients. * p <0.05 for paired comparison.

Multifactorial treatment target attainment

Rates of multifactorial treatment goal achievement in the elderly participants are described in Table 24. Patients at very high CV risk were less likely to achieve optimal LDL-C levels compared with those at high and moderate risk, respectively (27% vs 48% vs 62%, p <0.05). Individuals on combination treatment with statin + ezetimibe were more likely to achieve optimal levels of LDL-C according to the ESC/EAS 2011 guidelines compared with those on statin monotherapy (48% vs 33%, p <0.05 for the comparison between the 2 groups). Across CV risk groups, the favourable impact of combination therapy on LDL-C target attainment was most evident in subjects at very high CV risk (the respective rates were 46% vs 23%, p <0.05). Despite not being significant, a similar trend was noticed in individuals at high (56% vs 52%) and moderate CV risk (92% vs 60%).

The rates of BP target attainment as proposed by the ESC/ESH 2013 guidelines in the diabetic patients were similar to those noticed in the individuals without DM (Table 24).

A higher proportion of the latter group (86%) achieved the less strict BP target <150/90 mmHg. Almost half of the patients with DM had HbA1c levels <7%, while a higher proportion had HbA1c <7.5% or <8% (68% and 88%, respectively) (Table 24).

Higher rates of overall control of CV risk factors were noticed in non-diabetic subjects compared with those with DM. Of non-diabetic individuals, 28% had optimal LDL-C and BP levels according to the ESC/EAS 2011 and ESH/ESC 2013 guidelines, while only 13% of diabetics had achieved all proposed LDL-C, BP and HbA1c targets.

Table 24 *Rates of multifactorial treatment target attainment in the elderly at the most recent visit*

Risk factors	Subjects	Treatment targets	Target attainment,%
Low-density lipoprotein cholesterol	Very high risk	<70 mg/dL	27
	High risk	<100 mg/dL	48*
	Moderate risk	<115 mg/dL	62*
Blood pressure	Non diabetic	<140/90 mmHg	78
	Diabetic	<140/85 mmHg	71
Glycated hemoglobin	Diabetic	<7%	47

Values are expressed as percentages. To convert from mg/dL to mmol/L multiply by 0.02586 for cholesterol. * p <0.05 for the comparison with patients at very high risk.

4.6 Targets of lipid-lowering therapy: correlation of apolipoprotein B with low- and non-HDL-C

After excluding those taking lipid-lowering therapy at baselines (n=179), 821 subjects were eligible for inclusion in the present analysis. Of those, 10% were diagnosed with DM and 41% fulfilled the criteria of MetS. Baseline characteristics are shown in Table 25. Briefly, those with DM or MetS were older and had higher levels of waist circumference, BMI, FPG, HbA1c, BP, and lower HDL-C, apoA-I, Lp(a) levels compared with non-DM non-MetS individuals (Table 25). As expected, subjects with DM/MetS were more likely to have high TGs (≥200 mg/dL) but lower TC and LDL-C levels (Table 25).

Table 25 *Baseline demographic and clinical characteristics of study participants classified according to the presence of diabetes mellitus or metabolic syndrome*

	Diabetic subjects	Subjects with MetS	no DM/MetS dyslipidemic subjects
N	83	336	402
Sex (male), %	40*	43	42
Age, years	61 (55-69)*	57 (50-64)*	52 (43-61)
Smoking, %	14	17	16
Fasting plasma glucose, mg/dL	138 (123-169)*	100 (91-107)*	90 (85-96)
Glycated hemoglobin, %	7.8 ± 1.4*	6.2 ± 0.8	5.8 ± 0.3
Body mass index, kg/m^2	28.7 (25.8-31.8)*	28.9 (26.7-31.2)*	25.7 (23.7-28)
Waist, cm	103 ± 10*	102 ± 10*	93 ± 11
Systolic blood pressure, mmHg	143 (130-160)*	140 (132-160)*	130 (120-150)
Diastolic blood pressure, mmHg	85 (76-93)	90 (80-100)*	81 (80-91)
Triglycerides >200 mg/dL, %	29*	36*	10
Total cholesterol, mg/dL	231 ± 49*	255 ± 45*	267 ± 48
Triglycerides, mg/dL	160 (106-220)*	169 (128-225)*	109 (84-144)
High-density lipoprotein cholesterol, mg/dL	48 ± 13*	49 ± 12*	58 ± 14
Low-density lipoprotein cholesterol, mg/dL	148 ± 41*	170 ± 41*	186 ± 43
Non-high-density lipoprotein cholesterol, mg/dL	180 ± 43*	206 ± 43	210 ± 45
Apolipoprotein A-I, mg/dL	145 ± 34	141 ± 30*	155 ± 30
Apolipoprotein B, mg/dL	107 ± 24*	122 ± 25	123 ± 31
Apolipoprotein E, mg/L	40 ± 11	47 ± 17	48 ± 19
Lipoportein (a), mg/dL	9.8 (2.7-21)*	10.1 (4.5-17.9)*	12.5 (7.6-27.3)

Parametric and non-parametric values are expressed as mean ± standard deviation or median (interquartile range), unless percentages as shown. DM/MetS subjects, subjects with diabetes or metabolic syndrome; no DM/MetS hyperlipidemic subjects, hyperlipidemic subjects without diabetes or metabolic syndrome. * $p < 0.05$ for the comparison with the no DM and no MetS hyperlipidemic subjects.

Correlations of apoB with LDL-C and non-HDL-C

Due to the small number of diabetic patients and the fact that both MetS and diabetic subjects exhibited common metabolic and lipid abnormalities, we merged DM and MetS in one group.

In the entire study population both LDL-C and non-HDL-C levels were significantly associated with apoB (r^2=0.689, p <0.01 for LDL-C; r^2=0.739, p <0.01 for non-HDL-C). The associations of apoB with LDL-C and non-HDL-C levels according to the presence of DM or MetS and baseline TG levels are presented in Table 26 and Figure 16.

For the individuals with TG levels <200 mg/dL apoB was correlated to the same degree with LDL-C and non-HDL-C levels, irrespective of the presence of DM or MetS. The corresponding correlations were r^2=0.755 and r^2=0.743 for subjects with DM/MetS having with TGs <200 mg/dL (p<0.01 for both correlations), and r^2=0.848 and r^2=0.838 for non-DM/nonMetS individuals (p <0.01 for both correlations).

The existence of high TG levels (≥200 mg/dL) reduced the correlation of apoB with LDL-C and non-HDL-C in both groups, with more profound reductions in DM/MetS groups (Table 26, Figure 16). ApoB was better correlated with LDL-C and non-HDL-C in nonDM/nonMetS and high TG group (r^2=0.710 and 0.714, p <0.01, respectively) compared DM/MetS group (r^2=0.600 and 0.604, p <0.01, respectively).

Table 26 *Correlations of apolipoprotein B with low- and non-high-density lipoprotein cholesterol in study participants classified according to the presence of diabetes mellitus or metabolic syndrome*

Subjects	TG levels	Correlation (r^2)	
		ApoB with LDL-C	**ApoB with non-HDL-C**
DM/MetS (n=419)	all individuals	0.662	0.702
non DM/MetS (n=402)		0.731	0.785
DM/MetS (n=272)	<200 mg/dL	0.755	0.743
non DM/MetS (n=362)		0.848	0.838
DM/MetS (n=147)	>200 mg/dL	0.600	0.604
non DM/MetS (n=40)		0.710	0.714

ApoB, apolipoprotein B; DM/MetS, subjects with diabetes or metabolic syndrome; LDL-C, low-density lipoprotein cholesterol; no DM/MetS, hyperlipidemic subjects without diabetes or metabolic syndrome, non-HDL-C, non-high-density lipoprotein cholesterol; TG, triglycerides. * p <0.01 for all correlations.

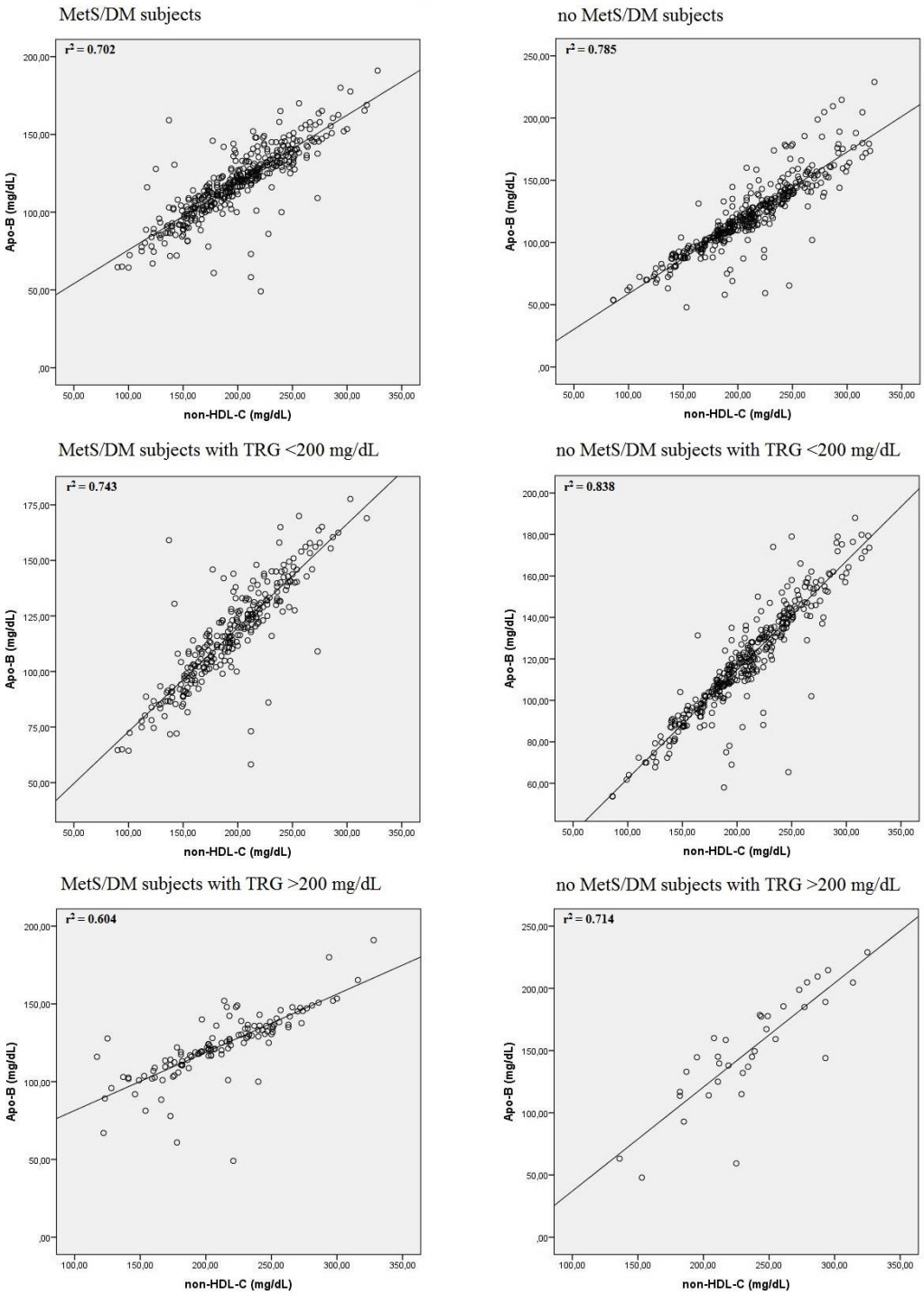


Figure 16 Correlation between apolipoprotein B and non-high-density lipoprotein cholesterol in different patient subgroups

Apo-B, apolipoprotein B; MetS/DM, hyperlipidemic subjects with metabolic syndrome or diabetes; non-HDL-C, non-high-density lipoprotein cholesterol; no MetS/DM, hyperlipidemic subjects without metabolic syndrome or diabetes; TG, triglycerides. p <0.01 for all correlations between ApoB and non-HDL-C.

4.7 Adverse effects and interactions of statin therapy

4.7.1 Effect of statins on muscle, liver and kidney function

In the present analysis, we evaluated the effect of statin therapy on muscle, liver and renal function (n=1,334) during a 6-year follow-up (4-10). As shown in Table 27, no significant changes were noticed apart from a decrease in alkaline phosphatase by 12% and an increase of CK by 10%. eGFR declined by 6 mL/min/1.73 m^2. The rates of liver enzymes and CK increase were 3% and 1%, whereas 2% of the participants experienced myalgias their follow-up.

Table 27 *Changes in muscle, liver and renal function of 1,334 study participants during 6-year follow-up*

	Baseline visit	Last Visit
Estimated glomerular filtration rate, mL/kg/1.73 m^2	81 (71-92)	75 (64-83)*
Aspartate aminotransferase, U/L	21 (18-26)	23 (20-27)*
Alanine aminotransferase, U/L	22 (17-29)	22 (17-29)
Gamma-glutamyltranspetidase, U/L	18 (13-28)	19 (13-27)
Alkaline phosphatase, U/L	67 (54-90)	59 (48-73)*
Creatine phosphokinase, U/L	95 (70-131)	105 (77-156)*

Values are expressed as median (interquartile range). * $p < 0.05$ for paired comparison.

4.7.2 Statin-associated risk of incident diabetes

4.7.2.1 Statin therapy with or without ezetimibe and the progression to diabetes

After enrolling a total of 1,000 consecutive subjects and excluding 123 with DM at baseline, 877 patients were eligible for the present analysis. Median age was 55 years; 44% were males and 33% had prediabetes. Ninety-one percent of subjects were on statin; of those, 75% were on statin monotherapy and 25% on statin + ezetimibe. Atorvastatin was the most commonly used statin (39%, median dose 20 mg) followed by rosuvastatin (29%, median dose 20 mg), simvastatin (20%, median dose 40 mg), and fluvastatin (3%, median dose 80 mg). Almost half of subjects were on moderate-intensity statin monotherapy, while 1 of 3 individuals were on a high-intensity statin.

Demographic and clinical characteristics across lipid-lowering treatment groups are shown in Table 28. Individuals taking statin plus ezetimibe were less likely to have MetS, PreDM or hypertension compared with those on statin monotherapy or those not

taking a statin at all (Table 28). On the contrary, they were more likely to receive high-intensity statin treatment as they had higher baseline LDL-C levels compared with the other 2 groups (Table 28).

During follow-up for a median of 7 years (IQR: 3-12 years), 12% of the study participants developed DM. As expected, individuals with PreDM at baseline had a higher risk of incident DM compared with those with normal FPG levels (OR: 11.71, 95% CI: 7.09-19.35, p <0.05).

Table 28 *Baseline characteristics and concomitant therapy at the most recent across lipid-lowering therapy groups*

Variables	Statin therapy		
	No statin therapy	**Monotherapy**	**Statin plus ezetimibe**
N	81	597	199
Sex (Male), %	44	43	45
Metabolic Syndrome, %	43*	44*	26
Smoking, %	12	17	18
Family history of diabetes mellitus, %	17	17	16
Levels of fasting plasma glucose, %			
<100 mg/dL (normoglycemia)	69	63*	77
100-125 mg/dL (prediabetes)	31	37*	23
Age, years	50 (40-61)	57 (49-64)*	53 (43-61)
Follow up, years	6 (4-10)	6 (4-10)	7 (4-11)
Body mass index, kg/m^2	27.2 (24.7-30.1)	27.4 (24.9-29.9)	27.1 (24-29.4)
Waist, cm	100 ± 12*	98 ± 11	96 ± 14
Fasting plasma glucose, mg/dL	92 (87-102)	95 (88-104)*	92 (94-99)
Systolic blood pressure, mmHg	140 (130-150)*	140 (130-155)*	130 (120-148)
Diastolic blood pressure, mmHg	90 (80-98)*	88 (80-95)*	80 (78-90)
Total cholesterol, mg/dL	225 (186-247)*	254 (225-288)*	282 (239-322)
Triglycerides, mg/dL	128(89-228)*	136 (97-194)*	115 (90-156)
High-density lipoprotein cholesterol, mg/dL	49 (40-60)*	52 (45-61)	53 (47-64)

Low-density lipoprotein cholesterol, mg/dL	138 (112-158)*	171 (143-198)*	198 (167-240)
Concomitant treatment at the most recent visit			
Intensity of statin therapy			
Low		1*	13
Moderate		71*	35
High		28*	52
Fibrates, %	24*	5*	1
Omega 3 fatty acids, %	7*	6*	1
Colesevelam, %	0*	0*	5
Beta blockers, %	15*	23	26
Angiotensin converting enzyme inhibitors, %	7	10	6
Angiotensin receptor blockers, %	56*	57*	40
Calcium channel blockers, %	38*	37*	24
Thiazide diuretics, %	29	41*	28
Corticosteroids, %	1	1	1

Values are expressed as mean ± standard deviation or median (interquartile range), unless percentages are shown. To convert from mg/dL to mmol/L multiply by 0.0555 for fasting plasma glucose, 0.02586 for cholesterol indices and 0.01129 for triglycerides. * p <0.05 for the comparison with individuals on statin plus ezetimibe.

Predictors for new-onset diabetes

Univariate analyses showed that baseline age (OR: 1.04, 95% CI: 1.02-1.06, p <0.05), BMI (OR: 1.10, 95% CI: 1.05-1.16, p <0.05), waist (OR: 1.04, 95% CI: 1.01-1.06, p <0.05), FPG (OR: 1.12, 95% CI: 1.10-1.14, p <0.05), TGs (OR: 1.002, 95% CI: 1.001-1.003, p <0.05), SBP (OR: 1.03, 95% CI: 1.02-1.04, p <0.05), presence of MetS (OR: 8.00, 95% CI: 4.86-13.18, p <0.05), family history of DM (OR: 2.46, 95% CI: 1.50-4.01, p <0.05), follow-up duration (OR: 1.11, 95% CI: 1.06-1.16, p <0.05), treatment with antihypertensive drugs (OR: 1.58, 95% CI: 1.36-1.84, p <0.05) and high-intensity statin treatment (OR: 1.74, 95% CI: 1.15-2.62, p <0.05) were associated with increased risk of new-onset DM.

On the other hand, baseline TC (OR: 0.996, 95% CI: 0.992-0.999, p <0.05), HDL-C (OR: 0.984, 95% CI: 0.969-0.999, p <0.05) and LDL-C (OR: 0.993, 95% CI: 0.989-0.998, p <0.05) were associated with lower DM risk, whereas the use of ezetimibe was not associated with new-onset DM (OR: 0.63, 95% CI: 0.37-1.06, p >0.05).

Multivariate analysis demonstrated that baseline FPG (OR: 1.09, 95% CI: 1.07-1.12, p <0.05), presence of MetS (OR: 3.49, 95% CI: 1.92-6.35, p <0.05), family history of DM (OR: 3.03, 95% CI: 1.62-5.66, p <0.05), duration of follow-up (OR: 1.08, 95% CI: 1.02-1.15, p <0.05) and high-intensity statin therapy (OR: 2.04, 95% CI: 1.18-3.54, p <0.05) were independent predictors of new-onset DM.

Intensity of statin treatment and risk of new-onset diabetes

In the whole study population, a non-significant trend towards a higher risk of incident DM was noticed in statin treated individuals compared with those not taking a statin (adjusted OR: 2.63, 95% CI: 0.86-8.06, p >0.05). The same non-significant trend was also evident in the prediabetic individuals (adjusted OR: 2.85, 95% CI: 0.76-10.69, p >0.05) and in those with normal glucose values (adjusted OR: 1.91, 95% CI: 0.22-16.28, p >0.05).

None of the individuals receiving low-intensity statin treatment was diagnosed with DM during the study. As shown in Figure 17A, study participants on high-intensity statin therapy were at higher risk of developing DM compared with those on moderate-intensity statin treatment (adjusted OR: 1.84, 95% CI: 1.05-3.23, p <0.05) and those not taking a statin (adjusted OR: 4.29, 95% CI: 1.29-14.21, p <0.05). In sub-group analyses the same pattern was evident for the prediabetic subjects taking high-intensity statin therapy (adjusted OR: 2.12, 95% CI: 1.06-4.24, p <0.05, vs those on moderate-intensity statin therapy and adjusted OR: 4.90, 95% CI: 1.16-20.66, p <0.05, vs those not taking a statin), but not for those with fasting FPG <100 mg/dL (5.5 mmol/L) (Figure 17A). There were no differences between statins regarding DM development (Figure 17B).

Ezetimibe and risk of new-onset diabetes

As depicted in Figure 18A, there was no difference regarding new-onset DM between statin + ezetimibe and statin monotherapy groups (adjusted OR: 1.008, 95% CI: 0.51-1.99, p >0.05). The same pattern was evident for prediabetic individuals (adjusted OR: 0.89, 95% CI: 0.36-2.22, p >0.05) and those with normal FPG (adjusted OR: 1.05, 95% CI: 0.34-3.23, p >0.05) (Figure 18A).

Similar comparisons based on the intensity of statin treatment were performed (Figure 18B). The use of ezetimibe was not associated with new-onset DM among subjects taking moderate-intensity statin treatment (adjusted OR: 1.39, 95% CI: 0.50-3.87, p >0.05). The same pattern was again evident for those receiving high-intensity statin

treatment (adjusted OR: 0.63, 95% CI: 0.22-1.76, p >0.05). Despite not being significant, a trend towards a lower risk of incident DM was noticed in prediabetic individuals taking a moderate-intensity statin plus ezetimibe compared with those on high-intensity statin monotherapy (adjusted OR: 0.49, 95% CI: 0.12-2.02, p >0.05).

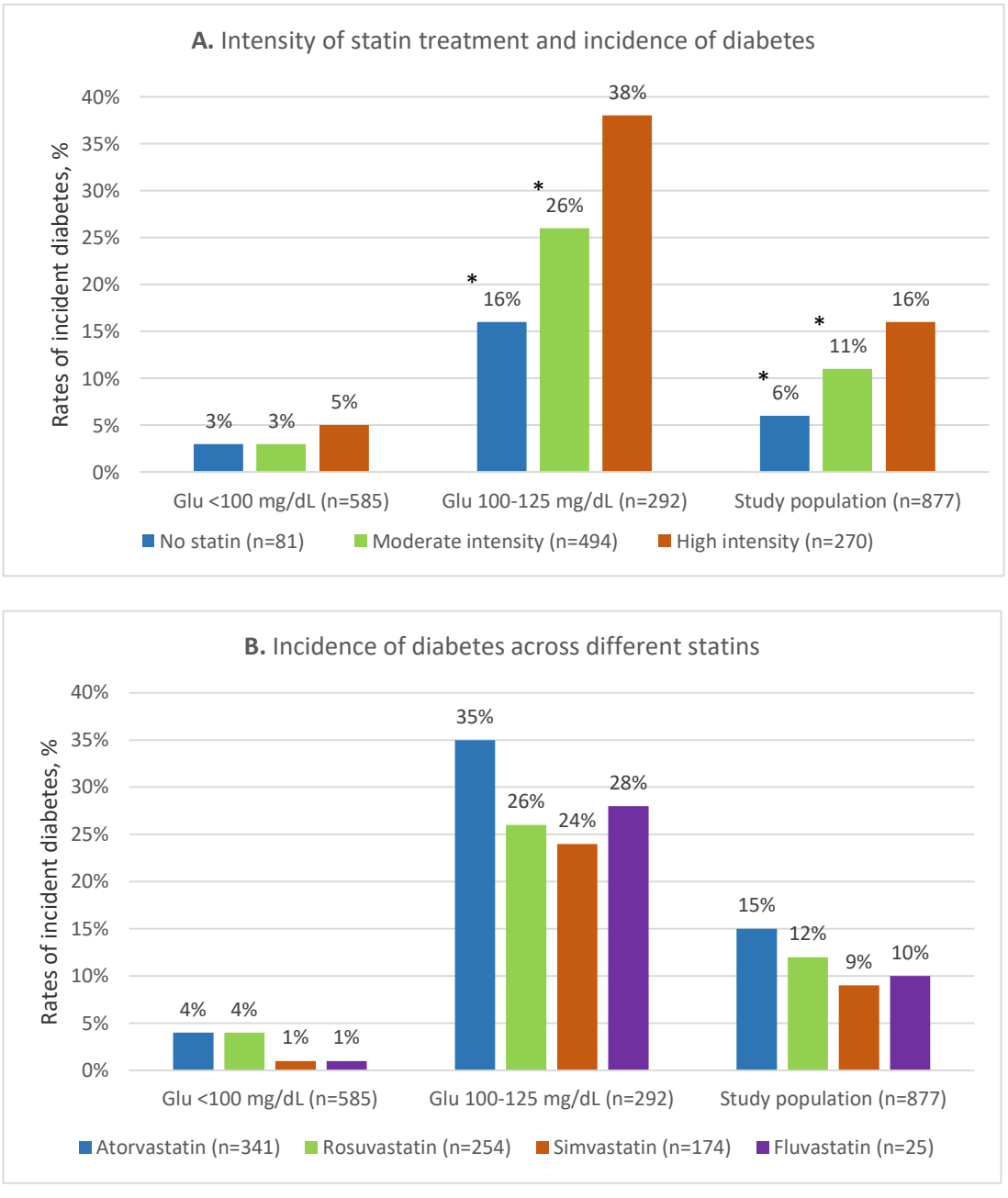
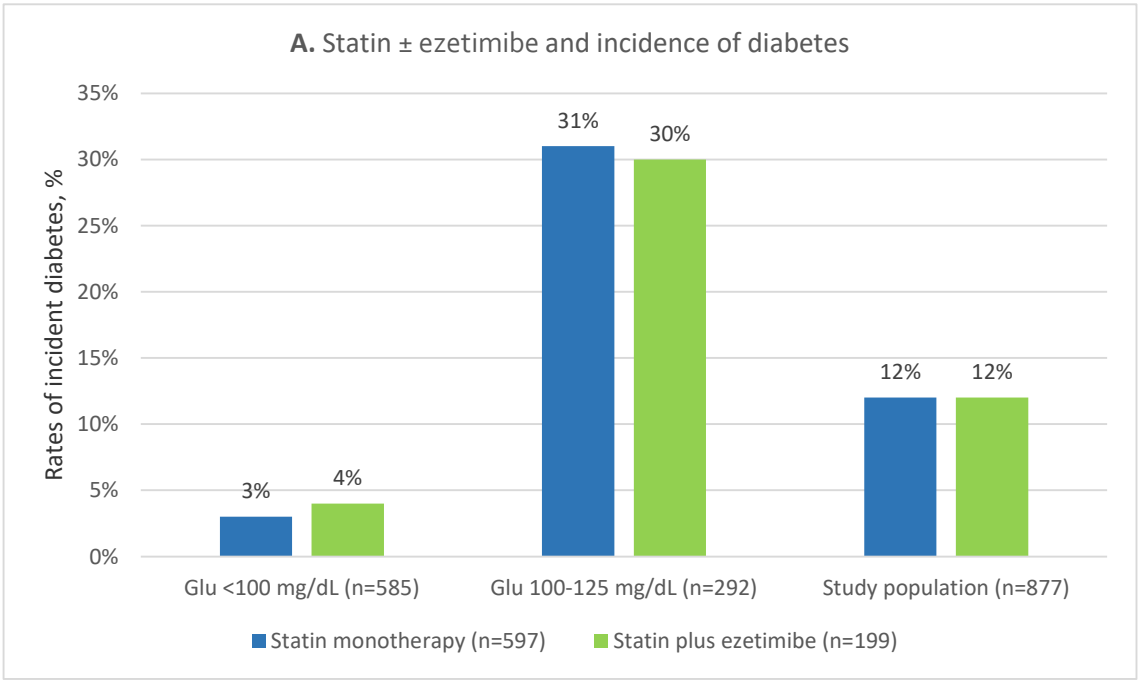


Figure 17 Statin treatment and rates of incident diabetes over 7 years

To convert from mg/dL to mmol/L multiply by 0.0555 for fasting plasma glucose. ANCOVA was performed across treatment groups after adjusting for the log-transformed baseline fasting plasma glucose levels and follow-up duration, the presence of metabolic syndrome and family history of diabetes. Glu, fasting plasma glucose. * p <0.05 for the comparison with high-intensity statin treatment.



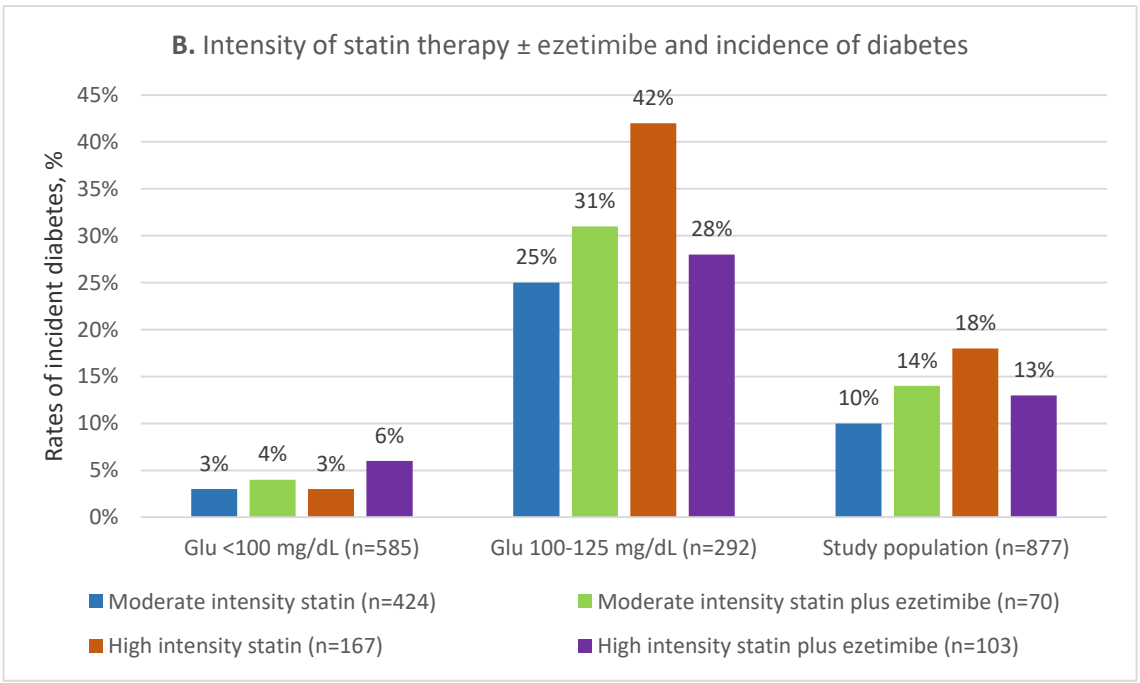


Figure 18 Statin with or without ezetimibe and rates of incident diabetes over 7 years

To convert from mg/dL to mmol/L multiply by 0.0555 for fasting plasma glucose. ANCOVA was performed across treatment groups after adjusting for the log-transformed baseline fasting glucose levels and follow-up duration, the presence of metabolic syndrome and family history of diabetes. Glu, fasting plasma glucose. p >0.05 for the comparisons between therapy groups.

4.7.2.2 Atherogenic dyslipidemia and risk of incident diabetes in statin-treated subjects

After excluding 166 patients with T2DM and 193 subjects taking lipid-lowering therapy at baseline, a total of 882 individuals were included in the present analysis. At baseline, 31% had IFG, 52% had BMI ≥25 kg/m^2, 10% were diagnosed with mixed dyslipidemia (MixDys), 57% with hypertension and 9% with ASCVD. Ninety-four (11%) of study participants developed T2DM and 58 (7%) suffered from a new CV event during follow-up (median 6 years; IQR: 4-10). Detailed subject characteristics are presented in Table 29. Individuals who developed T2DM had higher levels of FPG, BMI, TGs, BP and lower HDL-C levels compared with non-new T2DM group (Table 29). In addition, new-T2DM patients had higher prevalence of MetS, IFG, MixDys and hypertension and they were more likely to be on high-intensity statins and TG-lowering therapy (i.e. fibrates and n-3 fatty acids) (Table 29).

Univariate analysis showed that age, family history of DM, MetS, IFG, increased TG levels, low HDL-C levels, MixDys, and overweight/obesity, along with treatment with high-intensity statins, antihypertensive drugs or fibrates were significantly associated with incident T2DM (Table 30). In multivariate regression analysis, age, family history of DM, IFG, MixDys, overweight/obesity and high-intensity statin therapy remained significantly associated with increased risk of incident T2DM (Table 30).

Within the IFG subgroup, MixDys consistently increased T2DM risk (adjusted OR: 3.44, 95% CI: 1.31-9.04, p <0.05, after adjusting for age, family history of DM, overweight/obesity and high-intensity statin therapy). As shown in Figure 19A, IFG patients with MixDys exhibited the highest rate of incident T2DM compared with non-IFG/non-MixDys participants (adjusted OR: 21.01, 95% CI: 7.64-57.78, p <0.01). Moreover, in IFG patients, overweight/obesity consistently increased T2DM risk despite smaller sample size (adjusted OR: 2.54, 95% CI: 1.14-5.66, p <0.05, after adjusting for age, family history of DM, MixDys and high-intensity statin therapy). As shown in Figure 19B, overweight/obese patients with IFG exhibited the highest rate of incident T2DM compared with non-IFG/non-overweight/obese participants (adjusted OR: 20.10, 95% CI: 6.72-60.15, p <0.05)

Within the subgroup of overweight/obese participants, MixDys consistently increased the risk of T2DM (adjusted OR: 5.60, 95% CI: 2.19-14.30, p <0.01, after adjusting for age, family history of DM, IFG and high-intensity statin therapy). As shown in Figure

19C, overweight/obese patients with MixDys exhibited the highest rate of incident T2DM (adjusted OR: 10.61, 95% CI: 3.92-28.70, p <0.01, for the comparison with those having BMI <25 kg/m^2 without MixDys).

Table 29 *Baseline characteristics of subjects with and without new diabetes*

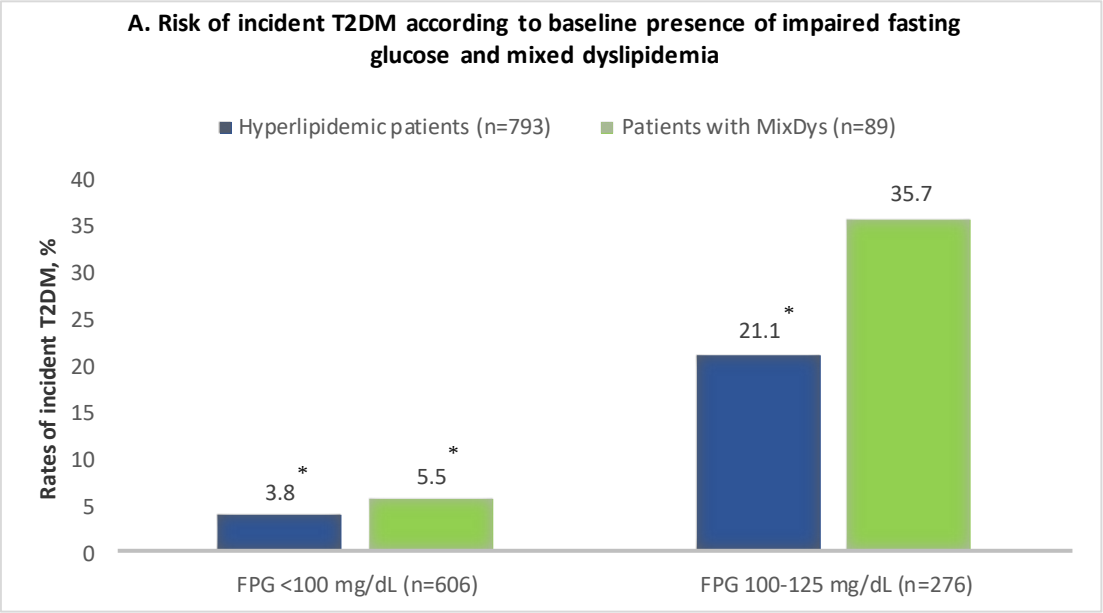
	Patients without new T2DM	Patients with new T2DM
N	788	94
Sex (male), %	57	61*
Age, years	54 (46-62)	59 (54-64)
Family history of diabetes mellitus, %	14	28*
Atherosclerotic cardiovascular disease, %	9	12
Metabolic syndrome, %	34	77*
Impaired fasting glucose,%	26	75*
Body mass index ≥25 kg/m^2, %	50	76*
Hypertension, %	56	72*
Triglycerides ≥200 mg/dL, %	19	36*
Low high-density lipoprotein cholesterol levels, %	25	42*
Mixed dyslipidemia, %	8	24*
Systolic blood pressure, mmHg	140 (125-150)	150 (138-160)
Diastolic blood pressure, mmHg	87 (80-95)	90 (80-100)
Body mass index, kg/m^2	27.1 (24.6-29.7)	29.2 (27.3-32.2)*
Fasting plasma glucose, mg/dL	93 (86-100)	108 (99-117)
Total cholesterol, mg/dL	261 (232-297)	257 (214-293)
Triglycerides, mg/dL	127 (92-181)	148 (102-233)*
High-density lipoprotein cholesterol, mg/dL	53 (45-64)	48 (41-62)*
Low-density lipoprotein cholesterol, mg/dL	176 (152-209)	175 (134-202)
Assigned treatment		
High-intensity statin, %	29	42*
Ezetimibe, %	21	22
Fibrates, %	4	11*
Omega-3 fatty acids, %	3	8*
Colesevelam, %	1	0
Antihypertensive drugs, %	66	82*

Values are expressed as median (interquartile range), unless percentages are shown. Conversion factors for units: fasting plasma glucose in mg/dL to mmol/L, ×0.05551; cholesterol, in mg/dL to mmol/L, ×0.02586; Triglycerides in mg/dL to mmol/L ×0.01129. T2DM, type 2 diabetes mellitus. *p <0.05, for the comparison with the patients not developing T2DM.

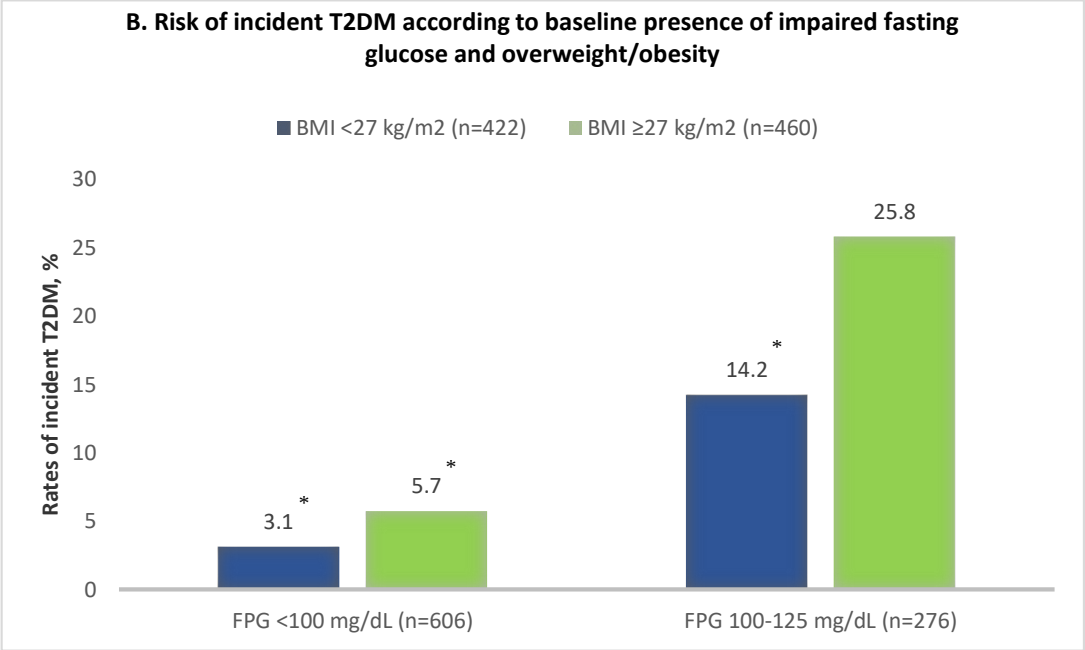
Table 30 *Univariate and multivariate analysis of factors associated with incident diabetes*

Variables	Univariate analysis	Multivariate analysis
Baseline parameters		
Age, per 1 year increase	1.04 (1.02-1.06), p <0.01	1.05 (1.02-1.08), p <0.01
Family history of diabetes	2.40 (1.42-4.06), p=0.01	3.58 (1.86-6.91), p <0.01
Hypertension	2.05 (1.28-3.30), p <0.05	-
Metabolic syndrome	6.59 (3.96-10.97), p <0.01	-
Impaired fasting glucose	8.35 (5.07-13.76). p <0.01	6.56 (3.53-12.18), p <0.01
Body mass index ≥25 kg/m^2	3.23 (1.86-5.62), p <0.01	2.65 (1.39-5.05), p <0.01
Triglycerides ≥200 mg/dL	2.39 (1.49-3.81), p <0.01	-
Low high-density lipoprotein cholesterol levels	2.14 (1.36-3.36), p=0.01	-
Mixed dyslipidemia	3.58 (2.08-6.17), p <0.01	3.27 (1.50-7.15), p <0.01
Assigned treatment		
High-intensity statin	1.94 (1.24-3.02), p <0.01	3.51 (1.89-6.51), p <0.01
Antihypertensive drugs	2.38 (1.54-3.68), p <0.01	-
Fibrates	2.99 (1.41-6.33), p <0.01	-

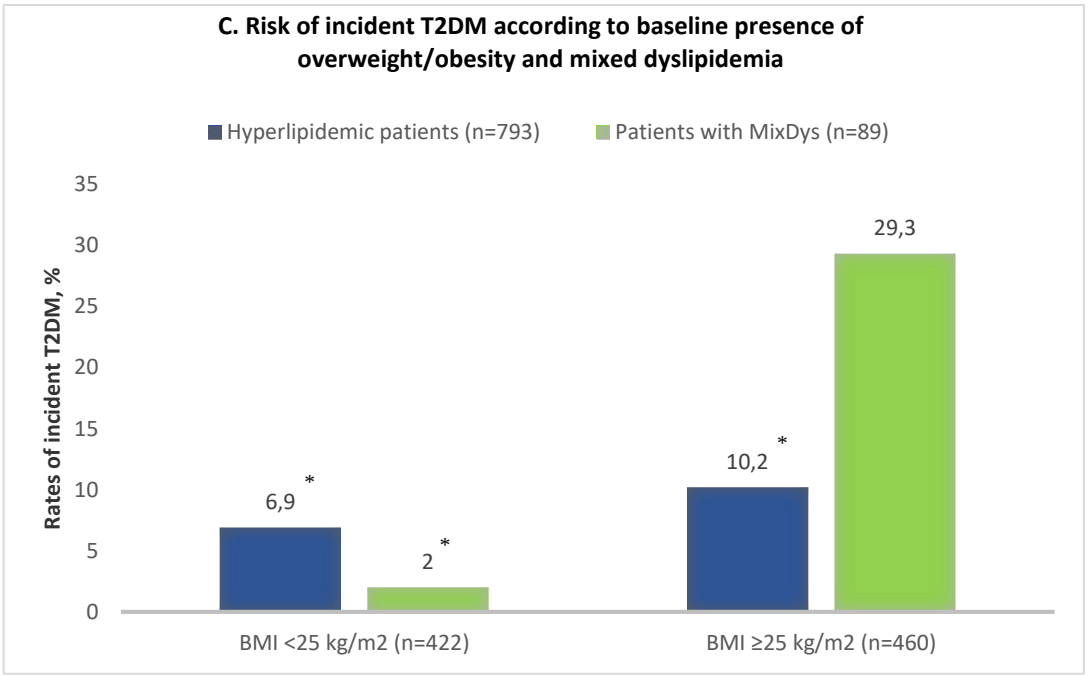
The results are expressed as odds ratios (95% confidence intervals).



* p <0.05, for the comparison with the subjects with impaired fasting glucose and mixed dyslipidemia



* p <0.05, for the comparison with the subjects with impaired fasting glucose and overweight/obesity



* p <0.05, for the comparison with the subjects with overweight/obesity and mixed dyslipidemia

Figure 19 Risk of incident diabetes according to the baseline presence of impaired fasting glucose, mixed dyslipidemia and obesity

BMI, body mass index; FPG, fasting plasma glucose; MixDys, mixed dyslipidemia; T2DM, type 2 diabetes mellitus

4.7.2.3 Metabolically healthy obesity and risk of incident diabetes in statin-treated subjects

After excluding 184 patients with T2DM at baseline visit and 112 not prescribed any lipid-lowering treatment, 1,077 subjects were included in the present analysis. Of those, 60.5% (n=651) were metabolically healthy non-obese (MHNO), 17.6% (n=190) metabolically healthy obese (MHO), 15% (n=162) metabolically unhealthy non-obese (MUNO) and 6.9% (n=74) metabolically unhealthy obese (MUO). A total of 139 study participants (12.9%) developed T2DM during a 6-year follow-up (IQR: 4-10 years). Baseline characteristics are presented in Table 31. MHO patients had higher SBP and DBP but lower LDL-C levels compared with MHNO subjects. MHO had fewer metabolic abnormalities (increased FPG and TG and low HDL-C) compared with the MUNO and MUO patients (Table 31).

Table 31 *Baseline characteristics of study participants classified according to metabolic and weight phenotype*

	Metabolically healthy non-obese (n=651)	Metabolically healthy obese (n=190)	Metabolically unhealthy non-obese (n=162)	Metabolically unhealthy obese (n=74)
Sex (male), %	47*	32	55*	28
Age, years	54 (45-62)*	60 (52-69)	59 (51-65)	58 (50-65)
Family history of diabetes mellitus, %	16	23	20	25
Hypertension, %	45*	70	75	87*
Systolic blood pressure, mmHg	130 (120-146)*	140 (130-155)	140 (130-160)	150 (135-160)
Diastolic blood pressure, mmHg	82 (75-90)*	90 (80-95)	90 (80-96)	92 (85-100)
Fasting plasma glucose, mg/dL	92 (86-99)	93 (87-98)	104 (95-110)*	103 (93-111)*
Body mass index, kg/m^2	25.8 (23.9-27.6)*	32.0 (30.8-34.1)	27.6 (25.8-28.7)*	33.3 (31.6-35.8)*
Total cholesterol, mg/dL	264 (227-295)*	248 (221-278)	253 (217-287)	251 (214-296)
Triglycerides, mg/dL	114 (85-153)	123 (99-158)	189 (158-227)*	195 (150-239)*
High-density lipoprotein cholesterol, mg/dL	54 (47-66)	56 (48-67)	44 (39-50)*	48 (40-52)*
Low-density lipoprotein cholesterol, mg/dL	178 (148-209)*	161 (138-191)	166 (136-191)	164 (121-204)
Intensity of statin therapy [a]				
High-intensity, %	37*	28	35	23
Moderate-intensity, %	55	61	49	67
Low-intensity, %	8*	11	16	10
Fibrates, %	3	3	10*	7
Ezetimibe, %	28	26	12*	18

Values are expressed as median (interquartile range) unless percentages are shown. Conversion factors for units: fasting plasma glucose in mg/dL to mmol/L ×0.05551; cholesterol indices in mg/dL to mmol/L ×0.02586; triglycerides in mg/dL to mmol/L × 0.01129. [a] Prescribed at baseline visit *p <0.05 for the comparison with the metabolically healthy obese patients.

Multivariate analysis showed that age and metabolic phenotype, along with family history of DM and high-intensity statin treatment were independently associated with the risk of incident T2DM (Table 32).

Table 32 *Univariate and multivariate analysis of factors associated with incident diabetes after the inclusion of metabolically healthy obesity*

Variables	Univariate analysis	Multivariate analysis
Baseline parameters		
Age, per 1-year increase	1.04 (1.02-1.05), p <0.01	1.04 (1.02-1.06), p <0.01
Family history of diabetes	2.63 (1.71-4.05), p <0.01	2.77 (1.68-4.55), p <0.01
Hypertension	2.76 (1.82-4.18), p <0.01	-
Metabolic syndrome	6.51 (4.26-9.93), p <0.01	-
Fasting plasma glucose ≥100 mg/dL	10.33 (6.91-15.47) p <0.01	-
Body mass index ≥30 kg/m^2	2.03 (1.32-3.11), p <0.01	-
Triglycerides ≥150 mg/dL	2.79 (1.93-4.02), p <0.01	-
Low high-density lipoprotein cholesterol levels	2.55 (1.72-3.79), p <0.01	-
Metabolically healthy status & obesity		
Metabolically healthy non-obesity	1	1
Metabolically unhealthy non-obesity	3.88 (2.29-6.57), p <0.01	3.17 (1.76-5.68), p <0.01
Metabolically healthy obesity	1.65 (0.90-3.03), p >0.05	1.46 (0.76-2.82), p >0.05
Metabolically unhealthy obesity	8.03 (4.33-14.91), p <0.01	7.87 (4.02-15.42), p <0.01
High-intensity statin	1.46 (1.01-2.10), p <005	2.08 (1.29-3.35), p <0.05
Fibrates	3.02 (1.54-5.93), p <0.01	-

Values are expressed as odds ratios (95% confidence intervals).

Adjusted rates of incident T2DM among groups based on obesity and metabolic phenotype are presented in Figure 20. No significant difference regarding T2DM risk was noticed between MHO and MHNO patients (adjusted OR: 1.46, 95% CI: 0.76-2.82, p >0.05). MUNO phenotype was associated with increased T2DM risk compared with MHNO (adjusted OR: 3.17, 95% CI: 1.76-5.68, p<0.01). Likewise, MUNO was associated with a higher T2DM risk compared with MHO phenotype (adjusted OR: 2.06, 95% CI: 1.01-4.20, p <0.05). MUO phenotype was associated with the highest T2DM risk across all groups (adjusted ORs: 7.87, 95% CI: 4.02-15.42, p <0.01 for the comparison with MHNO; 5.45, 95% CI: 2.47-12.04, p <0.01, for the comparison with MHO; and 2.68, 95% CI: 1.28-5.64, p <0.01 for the comparison with MUNO).

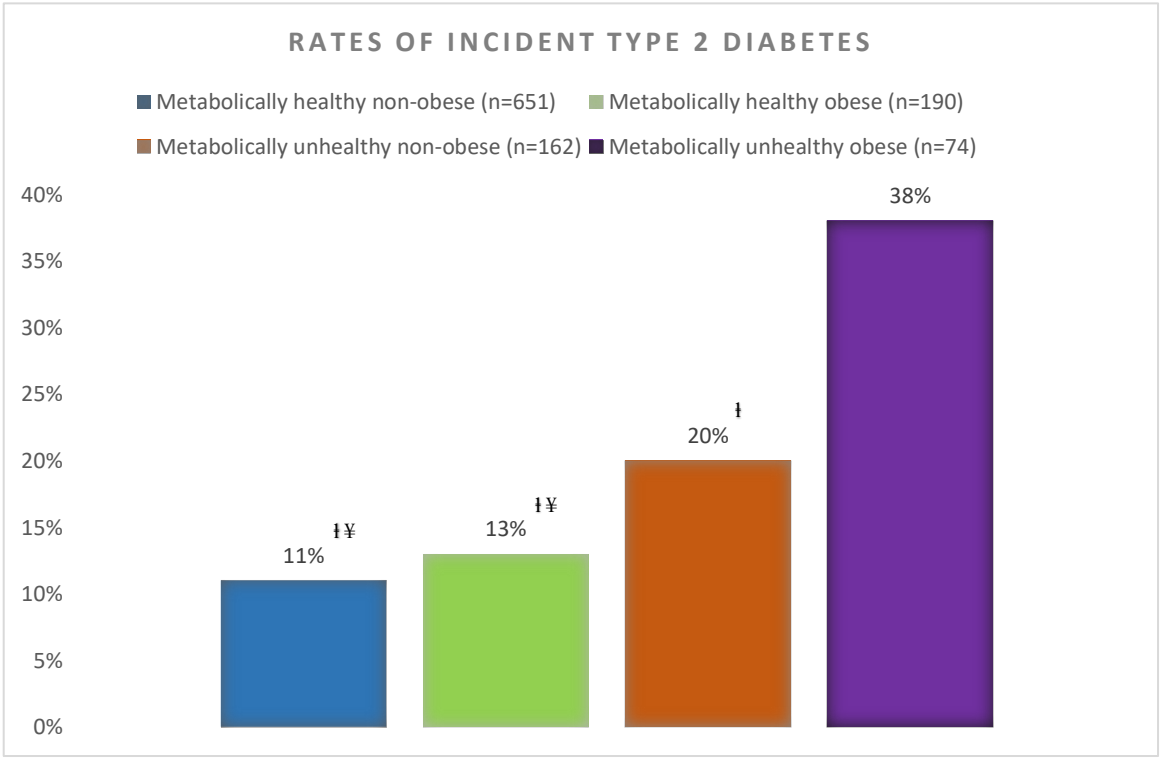


Figure 20 Rates of incident diabetes across subject groups defined by metabolic and weight phenotype during 6-year follow-up

Comparison within groups were adjusted for age, family history of diabetes and high-intensity statin treatment. ¥ p <0.05 for the comparison with metabolically unhealthy non-obese phenotype. ł p <0.05 for the comparison with the metabolically unhealthy obese phenotype.

4.7.3 Interaction between proton pump inhibitors and statins

Of 1,000 consecutive patients being assessed, 648 subjects were eligible for inclusion in the present analysis after excluding those taking lipid-lowering treatment at baseline visit and those with active GI disease. Of those, 607 individuals (93%) were on a statin and 41 (7%) on a statin + chronic proton pump inhibitors (PPIs) during follow-up. Chronic treatment with PPIs was defined as a 2-year supply of PPIs up to the last visit. Mean age was 56 ± 11 years; 45% were males and the study participants were followed-up for a median of 7 years (4-11). Baseline demographic and clinical characteristics are shown in Table 33. Patients taking statin + PPIs were older, had higher CV risk, higher prevalence of hypertension and CVD, HDL-C levels and were more likely to receive clopidogrel compared with those on statin alone (Table 33). No difference was noticed between 2 groups regarding their lipid-lowering therapy and compliance with treatment (Table 33).

Table 33 *Baseline characteristics of 648 subjects treated with statin or a statin plus a proton pump inhibitor*

	Statin alone	Statin + Proton pump inhibitor
N	607	41
Sex (male), %	45	39
Age, years	56 ± 11	61 ± 9*
Follow-up, years	7 (4-10)	8 (5-13)
Smoking, %	17	15
Systolic blood pressure, mmHg	140 (128-155)	148 (130-159)
Diastolic blood pressure, mmHg	89 (80-95)	90 (78-92)
Fasting plasma glucose, mg/dL	95 (88-105)	97 (84-106)
Waist, cm	98 ± 11	99 ± 12
Body mass index, kg/m^2	27.5 ± 3.5	27.6 ± 3.8
Total cholesterol, mg/dL	265 ± 46	259 ± 43
Triglycerides, mg/dL	135 (97-190)	138 (101-169)
High-density lipoprotein cholesterol, mg/dL	54 ± 14	59 ± 17*
Low-density lipoprotein cholesterol, mg/dL	181 ± 41	172 ± 39
Estimated glomerular filtration rate, mL/min/1.73 m^2	79 ± 14	74 ± 12*
Uric acid, mg/dL	5.1 ± 1.5	4.8 ± 1.5
Hypertension, %	73	89*

Metabolic syndrome, %		55	58
Cardiovascular disease, %		19	39*
Diabetes mellitus, %		20	29
Chronic kidney disease, %		12	22
Cardiovascular risk	Moderate	12	0*
	High	42	29*
	Very high	46	71*
Treatment with antiplatelet agents, %	Aspirin	19	27
	Clopidogrel	12	24*
Antihypertensive therapy, %		71	88*
Statins (median dose, mg)	Atorvastatin, %	42 (20)	39 (30)
	Rosuvastatin, %	29 (10)	34 (15)
	Simvastatin, %	24 (40)	27 (40)
	Fluvastatin, %	4 (80)	0
	Pravastatin, %	1 (40)	0
Intensity of statin treatment, %	High	29	37
	Moderate	67	61
	Low	4	2
Ezetimibe, %		19	27
Fibrates, %		3	5
Omega-3 fatty acids, %		4	2
Colesevelam, %		1	0
Compliance with lipid-lowering treatment	Good (≥80%)	94	90
	Poor (<80%)	6	10

Parametric and non-parametric values are expressed as mean ± standard deviation and median (interquartile range), respectively, unless percentages are shown. To convert from mg/dL to mmol/L multiply by 0.02586 for cholesterol indices, by 0.01129 for triglycerides and by 0.06 for fasting plasma glucose. *p <0.05 for the comparison between subjects on statin alone and those on statin + proton pump inhibitor.

Changes in metabolic and safety profile from baseline to most recent visit are shown in Table 34. No significant differences were found between 2 groups regarding changes in all parameters except for the reductions noticed in DBP and TC and LDL-C levels (Table 34).

Table 34 *Changes in metabolic profile, liver and muscle enzymes of 648 study participants taking statin or statin and proton pump inhibitor*

	Baseline visit	Recent visit	P vs baseline	Change, %
Glucose (fasting), mg/dL				
Statin	95 (88-105)	97 (90-109)	<0.001	+2.1%
Statin + PPIs	97 (84-106)	96 (91-109)	0.183	-1.0%
Body mass index, kg/m^2				
Statin	27.5 ± 3.5	28.5 ± 3.8	<0.001	+3.6%
Statin + PPIs	27.6 ± 3.8	28.3 ± 4.9	0.173	+2.5%
Uric acid, mg/dL				
Statin	5.1 ± 1.5	5.3 ± 1.5	0.002	+3.9%
Statin + PPIs	4.8 ± 1.5	5.2 ± 1.5	0.142	+8.3%
Systolic blood pressure, mmHg				
Statin	140 (128-155)	129 (120-136)	<0.001	-7.8%
Statin + PPIs	148 (130-159)	132 (121-138)	<0.001	-10.8%
Diastolic blood pressure, mmHg				
Statin	88 (80-95)	79 (73-84)	<0.001	-10.2%
Statin + PPIs	90 (78-92)	74 (70-80)*	<0.001	-17.7%*
Estimated glomerular filtration rate, mL/min/1.73 m^2				
Statin	79 ± 14	74 ± 16	<0.001	-6.3%
Statin + PPIs	74 ± 12	67 ± 16	0.007	-9.4%
Total cholesterol, mg/dL				
Statin	265 ± 46	174 ± 31	<0.001	-34.3%
Statin + PPIs	259 ± 43	162 ± 27*	<0.001	-37.5%*
Triglycerides, md/dL				
Statin	135 (97-190)	111 (85-148)	<0.001	-17.8%
Statin + PPIs	138 (101-169)	108 (93-134)	0.002	-21.7%
High-density lipoprotein cholesterol, mg/dL				
Statin	54 ± 14	55 ± 14	0.002	+1.9%
Statin + PPIs	59 ± 17	57 ± 15	0.568	-3.4%

Low-density lipoprotein cholesterol, mg/dL				
Statin	181 ± 41	95 ± 25	<0.001	-47.5%
Statin + PPIs	172 ± 39	82 ± 25*	<0.001	-52.3%*
Aspartate aminotransferase, IU/L				
Statin	21 (18-25)	23 (20-27)	<0.001	+9.5%
Statin + PPIs	21 (19-25)	22 (18-30)	0.260	+4.8%
Alanine aminotransferase, IU/L				
Statin	21 (17-28)	23 (18-29)	0.036	+9.5%
Statin + PPIs	20 (16-24)	19 (14-28)	0.993	-5.0%
Gamma-glutamyltranspetidase, IU/L				
Statin	18 (13-27)	19 (14-26)	0.227	+5.5%
Statin + PPIs	17 (11-26)	17 (12-38)	0.927	0%
Alkaline phosphatase, IU/L				
Statin	71 (57-94)	58 (47-73)	<0.001	-18.3%
Statin + PPIs	80 (58-111)	59 (43-75)	<0.001	-26.2%
Creatine phosphokinase, IU/L				
Statin	94 (72-130)	105 (78-155)	<0.001	+11.7%
Statin + PPIs	111 (74-143)	111 (82-179)	0.178	0%

Median follow-up=7 years, n=648: 607 on a statin alone and 41 on a statin + chronic PPIs. Parametric and non-parametric values are expressed as mean ± standard deviation and median (interquartile range), respectively, unless percentages are shown. To convert from mg/dL to mmol/L multiply by 0.02586 for cholesterol indices, by 0.01129 for triglycerides and by 0.06 for fasting plasma glucose. PPIs, proton pump inhibitors. *p <0.05 for the comparison with statin alone vs statin + PPIs, after adjusting for corresponding baseline values.

Correlation coefficient analyses indicated that baseline LDL-C levels (r=0.495, p <0.001), follow-up duration (r=0.133, p=0.001), treatment with aspirin (r=0.126, p=0.001), clopidogrel (r=0.098, p <0.05), ezetimibe (r=0.384, p <0.001), PPIs (r=0.121, p <0.001), along with the intensity of statin therapy (r=0.241, p <0.001), compliance with lipid-lowering treatment (r=0.161, p <0.001), DM (r=0.156, p <0.001) and CV risk (r=0.169, p <0.001) were significantly associated with LDL-C reduction.

Stepwise linear regression analysis taking account all the above parameters indicated that chronic PPI treatment remained an independent predictor for LDL-C reduction (beta=0.104, p <0.01) (Table 35). Specifically, a higher LDL-C reduction by 6.4% was found in individuals on statin + PPIs compared with controls (95% CI: 1.9-10.9%, p <0.01, after adjusting for the effect of baseline LDL-C levels, DM, ezetimibe use, compliance with treatment, intensity of statin treatment and CV risk). In sub-group analysis,

this difference remained significant in individuals receiving rosuvastatin (10.8%, 95% CI: 3.3-18.4%, p <0.01, after adjusting for the same covariates). Despite not being significant, a similar trend towards a higher LDL-C reduction between case and control subjects was noticed among those taking atorvastatin (3.9%, 95% CI: -3.2-11.2%, p >0.05) and simvastatin (2.9%, 95% CI: -6.5-12.4%, p >0.05).

Table 35 *Stepwise multivariate linear regression analysis taking into account the use of proton pump inhibitors and other factors affecting the changes of lipid parameters*

Regressors	Reduction of low-density lipoprotein cholesterol (beta/p)
Baseline low-density lipoprotein cholesterol	0.482 (<0.001)
Ezetimibe	0.198 (<0.001)
Diabetes mellitus	0.168 (<0.001)
Compliance with lipid-lowering therapy	0.205 (<0.001)
Proton pump inhibitors	0.104 (0.005)
Intensity of statin therapy	0.101 (0.009)
Cardiovascular risk	0.082 (0.049)
R^2 X 100	43.2

4.7.4 Statin escape phenomenon

After excluding 225 subjects treated with statins at baseline visit, 108 subjects who discontinued statin treatment at most recent visit, 712 subjects in whom statin therapy changed during follow-up and 14 poor compliers, 181 were considered eligible for the present analysis. Study participant baseline characteristics are shown in Table 36. Of 181 eligible subjects, 56 (31%) exhibited the statin escape phenomenon and 125 (69%) did not.

There were no differences between these 2 groups apart from higher baseline prevalence of CHD noticed in the escape group (7 vs 1%, p <0.05). As shown in Table 36, there was no difference between the 2 groups regarding statin treatment. No participant received any non-statin lipid-lowering therapy (i.e. fibrate, ezetimibe). In addition, no difference was found regarding drugs interfering with cholesterol or statin metabolism (i.e. beta blockers, thiazides, pioglitazone, atypical antipsychotics, levothyroxine, clopidogrel or proton-pump inhibitors; Table 36).

Table 36 *Baseline characteristics of statin escapers and non-escapers*

Variable	Escape group	Non-escape group
N	56	125
Sex (male), %	43	52
Current smoking, %	9	14
Age, years	56 (51-63)	57 (49-65)
Waist, cm	97 (90-101)	98 (90-105)
Systolic blood pressure, mmHg	134 (127-146)	140 (129-150)
Diastolic blood pressure, mmHg	83 (79-95)	87 (80-92)
Follow-up, years	4 (3-6)	4 (4-7)
Metabolic syndrome, %	39	40
Hypertension, %	59	57
Diabetes mellitus, %	11	9
Stroke, %	5	4
Coronary heart disease, %	7	1*
Abdominal aortic aneurysm, %	2	0
Carotid stenosis ≥50%, %	0	2
Peripheral arterial disease, %	0	1
Statin therapy, % (median dose, mg)		
Atorvastatin	38 (20 mg)	34 (20 mg)
Rosuvastatin	29 (10 mg)	24 (10 mg)
Simvastatin	21 (40 mg)	26 (40 mg)
Fluvastatin	7 (80 mg)	6 (80 mg)
Pravastatin	0	1 (40 mg)
Beta blocker, %	9	7
Thiazides, %	11	19
Pioglitazone, %	4	1
Antipsychotics, %	0	1
Levothyroxine, %	4	5
Clopidogrel, %	2	2
Proton-pump inhibitors, %	4	4

Median follow-up duration: 4 years (3-6 years). Values are expressed as median (interquartile range), unless percentages as shown. * $p < 0.05$ for the comparison with the escape group.

Baseline lipid and metabolic profile did not differ between the 2 study groups (Table 37). Six months after the initiation of statin treatment, LDL-C levels were lower in the escape compared with the non-escape group [88 (78-97) vs 109 (91-129) mg/dL, p <0.01; Figure 21]. On the contrary, LDL-C levels at the most recent visit were lower in the non-escape compared with the escape group [103 (96-118) vs 94 (79-114) mg/dL, p <0.01; Figure 21]. Similarly, non-HDL-C levels were lower 6 months after the initiation of statin therapy in the escape compared with the non-escape group among non-diabetic individuals [107 (97-121) vs 132 (115-153) mg/dL, p <0.01; Table 37). On the other hand, higher non-HDL-C levels were noticed in the former group at the most recent visit (Table 37). TGs significantly declined by 11 and 18% in the escape and non-escape group during follow-up, respectively (p <0.01 respectively for the change within each group; Table 37). Despite the fact, that the non-escape group exhibited higher TG levels than the escape group 6 months after the initiation of statin therapy [104 (83-140) vs. 97 (69-117) mg/dL, p <0.05], there was no difference between 2 groups regarding TG levels at the most recent visit and the change of TG levels during follow-up (p >0.05 for the comparison between 2 groups). HDL-C levels did not change during follow-up and were not different between the 2 groups (Table 37).

There was no significant difference between the 2 groups regarding BMI change. As also shown in Table 37, FPG levels did not change during follow-up and were not different between the 2 groups. eGFR declined by 0.5 and 4.1 mL/min/1.73 m^2 in the escape and non-escape group, respectively (p <0.05 respectively for the change within each group), but the difference between the 2 groups was not significant. The same was true for the change in HbA1c levels in diabetics (Table 37, p >0.05 for the comparison between the 2 groups).

Binary logistic regression assessing baseline characteristics along with the changes in BMI, eGFR or HbA1c levels during follow-up did not reveal any significant predictor for the statin escape phenomenon.

During a median follow-up of 4 years, 1 of 56 escape individuals and 6 of 125 non-escape subjects were diagnosed with incident CVD (p >0.05 for the comparison between the 2 groups).

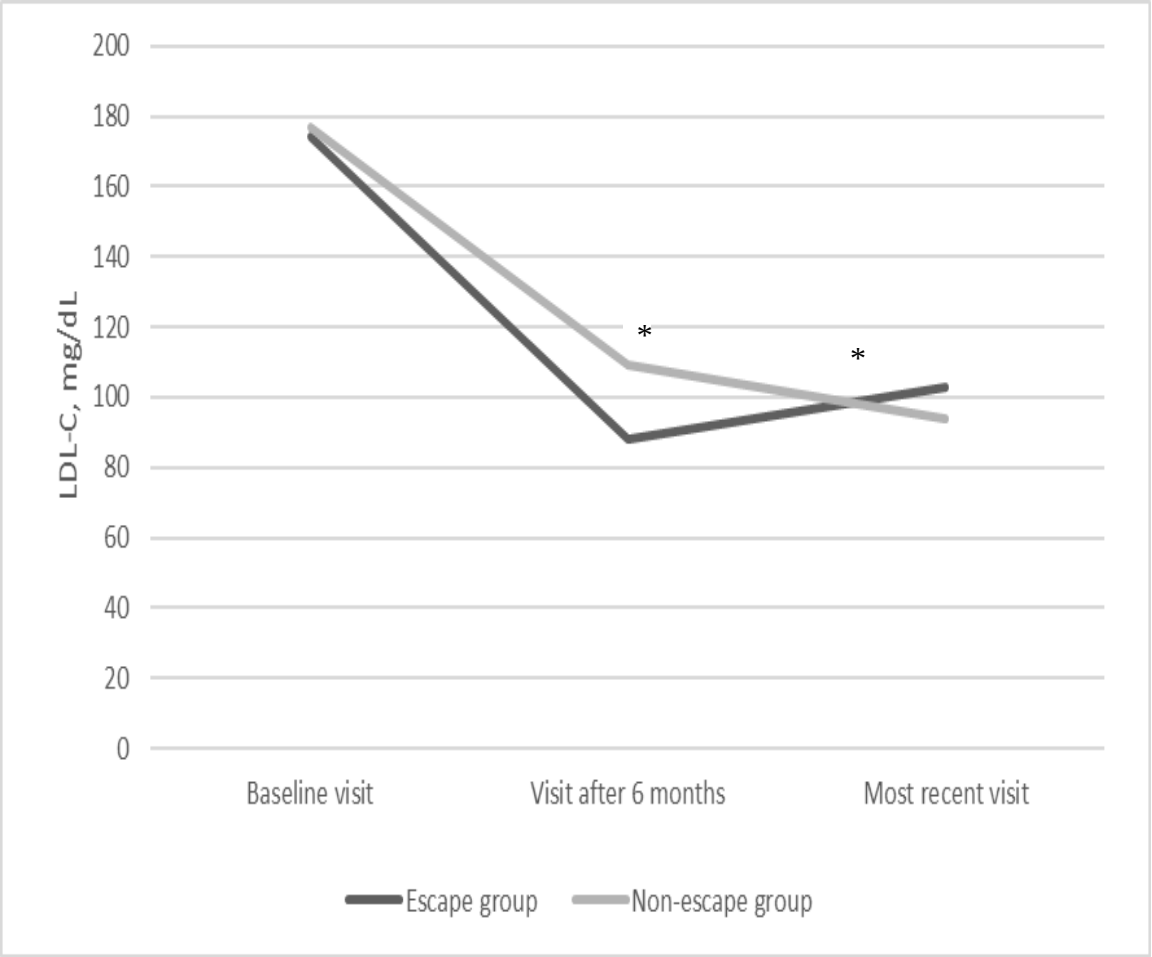


Figure 21 Change in low-density lipoprotein cholesterol levels in statin escapers and non-escapers during their follow-up

LDL-C, low-density lipoprotein cholesterol. *p <0.05 for the comparison between the 2 groups.

Table 37 *Lipid and metabolic profile of statin escapers and non-escapers*

	Baseline visit	Visit at 6 months	Most recent visit
Total cholesterol, mg/dL			
Escape group	258 (233-283)	162 (147-174)	182 (170-201)
Non-escape group	259 (235-295)	184 (162-206) *	172 (154-193) *
Triglycerides, mg/dL			
Escape group	117 (89-175)	97 (69-117)	104 (87-129)
Non-escape group	132 (99-181)	104 (83-140) *	108 (79-130)
High-density lipoprotein cholesterol, mg/dL			
Escape group	53 (47-68)	55 (43-64)	54 (48-68)
Non-escape group	53 (46-65)	52 (44-60)	56 (46-62)
Low-density lipoprotein cholesterol, mg/dL			
Escape group	174 (152-189)	88 (78-97)	103 (96-118)
Non-escape group	177 (152-205)	109 (91-129) *	94 (79-114) *
Non-high-density lipoprotein cholesterol, mg/dL[a]			
Escape group	204 (181-223)	107 (97-121)	127 (116-143)
Non-escape group	209 (182-241)	132 (115-153) *	118 (102-137) *
Body mass index, kg/m^2			
Escape group	27.3 (23.5-29.9)	27.2 (23.5-30.1)	27.6 (24-30.2)
Non-escape group	27.9 (25.5-30.6)	28.3 (25.1-30.9)	28.4 (25.5-31.5)
Fasting plasma glucose, mg/dL			
Escape group	95 (88-105)	95 (87-129)	95 (88-106)
Non-escape group	93 (87-103)	94 (88-104)	96 (89-106)
Glycated hemoglobin, % [b]			
Escape group	8.5 (6.7-8.6)	6.6 (5.6-5.9)	6.7 (6.6-7.1)
Non-escape group	8.4 (7.7-10.9)	6.7 (6.3-7.9)	6.9 (6.3-7.6)
Estimated glomerular filtration rate, mL/min/1.73 m^2			
Escape group	77 (69.6-86.7)	76.6 (67.9-84.8)	76.5 (65.4-81)
Non-escape group	81 (70.7-91.4)	79.7 (69-89.7)	76.9 (65.5-85.7)

Values are expressed as median (interquartile range). To convert from mg/dL to mmol/L multiply by 0.0555 for glucose, 0.02586 for cholesterol, and 0.01129 for triglycerides. [a] Non-high-density lipoprotein cholesterol values refer to non-diabetic individuals (n=164). [b] Glycated hemoglobin values refer to diabetic individuals (n=17). * p <0.05 for the comparison with the escape group

4.8 Risk factors for incident chronic kidney disease in dyslipidemic individuals: the role of uric acid

After excluding 102 patients with baseline CKD, 32 with previous history of gout, 12 subjects treated with xanthine oxidase inhibitors, 19 with losartan and 9 with fenofibrate, a total of 1,095 individuals were eligible for inclusion in the present analysis. Of those, 129 patients (12%) developed CKD during follow-up (6 years; IQR:4-10) and eGFR decreased from 74 (64-83) to 54 (48-57) ml/min/1.73 m^2 ($p < 0.001$). Of note, the median annual decrease in eGFR was 0.69 ml/min/1.73 m^2 (IQR: 0.45-2.33) in the entire study population.

Baseline demographic and clinical characteristics according to uric acid levels are shown in Table 38. Briefly, subjects in the higher uric acid quartiles were more likely to be men, smokers and heavy drinkers. With increasing uric acid groups, we observed lower eGFR, higher FPG, higher BMI, higher TGs, lower HDL-C and higher antihypertensive drug use (Table 38). Differences were also noticed regarding antihypertensive medications across groups (Table 38). Moreover, higher uric acid levels were associated with higher prevalence of ASCVD and MetS (Table 38).

The majority of study participants were treated with statins (91%) and antihypertensive drugs (69%) at the most recent visit. As a result, a significant decline by 29%, 22% and 43% was noticed in TC, TGs and LDL-C levels, respectively ($p < 0.001$), whereas HDL-C levels significantly increased by 2% ($p < 0.001$). Similarly, SBP and DBP significantly decreased by 12 mmHg and 8 mmHg, respectively ($p < 0.001$). No major differences were noticed across study groups regarding concomitant therapies at the most recent visit.

Univariate Cox regression analysis demonstrated that female subjects, patients with DM, decreased baseline renal function (eGFR: 60-90 mL/min/1.73 m^2) and ASCVD exhibited a higher risk of incident CKD during follow-up (Table 39). Similarly, baseline age, TC, LDL-C and uric acid levels were associated with incident CKD (Table 39). Of note, no association was found between concomitant treatment and the risk of incident CKD. The same was evident for the changes in metabolic profile and BP levels, apart from subject LDL-C reduction, which was significantly associated with incident CKD risk (Table 39).

Table 38 *Baseline characteristics of study participants across uric acid quartiles*

	Uric acid quartiles (mg/dL)				p for trend
	<4	4-5	5-6	>6	
N	266	275	287	267	
Sex (male), %	28	38	53	67	<0.001
Age, years	54 (49-62)	57 (50-65)	55 (48-63)	55 (44-63)	0.08
Smoking, %	6	10	21	23	<0.001
Heavy drinkers, %	2	2	7	9	<0.001
Fasting plasma glucose, mg/dL	93 (85-102)	94 (89-104)	96 (89-104)	99 (91-109)	<0.001
Body mass index, kg/m^2	25.9 (23.8-28.9)	27.3 (24.6-30.1)	27.5 (25.8-30.6)	27.8 (26-30.5)	<0.001
Systolic blood pressure, mmHg	137(123-155)	140 (130-150)	140 (125-150)	140 (125-150)	0.59
Diastolic blood pressure, mmHg	85 (76-95)	85 (80-93)	85 (80-95)	87 (80-94)	0.39
Total cholesterol, mg/dL	259 (224-294)	251 (214-294)	252 (220-291)	247 (205-282)	0.04
Triglycerides, mg/dL	111 (85-95)	124 (89-169)	133 (99-193)	148 (107-209)	<0.001
High-density lipoprotein cholesterol, mg/dL	57 (49-69)	54 (46-65)	50 (44-59)	48 (41-56)	<0.001
Low-density lipoprotein cholesterol, mg/dL	173 (140-200)	171 (137-205)	169 (140-202)	162 (130-190)	0.08
Comorbidities					
Estimated glomerular filtration rate 60-90 mL/min/1.73 m^2, %	54	63	69	67	0.01
Hypertension, %	28	30	26	25	0.60
Diabetes mellitus, %	11	10	9	16	0.09
Metabolic syndrome, %	29	42	45	56	<0.001
Baseline atherosclerotic cardiovascular disease, %	10	14	13	20	0.03
Concomitant therapy					
Statins, %	15	17	18	21	0.31
Ezetimibe, %	0	1	0	2	0.35

Antihypertensive treatment, %	30	43	45	50	<0.001
Angiotensin converting enzyme inhibitors, %	9	13	14	18	0.03
Angiotensin receptor blockers, %	11	18	24	20	0.01
Beta blockers, %	6	12	15	18	0.001
Thiazide diuretics, %	9	16	20	27	<0.001
Calcium channel blockers, %	14	14	15	20	0.24
Aldosterone receptor blockers, %	0	0	0	0	0.78
Antidiabetic treatment, %	8	7	5	9	0.48
Metformin, %	5	4	4	8	0.27
Sulphonylureas, %	3	4	2	4	0.60
Pioglitazone, %	1	0	0	1	0.24
Dipeptidyl peptidase 4 inhibitors, %	0	0	0	0	0.60
Insulin therapy, %	2	2	0	1	0.45

Values are expressed as mean ± standard deviation or median (interquartile range), unless percentages are shown. Conversion factors for units: fasting plasma glucose in mg/dL to mmol/L, ×0.05551; cholesterol indices in mg/dL to mmol/L, ×0.02586; triglycerides in mg/dL to mmol/L ×0.01129; uric acid in mg/dL to μmol/L, ×59.48.

Table 39 *Multivariate analysis of factors for incident chronic kidney disease*

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p	HR (95% CI)	p
Baseline variables				
Sex, female	1.87 (1.35-2.57)	<0.001	1.74 (1.14-2.65)	0.01
Age, per 1 year increase	1.10 (1.08-1.12)	<0.001	1.10 (1.07-1.12)	<0.001
Smoking	1.83 (1.01-3.30)	0.05	-	
Alcohol consumption	2.22 (0.95-5.23)	0.07	-	
Uric acid, per 1 mg/dL increase	1.25 (1.10-1.43)	0.001	1.26 (1.09-1.45)	0.001
Total cholesterol, per 1 mg/dL increase	0.996 (0.993-1.000)	0.03	-	
Low-density lipoprotein cholesterol, per 1 mg/dL increase	0.995 (0.991-0.998)	0.01	-	
Baseline characteristics				
Estimated glomerular filtration rate 60-90 mL/min/1.73 m^2	2.13 (1.20-3.79)	0.01	2.38 (1.18-4.81)	0.02
Diabetes mellitus	1.81 (1.17-2.81)	0.01	1.67 (1.05-2.65)	0.03
Atherosclerotic cardiovascular disease	1.87 (1.23-2.84)	0.01	1.62 (1.02-2.58)	0.04
Baseline treatment with beta blockers	1.53 (0.95-2.48)	0.08	-	
Changes in metabolic profile				
Low-density lipoprotein cholesterol reduction by 1 mg/dL	0.996 (0.993-1.000)	0.03	0.995 (0.991-0.998)	0.01

Only those factors that contributed to the outcome in the initial univariate analyses at p values <0.1 are presented. These factors were included in the multivariate model as candidate variables and then removed by backward stepwise selection procedure. Conversion factors for units: cholesterol indices in mg/dL to mmol/L, ×0.02586; uric acid in mg/dL to μmol/L, ×59.48. HR; hazard ratio, 95% CI; 95% confidence intervals.

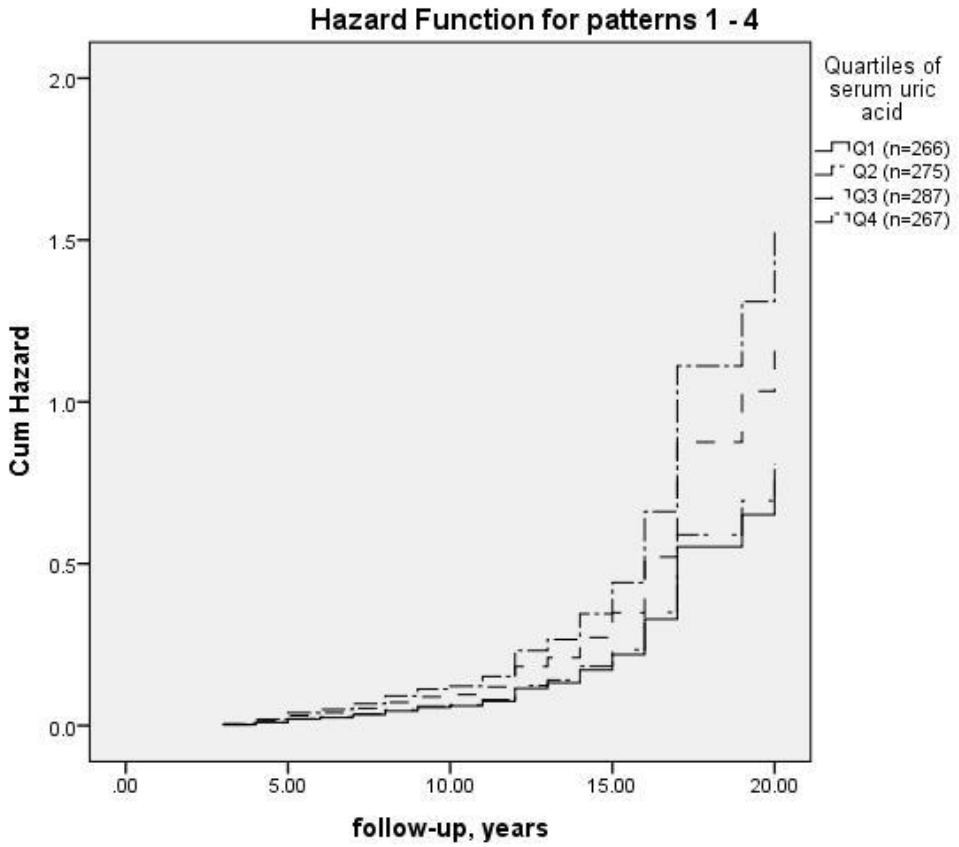


Figure 22 Risk of incident chronic kidney disease across uric acid quartiles

Uric acid quartiles we defined as: Q1: <4, Q2: 4-5, Q3: 5-6 and Q4: >6 mg/dL. Multivariate Cox regression analysis compared the risk of incident chronic kidney disease between the higher uric acid quartiles and the lowest (Q1). The adjusted HRs (95% CI) for each quartile was: Q2: 1.07 (0.60-1.88), p >0.05; Q3: 1.59 (0.88-2.87), p >0.05; Q3: 2.01 (1.11-3.65), p <0.05. Conversion factors for units: Uric acid in mg/dL to μmol/L, ×59.48. HRs; hazard ratios; 95% CI; 95% confidence intervals

According to the multivariate Cox regression analysis, uric acid levels along with female gender, age, baseline ASCVD, DM, decreased baseline renal function and LDL-C reduction remained independent predictors for incident CKD (Table 39). Uric acid levels >6 mg/dL were associated with a 2-fold risk of incident CKD compared with <4 mg/dL (adjusted HR: 2.01, 95% CI: 1.11-3.65, p <0.05; Figure 22).

4.9 Risk factors for incident hyponatremia

A total of 1,334 dyslipidemic individuals were included in the present analysis and were followed-up for a median of 6 years (4-10). Of those, 94% were on lipid-lowering drugs (91% on statins) and 70% on antihypertensive drugs (38% on diuretics). A total of 12% (n=160) of patients developed hyponatremia (sodium <138 mEq/L) during follow-up. After including factors predisposing to hyponatremia and those associated with hyponatremia in univariate analyses (smoking DM, CVD, baseline FPG, sodium, TC, LDL-C and diuretic therapy), multivariate proportional hazard model confirmed that high HDL-C levels increase the risk of hyponatremia (Table 40). This association remained significant in both normotensive individuals (adjusted HR: 1.03, 95% CI: 1.002-1.05, $p < 0.05$) and hypertensive patients (adjusted HR: 1.02, 95% CI: 1.004-1.04, $p < 0.05$).

Table 40 *Multivariate Cox proportional hazards model for hyponatremia*

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	**p**	**HR (95% CI)**	**p**
Baseline characteristics				
Gender (male)	0.80 (0.57-1.11)	NS	-	
Age, per 1 year increase	1.01 (0.99-1.02)	NS	-	
Smoking	1.33 (1.10-1.61)	<0.01	1.50 (1.21-1.87)	<0.01
Metabolic syndrome	1.04 (0.75-1.45)	NS	-	
Diabetes	2.27 (1.47-3.50)	<0.01	-	
Cardiovascular disease	1.80 (1.19-2.70)	<0.01	-	
Fasting plasma glucose, per 1 mg/dL increase	1.008 (1.003-1.012)	<0.01	1.006 (1.001-1.012)	<0.05
Body mass index, per 1 kg/m^2 increase	1.04 (0.82-1.31)	NS	-	
Estimated glomerular filtration rate, per 1 mL/min/1.73m^2 increase	1.001 (1.000-1.003)	NS	-	
Sodium, per 1 mEq/L increase	0.98 (0.97-0.99)	<0.05	0.97 (0.96-0.98)	<0.01
Uric acid, per 1 mg/dL increase	1.11 (0.99-1.22)	NS	-	
Total cholesterol, per 1 mg/dL increase	0.995 (0.992-0.998)	0.01	-	
High-density lipoprotein cholesterol, per 1 mg/dL increase	1.011 (1.000-1.023)	0.05	1.02 (1.01-1.04)	<0.01
Low-density lipoprotein cholesterol, per 1 mg/dL increase	0.993 (0.990-0.997)	<0.01	0.994 (0.991-0.998)	<0.01
Thyroid stimulating hormone, per 1 mIU/L increase	0.99 (0.94-1.06)			
Assigned therapy				
Statins	0.97 (0.59-1.56)	NS		
Antihypertensive drugs	1.04 (0.71-1.52)	NS	-	
Diuretics	1.29 (1.07-1.55)	<0.01	1.27 (1.04-1.56)	<0.05
Selective serotonin reuptake inhibitors	0.89 (0.39-2.02)	NS		

HR: hazard ratio, 95% CI: 95% confidence intervals; NS: statistically no significant (p >0.05)

CHAPTER V. DISCUSSION

5.1 Incidence of cardiovascular disease and risk factors in patients with dyslipidemia

As shown in Tables 5 and 6, baseline ASCVD, obesity, hypertension, dyslipidemia and DM were frequent in our study participants, but were intensively treated during follow-up. Of great importance, the annual rate of incident ASCVD in our cohort was similar to that of another Hellenic cohort representing general population (10.4 vs 15.7/1,000 patient-years, respectively).(207) Therefore, it seems that intense cardiovascular therapy in patients with dyslipidemia reduces ASCVD incidence to that of the general population. Our study also showed that age, previous ASCVD, T2DM and smoking were associated with ASCVD incidence in well-treated dyslipidemic patients.

ASCVD remains the leading mortality cause in the developed countries and a considerable proportion of persons develop ASCVD nowadays, despite available therapies for CV prevention.(2, 3) More than 85 million people in Europe were living with CVD in 2015 and 11.3 million new cases of CVD were diagnosed during that year.(2) Based on National Health and Nutrition Examination Survey (NHANES) 2013-2016, CVD prevalence (CHD, HF and stroke) in adults ≥20 years of age, was estimated up to 9% (24.3 million in 2016) in US.(3) The most prevalent CV conditions are peripheral vascular disease (stroke/PAD) and CHD in Europe.(2) The former accounted for 15.3 million cases (37% of all CVD) among males and for over 21 million cases (48% of all CVD) among females, while CHD was responsible for almost 17 million cases (41% of all CVD) in males and over 13 million cases (30% of all CVD) in females.(2) Over half of all cases of incident CVD in Europe were due to CHD during 2015, which was more evident in men, whereas the incidence of stroke, which accounted for around 14% of all new CVD cases, was slightly higher in females.(2) As far as CV risk factors are concerned, the prevalence of smoking (38%) and hypertension (15-32%) has declined during the last decade in Europe, but obesity and T2DM have become epidemic.(2) Indeed, over half of the European citizens are overweight/obese and the prevalence of T2DM (5.1%) has increased by 28% during the last decade.(2)

Data regarding CVD in Greece come from a few observational studies, whith ATTICA study being the largest with the longest follow-up.(208-214) ATTICA study was a population-based health and nutrition survey which enrolled 1,514 adult men and 1,528 adult women from the greater area of Attici, Greece (May 2001 to December 2002),

while a 10-year follow-up was performed in 2011-2012.(207, 208) Similarly, our cohort was conducted during the same period (1999-2015). Although a lower smoking prevalence was noticed in our study (17 vs 45%), our subjects were older (55 vs 46 yrs old) and at higher CV risk compared with those enrolled on ATTICA study; baseline ASCVD prevalence was higher (16 vs 4%) as was overweight/obesity (75 vs 56%), dyslipidemia (100 vs 43%), hypertension (60 vs 31%) and T2DM (11 vs 7%).(208) As shown in Table 6, our subjects were intensively treated during follow-up; at the most recent visit, 94% of our cohort were on lipid-lowering therapies, 70% were taking antihypertensive drugs and 31% were receiving antiplatelets. Considering the fact that the annual rate of incident ASCVD in our cohort was similar to that noticed in ATTICA study (10.4 versus 15.7/1,000 patient-years),(207) it seems that intense cardiovascular therapy in patients with dyslipidemia reduces ASCVD incidence to that of the general population.

Concerning the role of risk factors in the development of ASCVD, male sex, age, previous ASCVD, DM, CKD, hypertertension and smoking were associated with new ASCVD in our cohort (Table 7). In multivariate analysis, age, previous ASCVD, T2DM and smoking remained significant factors associated with incident ASCVD (Table 7). An heterogeneity of CV risk factors contributing to ASCVD in clinical practice has also been noticed in previously published observational cohorts.(207, 215, 216) ATTICA study showed that determinants of CVD events were increased age, CRP levels and adherence to Mediterranean diet.(207) Based on data from Royal College of General Practitioners Research and Surveillance Centre (n=1,275,174), sex, age, index of multiple deprivation, smoking BMI, DM, hypertension and CKD were predisposing factors for CVD development.(216) The controversial results of cohorts reporting on ASCVD incidence could be due to study design and popolulation characteristics. According to our results, T2DM and smoking were the only modifiable CV risk factors. In this context, public strategies and effective therapeutic plans aiming at smoking cessation are imperative, whereas treatment with SGLT2 inhibitors and GLP1-RAs could help to protect against residual CV risk in diabetic patients.(169)

Certain limitations should be considered before interpretation of our results. First, the retrospective design of our study and its relatively small sample limit the investigation of ASCVD incidence. The lack of report on other CV risk factors (ie. diet, physical

activity, inflammatory markers) could have influenced our results. However, our study was the first to evaluate ASCVD incidence and CV risk factors in dyslipidemic patients at high CV risk who were intensively treated and had a long follow-up.

5.2 Prognostic value of tools estimating the risk of atherosclerotic cardiovascular disease

The present study demonstrated that $CHADS_2$ and CHA_2DS_2-VASc scores exhibit a strong predictive value for ASCVD events in dyslipidemic individuals without AF.(217) However, SCORE (multiplied by 2.5) and PCE exhibited higher prognostic values for incident ASCVD in our population.(217)

A variety of tools estimating CV risk have been developed worldwide during the last decades. SCORE has been used for 10-year CV mortality estimation in Greece and the majority of the European countries.(25, 37) Framingham risk score (FRS) and its modifications had long been used in US adults.(16) The applicability of Framingham-based algorithms to modern populations had been questioned with multiple studies in diverse populations suggesting that FRS might misclassify risk, particularly in women and non-US populations.(19, 218-220) In response, ACC/AHA developed PCE designed to predict 10-year risk of 'hard' ASCVD events (nonfatal MI, fatal CHD, nonfatal or fatal stroke).(22)

There is considerable debate which of these tools is more accurate in predicting CV risk in clinical practice.(221-227) In this context, Qureshi et al used baseline data from the Multi-Ethnic Study of Atherosclerosis and 10-year adjudicated ASCVD events to compare the predictive accuracy of PCE, modified FRS and SCORE.(226) A total of 5,654 subjects were included in final analysis; mean age was 61.4 ± 10.3 and 47.1% were men.(226) After a median follow-up of 8.5 years (IQR: 7.6-8.6 years), 342 subjects (6.0%) developed ASCVD.(226) All of these scores had acceptable discriminative ability for predicting incident ASCVD.(226) The corresponding C-statistics (95% CI) of the ROC curve analysis were 0.737 (0.713-0.762) for PCE, 0.717 (0.691-0.743) for FRS, 0.722 (0.696-0.747) for SCORE (high risk countries), and 0.721 (0.696-0.746) for SCORE (low risk countries).(226) Thus, PCE had the best discrimination capacity for ASCVD risk assessment in a US-based multiethnic cohort compared with SCORE and FRS.(226) On the other hand, an analysis of the Rotterdam study, a prospective population-based cohort study including 4,854 persons aged 55

years or older without previous ASCVD, demonstrated that SCORE model was more suitable in a European population than PCE.(228) The C statistic was 0.67 (95% CI, 0.63-0.71) in men and 0.68 (95% CI, 0.64-0.73) in women for hard ASCVD events (PCE), and 0.76 (95% CI, 0.70-0.82) in men and 0.77 (95% CI, 0.71-0.83) in women for CVD mortality (SCORE).(228)

None of these tools has been tested in very high-risk individuals, such as those with previous ASCVD. In this context, a few studies have evaluated the efficacy of tools for CV risk estimation, such as $CHADS_2$ score.(229-232) The largest of those was a multicenter, observational cohort study which included 7,082 consecutive Japanese CHD patients requiring PCI without clinical evidence of AF.(230) Its primary aim was to evaluate the prognostic value of $CHADS_2$ score for CV events.(230) In that study, $CHADS_2$ score was significantly associated with ASCVD development during 1-year follow-up for (HR: 1.31, 95% CI: 11.7-1.47, p <0.001).(230) In addition, Kaplan-Meier analysis showed a significantly higher incidence of CV events in patients having higher $CHADS_2$ score (log-rank test, p <0.001).(230) Likewise, a meta-analysis of 7 prospective and 1 retrospective cohorts including 31,509 patients with CHD, demonstrated that $CHADS_2$ score ≥2 was associated with increased CV mortality in patients without AF (pooled RR: 3.14, 95% CI: 2.14-4.61).(229)

Our results arguing for an association between $CHADS_2$/CHA_2DS_2-VASc scores and incident ASCVD risk are in line with previous studies.(229-232) Although $CHADS_2$ and CHA_2DS_2-VASc scores were originally developed to predict thromboembolism risk in AF patients, our findings suggest that they do predict ASCVD risk in a high-risk population, irrespective of the presence of AF. This is no surprise since $CHADS_2$ and CHA_2DS_2-VASc capture major ASCVD risk factors. Nevertheless, physicians should keep in mind that prognostic value $CHADS_2$ and CHA_2DS_2-VASc are not superior to SCORE or PCE.(217)

5.3 Prognostic value of $CHADS_2$ and CHA_2DS_2-VASc scores for new atrial fibrillation in dyslipidemic individuals: role of incorporating low high-density lipoprotein cholesterol levels

Our study showed that both $CHADS_2$ and CHA_2DS_2-VASc scores have a strong predictive power for incident AF in dyslipidemic individuals, with modest further improvement when low HDL-C levels are incorporated.(233)

In 2010, the estimated number of patients with AF worldwide was 33.5 million, with higher rates in developed countries.(170) One in 4 middle-aged adults in Europe and the US will develop AF, whereas the prevalence of AF is approximately estimated up to 3% in adults aged ≥20 years.(170) The prevalence of AF is greater in older individuals and in patients with predisposing conditions for AF, such as hypertension, HF, CHD, valvular heart disease, obesity, DM and CKD.(170) As shown in Table 9, age, hypertension and CKD were independent predictors for AF, whereas DM and CVD were associated with a non-significant trend towards a higher risk of new-onset AF in our study.(233) Although ACE inhibitors have been reported to protect against AF, (234) this was not the case in our study. This could be attributed to their relation with other potential confounding by indication factors, such as hypertension and coronary artery disease. Indeed, the use of ACE inhibitors as well as of antiplatelets was not an independent factor for incident AF in our multivariate analysis.(233)

Although AF and CVD share common risk factors, controversial data exist regarding the association between the various cholesterol subclasses and AF risk.(235-239) LDL-C, which is undoubtedly a causal risk factor for CVD, has been reported to have a paradoxical association with AF.(235-238) The inverse association between LDL-C levels and AF has been attributed to the stabilizing effect of cholesterol on myocardial cell membranes, which may impact ion channel density and function and other aspects of membrane excitability.(240-242) Another prospective study with 23,738 healthy subjects demonstrated that the inverse association between LDL-C and AF is extended to other atherogenic lipoproteins suggesting that these associations were unlikely to be mediated by direct cholesterol effects.(236) Although in our study LDL-C was inversely associated with incident AF, this association became insignificant after adjustment for confounding factors.(233) Similarly, the analysis of 2 large community-based cohorts (Multi-Ethnic Study of Atherosclerosis and Framingham Heart Study) with a total of 7,142 participants showed that high LDL-C levels were related with a lower risk of AF in minimally adjusted models but not after multivariable adjustment.(239) There are several reasons that could account for inconsistent results between studies, such as lack of adjustment for confounding risk factors, differences in population characteristics (i.e. co-existing CV risk factors, concomitant treatment), AF ascertainment methods and length of follow-up.

Furthermore, we showed that baseline HDL-C is an independent predictor for AF, which is in agreement with most studies.(233, 235, 237, 239, 243, 244) The observed

inverse association between HDL-C and AF risk may be explained by different mechanisms. Firstly, low HDL-C might indirectly increase the risk of AF through the well-known association with CHD and HF (245, 246), which are established risk factors for AF.(170) In addition, the anti-inflammatory and antioxidant properties of HDL particles (247, 248) could inhibit several pathophysiological pathways in AF.(249, 250) Of note, we have shown that HDL-C levels were not associated with QTc interval or indexes of repolarization dispersion in patients with primary hypercholesterolemia.(251) In this context, HDL-C may merely be a marker of good CV and general health without any cause-and-effect association with AF.(252, 253)

The most relevant finding in of study was that $CHADS_2$ and CHA_2DS_2-VASc scores are strongly predictive for new-onset AF.(233) Recent evidence supports that both scores are associated with risk of incident or recurrent AF. Two prospective studies with either patients who underwent cardiac surgery or patients with paroxysmal AF who received catheter ablation reported that $CHADS_2$ and CHA_2DS_2-VASc scores were significant predictors for postoperative or recurrent AF.(254, 255) Similar results were also demonstrated in other prospective cohorts including general population or hypertensive patients.(206, 256-258) These findings are not surprising since $CHADS_2$ and CHA_2DS_2-VASc scores include causal risk factors for AF.(170) Considering that newly diagnosed AF is an independent factor for future major CV events and that traditional CV risk factors are included in $CHADS_2$ and CHA_2DS_2-VASc scores,(170) there is bound to be a correlation between these entities. Indeed, higher $CHADS_2$ and CHA_2DS_2-VASc scores, along with a non-significant trend towards a higher baseline prevalence of CVD were noticed in patients who developed AF in our study.(233) Nevertheless, our results are in line with those of previous cohorts showing that these scores remained independent predictors for incident AF after adjustment for CV comorbidities. On the basis of these results, it is possible to suggest that AF may be considered a time-integrated marker of exposure to multiple CV risk factors and as a sensitive indicator of high atherothrombotic risk.(233)

In light of this evidence, our study may have implications for AF screening, especially amongst high-risk groups.(233) Physicians should rigorously screen for AF in patients with high $CHADS_2$/CHA_2DS_2-VASc scores and/or low HDL-C, especially when reporting symptoms of cardiac arrhythmias or diagnosed with thromboembolic CV events. In these cases, AF should be ruled out with a 24-h or longer ambulatory monitor of heart rhythm.

Limitations of this analysis were its retrospective nature along with the small number of events.(233) This could be attributed to the relatively young age of our population, since AF is much more prevalent in older individuals.(233) Considering that many AF episodes, especially in the elderly, are asymptomatic (clinically silent), the incidence of AF in our population might have been underestimated.(233) Moreover, no data on subclinical structural heart disease were available and echocardiographic data related to AF development were.(233) In addition, we did not report on biomarkers associated with AF, such as natriuretic peptides and inflammation markers.(235, 239) Also, the prescription of statin therapy to the majority of study participants during follow-up (259, 260) might have altered the associations between cholesterol indices and the risk of new-onset AF.(233) We investigated the effect of baseline lipid parameters but not their variations overtime on the risk of incident AF.(233) Furthermore, no data were available regarding some parameters, such as alcohol consumption and exercise status that seem to be related to HDL-C levels as well as to AF.(233) These limitations could have decreased the sensitivity and specificity of our analyses.(233) Thus, future prospective studies are needed to confirm the predictive value of $CHADS_2$ and CHA_2DS_2-VASc scores and/or low HDL-C for incident AF and whether a screening strategy based on these scores may improve prognosis.

On the other hand, our study was among the largest with a long follow-up which confirmed the limited literature on the association of $CHADS_2$/CHA_2DS_2-VASc scores with AF risk.(233) Unlike previous cohorts referring to patients with hypertension, cardiac interventions or general population, our study confirmed the association of these scores with AF risk in dyslipidemic individuals and shows a modest improvement in prediction after incorporating low HDL-C levels.(233)

5.4 Association between high-density lipoprotein cholesterol levels and ventricular repolarization indexes

Our study demonstrated that serum HDL-C levels do not correlate with the duration of ventricular repolarization as estimated by the QTc interval or with the dispersion of ventricular repolarization as reflected by novel indexes such as Tpe interval and Tpe/QT ratio in subjects with primary hypercholesterolemia.(251)

Increased QT interval, which reflects prolonged ventricular repolarization, has been clearly associated with increased risk for mortality, including sudden cardiac death, in the general population.(261, 262) In fact, longer QT intervals tend to be more spatially and temporally heterogeneous because of reduction in repolarization reserve.(263) However, heterogeneity of repolarization with unstable intramural reentry is the underlying mechanism in many forms of polymorphic VT, regardless of the QT interval.(263)

Tpe represents a novel index of arrhythmic risk beyond the conventional QTc interval. Regardless of the controversy whether it is a marker of transmural or global dispersion of repolarization,(191, 264, 265) it has been clearly associated with increased risk for malignant ventricular arrhythmias in a variety of conditions.(191, 193, 266-272) Also, increased Tpe has been independently associated with increased risk for sudden cardiac death in the general population,(273) while it is a strong predictor of mortality during the first year after an acute myocardial infarction.(274) Spatial dispersion of repolarization reflects the heterogeneity of repolarization which creates voltage gradients and thus promoting ventricular arrhythmias.(191, 193, 272) The Tpe/QT ratio appears to be a more sensitive arrhythmogenic index since it remains constant despite changes in the heart rate (dynamic changes in Tpe and QT interval occur in a proportional and parallel fashion).(191, 193, 272) Tpe/QT ratio is increased in various pathological conditions.(191, 193) Remarkably, an increased Tpe/QT ratio has been associated with arrhythmic events in patients with acquired long QT syndrome and in patients with hypertrophic cardiomyopathy.(269, 272) Moreover, it has been shown that beta blockers reduce the QT and the Tpe intervals during exercise and recovery in patients with long QT syndrome.(275) In the setting of stable coronary artery disease, Tpe/QT ratio significantly increases at peak exercise.(192) In addition, it has been demonstrated that Tpe interval and Tpe/QT ratio are increased in individuals with early repolarization.(193) In the same line, Karim Talib et al demonstrated that in patients who suffered from ventricular fibrillation in the setting of J wave syndromes, the Tpe interval and Tpe/QT ratio are significantly increased compared to matched individuals with benign early repolarization.(276) A common genetic variant that affects the duration of the Tpe interval in the general population has also been identified.(277)

Taking into account the aforementioned considerations we focused on the measurement of the novel indexes Tpe and Tpe/QT to investigate the association between HDL-C and the dispersion of ventricular repolarization in patients with primary hypercholesterolemia.(251) We did not measure the older index 'QTc dispersion' since accumulated evidence suggests that it does not actually reflects the dispersion of ventricular repolarization.(278)

Data on the association of lipid parameters with the ventricular repolarization are sparse. In a small case-control study a significant positive correlation was demonstrated between TC, TGs, LDL-C and the longest QT interval (QTmax) and QT dispersion (QTd).(279) Furthermore, a positive correlation between HDL-C levels and QTmax was evident.(279) It has also been indicated that simvastatin treatment in diabetic patients with hyperlipidemia is associated with reduced heterogeneity of repolarization as assessed by QTc.(280) However, in this study no significant change in HDL-C levels was observed over 1-year treatment with simvastatin.(280) Therefore, other antiarrhythmic mechanisms may be operative in this setting. In an experimental protocol using rabbits, Liu et al. showed that hypercholesterolemia resulted in nerve sprouting, sympathetic hyperinnervation, and electrical remodeling associated with longer QTc intervals, increased repolarization dispersion and increased vulnerability to ventricular fibrillation.(281)

Den Ruijter et al. studied the effects of reconstituted HDL administration in isolated rabbit cardiomyocytes as well as in human subjects.(282) Remarkably, reconstituted HDL significantly shortened the action potential duration in isolated cardiomyocytes, while its infusion in healthy humans shortened the QTc interval (estimated by the Bazett's formula) independently of baseline apoA-I levels.(282) Of note, apoA-I exhibited similar effect as reconstituted HDL in the in vitro experiment.(282) Despite these promising results we failed to show any association of HDL-C levels with the duration of repolarization as well as with markers of dispersion of repolarization in a real-life population of hypercholesterolemic patients (Table 11, Figures 8 and 9).(251) It should be noted that reconstituted HDL may have different effects compared to native HDL. Moreover, levels of HDL-C do not differentiate HDL subpopulations which may exhibit different antiarrhythmic properties. It should also be noted that besides hypertension, the prevalence of other comorbidities in our population that may affect repolarization, such as DM and coronary artery disease was low (Table 10).(251) Also,

it is recognized that a complex interaction between triggers and substrate that often have a dynamic behavior leads to the development of malignant ventricular arrhythmias.(76, 283) Thus, the possibility of an antiarrhythmic effect of HDL under specific triggers and substrates cannot be excluded. For example, acute myocardial ischemia promotes local heterogeneity of repolarization and therefore the effect of HDL on ventricular repolarization may be prominent during an acute ischemic event.(284) However, this antiarrhythmic effect remains a speculation.

Although our analysis adds to the current knowledge on the association of lipid parameters on ventricular repolarization and arrhythmic risk in general, some potential limitations were apparent.(251) Firstly, this was a relatively small cross-sectional study.(251) Secondly, no echocardiographic data were available.(251) Thirdly, we did not measure if an alteration in the HDL-C levels in an individual basis alters ventricular repolarization.(251) Also, we did not have data with regard to changes of electrocardiographic parameters in relation to HDL-C changes over time in the whole population, especially after treatment with hypolipidemic drugs.(251)

5.5 Target attainment of cardiovascular therapy

5.5.1 Lipid target attainment among patients at very high and high cardiovascular risk according to National Cholesterol Education Program Adult Treatment Panel III and European Society of Cardiology/European Atherosclerosis Society 2011 guidelines

As shown in Table 14, our study showed that up to 4 out of 5 patients attending a University Hospital Lipid Clinic failed to achieve the ESC/EAS 2011 lipid targets.(259) This failure was particularly relevant in very high CV risk patients where LDL-C targets are more aggressive.(259)

Our findings are consistent with previous studies in lipid clinics. However, data are limited. In a retrospective analysis of Asian patients (n=267) with acute coronary syndrome in a tertiary hospital, the rate of LDL-C target attainment <70 mg/dL (1.8 mmol/L) was 36.7%.(285) In a lipid clinic in Italy, only 10% of untreated and 20% of treated high CV risk patients achieved LDL-C levels <100 mg/dL (2.6 mmol/L).(286) Suboptimal management of hypercholesterolemia in patients with and without CVD and DM has been demonstrated by many studies.(287-292) In a US cohort only 62.5% of treated adult patients with hyperlipidemia attained the recommended LDL-C goals

according to NCEP ATP III guidelines.(293) Very high CV risk patients with either CVD or a FRS >20% were less likely to achieve LDL-C goal compared with those having a FRS 10-20% (the respective rates for LDL-C target attainment were 34.7, 49.5 and 77.6%).(293) Almost half of CHD patients had LDL-C <100 mg/dL (2.6 mmol/L) and a lower percentage (16.7%) had LDL-C <70 mg/dL (1.8 mmol/L).(293) Also, low proportions of LDL-C goal attainment <70 mg/dL (1.8 mmol/L) were noted in patients with stroke, DM and CKD (21.9, 38.6 and 27.7%, respectively).(293) A Chinese study included 1,355 patients with acute coronary syndrome on atorvastatin 20 or 40 mg/day.(294) Only 41% of these patients had LDL-C <70 mg/dL (1.8 mmol/L) after 2 years.(294) Among 9,995 individuals, 30% and 67% of very high and high CV risk patients, respectively, achieved the NCEP ATP III LDL-C targets.(295) A similar analysis was performed in the Incremental Decrease in End Points through Aggressive Lipid Lowering (IDEAL) study.(296) Of patients receiving simvastatin 20 or 40 mg/day, 12% had LDL-C <100 mg/dL (2.6 mmol/L) after 1 year.(296) Only 31% of statin-treated patients with CHD (n=382) achieved the LDL-C goal <70 mg/dL (1.8 mmol/L) in another registry.(297) In DYSIS, LDL-C was not at goal in 41% of patients with CVD (n=11,104).(298) Across disease groups, 59% of patients with PAD and 38% of those with CHD were not at goal.(298) Likewise, almost half of hospitalized patients with CHD (n=136,905) had admission LDL-C levels <100 mg/dL (2.6 mmol/L) and only 17.6% <70 mg/dL (1.8 mmol/L).(299) One out of 3 high CV risk patients (n=13,942) on simvastatin 40 mg/day had LDL-C <100 mg/dL (2.6 mmol/L) at entry in outpatient centers throughout Germany.(300) In EUROASPIRE IV, only 16% of very high CV risk patients in Greece had LDL-C <70 mg/dL (1.8 mmol/L).(301) EUROASPIRE V also demonstrated poor target attainment; 42% of CHD patients had BP $\geq$ 140/90 mmHg and 71% had not optimal LDL-C levels.(178) In our study, patients with CKD had the lowest rate of LDL-C goal attainment compared with other disease state groups.(259) A comparable rate (61%) of LDL-C goal achievement <100 mg/dL (2.6 mmol/L) was reported in 3,157 patients with stage 3-4 CKD.(302) Our findings were consistent with those of other studies in Greece. CEPHEUS-Greece showed that almost half of patients did not reach recommended LDL-C targets.(303) Only 14.7% of very high CV risk patients had LDL-C <70 mg/dL (1.8 mmol/L).(303) Also, almost half of patients with CHD or its equivalents had LDL-C <100 mg/dL (2.6 mmol/L).(303) This proportion was 26.6% in those with FRS 10-20%.(303) The proportion of those with FRS <10% having

LDL-C <130 mg/dL (3.4 mmol/L) was much higher (70.7%).(303) Similarly, the DYSIS-Greece showed that 61% of very high CV risk patients did not achieve the recommended LDL-C target <100 mg/dL (2.6 mmol/L).(304)

Lipid-lowering treatment

In our study, the vast majority of patients were on statins.(259) In EUROASPIRE III, almost half of asymptomatic high and 78% of very high CV risk patients were on statins.(305, 306) The corresponding rates were higher in EUROASPIRE IV: 86% of patients were on statins, while the respective rate in Greece was higher (96%).(301) In EUROASPIRE V, 80% of CHD participants were treated with statins.(178) Low rates of lipid-lowering treatment have been demonstrated by another study (n=1,129).(293) One out of 3 very high and 65.3% of high CV risk patients were on treatment.(293) Four out of 5 patients with CVD were on statin monotherapy and 10.8% in statin combinations with other lipid-lowering drugs.(293) The respective proportions in patients with FRS 10-20% were 80.6 and 11.3%.(293) A large outpatient registry demonstrated that 83% of patients with known ASCVD was on lipid-lowering treatment, of those 77% were on statins.(307)

The maximum recommended dose of a statin was rarely used in our study.(259) Our findings are consistent with a cohort of 59,094 new statin users.(308) In that study statins were sub-optimally dose-titrated and used over too short periods to offer a maximal benefit on prevention of acute myocardial infarction.(308) Of note, only 1/3 of patients received combination therapy in our population.(259) This might have contributed to low success rates in LDL-C target achievement. Indeed, in our study those on combination treatment were more likely to achieve ESC/EAS 2011 targets compared with those on statin monotherapy (Table 16).(259, 260) Additionally, according to ESC/EAS 2011 guidelines high CV risk patients with TGs >200 mg/dL (1.7 mmol/L) may be treated with fibrates.(37) Indeed, in our cohort subjects with high baseline TG levels were more likely to be on a fibrate at last visit.(259)

Strategies for confronting poor lipid target achievement

Low rates of lipid target achievement are associated with increased CV risk.(309) Among patients with CHD and hypercholesterolemia, those sub-optimally statin-treated had a 2-fold increased risk of non-fatal MI and coronary death compared with those on optimal statin treatment.(309)

In this context, additional treatment strategies are needed to increase rates of lipid target attainment. First, compliance to treatment should be considered. In our cohort 'poor' compliers had lower rates of LDL-C and non-HDL-C target attainment compared with 'good' compliers.(259) This is relevant since poor compliance to lipid-lowering treatment has been associated with increased CV morbidity and mortality.(310) Some strategies can increase compliance to treatment. For example, fixed-dose combinations of lipid-lowering medications can improve compliance leading to a long overdue reduction in CV events.(183) Smoking, excess alcohol drinking and increased BMI are strongly connected with high CV risk.(203, 311) Despite not being significantly associated with lipid target attainment in our study, a trend towards a better LDL-C goal achievement by non-smokers and 'never' or 'occasional' drinkers was demonstrated, while the normal weight patients had better rates of non-HDL-C goal achievement.(259) A larger study might have shown significant differences. Nevertheless, a multifactorial approach to attain multiple treatment targets could maximize vascular benefits.(312)

The complexity of cases referred to a lipid clinic can also help explain low rates of lipid target attainment. Patients with genetic dyslipidemias or intolerant to statins are less likely to achieve lipid targets. In our cohort 12% of patients were clinically diagnosed with FH and 3% were statin intolerant.(259) Among FH patients only 42% achieved the recommended LDL-C goal, while none of statin intolerant patients achieved this target.(259) Of note, all these results were obtained in the pre-PCSK9 inhibitor era. Use of PCSK9 inhibitors markedly increased LDL-C target achievement in FH and statin intolerant patients.(313-315)

Physician reluctance to follow guidelines and underestimation of individual risk . might also play a role. It has been shown that physicians estimate correctly individualized CV risk in only 50% of cases.(316) Also, lacking of consensus on whether or not DM and CKD are CHD equivalents could have contributed to poor physician compliance with guidelines.(317-319) Furthermore, various reports showed that treatment intensity increases at a late stage, once complications have occurred.(320) Moreover, the fear of side effects due to prescription of high-dose statin treatment might contribute.(321, 322) In contrast, using high-dose statin treatment, combination therapies or switching from less to more potent statins result in better outcomes.(323, 324)

5.5.2 Lipid target attainment according to European Society of Cardiology/European Atherosclerosis Society 2011 and American College of Cardiology/American Heart Association 2013 guidelines

High-intensity statin therapy as suggested by the ACC/AHA 2013 guidelines failed to achieve the proposed LDL-C reduction ≥50% in at least half of the high risk patients.(260) In contrast, high-dose statin + ezetimibe combination was significantly more effective in this regard (Figure 10).(260)

The use of ezetimibe, not high-intensity statin, improves LDL-C goal achievement proposed by the ESC/EAS 2011 guidelines

As shown in Table 16, even in the setting of a specialized lipid clinic, only 1 in 4 patients at very high CV risk and almost half of those at high and moderate CV risk achieved therapeutic goals according to the ESC/EAS 2011 guidelines.(259) Our observations concerning the additional use of a non-statin drug, i.e ezetimibe, are in agreement with published studies.(325, 326) In addition, our data showed that combination treatment with statin + ezetimibe increases the rates of LDL-C goal achievement, while this was not the case with high-intensity statin treatment (Figure 10, Tables 16 and 17).(260) In this context, novel treatment modalities, such as antibodies against PCSK9 should be considered.(327)

The ACC/AHA 2013 guidelines may lead to undertreatment of high-risk individuals

The ACC/AHA 2013 guidelines introduced a different approach for the management of dyslipidaemias and CVD prevention suggesting the use of appropriate-intensity statin treatment instead of specific LDL-C targets.(22) Although our study included patients treated according to ESC/EAS 2011 guidelines prior to the publication of ACC/AHA 2013, useful conclusions regarding their feasibility and efficacy in the ‘real world’ could be drawn.(260) ACC/AHA 2013 emphasized using the most intensive statin treatment in certain high-risk groups.(22) Our data demonstrated that these recommendations were not very far away from the application of ESC/EAS 2011 guidelines in clinical practice, since very high CV risk patients according to ESC/EAS were more likely to receive high-intensity statins (Table 16).(260) The abolition of LDL-C targets in favour of the use of the most appropriate-intensity statin therapy proposed by the ACC/AHA 2013 ignored the fact that patient response to statin treatment varies in the ‘real world’.(22,

328, 329) Our observations concerning less than expected response to high-intensity statin treatment were in agreement with the recent results of the VOYAGER meta-analysis (Individual Patient Meta-Analysis of Statin Therapy in At Risk Groups: Effects of Rosuvastatin, Atorvastatin and Simvastatin).(260, 329) Indeed, our study showed that patient response to high-intensity statin treatment could be much lower (Figure 10).(260) Our cohort reflected the 'real word' after an extensive follow-up, instead of an 'ideal' setting provided by a short-term clinical studies.(260) Poor response to statin treatment may be explained, at least in part, by several factors. The most important is poor compliance to treatment, which is a common problem in everyday clinical practice even in high-risk patients.(330, 331) Another issue is that an inter-individual difference in LDL-C response to statin treatment may be genetically determined.(332) Therefore, high-risk individuals might be undertreated under the ACC/AHA guidelines since a significant number of those taking high-intensity statin therapy exhibit inadequate LDL-C lowering in clinical practice.(260)

The use of ezetimibe boosts achievement of LDL-C reduction ≥50% in high-risk individuals according to the ACC/AHA 2013 guidelines

The ACC/AHA 2013 guidelines were essentially *"statin"* guidelines.(22) However, they did suggest that combination treatment with non-statin lipid-lowering drugs should be considered if the expected 50% LDL-C reduction cannot be achieved with 'high-intensity' statin treatment alone.(22) Our observations concerning the role of ezetimibe in further LDL-C lowering are in agreement with other studies.(325) Our analyses showed that high risk patients treated with a 'high-intensity' statin + ezetimibe were more likely to achieve the optimal target of LDL-C reduction ≥50% compared with those on 'high-intensity' statin monotherapy (Figure 10).(260) Therefore, combination treatment should be considered in these individuals.

The ACC/AHA risk calculation may underestimate cardiovascular risk

A major concern regarding the ACC/AHA 2013 guidelines was that a reduction in the threshold for treatment in primary prevention would lead to a greater number of individuals being treated with a statin.(333) Our study included subjects who were referred for the management of documented hyperlipidemia and did not address statin treatment eligibility.(260) Nevertheless, a significant proportion of subjects at very high

risk may be missed or undertreated by applying the ASCVD risk algorithm proposed by the ACC/AHA.(334, 335) Specifically, individuals with CKD, carotid stenosis, abdominal aortic aneurysm or with DM aged <40 or >75 years would be mistreated; those having ASCVD risk ≥7.5% would be probably undertreated, since they would not be candidate for high-intensity statin therapy or those having ASCVD risk <7.5% (SCORE <2.5%) would not be eligible for taking a statin. Indeed, a number of subjects having ASCVD risk <7.5% in our study had high TG levels or were diagnosed with NAFLD, metabolic syndrome or an autoimmune disease.(260)

Our findings should be interpreted in light of certain limitations. Namely, our study was retrospective and involved patients treated according to the ESC/EAS 2011 guidelines.(260) Therefore, the intensity of statin treatment was decided on the basis of reaching the specific LDL-C target and not aimed at achieving the ACC/AHA 2013 target.(260) Nevertheless, our study applied AHA/ACC 2013 guidelines in a European cohort, providing useful information on their clinical relevance and feasibility in the 'real world', instead of an 'ideal' setting of clinical trials.(260)

5.5.3 Cholesterol target attainment in patients with familial hypercholesterolemia

Our study confirmed previously published data demonstrating that untreated FH individuals develop premature CHD, whereas no difference were noticed regarding the prevalence of non-coronary CVD (Figure 11).(159) A high proportion of these patients do not achieve LDL-C targets in clinical practice (Figure 12).(159)

The prevalence of HeFH has been estimated to 1/500, while recent data have shown that it might be much higher (~1/200-300).(161, 336, 337) In Greece, it is estimated that 1 in 250 people have FH.(338) Our data showing a higher prevalence of FH (12%) are explained by the present study conducted in the setting of a lipid clinic.(159) FH is most often caused by mutations in the LDLR gene, resulting in the absence or dysfunction of LDLR on the surface of hepatocytes.(160, 161, 339, 340) Defects in the genes encoding apoB and PCSK9 account for ~5% and <1% of FH cases, respectively.(160, 161, 339, 340) However, 5-30% of cases of phenotypic FH could not be attributed to already known mutations.(160, 161, 339, 340) Because DNA testing was not routinely performed in FH individuals, no data on FH mutations are available in our study.(159) Study participants fulfilling the DLCN criteria of FH had higher levels of atherogenic indices, such as LDL-C, apoB and Lp(a) compared with the non-FH subjects (Table

18).(159) Nevertheless, FH subjects exhibited a better profile regarding markers of MetS and glucose homeostasis.(159) These results along with the lower prevalence of DM noticed in FH subjects are in agreement with previous studies and could be attributed to the possible role of LDLR in the development of T2DM.(341, 342)

If left untreated, FH is undoubtedly related with a high risk of premature CHD, while controversial data exist regarding non-coronary CVD.(131, 161, 162) Indeed, our results demonstrated an approximately 3-fold higher prevalence of CHD in FH individuals compared with non-FH subjects, whereas no difference was noticed regarding the prevalence of stroke, PAD and carotid stenosis (Figure 11).(159) Despite their increased CV risk, only 1 of 10 FH individuals was on statin therapy at the time of referral.(159) These rates were in agreement with other studies underlying the undertreatment of such individuals in the general population.(337, 343) Indeed, the Hellenic Familial Hypercholesterolemia (HELLAS-FH) Registry has recently evaluated the characteristics and management of patients with FH in Greece.(181) Among 1,093 FH patients, 63.1% were receiving hypolipidemic drug treatment, mainly statins, at inclusion in the registry, whereas the majority of treated patients (87.9%) did not achieve LDL-C targets.(181)

As shown in Table 19, a high proportion of FH individuals, but not all, was on statin treatment at the most recent visit.(159) In addition, these patients were more likely to take a high-intensity statin or a combination treatment of a statin plus ezetimibe compared with the non-FH individuals.(159) These results are in agreement with previous reports of WHO and Make Early Diagnosis to Prevent Early Death (MED PED) underlining a significant progress on the treatment of FH patients during the last 20 years, due to the establishment of specialized lipid clinics and the use of new lipid-lowering drugs.(30, 31) As a result, a satisfactory increase in the percentage of these patients receiving lipid-lowering therapy has been observed.(30, 31) Nevertheless, a high proportion of those remain undertreated.(30, 31) Indeed, a low proportion of both groups in our study achieved optimal LDL-C levels and only 15% of FH individuals with established CVD had optimal LDL-C levels <70 mg/dL (Figure 12).(159) Thus, it seems that the therapeutic gap in treating hypercholesterolemia is even greater in FH individuals with CHD.(344, 345) These results are in agreement with other studies conducted in lipid clinics showing that FH individuals are undertreated and remain at high CV risk and mortality.(158, 181, 344-348) Indeed, in our study 40% of the

individuals with LDL-C ≥190 mg/dL receiving high intensity statin monotherapy and 20% of those taking a high intensity statin plus ezetimibe do not achieve the anticipated LDL-C reduction ≥50%,(159) as proposed by ESC/EAS 2011 guidelines (Figure 10).(36, 159)

There are certain study limitations in this analysis.(159) This was a retrospective observational study with an extensive follow-up of 6 years in a real-world outpatient lipid clinic.(159) Thus, our findings regarding the incidence of CVD should be interpreted in light of this limitation.(159) Due to the adjustment for potential confounding factors, the trend towards a higher risk of incident CVD in the FH individuals compared with the non-FH subjects is insignificant.(159) Under these circumstances, our results confirmed that CV risk of statin-treated FH individuals becomes equal to that of the general population.(159) Otherwise, after taking into consideration the low-rates of LDL-C target attainment noticed in our FH study participants and small sample size, along with the retrospective nature of our study and other potential confounding factors not included in the present analysis, this no-significant trend should be underlined.(159) Nevertheless, our study representing a ‘‘pragmatic study’’ provided real data of the everyday clinical practice and replicates previous findings regarding the undertreatment of patients with FH in Hellenic population.(159)

5.5.4 Cholesterol target attainment in patients at ‘extreme’ CV risk according to American Association of Clinical Endocrinologists/American College of Endocrinology 2017 guidelines

This analysis demonstrated that patients at ‘extreme’ CV risk, as proposed by AACE/ACE, are far from optimally treated.(349)

A previous study has evaluated whether achieving LDL-C less than 55 mg/dL in patients at ‘extreme risk’ is feasible in clinical practice.(350) According to that study, more than half of all patients with stable coronary artery disease were at ‘extreme CV risk’ as proposed by AACE/ACE,(127) whereas only 5% of those achieved LDL-C levels <55 mg/dL.(350) In contrast to Rallidis et al., we enrolled patients not only with CHD, but also with stroke, PAD and carotid stenosis.(349) Nevertheless, our results similarly showed that half of patients with CVD belonged to ‘extreme CV’ risk category.(349) The results of Rallidis’ study along with ours are in agreement with

previously published studies.(351) Patient comorbidities, such as FH and statin intolerance, along with poor adherence to treatment could account for the low rates of LDL-C goal achievement.(259, 260, 351) Nevertheless, physician reluctance to prescribe high doses of statins or combinations of lipid-lowering therapies are quite often in clinical practice.(259, 260, 351) Although intense lipid-lowering therapy was prescribed only to half of patients at 'extreme CV risk', it increased the rates of LDL-C target attainmen.(349) Indeed, the combination treatment of a high-intensity statin with ezetimibe boosts LDL-C reduction and target attainment.(260) However, this was not the case for the most stringent LDL-C goal proposed by AACE/ACE.(349) Despite that more patients at 'extreme risk' achieved LDL-C <55 mg/dL in our study compared with Rallidis (15% vs 5%), the majority of those remained sub-optimally treated, even those taking intense lipid-lowering therapy (Figure 13).(349) In this context, novel therapies such as PCSK9 inhibitors could benefit such patients. However, all of our study participants at 'extreme risk' had LDL-C <100 mg/dL and were not eligible for therapy with PCSK9 inhibitors according to current national policy in Greece.(156)

5.5.5 Eligibility for treatment with proprotein convertase subtilisin/kexin type 9 inhibitors

Our study showed that a considerable proportion of hyperlipidemic patients at high CV risk, and especially those with previous ASCVD or FH, could not achieve optimal LDL-C levels despite intense lipid-lowering therapy and therefore would be candidates for treatment with PCSK9 inhibitors.(313-315)

As previously reported, LDL-C goal achievement remains far from optimal in everyday clinical practice, mostly in patients with ASCVD,(179, 259, 260, 301, 303, 352-354) but also in other high risk patients, such as those with DM and FH.(355-357) In this context, several trial and meta-analyses have proved the effectiveness of PCSK9 inhibitors in LDL-C reduction.(358-360) Considering the recent results of the FOURIER and ODYSSEY trial showing that the use of evolocumab or alirocumab on a background of statin therapy reduced the risk of CV events by ~15%,(144, 145) current guidelines propose the use of PCSK9 inhibitors in certain patient groups.(27, 28, 156, 196) Several analyses have argued that PCSK9 inhibitor use even in patients with FH or CVD does not meet generally acceptable incremental cost-effectiveness thresholds and therefore significant discounts are necessary to meet conventional cost-effectiveness

standards.(361-363) All things considered, there is a need for identifying the right candidates for PCSK9 inhibitor therapy in clinical practice. An observational study using the Information System for the Development of Research in Primary Care in Catalonia in Spain estimated the number of patients eligible for treatment with PCSK9 inhibitors according to local guidelines.(364) Among those taking optimized lipid-lowering therapy, 12.5% of the FH patients without CVD would be eligible for treatment with PCSK9 inhibitors according to ESC/EAS 2017 recommendations,(365) whereas the corresponding rates for those with CVD would be 25%.(364) Among those with CVD, FH increased the rate of patients being candidates for PCSK9 inhibitors (23.4% for FH patients vs 3.7% for non-FH).(364) Another analysis of 2 prospective Hellenic trials which included 1,303 consecutive patients with stable CHD <75 years old evaluated the eligibility for treatment with PCSK9 inhibitors, after calculating the expected LDL-C levels if maximum lipid-lowering therapy had been implemented (20/40 mg rosuvastatin or 40/80 mg atorvastatin + ezetimibe 10 mg daily).(366) According to these studies, 4.5% of CHD patients and 34.1% of those with CHD plus FH would have LDL-C >100 mg/dL and should be consequently treated with a PCSK9 inhibitor according to the Hellenic consensus.(366) According to ESC/EAS recommendations, the corresponding rates would be 1% and 7%, respectively.(366) On the other hand, a prospective Swiss cohort of 2,023 patients hospitalized for acute coronary syndrome assessed suitability for PCSK9 inhibitors as proposed by ACC/AHA 2018 and ESC/EAS 2017.(367) After simulating a fixed relative reduction of 24% in LDL-C levels at 1 year in all patients not treated with ezetimibethe proportion of patients who would be eligible for PCSK9 inhibitors was 13.4% using ACC/AHA 2018 criteria and 2.7% using those of ESC/EAS 2017.(367) Patients with possible or probable/definite FH (n=25.6%) were more frequently eligible for PCSK9 inhibitors compared with non-FH: 27.6% vs 8.8% according to ACC/AHA 2018 and 6.6% vs 1.8% according to ESC/EAS 2017.(367) Therefore, recommendations made by the ACC/AHA 2018 guidelines would lead to 5-fold higher eligibility rates for PCSK9 inhibitors compared to ESC/EAS 2017 consensus in acute coronary syndrome patients.(367)

According to local guidelines, 22% of patients taking maximally tolerated statin therapy plus ezetimibe and diagnosed with ASCVD, FH, DM or being statin intolerant would be eligible for treatment with PCSK9 inhibitors in our study.(313-315) The application of

ACC/AHA 2018 would lead to higher eligibility rates (36%) very-high risk ASCVD patients or those with LDL-C ≥190 mg/dL.(313, 314) Furthermore, we showed that recently announced stricter LDL-C targets by ESC/EAS 2019 will result in even less goal achievement and therefore in higher rate of eligibility for PCSK9 inhibitor treatment (Figure 15).

5.5.6 Attainment of multifactorial treatment targets in the elderly patients

Our study showed that a high proportion of the elderly attending a lipid clinic failed to achieve targets of lipid-lowering, antihypertensive and antidiabetic treatment (Table 24).(368) One out of 4 patients had optimal LDL-C levels according to ESC/EAS 2011 guidelines, 76% of those diagnosed with hypertension achieved the proposed BP targets by the ESH/ESC 2013, while only half of those with DM had HbA1c <7%.(368) Of note, almost 1 out of 3 non-diabetic and 1 out of 10 diabetic individuals achieved all treatment targets.(368)

It has been demonstrated that the combination treatment of statin plus ezetimibe provides a more effective therapeutic option for LDL-C lowering in the elderly compared with statin monotherapy.(369) In our study, individuals receiving statin + ezetimibe achieved higher rates of LDL-C goal achievement compared with those receiving statin monotherapy (48 vs 33%, p <0.05).(368) Therefore, the additional use of ezetimibe should be considered in the elderly to achieve LDL-C.(325) In this context, novel treatment modalities, such as antibodies against PCSK9, would be a suitable therapeutic option for further LDL-C lowering.(327)

A large proportion of hypertensive individuals fail to achieve BP targets in clinical practice,(370) which is more prominent in the elderly.(371) In a community-based cohort study based on all Framingham Heart Study Examinations attended in the 1990s, BP control rates (BP <140/90 mmHg) for male patients aged 60-79 and >70 years old were 36% and 38%, respectively.(371) The corresponding rates for the females were 28% and 23%, respectively.(371) A similar low rate of BP target attainment (36%) was noticed in hypertensive patients in the Second Australian National Blood Pressure (ANBP2) on antihypertensive treatment and followed for a median of 4.1 years.(372) Higher rates were observed in the Anti-hypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) trial and the Controlled Onset Verapamil Investigation of CV Endpoints (CONVINCE) trial, where the corresponding rates were

66% and 67%, respectively.(373, 374) In our cohort, a higher proportion of hypertensive individuals (76%) had optimal BP levels according to ESH/ESC 2013 guidelines.(368) This could be attributed to patients attending a specialist clinic.(368) BP targets in the elderly have been an area of discussion.(375) Some studies argued that the BP target <140/90 mmHg in older individuals might not be more beneficiary compared with a less strict one (<150/90 mmHg), while the former increases the adverse event risk.(376-378) In addition, it was noticed that the elderly hypertensive patients were more likely to reduce SBP between 150 and 140 mmHg, rather than <140 mmHg.(376-378) In agreement, a higher proportion of non-diabetic patients had BP levels <150/90 mmHg rather than <140/90 mmHg in our study.(368) Therefore, the less intense SBP lowering is more 'achievable' in older patients.(368)

It has been estimated that almost 1 out of 3 diabetic patients achieve good glycemic control in the US and Europe.(379, 380) In our cohort, a higher but still low proportion of the elderly diabetic subjects (47%) achieved the HbA1c target <7%.(368) Professional organizations emphasize on the individualization of HbA1c targets.(381) The limited available evidence suggests that a near-normal glycemic target should be achieved in younger DM patients with a recent onset of DM to prevent complications.(381) On the other hand, more relaxed targets may be considered in the elderly, since intensive glycemic may not result in more benefit on macrovascular outcomes compared with standard therapy.(381) In our cohort, a higher proportion of elderly diabetic subjects (88%) achieved an HbA1c target <8%.(368) In this context, a less strict glycemic target could be more easily achieved in clinical practice.

Our results showing suboptimal treatment and CV risk factor control in the elderly are similar to those of previous studies.(382, 383) In those cohorts, 74-89% of the diabetic patients aged ≥65 years had SBP <140 mmHg, 8-52% had LDL-C <100 mg/dL and 76-83% had HbA1c <8%.(382, 383) The corresponding rates of BP and LDL-C target attainment in those without DM were 75 and 55%, respectively.(382) Thus, despite the available modern treatment options, no impressive change in the rate of target achievement in the elderly have occurred over the years.

There are several reasons that might account for this poor goal achievement in clinical practice. Firstly, patient adherence to treatment plays a major role.(259, 372, 381) Advancing age is related with an increased number of concomitant diseases.(183) Therefore, the complexity of prescribed scheme, such as the increased number of

prescribed medications might decrease patient compliance.(183) In this setting, patient education and fixed-dose combinations may improve adherence.(183) Secondly, fear of adverse effects and physician reluctance to prescribe the most potent treatments may play a role.(259, 372, 381) Indeed, most potent therapies were infrequently prescribed in our study.(368) As shown in Table 22, maximal doses of the most potents statins were not frequently given, while only 20% of subjects were receiving combination treatment of statin + ezetimibe.(368) In addition, only half of diabetic subjects were receiving a combination therapy of oral antidiabetic drugs and 13% were on insulin treatment.(368) Indeed, combination therapy with statin + ezetimibe led to higher rates of LDL-C target attainment.(368) Of note, rates of adverse events were low in our study.(368) In addition, considering the expected annual decline of about 1 mL/min/1.73 m^2 (259) (or 8 mL/min/1.73 m^2 over the 8-year study period), eGFR declined by 5 mL/min/1.73 m^2 in our cohort.(368) These results come in agreement with other studies demonstrating that multifactorial treatment, including statin therapy, may have a favourable impact on liver and kidney function.(384, 385)

5.6 Correlation of apolipoprotein B with low- and non-high-density lipoprotein cholesterol

Our findings demonstrated that apoB correlation with LDL-C or non-HDL-C decreased if TG levels were greater than 200 mg/dL, and this decrease was more evident in individuals with DM or MetS (Figure 16).(197)

LDL-C represents the mass of cholesterol within LDL.(37, 386) Non-HDL-C represents the sum of cholesterol in TRLs, such as VLDL, chylomicrons and their remnants, in LDL and in Lp(a), while each of these atherogenic particles contain one molecule of apoB.(387) Normally, LDL particles account for more than 90% of total apoB particles, whereas VLDL particles make up a little less than 10%.(387) In this context, the correlations between apoB and LDL-C or non-HDL-C is expected to be strong. Indeed, several studies have indicated that apoB is highly correlated with LDL-C ($0.61 < r < 0.86$, $p < 0.05$) and non-HDL-C ($0.79 < r < 0.94$, $p < 0.05$). (388-392) Nevertheless, a lot of debate has focused on whether apoB or non-HDL-C should be used instead of LDL-C as alternative targets for CV risk prevention.(393) Both, apoB and non-HDL-C are considered as better CV risk markers in both untreated and treated individuals compared with LDL-C.(45, 394, 395) A few studies have shown a stronger correlation between

apoB and LDL-C in individuals with normal TG compared with higher TG levels, while the correlation between apoB and non-HDL-C was less affected.(388, 396-398) In this context, EAS/EAS 2019 guidelines propose apoB or non-HDL-C as alternative targets to LDL-C for the management of dyslipidemias in individuals with DM, MetS, high TG and low LDL-C levels.(27) In our analysis high TG levels were associated with decreased correlation between apoB and LDL-C, especially in with the presence of DM or MetS.(197) This could be attributed to IR causing higher free fatty acid burden on hepatocytes and downregulating lipoprotein lipase, thus resulting in high preponderance of TRLs, such as VLDL and remnants.(399) LDL-C could be 'normal' in such individuals, but consist of more small-dense atherogenic particles.(386, 387, 400) On the other hand, non-HDL-C, which depicts cholesterol in all apoB particles, should be expected to highly correlate with apoB irrespective of TG levels.(388, 396-398) However, our study along with others showed that correlation between apoB and non-HDL-C was also significantly affected by TG levels, mainly in subjects with DM or MetS.(197, 400) Indeed, non-HDL-C could be highly discordant with regard to apoB in such individuals due to the large number of TRLs and small dense LDL particles.(386, 387) Thus, apoB seems a more attractive risk marker for the prevention of CVD, since its measurement provides a precise estimate of all atherogenic particles. In addition, it has been established that atherosclerosis progression does not depend on the amount of cholesterol, but on the number and size of apoB particles entering in the vessel wall.(391, 399)

The retrospective analysis could be regarded as a limitation of our study.(197) Nevertheless, analysis of correlations between apoB and non-HDL-C or LDL-C was not influenced by this particular design.(197) Another limitation was the integration of diabetics with MetS individuals in one group.(197) However, diabetics and MetS subjects have similar lipid abnormalities, known as atherogenic dyslipidemia. (197, 401) Nevertheless, this analysis represented a real-life study from a lipid clinic with 821 participants and was the first to assess the correlations of apoB with LDL-C and non-HDL-C on the basis of MetS or DM presence in combination with TG stratification.(197) The implication of our findings is that apoB could represent an attractive marker for the management of dyslipidemic individuals with DM or MetS and high TG levels.(197) Future studies should be focused on the role of apoB as a marker of CV risk as well as a therapeutic target in such individuals.

5.7 Adverse effects and interactions of statins

5.7.1 Effect of statins on muscle, liver and kidney function

Our study showed that rates of adverse effects caused by statin therapy are actually low in clinical practice, whereas a neutral effect, if not favorable, on renal function was also noticed (Table 27).(259, 368)

Although statins are generally very well tolerated, they do have some specific adverse effects on muscle, liver, whereas there is a debate whether they affect renal function.(27) However, rates of adverse effects are low in clinical practice and the overall benefit of statins far outweigh this risk.(402, 403) Previous observational studies have reported a frequency of SAMS varying between 10-15%.(404-406) Although our study was conducted in a specialized lipid clinic to which more statin intolerant patients usually refer, the corresponding rates were lower (2%).(368, 407) Our results are in line with blinded RCTs of statins vs placebo which have demonstrated that there is no, or only a slightly, increased frequency of muscle symptoms in statin allocated groups.(408, 409) The Anglo-Scandinavian Cardiac Outcomes Trial Lipid-Lowering Arm (ASCOT-LLA) study addressed this issue by comparing the incidence of 4 different adverse events, including muscle-related symptoms, during both the blinded, placebo-controlled period and its open-label extension study.(405) During the blinded phase, muscle-related adverse events were reported at a similar rate by participants randomly assigned to atorvastatin or placebo [298 (2.03% per annum) vs 283 (2.00% per annum); HR: 1.03, 95% CI: 0.88-1.21, $p < 0.05$].(405) On the other hand, during the open label extension muscle-related adverse events were reported at a significantly higher rate by participants taking statins than by those who were not [161 (1.26% per annum) vs 124 (1.00% per annum); HR: 1.41, 95% CI: 1.10 - 1.79, $p < 0.01$].(405) Therefore, a nocebo effect (i.e. one caused by negative expectations) may partly explain the higher frequency of SAMS in previous observational studies and in clinical practice.(405)

Our rates of LFTs increase (3%) are similar to those previously reported.(27, 406) However, mild elevation of LFTs has not been shown to be associated with true hepatotoxicity or changes in liver function.(27) Progression to liver failure is exceedingly rare and thus, routine monitoring of LFTs during statin treatment is no longer recommended.(27) Patients with mild LFTs elevation due to steatosis have been studied during statin treatment with no indication that statins cause any worsening of the underlying liver disease.(410) On the contrary, statin therapy might be beneficially in

such patients. A post-hoc analysis of the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study showed that statin treatment not only was safe and improved liver tests, but also reduced CV morbidity in patients with mild-to-moderately abnormal liver tests.(385)

There is a debate regarding the effect of statins on renal function.(411) An increased frequency of proteinuria has been reported for all statins and especially rosuvastatin.(412, 413) This proteinuria is considered to be of tubular origin, usually transitory, and has been attributed to reduced tubular reabsorption and not to glomerular dysfunction.(412, 413) The annual decline of renal function in our subjects was within the ranges of the expected annual eGFR decline of 0.5-1.0 mL/min/1.73 m^2 in healthy individuals (6 mL/kg/1.73 m^2 during a 6-year follow-up).(259, 368, 414) Therefore, our results are in line with previous reports suggesting that statins might have a long-term benefit on renal function.(411, 415)

5.7.2 Statin-associated risk of incident diabetes

5.7.2.1 Statin therapy with or without ezetimibe and the progression to diabetes

Our study demonstrated that high-intensity statin treatment is associated with a higher risk of incident DM, mostly in the prediabetic individuals, whereas the addition of ezetimibe seems to have a neutral effect on glucose metabolism over an average follow-up of 7 years (Figures 17 and 18).(416)

Statins are the cornerstone for primary and secondary CVD prevention.(22, 37) However, evidence of large clinical trials and meta-analyses demonstrated that statins might be related with DM onset.(34, 417) Two meta-analyses including up to 13 randomised trials have shown that statin treatment increased the risk for incident DM by 9-13% compared with placebo after a mean follow up of 4 years.(137, 417) There was no difference in new DM between different statins.(137, 417) In our study, a higher risk of new-onset DM was observed in subjects taking high-intensity statin treatment compared with those on lower-intensity or no statin, while no apparent differences between different statins were noticed (Figure 17).(416) These results are in agreement with existing reports on high-intensity statin treatment and incident DM.(135, 418, 419) Those at greater risk for DM onset were the prediabetic individuals.(416) This is in line with previous studies demonstrating that baseline FPG levels and MetS presence are strong predictors for new-onset DM in statin-treated individuals.(136, 420) Nevertheless,

the well-established benefits of statin therapy in CV risk reduction far outweigh the moderate risk of new DM, especially in individuals at higher CV risk.(421-424) In this context, guidelines recommend a closer follow-up by measuring levels of HbA1c and FPG in individuals being at higher DM risk, while lifestyle management should be emphasized.(422, 423)

Ezetimibe on the other hand is a non-statin lipid lowering drug which has been reported to reduce CV risk by 6.4% in patients with acute coronary syndrome when added to statin therapy.(140) As previously reported, the use of ezetimibe in addition to statins improves LDL-C target attainment proposed by ESC/EAS guidelines.(27, 259, 260) Moreover, achievement of LDL-C reduction by ≥50%, as proposed for high risk individuals by current guidelines, is more frequently accomplished with the combination of statin plus ezetimibe rather than high-intensity statin monotherapy.(27, 260) There are limited data on the effect of ezetimibe on glucose metabolism.(425, 426) Experimental animal studies showed that ezetimibe might have a positive impact on glycemic control, whereas human studies have demonstrated controversial results regarding the effect of ezetimibe on various markers of glucose metabolism (i.e. IR, non-alcohol fatty liver disease, HbA1c).(426-429) As shown in Figure 18, the rate of incident DM in our subjects on statin plus ezetimibe were similar to those on statin monotherapy.(416) Interestingly, a non-significant trend towards lower risk of incident DM was noticed in individuals receiving a moderate-intensity statin plus ezetimibe compared with those on high intensity statin monotherapy.(416) One unanswered question is whether would be preferable to use combination therapy of moderate-intensity statin plus ezetimibe rather than high intensity statin monotherapy, since a higher LDL-C reduction could be accomplished without increasing the risk of incident DM.

One limitation of this analysis was the study design.(416) This was a retrospective observational study with an extensive follow-up of 7 years based in a real-world outpatient lipid clinic.(416) Our study population was large enough to detect the observed effect with 90% power at an alpha of 0.05.(416) Overall, our study represented a ‘pragmatic study’ and provided real data of everyday clinical practice and not a selected sample of patients with a close monitoring like those from a randomized control trial.(416) We did not perform any analyses on the impact of statin and ezetimibe treatment on IR and HbA1c levels.(416) In addition, we had no data on

pravastatin or lovastatin, two statins that are rarely prescribed in Greece.(416) Although this was a retrospective study, there was no major heterogeneity regarding sample size of each statin group and follow-up duration.(416) On the other hand, our study was the first to report that prediabetic individuals might be at a higher risk for incident DM after taking high-intensity statin treatment, whereas ezetimibe does not improve nor deteriorates glucose homeostasis.(416) Further data on the role of ezetimibe on glucose metabolism were reported in the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) study.(140) In concert to our study, the addition of ezetimibe to simvastatin vs simvastatin alone did not increase the risk of new-onset DM (HR: 1.04, 95% CI: 0.94-1.15, p >0.05).(430) However, in contrast to our study, the available information from IMPROVE-IT is limited only to simvastatin 40 mg, a moderate-intensity statin. Therefore, future studies should investigate the effect of ezetimibe on high-intensity statin treatment, which is the current practice for high risk individuals. Physicians should be aware that high-intensity statins in preDM individuals increase the risk for new-onset DM whereas ezetimibe has a neutral effect.

5.7.2.2 Atherogenic dyslipidemia and risk of incident diabetes in statin-treated subjects

As shown in Figure 19, our study showed that the normoglycemic non-overweight individuals without MixDys exhibited the lowest risk of new-onset T2DM among statin-treated individuals.(431) T2DM event rates increased in patients with normal FPG and either MixDys or overweight/obesity and became highest for those with IFG and overweight/obesity or MixDys.(431)

Waters et al. were the first to demonstrate that preDM, obesity, hypertension and high levels of TG increased the risk of incident T2DM in statin-treated patients.(136) After taking into account that this constellation of abnormalities are tightly related with IR, they proposed that insulin-resistant candidates for statin treatment are prone to T2DM development.(432) Although the measurement of insulin levels has been used for the estimation of IR,(433) the absence of a standardized insulin assay limits its clinical utility.(434) PreDM indicates IR and undoubtedly increases T2DM risk in statin-treated patients.(138, 416, 435) Nevertheless, preDM encompasses different entities not always related with IR.(436) For instance, patients with IFG might have similar IR to either normoglycemic individuals or patients with impaired glucose tolerance.(436) Thus,

using only the cut-off FPG values of IFG to identify high T2DM risk patients could under- or over-estimate the potential diabetogenic impact of statin therapy. Likewise, although overweight/obesity has been considered to be related with IR, a considerable proportion of overweight/obese individuals, the so called 'metabolically healthy obese' patients who have normal FPG and TG levels, exhibit lower rates of metabolic complications than expected, such as new-onset T2DM and CVD.(200, 437, 438) On the other hand, overwhelming evidence suggests the association of MixDys with IR.(432, 439) Compensatory hyperinsulinemia due to IR has been considered to induce increased flux of free fatty acids, raise TG production and decrease HDL-C.(432, 439, 440) Recent evidence from epidemiological, genetic and intervention studies supports the 'hypertriglyceridemia-IR-hyperinsulinemia' vicious cycle suggesting that atherogenic dyslipidemia itself induces IR.(441) Studies evaluating the association between lipid parameters and IR or T2DM risk demonstrated that markers including FPG, TGs and HDL-C levels have a strong predictive value for T2DM incidence in the general population.(442-445) For 469 statin-treated patients classified as being at high risk for T2DM, Armato et al showed that those with elevated TG levels displayed markers of IR and compensatory hyperinsulinemia, despite their similar baseline FPG and glycated hemoglobin levels to those with isolated hypercholesterolemia.(444)

Our study evaluated whether IR, identified by the presence of IFG, MixDys or overweight/obesity, predicts incident T2DM in statin-treated individuals.(431) We showed that these combinations dramatically increase the diabetogenic impact of statin therapy, similarly to the findings of ananalysis of TNT and SPARCL trials (n=11,354).(431, 446) The majority of our study participants who were normoglycemic, non-obese and had normal TG and HDL-C levels (~30%) exhibited the lowest rates of T2DM (~3-4%).(431) On the other hand, the prediabetic patients with either MixDys (~5%) or obesity (~16%) exhibited the highest rates of incident DM on statin therapy (36% and 26%, respectively).(431) When presented alone, IFG, MixDys and obesity were associated with new DM rates intermediate between the high- and low-risk groups described above (Figure 19).(431)

Our results provide a simplified tool for the physician to identify patients at high risk of developing T2DM on statin treatment.(431) In contrast to RCTs, the rate of new-onset T2DM was greater than incident ASVCD in our study (11 vs 7% during a median of 6 years).(136, 137, 447) Thus, our study underlines the need to identify and minimize this

risk in everyday clinical practice. Obtaining simple measurements, such as FPG, BMI and TGs, would help to tailor different pharmacological and non-pharmacological treatment plans before and after initiating statins. Also, a more frequent monitor of glycemic status would be reasonable for obese patients with IFG and MixDys.(431) Considering that weight gain is associated with increased risk of new-onset T2DM,(448) obese patients with IFG should be encouraged to lose weight to minimize the risk of statin-induced T2DM. One might consider statins with a more neutral effect on glucose homeostasis, especially in patients at low CV risk.(449)

Study limitations for this analysis was the retrospective design of our study.(431) Potential confounding factors, such as dietary composition, physical activity and duration of statin therapy could have influenced our results.(431) Nevertheless, our study had a long follow-up of 6 years in a real-world outpatient lipid clinic setting.(431) As such, this is a 'pragmatic study' of everyday clinical practice and not a selected sample of patients with a close monitoring like those in a randomized control trial.(431) In contrast to TNT, IDEAL and SPARCL trials,(136, 446) our participants were all statin-treated and followed-up for a longer period, whereas the rate of incident T2DM was greater in our study.(431) We showed that both increased TGs and low HDL-C (and not only elevated TGs as shown by TNT, IDEAL and SPARCL) were associated with increased risk of statin-induced T2DM and highlighted the prognostic value of MixDys for statin-associated T2DM.(431)

5.7.2.3 Metabolically healthy obesity and risk of incident diabetes in statin-treated subjects

This was the first study to examine the risk of incident T2DM in patients receiving statin therapy according to their metabolic health and obesity status.(450) As shown in Figure 20, MHO was not significantly associated with T2DM onset compared with MHNO phenotype in statin-treated patients.(450) On the other hand, MUNO and mostly MUO were associated with a significant increase in new-onset T2DM risk.(450) Therefore, it seems that the risk of statin-associated new-onset T2DM depends mainly on the metabolic rather than obesity status.

Although statins undoubtedly decrease CV risk, the development of T2DM is one of their well-established adverse effects.(135, 137) Various pathways leading to increased IR and decreased insulin secretion have been proposed by experimental studies.(451-

453) Indeed, insulin resistant patients with components of MetS, such as hypertension, obesity, atherogenic dyslipidemia and preDM exhibit the highest risk of incident statin-associated T2DM.(135, 137) More interestingly, the co-existence of these risk factors seem to dramatically accentuate the diabetogenic impact of statin therapy.(416, 431, 446)

During the last decade, it has become evident that a proportion of obese individuals do not exhibit related metabolic abnormalities, the so-called MHO.(199-201) Because of the lack of universally accepted criteria to identify MHO, its prevalence varies widely among studies and ranges between 6 to 40%.(199, 454) The definition of the MHO phenotype in our study comes in agreement with the vast majority of previously published studies (i.e. ≤2 metabolic syndrome criteria).(199, 455) Although the mechanisms involved in the pathogenesis of MHO have not been clarified, several potential pathways leading to less decrease of insulin sensitivity despite obesity have been proposed.(199-201) These include increased de-novo lipogenesis in adipocytes from subcutaneous tissue and adiponectin production, along with decreased inflammatory pathway signaling and mitochondrial iron transport into the mitochondrial matrix.(199-201) Prospective cohorts have shown that MHO is associated with a lower T2DM risk when compared with the MUO phenotype.(456-459) Likewise, meta-analyses have shown that MHO is associated with approximately half the risk of developing T2DM compared with MUO and MUNO.(460-463) Nevertheless, MHO is still associated with a 2-fold increase in the risk of T2DM compared with MHNO.(456-459) Although the corresponding OR suggested a trend towards an increased T2DM risk in our cohort, the association between MHO and new T2DM onset was not significant (Table 32).(450)

According to our results, patient metabolic phenotype account for T2DM development on statin treatment rather than weight status.(450) Indeed, previously published analyses have shown that both MUO and MUNO individuals exhibit the highest risk of incident T2DM.(456, 459, 464) Therefore, in case of metabolically unhealthy patients, a more frequent monitor of glycemic status would be reasonable during statin treatment, together with an intense lifestyle intervention.(201, 455, 465) Furthermore, statins with a possibly more favorable effect on glucose homeostasis, such as pitavastatin, may be considered.(449) Nevertheless, MHO subjects should be closely followed-up, since a considerable proportion may transit to MUO and finally develop T2DM.(466-469)

Major limitations of this analysis are its retrospective nature, and the lack of data on dietary habits and physical activity.(450) Furthermore, the marked heterogeneity of MHO definitions was a major limitation also underlined in previous studies.(199, 201, 454) In addition, the effect of changes in weight, metabolic phenotype and drug treatment during follow-up was not evaluated.(466, 468) To the best of our knowledge however, this was the first study to investigate the association between MHO and the risk of statin-associated T2DM in a relatively large cohort with a long follow-up.(450)

5.7.3 Interaction between proton pump inhibitors and statins

Our study suggested, for the first time to our knowledge, that treatment with PPIs may modestly increase statin-mediated LDL-C reduction without increasing the risk of liver and muscle toxicity.(470)

It has been reported that PPIs may be involved in cholesterol metabolism.(471, 472) A study investigating whether helicobacter pylori infection was associated with changes in serum lipid levels indicated that its eradication significantly increased HDL-C after taking amoxicillin, clarithromycin, and omeprazole.(473) Despite not being significant, a trend towards a reduction in TC and LDL-C levels was noticed in that study.(473) PPIs can decrease the intra-lysosomal acidity through the inhibition of the lysosomal membrane H^+/K^+ ATPase.(471) Therefore, these drugs could inhibit the intra-lysosomal oxidation of LDL-C.(471) In addition, lansoprazole and other PPIs with structure similarities might act as liver X receptor (LXR) agonists.(472) Lansoprazole can activate endogenous LXR in a concentration-dependent manner, followed-up by transcriptional up-regulation of LXR related genes leading to the increase of their proteins.(472) These proteins are involved in cholesterol metabolism and various steps of atherosclerosis.(472) Indeed, a synthetic LXR ligand reduced LDL-C in nonhuman primates with normal lipid levels.(474)

Furthermore, the possible cholesterol-lowering effect of PPIs on statin-treated individuals could be attributed to the liver metabolism of both drugs (CYP450).(475, 476) It is known that atorvastatin and simvastatin are metabolized by the cytochromes CYP3A4 and CYP2C8, while rosuvastatin is metabolized by CYP2C9 and CYP2C19.(475) PPIs also undergo similar hepatic metabolism, involving the cytochromes CYP3A4 and CYP2C19.(476) Most PPIs are weak inhibitors of CYP3A4, while omeprazole and esomeprazole are the most potent CYP2C19 inhibitors.(476) By

competing with such isoforms, PPIs may reduce the metabolism of statins resulting in an increase of their LDL-C-lowering efficacy.(406, 475) In a similar way, esomeprazole and omeprazole have been suggested to reduce the antiplatelet effect of clopidogrel by competing the same cytochrome.(477) Nevertheless, PPIs have not been considered yet to interact with statins.(478, 479)

In our study, a high proportion of the participants taking statin + PPI were also receiving clopidogrel (Table 33).(470) Despite the fact that few reports have demonstrated a statin-clopidogrel interaction, post-hoc analyzes from RCTs have not associated the co-administration of statins and clopidogrel with an increased CV risk.(480) In addition, the effect of clopidogrel on LDL-C reduction did not remain significant in our multivariate regression analysis (Table 35).(470) Thus, the use of clopidogrel may not account for the higher LDL-C reduction noticed in the subjects taking statin + PPI in our study.(470)

Inhibitors of CYP450 are associated with skeletal muscle or liver toxicity by increasing the plasma concentrations of statins.(406, 481) In this context, PPIs have been related to myopathy including polymyositis in statin-treated individuals.(482-485) Nevertheless, no differences were found regarding the changes in liver or muscle enzymes and the rates of statin-induced adverse events between cases and controls in this study (Table 34).(470)

It has to be noticed that this was a retrospective observational study not specifically designed to investigate the effect of PPIs on statin-induced LDL-C lowering.(470) Unfortunately, there were no data available on the specific PPIs used.(470) Therefore, we were not able to assess possible differences among various PPIs.(470) Also, the numbers of patients on statin + PPIs was small.(470) Despite careful adjustment, residual confounding may still be present. Diet could account for the noticed difference in LDL-C reduction between the 2 groups. Indeed, individuals taking PPIs due to GI disorders usually follow a fatless diet. In order to avoid this bias, subjects diagnosed with active ulcer, gastritis or gastroesophageal reflux disease were excluded.(470) Adherence to a healthy diet confers to a significant CV risk reduction, even in statin-treated individuals.(486, 487) Thus, individuals at very high CV risk, such as the majority of those taking PPIs in our cohort, might have followed a stricter diet leading to a higher cholesterol reduction.(470) On the other hand, a less strict diet followed by those not receiving a PPI could explain the increase in markers of MetS and non-

alcoholic fatty liver disease noticed in our study (i.e. glucose, BMI, uric acid and liver enzymes), although there was no significant difference between the 2 groups.(470) Unfortunately, we had no data on participant diet.(470) Another residual factor could be the lower eGFR in the group of statin + PPI.(488) Nevertheless, no association between eGFR and LDL-C reduction was evident.(470)

5.7.4 Statin escape phenomenon

Our analysis additionally confirmed the existence of statin escape phenomenon in clinical practice.(489)

Two small studies including patients with FH were the first to notice cases of paradox rebound cholesterol increase following statin dose increase.(490, 491) Since then, the EXCEL study along with others, has described this so-called statin escape phenomenon.(491-494) Our results showing an initial marked LDL-C reduction but followed by a >10% LDL-C increase after prolonged statin treatment in subjects exhibiting the statin escape phenomenon are in line with the results of these studies.(491-493) Similar to previous studies, we did not find any predictors for this phenomenon.(491-493) A recent study showed that statin escape phenomenon not only exists, but also might be an independent predictor of CVD.(492) The mechanisms attributing to the statin escape phenomenon have not yet been elucidated. The failure of statin therapy to decrease LDL-C levels on a long-term basis may be attributed to poor compliance with lipid-lowering treatment and diet. Particularly, an increased intake of cholesterol in the diet may contribute to intermittent variations in cholesterol levels. In addition, weight changes or a poor glycemic control in diabetic individuals could also cause an LDL-C increase, which could be wrongfully considered as statin escape phenomenon. After excluding subjects with these characteristics, one study concluded that only 1.2% of 161 study participants exhibited the statin escape phenomenon, although 28% of those were initially considered to meet the criteria of statin escape.(493) Despite the fact that no data regarding diet and exercise was available in our study, there was no significant difference between groups in terms of BMI change, glycemic control and kidney function (Table 37).(489)

We also assessed non-HDL-C levels in non-diabetic individuals considering that atherogenic dyslipidemia may alter LDL-C changes.(197) Statin escapers had higher non-HDL-C levels after prolonged statin therapy in comparison with non-escapers, although they had a higher non-HDL-C reduction 6 months after treatment onset (Table 37).(489)

Although we checked for adherence to therapy, our study might have included non-compliant individuals.(489) It may be possible that escapers adhered less to statin therapy and diet after seeing a large drop in their LDL-C levels. Another possible explanation for the statin escape phenomenon could be the concomitant therapy, since a variety of drugs could increase LDL-C lowering action of statins by inducting cytochromes CYP450-3A4 and 2C9.(260, 406) According to a few experimental studies, statin escape phenomenon could be attributed to a slow increase in the HMG-CoA reductase activity or to an increase in PCSK9 levels caused by prolonged statin therapy.(495-500)

Although this was a retrospective observational study with a small sample size, only the EXCEL study, which was the only randomized trial reporting on statin escape phenomenon and a retrospective cohort had larger samples.(489, 492, 494) The small number of eligible participants did not allow any analysis to identify potential predictors for the statin-escape phenomenon.(489) Additionally, due to small sample and low incidence of CVD this study did not have the power to establish an association between statin escape and CVD incidence.(489) Nevertheless, our study confirmed the limited bibliography reporting on statin escape phenomenon and its quite high prevalence (28-31%).(492, 493) Therefore, further investigation on the underlying pathophysiology of this phenomenon and its potential clinical ramifications is required.

5.8 Risk factors for incident chronic kidney disease in dyslipidemic individuals: the role of uric acid

The present analysis showed that hyperuricemia was an independent factor for CKD in dyslipidemic individuals receiving multifactorial treatment in the setting of a tertiary lipid clinic.(501)

CKD has become a major health issue due to its accelerating prevalence, estimated to 8-16% worldwide, and is associated with CV and all-cause mortality.(202, 502) Sex, age, DM, hypertension, dyslipidemia and obesity are the leading causes of CKD in the developed countries.(202, 502) Our cohort confirmed that female sex, increasing age, ASCVD and DM increased the risk of incident CKD, but hypertension and dyslipidemia were not associated with CKD incidence (Table 39).(501) This could be attributed to the fact that lipid-lowering and antihypertensive therapy were prescribed to the majority

of study participants during follow-up.(501) Various guidelines suggest that treatment with statins, ACE inhibitors and ARBs may retard the progression of renal disease.(202, 503-505) Indeed, the statin-mediated LDL-C reduction was an independent factor against CKD onset in our study (Table 39).(501) In addition, the annual decline of renal function was within the ranges of the expected annual eGFR decline of 0.5-1.0 mL/min/1.73 m^2 in healthy individuals.(414) Thus, careful screening and proper intervention may prevent CKD onset and progression.(502) Strategies to reduce burden and costs related to CKD need to be included in national programs for the identification of the potential risk factors for CKD.(502)

Hyperuricemia has been recently proposed as a potential risk factor for CKD.(202) Although increased levels of uric acid are associated with CKD, it not clear yet whether hyperuricemia plays a causal role in CKD onset or it is merely a consequence of its association with other risk factors for CKD, such as hypertension and MetS.(506, 507) Experimental studies have supported a causal relationship between hyperuricemia and CKD with several potential mechanisms. Although a few trials showed that hyperuricemia can increase the risk of incident CKD directly through the inhibition of endothelial nitric oxide, activation of the renin-angiotensin system and increase in the renal microvascular damage via vascular cell proliferation and endothelial dysfunction,(508-510) others have shown that uric-acid lowering therapy had no impact on endothelium.(511, 512) On the other hand, it is possible that hyperuricemia can increase the risk of CKD by causing salt-sensitive hypertension.(513)

In the light of the experimental evidence, Mendelian randomization analyses have been performed to investigate the possible role of uric acid in CKD. A prospective cohort adopting the Mendelian randomization approach in 755 patients with CKD showed that a polymorphism in a gene encoding a urate transporter, strongly associated with serum uric acid levels in healthy individuals with normal renal function, held a strong predictive power for CKD progression.(514) On the other hand, a larger Mendelian randomization analysis using data from 7,979 patients of the Atherosclerosis Risk in Communities and Framingham Heart studies showed that the activity of renal uric acid transporters in raising serum uric acid was beneficial to renal function.(515)

Similarly, the results of epidemiological studies remain controversial. The Cardiovascular Health Study, a prospective community-based cohort with 5,888 study participants in the United States, found no association between uric acid levels and

incident CKD (OR: 0.96, 95% CI: 0.87-1.06, p >0.05).(516) Similar were the results of other studies showing a weak association between uric acid levels and renal function,(517-519) which was no longer significant after adjustment for confounding factors.(520) On the other hand, a large Japanese retrospective study including 48,177 healthy individuals followed-up for 7 years showed that hyperuricemia (defined as uric acid ≥6 mg/dL) was associated with increased the risk of incident CKD in women (HR: 5.77, 95% CI: 2.309-14.421, p <0.001), but not in men (OR: 2.004, 95% CI: 0.904-4.444, p >0.05).(521) Additionally, the results of a prospective Korean cohort study (n=14,939) showed an increased CKD risk for both men (HR: 2.1, 95% CI: 1.6-2.9, p <0.001) and women (HR: 1.3, 95% CI: 1.0-1.8, p <0.001) in the highest uric acid quartiles (522) and were further confirmed by other community-based cohorts conducted in Asia.(523-528) The analysis of 2 community-based cohorts, the Atherosclerosis Risks in Communities and the Cardiovascular Health Study (n=13,338), showed that hyperuricemia increased the risk for incident CKD (OR: 1.07 per 1-mg/dL increase, 95% CI: 1.01-1.14, p <0.05).(529) Another European cohort with 17,735 healthy volunteers followed-up for 7 years confirmed the association between uric acid levels and incident CKD risk (OR: 1.69 per 2 mg/dL increase, 95% CI: 1.59-1.80, p <0.0001),(530) which remained significant after adjustment for baseline concomitant diseases and therapies.(531) Similarly, a meta-analysis including 13 observational cohorts containing 190,718 subjects found an increase in the risk of incident CKD in those with hyperuricemia (OR: 2.35, 95% CI: 1.59-3.46, p <0.001).(532) Interestingly, the Rotterdam study including 2,601 subjects aged ≥55 years old showed that the association of uric acid concentration with renal decline was more evident in the hypertensive patients.(533) In this context, our results further elucidate the role of hyperuricemia as an independent factor for CKD even in dyslipidemic patients who received multifactorial treatment in the setting of a tertiary lipid clinic.(501)

A major limitation of this analysis was its retrospective nature.(501) The lack of data on potential confounding factors, such as diet and exercise could have influenced our results.(501) Also, no data on albuminuria were available, which is an important element in defining CKD, especially in patients with MetS and DM.(202, 501, 534) However, the CKD definition based on eGFR is acceptable in population-based research settings.(535) On the other hand, our study had several strengths. First, our cohort had an extensive follow-up of 6 years, similar to those of most previously

published studies.(501) Second, we excluded patients with baseline CKD or gout, which are well established predictors for CKD progression.(501) Third, our results provided further data on the limited bibliography regarding the effect of hyperuricemia on incident CKD risk in white-race population.(313, 516, 517, 520, 529-531, 533) Unlike most studies, we used the CKD-EPI equation for the definition of CKD, which is more generalizable and accurate equation for eGFR in comparison with the Modification of Diet in Renal Disease (MDRD) equation.(313, 501, 536) Only a few trials along with ours have included various comorbidities and concomitant treatment in analyses.(313, 501, 516, 520, 527, 531, 533) Last but not least, our study was not community-based but the first including dyslipidemic patients who received multifactorial treatment.(501) Although treatment with statins and ARBs or ACE inhibitors may have delayed the progression of renal disease, hyperuricemia remained an independent factor for CKD.(501) In this context, larger RCTs are needed to evaluate whether treatment with uric acid lowering drugs should be considered in such individuals.

5.9 Risk factors for incident hyponatremia

Our study confirmed previous reports indicating a relationship between high levels of HDL-C and hyponatremia.(537)

Israel et al. was the first to report that high levels of HDL-C are associated with hyponatremia in hypertensive and normotensive individuals.(538) This finding was derived from the prospective Systolic Blood Pressure Intervention Trial (SPRINT) and a cross-sectional analysis of NHANES datasets, respectively.(539) Of note, data on medications, especially antihypertensives and mainly diuretics, or comorbidities predisposing to hyponatremia were not available.(538)

Our study confirmed that high HDL-C levels were an independent factor for hyponatremia in dyslipidemic individuals, regardless of hypertension presence (Table 40).(540) Israel et al. suggested that this could be attributed to decreased sensitivity of arginine vasopressin receptors noticed in subjects with obesity and MetS, 2 states inversely correlated with HDL-C levels.(538) However, our study showed that neither obesity nor MetS were associated with hyponatremia (Table 40).(537) Another hypothesis suggesting that hypouricemia could explain both elevated HDL-C levels and hyponatremia was not supported by our results. On the contrary, high uric acid levels increased the risk of hyponatremia in hypertensive study participants (adjusted HR:

1.16, 95% CI: 1.03-1.31, p <0.05).(540) We also found an association between low LDL-C levels and hyponatremia, possibly insinuating a different metabolic pathway from those previously proposed.(538, 539) In the light of this evidence, further research is needed to elucidate the association between elevated HDL-C levels and hyponatremia. Until then, physicians should be aware of this association before initiating therapies predisposing to hyponatremia.

CHAPTER VI. CONCLUSIONS

In the present doctorate thesis:

1. We showed that CVD incidence in high risk dyslipidemic subjects intensively treated was similar to a Hellenic cohort at lower CV risk.
2. We investigated which CV risk factors are associated with new ASCVD events in high risk patients intensively treated in the setting a tertiary lipid clinic. DM, history of previous ASCVD, smoking and age were independent factors for ASCVD risk in dyslipidemic subjects on multifactorial cardiovascular therapy.
3. We confirmed that $CHADS_2$ and CHA_2DS_2-VASc scores exhibit a strong predictive value for incident ASCVD in dyslipidemic individuals without AF, without being superior to SCORE and PCE.
4. Although no association was found between HDL-C and ventricular repolarization indexes, our study was the first to show that $CHADS_2$ and CHA_2DS_2-VASc scores predict incident AF among dyslipidemic patients, with modest further improvement of performance when low HDL-C levels were included.
5. Even in the setting of a lipid clinic, we confirmed previous data reporting that the majority of patients and especially those at high CV risk, such as patients with ASCVD or FH, remain sub-optimally treated in everyday clinical practice.
6. We underlined the imperative need for combination therapies of most potent statins with ezetimibe ± PCSK9 inhibitors to achieve optimal LDL-C levels in clinical practice. In addition, we confirmed that a considerable proportion of patients with ASCVD or FH are eligibile for treatment with PCSK9 inhibitors.
7. We were the first to assess the correlations of apoB with LDL-C and non-HDL-C on the basis of the presense of MetS or DM in combination with TG stratification. In this setting, our study showed that apoB correlation with both LDL-C and non-HDL-C is reduced in individuals with high TG levels and mostly in those with DM or MetS.
8. We confirmed previous evidence arguing that rates of adverse effects caused by statin therapy are actually low in clinical practice, whereas a neutral effect, if not favorable, on renal function was noticed.
9. We showed that high-intensity statin therapy is associated with a higher risk of incident DM in prediabetic individuals compared with previous results from RCTs. Moreover, we confirmed that ezetimibe has a neutral effect on glucose metabolism.

10. We were the first to demonstrate that atherogenic dyslipidemia increases T2DM risk in statin-treated patients, while its combination with IFG and overweight/obesity dramatically increases the diabetogenic impact of statin therapy. These results could help physicians tailor therapeutic strategies minimizing DM risk before initiating statin therapy.
11. We were the first to show that metabolically healthy obesity does not seem to significantly increase T2DM risk in statin-treated individuals in contrast to metabolically unhealthy non-obesity and especially metabolically unhealthy obesity. Thus, the risk of statin-associated new-onset T2DM may depend mainly on the metabolic rather than obesity status.
12. We confirmed limited evidence arguing for the existence of statin escape phenomenon in clinical practice, although its clinical significance remains uncertain. In this context, patients with larger than anticipated LDL-C reduction should be carefully monitored.
13. We were the first to show a potential interaction between PPIs and statins, that is chronic PPI use may be associated with a modest enhancement in LDL-C lowering efficacy of statins.
14. We confirmed that hyperuricemia increases CKD risk in dyslipidemic individuals treated with statins and reno-protective antihypertensive drugs.
15. We confirmed limited evidence arguing that high HDL-C levels are associated with hyponatremia in dyslipidemic individuals.

SUMMARY

Introduction: Despite available therapies used for cardiovascular (CV) prevention and their increased prescription rates during the last decade, cardiovascular disease (CVD) remains the leading mortality cause worldwide. There are limited data regarding CV and metabolic risk in dyslipidemic patients treated in the setting of CV prevention.

Aims: To study CVD incidence in dyslipidemic patients taking multifactorial CV therapy and identify potential factors for residual CV and metabolic risk.

Methods: This was a retrospective study including consecutive adult patients with dyslipidemia who attended the Outpatient Lipid Clinic of the University Hospital of Ioannina in Greece for ≥3 years (from 1999 to 2015). A complete assessment of their clinical and laboratory profile was performed at baseline visit, after 6 months and most recent visit. Concomitant therapies were recorded, with a particular emphasis on lipid-lowering drugs. We depicted the incidence of atherosclerotic cardiovascular disease (ASCVD) and identified possible risk factors. We evaluated and compared prognostic values of tools estimating the risk of ASCVD and atrial fibrillation (AF). We also evaluated whether an association between lipid parameters and ventricular repolarization indices (QTc interval, the Tpe interval, and the Tpe/QT ratio) exists. We captured the rates of proposed lipid, blood pressure (BP) and glycemic target attainment, along with rate of eligibility for treatment with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. We assessed the correlations (r^2) of apolipoprotein B (apoB) with low-density lipoprotein cholesterol (LDL-C) and non-high-density lipoprotein cholesterol (non-HDL-C) according to the presence of high triglyceride (TG) levels, type 2 diabetes mellitus (T2DM) and metabolic syndrome (MetS). We recorded the rate of adverse effects related with lipid-lowering treatment and identified the corresponding risk factors. We assessed the overall effect of proton pump inhibitors (PPI) administration on LDL-C lowering and we investigated whether a statin escape phenomenon exists (as defined as an increase in low-density lipoprotein cholesterol (LDL-C) levels at the most recent visit by >10% compared with the value at 6 months following initiation of statin treatment). Also, we evaluated which factors were associated with incident chronic kidney disease (CKD) and hyponatremia in our study population.

Results: A total of 1,334 subjects were included in the present study and followed-up for a median of 6 years (4-10). During follow-up, lipid-lowering therapy was prescribed to the majority of study participants (94%) with statins being the cornerstone therapy (91%), whereas 70% of those were on antihypertensive therapy. During 6-year follow-up, a total of 95 subjects (7%) were diagnosed with incident ASCVD (rate of ASCVD incidence: 10.4/1,000 patient-years). ASCVD incidence in our cohort was similar to that of a Hellenic cohort (ATTICA study) representative of the general population (10.4 vs 15.7/1,000 patient-years, respectively). T2DM (HR: 2.09, 95% CI: 1.18-3.70, p <0.001), previous ASCVD (HR: 2.04, 95% CI: 1.21-3.43, p <0.001), smoking (HR: 1.82, 95% CI: 1.17-2.84, p <0.001) and age (HR: 1.07, 95% CI: 1.04-1.09, p <0.001) were independent risk factors.

ROC curve analysis indicated that $CHADS_2$ and CHA_2DS_2-VASc scores have a strong predictive value for ASCVD (C-statistic: CHADS 0.592, p <0.01; CHA_2DS_2-VASc: 0.568, p <0.05). Nevertheless, they were not superior to SCORE and PCE risk score (C-statistic: 0.612, p <0.001 and 0.717, p <0.001, respectively).

The correlation analysis (Spearman's) failed to show any association between HDL-C or other lipid parameters and studied ECG parameters. Nevertheless, ROC curve analyses showed that both $CHADS_2$ and CHA_2DS_2-VASc scores were significant predictors for new-onset AF (C-Statistic: $CHADS_2$ 0.679, p <0.001; CHA_2DS_2-VASc 0.698, p <0.001). After incorporating low HDL-C levels, both scores achieved slightly higher C-Statistic for AF prediction (0.690 and 0.707, respectively, p <0.001).

According to the ESC/EAS 2019 guidelines, patients at very-high CV risk (n=391) exhibited the lowest rate of LDL-C target attainment compared with those at high (n=457), moderate (n=105) and low CV risk (n=47) (7 vs 12 vs 42 vs 70%, respectively, p <0.05) If subjects were on high-intensity statin plus ezetimibe, the corresponding rates would be 36, 47, 95 and 97% for the patients at very high, high, moderate and low CV risk, respectively. In case of additional treatment with PCSK9 inhibitors, the corresponding rates would be 69, 79, 100 and 100%, respectively.

According to ACC/AHA 2018, 46% of patients with very high risk ASCVD and 31% of individuals with LDL-C ≥190 mg/dl both taking high-intensity statin therapy plus ezetimibe would be eligible for treatment with PCSK9 inhibitors. According to local Greek policy, the corresponding eligibility rate would be lower (22%) in patients with

ASCVD, familial hypercholesterolemia (FH), DM with target organ damage or statin intolerance who were on maximally tolerated statin therapy with ezetimibe.

Among elderly patients (≥65 years), LDL-C targets (ESC/EAS 2011), were attained by 27, 48 and 62% of those at very high, high and moderate risk, respectively. Of diabetic subjects, 71% had BP <140/85 mmHg, while 78% of non-diabetics had BP <140/90 mmHg. A higher proportion of non-diabetic individuals (86%) had BP <150/90 mmHg. Also, a higher proportion of diabetics had HbA1c <8% rather than <7% (88% and 47%, respectively). Of note, almost 1 out of 3 non-diabetic and 1 out of 10 diabetic individuals had achieved all 3 treatment targets.

The correlations between apoB and LDL-C or non-HDL-C were similar for individuals with TGs <200 mg/dL. Although these correlations remained significant for individuals with high TG levels (≥200 mg/dL), the correlation factor was markedly decreased mostly in those with T2DM or MetS (r^2=0.600, p <0.01, for the correlation between apoB and LDL-C; r^2=0.604, p <0.01, for the correlation between apoB and non-HDL-C). In contrast, the corresponding correlations were stronger in non-diabetic/non-MetS dyslipidemic individuals (r^2=0.710 and 0.714, respectively, p <0.01).

The rates of liver ezymes and CK increase were 3% and 1%, whereas only 2% of study participants experienced myalgias.

During follow-up ~12% of study participants developed T2DM. A higher risk of incident T2DM was observed in prediabetic individuals receiving high-intensity statin therapy compared with those on moderate-intensity (adjusted OR: 2.12, 95% CI: 1.06-4.24, p <0.05) and those not taking a statin (adjusted OR: 4.90, 95% CI: 1.16-20.66, p <0.05). The addition of ezetimibe to statin treatment did not increase the risk of incident T2DM in prediabetic individuals (adjusted OR: 0.89, 95% CI: 0.36-2.22, p >0.05). An additional analysis showed that among prediabetic subjects, atherogenic dyslipidemia increased T2DM risk (adjusted OR: 3.44, 95% CI: 1.31-9.04, p=0.01). The same was true for overweight/obese status (adjusted OR: 5.60, 95% CI: 2.19-14.30, p <0.01). There was no significant difference regarding T2DM risk between metabolically healthy non-obese (MHNO) and metabolically healthy obese (MHO) subjects (adjusted OR: 1.46, 95% CI: 0.76-2.82, p >0.05). Metabolically unhealthy obese (MUO) patients had greater T2DM risk than MHNO (adjusted OR: 7.87, 95% CI: 4.02-15.42, p <0.01), MHO (adjusted OR: 5.45, 95% CI: 2.47-12.04, p <0.01) and metabolically unhealthy non-obese (MUNO) subjects (adjusted OR: 2.68, 95% CI: 1.28-5.64, p <0.01).

Subjects receiving statin + PPI had a higher LDL-C reduction by 6.4% compared with those taking a statin alone (fully adjusted p <0.01), whereas 31% of 181 eligible subjects exhibited the statin escape phenomenon.

During follow-up (6 years; IQR:4-10), 11.9% of subjects developed CKD, whereas the median annual eGFR decline was 0.69 mL/min/1.73 m^2 (IQR: 0.45-2.33). Multivariate analysis showed that baseline uric acid levels (HR: 1.26, 95% CI: 1.09-1.45, p=0.001), female sex (HR: 1.74, 95% CI: 1.14-2.65, p=0.01), age (HR: 1.10, 95% CI: 1.07-1.12, p <0.001), T2DM (HR: 1.67, 95% CI: 1.05-2.65, p <0.05), ASCVD (HR: 1.62, 95% CI: 1.02-2.58, p <0.05), decreased baseline renal function (eGFR <90 mL/min/1.73 m^2) (HR: 2.38, 95% CI: 1.14-4.81, p <0.05) and LDL-C reduction (HR: 0.995, 95% CI: 0.991-0.998, p=0.01) were associated with incident CKD. High HDL-C levels were associated with risk of hyponatremia (adjusted HR: 1.02, 95% CI: 1.01-1.04, p <0.01).

Conclusions:

1. We showed that CVD incidence in high risk dyslipidemic subjects intensively treated was similar to a Hellenic cohort at lower CV risk.
2. We investigated which CV risk factors are associated with new ASCVD events in high risk patients intensively treated in the setting a tertiary lipid clinic. DM, history of previous ASCVD, smoking and age were independent factors for ASCVD risk in dyslipidemic subjects on multifactorial cardiovascular therapy.
3. We confirmed that $CHADS_2$ and CHA_2DS_2-VASc scores exhibit a strong predictive value for incident ASCVD in dyslipidemic individuals without AF, without being superior to SCORE and PCE.
4. Although no association was found between HDL-C and ventricular repolarization indexes, our study was the first to show that $CHADS_2$ and CHA_2DS_2-VASc scores predict incident AF among dyslipidemic patients, with modest further improvement of performance when low HDL-C levels are included.
5. Even in the setting of a lipid clinic, we confirmed previous data reporting that the majority of patients and especially those at high CV risk, such as those with ASCVD or FH, remain sub-optimally treated in everyday clinical practice.
6. We underlined the imperative need for combination therapies of most potent statins with ezetimibe ± PCSK9 inhibitors to achieve optimal LDL-C levels in clinical practice. In addition, we confirmed that a considerable proportion of patients with ASCVD or FH are eligibile for treatment with PCSK9 inhibitors.

7. We were the first to assess the correlations of apoB with LDL-C and non-HDL-C on the basis of the presense of MetS or DM in combination with TG stratification. In this setting, our study showed that apoB correlation with both LDL-C and non-HDL-C is reduced in individuals with high TG levels and mostly in those with DM or MetS.

8. We confirmed previous evidence arguing that rates of adverse effects caused by statin therapy are actually low in clinical practice, whereas a neutral effect, if not favorable, on renal function was noticed.

9. We underlined that high-intensity statin therapy is associated with a higher risk of incident DM in prediabetic individuals compared with previous results derived from randomized controlled trials. Moreover, we confirmed that ezetimibe has a neutral effect on glucose metabolism.

10. We were the first to demonstrate that atherogenic dyslipidemia increases T2DM risk in statin-treated patients, while its combination with IFG and overweight/obesity dramatically increases the diabetogenic impact of statin therapy. These results could help physicians tailor therapeutic strategies minimizing DM risk before initiating statin therapy.

11. We were the first to show that metabolically healthy obesity does not seem to significantly increase T2DM risk in statin-treated individuals in contrast to metabolically unhealthy non-obesity and especially metabolically unhealthy obesity. Thus, the risk of statin-associated new-onset T2DM may depend mainly on the metabolic rather than obesity status.

12. We confirmed limited evidence arguing for the existence of statin escape phenomenon in clinical practice, although its clinical significance remains uncertain. In this context, patients with larger than anticipated LDL-C reduction should be carefully monitored.

13. We were the first to show a potential interaction between PPIs and statins, that is chronic PPI use may be associated with a modest enhancement in LDL-C lowering efficacy of statins.

14. We confirmed that hyperuricemia increases CKD risk in dyslipidemic individuals treated with statins and reno-protective antihypertensive drugs.

15. We confirmed limited evidence arguing that high HDL-C levels are associated with hyponatremia in dyslipidemic individuals.

ΠΕΡΙΛΗΨΗ

Εισαγωγή: Παρά τις διαθέσιμες θεραπείες για την πρόληψη των καρδιαγγειακών νοσημάτων και τα αυξημένα ποσοστά συνταγογράφησής τους την τελευταία 10ετία, η καρδιαγγειακή νόσος (ΚΑΝ) παραμένει η κύρια αιτία νοσηρότητας και θνησιμότητας παγκόσμια. Υπάρχουν λίγα δεδομένα σχετικά με τον καρδιαγγειακό και μεταβολικό κίνδυνο σε ασθενείς με δυσλιπιδαιμία που λαμβάνουν θεραπεία στα πλαίσια της καρδιαγγειακής πρόληψης.

Σκοπός: Σκοπός μας ήταν να καταγράψουμε τη συχνότητα εμφάνισης ΚΑΝ σε ασθενείς με δυσλιπιδαιμία που λαμβάνουν πολυπαραγοντική θεραπεία και να προσδιορίσουμε τους πιθανούς παράγοντες για τον καρδιαγγειακό και μεταβολικό τους κίνδυνο.

Μέθοδοι: Πρόκειται για μια αναδρομική μελέτη παρατήρησης, στην οποία συμμετείχαν διαδοχικοί ενήλικες ασθενείς με δυσλιπιδαιμία που παρακολουθήθηκαν για ≥3 χρόνια (από το 1999 έως το 2015) στο εξωτερικό ιατρείο Διαταραχών του Μεταβολισμού των Λιπιδίων και Παχυσαρκίας του Πανεπιστημιακού Γενικού Νοσοκομείου Ιωαννίνων. Πραγματοποιήσαμε μια πλήρη αξιολόγηση του κλινικού και εργαστηριακού τους προφίλ στην αρχική επίσκεψη, μετά από 6 μήνες και στην πιο πρόσφατη επίσκεψη. Επίσης, καταγράφηκε η θεραπεία τους, με ιδιαίτερη έμφαση στα υπολιπιδαιμικά φάρμακα. Καταγράψαμε την επίπτωση της ΚΑΝ και εντοπίσαμε τους παράγοντες που σχετίζονται σημαντικά με τον κίνδυνο εμφάνισης ΚΑΝ στους συμμετέχοντες της μελέτης. Διερευνήσαμε και συγκρίναμε την προγνωστική αξία των διαθέσιμων μοντέλων εκτίμησης καρδιαγγειακού κινδύνου σε άτομα χωρίς κολπική μαρμαρυγή (ΚΜ) στην αρχική επίσκεψη και αξιολογήσαμε αν υπάρχει συσχέτιση μεταξύ των λιπιδαιμικών παραμέτρων και των δεικτών κοιλιακής επαναπόλωσης [διάστημα QTc, διάστημα T peak-to-end (Tpe) και αναλογία Tpe/QT]. Αξιολογήσαμε τα ποσοστά επίτευξης των προτεινόμενων στόχων της χοληστερόλης των χαμηλής πυκνότητας λιποπρωτεϊνών (LDL-C), αρτηριακής πίεσης (ΑΠ) και γλυκοζυλιωμένης αιμοσφαιρίνης (HbA1c), καθώς επίσης και τα ποσοστά των ασθενών που ήταν υποψήφιοι για θεραπεία με αναστολείς της proprotein convertase subtilisin/kexin τύπου 9 (PCSK9). Αξιολογήσαμε τις συσχετίσεις (r^2) της απολιποπρωτεΐνης B (apoB) με την LDL και τη χοληστερόλη των μη-υψηλής πυκνότητας λιποπρωτεϊνών (non-HDL-C) σε ασθενείς με τύπου 2 σακχαρώδη διαβήτη (ΣΔ2) ή μεταβολικό σύνδρομο και σε εκείνους χωρίς

ΣΔ2/μεταβολικό σύνδρομο ανάλογα με τα αρχικά επίπεδα των τριγλυκεριδίων (TGs) (< και >200 mg/dL). Επιπλέον, καταγράψαμε τα ποσοστά των ανεπιθύμητων ενεργειών που σχετίζονται με τις θεραπείες καρδιαγγειακής πρόληψης, με ιδιαίτερη έμφαση στην υπολιπιδαιμική αγωγή. Συγκρίναμε τη μείωση της LDL-C σε άτομα που λαμβάνουν στατίνη + αναστολείς αντλίας πρωτονίων (PPI) με εκείνα στα οποία χορηγήθηκαν μόνο στατίνη και ερευνήσαμε εάν υπάρχει το φαινόμενο της διαφυγής της δράσης των στατινών στην κλινική πράξη (δηλαδή αύξηση των επιπέδων της LDL-C κατά την πιο πρόσφατη επίσκεψη κατά >10% συγκριτικά με την τιμή στους 6 μήνες μετά την έναρξη της θεραπείας με στατίνη). Διερευνήσαμε τους παράγοντες κινδύνου για την εμφάνιση χρόνιας νεφρικής νόσου (ΧΝΝ) και υπονατριαιμίας στον πληθυσμό της μελέτης μας.

Αποτελέσματα: Συνολικά 1,334 άτομα συμμετείχαν στην παρούσα μελέτη, τα οποία παρακολουθήθηκαν για 6 έτη (4-10 έτη). Κατά τη διάρκεια της παρακολούθησης συνταγογραφήθηκε υπολιπιδαιμική αγωγή στην πλειοψηφία των συμμετεχόντων στη μελέτη (94%), με τις στατίνες να αποτελούν τον ακρογωνιαίο λίθο της (91%), ενώ το 70% ελάμβανε αντιϋπερτασική θεραπεία. Κατά τη διάρκεια της παρακολούθησής τους, 95 άτομα (7%) εμφάνισαν ΚΑΝ. Η επίπτωση της ΚΑΝ στη μελέτη μας ήταν παρόμοια με την αντίστοιχη μίας ελληνικής μελέτης (ΑΤΤΙΚΗ), αντιπροσωπευτικής του γενικού πληθυσμού (10.4 vs 15.7/1,000 ανθρωπο-έτη, αντίστοιχα). Το ιστορικό ΣΔ2 (HR: 2.09, 95% CI: 1.18-3.70, p <0.001), ΚΑΝ (HR: 2.04, 95% CI: 1.21-3.43, p <0.001) και καπνίσματος (HR: 1.82, 95% CI: 1.17-2.84, p <0.001), καθώς και η ηλικία (HR: 1.07, 95% CI: 1.4-1.9, p <0.001) αποτελούσαν ανεξάρτητους παράγοντες κινδύνου. Η ROC curve ανάλυση έδειξε ότι οι δείκτες $CHADS_2$ και CHA_2DS_2-VASc έχουν ισχυρή προγνωστική αξία για την εμφάνιση ΚΑΝ (C-statistic: $CHADS_2$ 0.592, p <0.01; CHA_2DS_2-VASc 0.568, p <0.05), η οποία ωστόσο δεν είναι ανώτερη σε σύγκριση με εκείνες των κλασικών εργαλείων εκτίμησης SCORE και PCE (C-statistic: 0.612, p <0.001 και 0.717, p <0.001, αντίστοιχα).

Η ανάλυση Spearman's δεν έδειξε σημαντική συσχέτιση μεταξύ HDL-C ή άλλων λιπιδίων με τις ηλεκτροκαρδιογραφικές παραμέτρους που μελετήθηκαν. Οι αναλύσεις ROC curve έδειξαν ότι οι δείκτες $CHADS_2$ και CHA_2DS_2-VASc είχαν ισχυρή προγνωστική αξία για την εμφάνιση νέας ΚΜ (C-statistic: $CHADS_2$ 0.679, p <0.001, CHA_2DS_2-VASc 0.698, p <0.001). Μετά την ενσωμάτωση των χαμηλών επιπέδων HDL-C βελτιώθηκε η προγνωστική αξία αυτών των δεικτών για την πρόβλεψη νέας ΚΜ (C-statistic 0.690 και 0.707, αντίστοιχα, p <0.001).

Σύμφωνα με τις κατευθυντήριες οδηγίες των ESC/EAS 2019, οι ασθενείς πολύ υψηλού καρδιαγγειακού κινδύνου (n=391) εμφάνισαν το χαμηλότερο ποσοστό επίτευξης της LDL-C σε σύγκριση με τους ασθενείς υψηλού (n=457), μέτριου (n=105) και χαμηλού καρδιαγγειακού κινδύνου (n=47) (7 vs 12 vs 42 vs 70%, αντίστοιχα, p <0.05). Αν τα άτομα αυτά ελάμβαναν στατίνη υψηλής αποτελεσματικότητας σε συνδυασμό με εζετιμίμπη, τα αντίστοιχα ποσοστά θα ήταν 36, 47, 95 και 97% για τους ασθενείς πολύ υψηλού, υψηλού, μέτριου και χαμηλού καρδιαγγειακού κινδύνου, αντίστοιχα. Σε περίπτωση επιπρόσθετης θεραπείας με αναστολείς της PCSK9, τα αντίστοιχα ποσοστά θα ήταν 69, 79, 100 και 100%, αντίστοιχα.

Σύμφωνα με τις Αμερικανικές κατευθυντήριες οδηγίες των ACC/AHA 2018, το 46% των ασθενών με ΚΑΝ και το 31% των ατόμων με LDL-C ≥190 mg/dL που ελάμβαναν στατίνη υψηλής αποτελεσματικότητας και εζετιμίμπη θα ήταν υποψήφιοι για θεραπεία με αναστολείς της PCSK9. Σύμφωνα με το κείμενο ομοφωνίας Ελλήνων ειδικών αυτό το ποσοσό θα ήταν χαμηλότερο (22%) για τους ασθενείς που ελάμβαναν εντατική υπολιπιδαιμική θεραπεία και είχαν διαγνωσθεί με ΚΑΝ, ΣΔ2 με βλάβη οργάνου στόχου ή οικογενή υπερχοληστερολαιμία (FH) ή είχαν δυσανεξία στις στατίνες.

Μεταξύ των ασθενών ηλικίας ≥65 ετών, τα ποσοστά επίτευξης των στόχων της LDL-C (ESC/EAS 2011) ήταν 27, 48 και 62% για τους ασθενείς πολύ υψηλού, υψηλού και μέτριου κινδύνου, αντίστοιχα. Από τους διαβητικούς ασθενείς, το 71% είχε ΑΠ <140/85 mmHg, ενώ το 78% των μη διαβητικών είχε ΑΠ <140/90 mmHg. Υψηλότερο ποσοστό των μη διαβητικών ατόμων ≥65 ετών (86%) είχε ΑΠ <150/90 mmHg. Επίσης, υψηλότερο ποσοστό διαβητικών ≥65 ετών είχε HbA1c <8% έναντι <7% (88% και 47%, αντίστοιχα). Σχεδόν 1 στους 3 μη διαβητικούς και 1 στους 10 διαβητικούς ασθενείς ≥65 ετών είχαν επιτύχει και τους 3 στόχους θεραπείας καρδιαγγειακής πρόληψης.

Η συσχέτιση μεταξύ της apoB και της LDL-C ή non-HDL-C ήταν παρόμοια για τα άτομα που είχαν TGs <200 mg/dL. Αν και αυτές οι συσχετίσεις παρέμειναν σημαντικές για τα άτομα με υψηλά επίπεδα TGs (≥200 mg/dL), ο βαθμός συσχέτισης ήταν μειωμένος κυρίως στους ασθενείς με ΣΔ2 ή μεταβολικό σύνδρομο (r^2=0.600, p <0.01 για τη συσχέτιση μεταξύ της ApoB και της LDL-C; r^2=0.604, p <0.01 για τη συσχέτιση μεταξύ της ApoB και της non-HDL-C). Αντίθετα, οι αντίστοιχες συσχετίσεις ήταν ισχυρότερες στους μη διαβητικούς ασθενείς χωρίς μεταβολικό σύνδρομο (r^2=0.710 και 0.714, αντίστοιχα, p <0.01).

Τα ποσοστά αύξησης των τρανσαμινασών και της κρεατινικής κινάσης ήταν 3% και 1%, ενώ μόνο το 2% των συμμετεχόντων στη μελέτη παρουσίασε μυαλγίες.

Κατά τη διάρκεια της παρακολούθησης, ένα ποσοστό ~12% των συμμετεχόντων εμφάνισε νέο ΣΔ2. Παρατηρήθηκε υψηλότερος κίνδυνος εμφάνισης ΣΔ2 στα άτομα με προδιαβήτη που έλαβαν θεραπεία με στατίνες υψηλής αποτελεσματικότητας σε σύγκριση με όσους ελάμβαναν στατίνες μέτριας αποτελεσματικότητας (προσαρμοσμένος OR: 2.12, 95% CI: 1.06-4.24, p <0.05) και εκείνους που δεν έλαβαν στατίνη (προσαρμοσμένος OR: 4.90, 95% CI: 1.16-20.66, p <0.05). Η προσθήκη εζετιμίμπης στη θεραπεία με στατίνη δεν αύξησε τον κίνδυνο εμφάνισης ΣΔ2 στα άτομα με προδιαβήτη (προσαρμοσμένος OR: 0.89, 95% CI: 0.36-2.22, p >0.05). Σε μια επιπρόσθετη ανάλυση μεταξύ των ατόμων με προδιαβήτη η αθηρογόνος δυσλιπιδαιμία (προσαρμοσμένος OR: 3.44, 95% CI: 1.31-9.04, p=0.01) και ο δείκτης μάζας σώματος >25 Kg/m^2 (προσαρμοσμένος OR: 2.54, 95% CI: 1.14-5.66, p <0.05) συσχετίσθηκε με αυξημένο κίνδυνο εμφάνισης ΣΔ2. Δεν παρατηρήθηκε σημαντική διαφορά αναφορικά με τον κίνδυνο εμφάνισης ΣΔ2 μεταξύ των μεταβολικά υγιών μη παχύσαρκων ατόμων (MHNO) και των μεταβολικά υγιών παχύσαρκων (MHO) ατόμων (προσαρμοσμένος OR: 1.46, 95% CI: 0.76-2.82, p >0.05). Οι μεταβολικά μη υγιείς παχύσαρκοι (MUO) ασθενείς είχαν υψηλότερο κίνδυνο εμφάνισης ΣΔ2 από τους MHNO (προσαρμοσμένος OR: 7.87, 95% CI: 4.02-15.42, p <0.01), τους MHO (προσαρμοσμένος OR: 5.45, 95% CI: 2.47-12.04, p <0.01) και τους μεταβολικά μη υγιείς μη παχύσαρκους (MUNO) ασθενείς (προσαρμοσμένος OR: 2.68, 95% CI: 1.28-5.64, p <0.01).

Τα άτομα που έλαβαν στατίνη + PPI είχαν υψηλότερη μείωση της LDL-C κατά 6.4% σε σύγκριση με εκείνα που έλαβαν μόνο στατίνη (p <0.01).

Από τα 181 άτομα που συμμετείχαν στην ανάλυση, ένα ποσοστό 31% εμφάνισε το φαινόμενο της διαφυγής της δράσης των στατινών.

Κατά τη διάρκεια της παρακολούθησης (6 έτη, IQR: 4-10), το 11.9% των ασθενών εμφάνισε ΧΝΝ, ενώ η μέση ετήσια μείωση του eGFR ήταν 0.69 mL/min/1.73 m^2 (IQR: 0.45-2.33). Η πολυπαραγοντική ανάλυση έδειξε ότι τα αρχικά επίπεδα ουρικού οξέος (HR: 1.26, 95% CI: 1.09-1.45, p=0.001), το θήλυ φύλο (HR: 1.74, 95% CI: 1.14-2.65, p=0.01), η ηλικία (HR: 1.10, 95% CI: 1.07-1.12, p<0.001), ο ΣΔ2 (HR: 1.67, 95% CI: 1.05-2.65, p<0.05), η ΚΑΝ (HR: 1.62, 95% CI: 1.02-2.58, p<0.05), η μειωμένη αρχική

νεφρική λειτουργία (eGFR <90 mL/min/1.73 m^2) (HR: 2.38, 95% CI: 1.14-4.81, p<0.05) και η μείωση της LDL-C (HR: 0.995, 95% CI: 0.991-0.998, p=0.01) συσχετίστηκαν με την εμφάνιση ΧΝΝ.

Αφού συμπεριελήφθησαν οι παράγοντες που προδιαθέτουν για την εμφάνιση υπονατριαιμίας και εκείνοι που σχετίσθηκαν με την υπονατριαιμία στις μονοπαραγοντικές μας αναλύσεις, η πολυπαραγοντική ανάλυση έδειξε ότι τα υψηλά επίπεδα HDL-C συσχετίζονται με αυξημένο κίνδυνο εμφάνισης υπονατριαιμίας (προσαρμοσμένος HR: 1.02, 95% CI: 1.01-1.04, p<0.01).

Συμπεράσματα:

1. Η παρούσα μελέτη έδειξε ότι η επίπτωση της ΚΑΝ δυσλιπιδαιμικών ασθενών υψηλού κινδύνου που ελάμβαναν εντατική αγωγή ήταν παρόμοια με την αντίστοιχη των ατόμων που συμμετείχαν σε μια ελληνική μελέτη (ΑΤΤΙΚΗ), αντιπροσωπευτική του γενικού πληθυσμού.
2. Ο ΣΔ, το κάπνισμα, η ηλικία και το προηγούμενο ιστορικό ΚΑΝ αποτελούν ανεξάρτητους παράγοντες εμφάνισης ΚΑΝ σε δυσλιπιδαιμικούς ασθενείς που λαμβάνουν εντατική αγωγή στα πλαίσια της καρδιαγγειακής πρόληψης.
3. Επιβεβαιώθηκε ότι οι δείκτες $CHADS_2$ και CHA_2DS_2-VASc εμφανίζουν ισχυρή προγνωστική αξία για την εμφάνιση ΚΑΝ σε δυσλιπιδαιμικά άτομα χωρίς ΚΜ, χωρίς ωστόσο να είναι ανώτεροι από τους κλασικούς δείκτες SCORE και PCE.
4. Παρά το γεγονός ότι δεν βρέθηκε συσχέτιση μεταξύ των δεικτών της κοιλιακής επαναπόλωσης με τις λιπιδαιμικές παραμέτρους, η μελέτη μας είναι η πρώτη που έδειξε ότι οι δείκτες $CHADS_2$ και CHA_2DS_2-VASc προβλέπουν την εμφάνιση ΚΜ σε δυσλιπιδαιμικούς ασθενείς, με περαιτέρω μικρή βελτίωση της απόδοσής τους όταν λαμβάνονται υπόψη και τα χαμηλά επίπεδα της HDL-C.
5. Επιβεβαιώσαμε ότι ακόμη και σε ένα εξειδικευμένο ιατρείο, η πλειοψηφία των ασθενών και ιδιαίτερα εκείνων με υψηλό καρδιαγγειακό κίνδυνο, όπως οι ασθενείς με ΚΑΝ ή FH, παραμένουν ανεπαρκώς θεραπευμένοι στην καθημερινή κλινική πρακτική.
6. Υπογραμμίσαμε την επιτακτική ανάγκη χορήγησης συνδυασμού ισχυρότερων στατινών με εζετιμίμπη με ή χωρίς αναστολείς της PCSK9 για την επίτευξη των βέλτιστων επιπέδων της LDL-C στην καθημερινή κλινική πρακτική και επιβεβαιώσαμε ότι ένα υψηλό ποσοστό ασθενών με ΚΑΝ ή FH είναι υποψήφιοι για αγωγή με PCSK9 αναστολείς.

7. Είμαστε οι πρώτοι που διερευνήσαμε τις συσχετίσεις της apoB με την LDL-C και non-HDL σε άτομα με ΣΔ2/μεταβολικό σύνδρομο ανάλογα με τα επίπεδα των TG και δείξαμε ότι μειώνονται εξίσου οι 2 συσχετίσεις στα άτομα με αυξημένα TG και κυρίως σε εκείνα με ΣΔ2/μεταβολικό σύνδρομο.

8. Επιβεβαιώσαμε τη βιβλιογραφία που υποστηρίζει ότι το ποσοστό των ανεπιθύμητων παρενεργειών από τη χορήγηση στατινών είναι χαμηλό στην κλινική πράξη. Επιπρόσθετα, φάνηκε ότι η πολυπαραγοντική θεραπεία έχει ουδέτερη, αν όχι προστατευτική επίδραση στην αναμενόμενη επιδείνωση της νεφρικής λειτουργίας με την πάροδο των ετών.

9. Επισημάναμε ότι η θεραπεία με στατίνη υψηλής αποτελεσματικότητας συσχετίζεται με υψηλότερο κίνδυνο εμφάνισης ΣΔ2 στα προδιαβητικά άτομα συγκριτικά με τα αντίστοιχα δεδομένα από τυχαιοποιημένες κλινικές μελέτες. Επιπρόσθετα, επιβεβαιώσαμε ότι η εζετιμίμπη έχει ουδέτερη επίδραση στην ομοιοστασία των υδατανθράκων.

10. Η παρούσα μελέτη έδειξε για πρώτη φορά ότι η αθηρογόνος δυσλιπιδαιμία αυξάνει τον κίνδυνο νεοεμφανιζόμενου ΣΔ2 σε ασθενείς που λαμβάνουν στατίνη, ενώ ο συνδυασμός της με τον προδιαβήτη και το αυξημένο σωματικό βάρος αυξάνει δραματικά την διαβητογόνο επίδραση των στατινών.

11. Η παρούσα μελέτη είναι η πρώτη που έδειξε ότι η μεταβολικά υγιής παχυσαρκία δεν φαίνεται να αυξάνει σημαντικά τον κίνδυνο εμφάνισης ΣΔ2 σε άτομα που λαμβάνουν στατίνη, σε αντίθεση με τη μεταβολικά μη υγιή μη παχυσαρκία και ιδιαίτερα τη μεταβολικά μη υγιή παχυσαρκία. Πιθανά η παρουσία μεταβολικών διαταραχών και όχι το βάρος καθεαυτό σχετίζονται με την εμφάνιση νέου ΣΔ2 σε ασθενείς που λαμβάνουν στατίνη.

12. Επιβεβαιώθηκαν τα λίγα δεδομένα για το φαινόμενο της διαφυγής της δράσης των στατινών, αν και η κλινική του σημασία παραμένει άγνωστη. Έτσι, ασθενείς με αρχικά μεγάλη μείωση της LDL-C αμέσως μετά την έναρξη της αγωγής πρέπει να ελέγχονται προσεκτικά για το ενδεχόμενο αυτό.

13. Επισημάνθηκε για πρώτη φορά η πιθανή αλληλεπίδραση μεταξύ των PPIs και των στατινών που οδηγεί στην ήπια ενίσχυση της υπολιπιδαιμικής δράσης.

14. Επιβεβαιώθηκε ότι η υπερουριχαιμία συσχετίζεται με αυξημένο κίνδυνο εμφάνισης ΧΝΝ σε άτομα με δυσλιπιδαιμία που λαμβάνουν στατίνες και αντιϋπερτασικά φάρμακα.

15. Η παρούσα μελέτη επιβεβαίωσε την περιορισμένη βιβλιογραφία που υποστηρίζει ότι τα υψηλά επίπεδα της HDL-C συσχετίζονται με την εμφάνιση υπονατριαιμίας σε ασθενείς με δυσλιπιδαιμία.

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