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Call for original research papers on
"THE LINK BETWEEN DIABETES AND CARDIOVASCULAR DISEASE"

The most recent observations from pathophysiological, epidemiological, and genetic studies are increasing substantially our knowledge on the close link between diabetes and cardiovascular disease.

Atherosclerosis, the journal of the European Atherosclerosis Society (EAS), is now **calling for the submission of Original Research Papers for a dedicated theme issue on "The link between diabetes and cardiovascular disease"**. Submissions are encouraged from all fields related to the topic including clinical, translational, and basic research.

The submitted Original Research Articles will be handled by Jan Borén, Alberico Catapano, and Katariina Öörni, Co-Editors of *Atherosclerosis*. All papers will be reviewed following standard reviewing procedures for the Journal. **Accepted manuscripts will be published with promotional open access for a one-year period, free of charges for the authors, together with invited reviews on the topic.**

For preparation of the Original Research manuscripts please see the "Guide for authors"

Deadline for submission of the first draft of the Original Research Papers is April 30, 2023. This call is only open for Original Research Articles and no review articles are allowed. Please select "Special issue: Diabetes and CVD" as article type at submission.

To submit your paper go to: Editorial Manager®

Atherosclerosis newsletter

Simona Negrini and Arnold von Eckardstein

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Hypercholesterolemia is a causal and treatable risk factor of atherosclerotic cardiovascular diseases. Like other hazards, its importance depends on both dosage (i.e., plasma concentration of LDL-cholesterol) and exposure (i.e., duration of LDL-cholesterol elevation). Here, we summarize the findings of several articles published in the January or February issues of *Atherosclerosis* that support this concept or describe therapeutic strategies to interfere with this interaction of time and space.

Impact of lipid lowering on coronary atherosclerosis moving from the lumen to the artery wall

Randomized clinical trials have demonstrated that increasingly intensive lowering of low-density lipoprotein cholesterol (LDL-C) reduces the rate of cardiovascular events in the primary and secondary prevention setting. Integration of serial coronary imaging within clinical trials has enabled evaluation of medical therapies on the natural history of coronary disease. These studies have extended from early investigation of coronary obstruction with angiography to more contemporary evaluation of plaque burden and composition with imaging modalities that directly visualize the artery wall. The findings of these trials have demonstrated that intensive lipid lowering promotes plaque regression and stabilization. The lessons of this body of research provide a biological rationale underscoring the ability of intensive lipid lowering to reduce cardiovascular risk and have the potential to promote greater uptake in clinical practice.

These issues are brilliantly discussed in the review by Di Giovanni et al..

Cumulative dyslipidemia with arterial stiffness and carotid IMT progression in asymptomatic adolescents: A simulated intervention longitudinal study using temporal inverse allocation model

Cumulative dyslipidemia measured during childhood or adolescence through mid-adulthood has been associated with markers of preclinical atherosclerosis measured at a single time-point in mid-adulthood. Conversely, higher adolescent arterial stiffness, a marker of arteriosclerosis, and carotid intima-media thickness (cIMT), a marker of atherosclerosis, may temporally precede cardiometabolic diseases in young adulthood. Agbaje et al. aimed to examine the longitudinal associations of total cholesterol (TC), non–high-density lipoprotein cholesterol (non–HDL-C), high-density lipoprotein

cholesterol (HDL-C), triglyceride, and low-density lipoprotein cholesterol (LDL-C) with carotid-femoral pulse wave velocity (cfPWV) and cIMT progression.

The authos studied 1779, 15-year-old participants from the Avon Longitudinal Study of Parents and Children, UK birth cohort, followed up for 9 years. Fasting TC, non–HDL-C, HDL-C, triglyceride, and LDL-C were measured at 15, 17, and 24 years and age-categorized as normal, elevated, and dyslipidemia based on National Heart, Lung, and Blood Institute lipid guidelines. cfPWV and cIMT were measured at 17 and 24 years. Associations were examined using linear mixed-effect models. To simulate the treatment of dyslipidemia, temporal inverse allocation model analyses were conducted.

Among 1779 participants, mean lipid levels and proportions at elevated or dyslipidemia categories increased from ages 15 through 24 years. Persistently elevated TC: effect estimate 0.026 mm, elevated non–HDL-C, and elevated LDL-C were cumulatively associated with cIMT progression. Persistent borderline-low HDL-C and very-low HDL-C levels were associated with cIMT progression. A temporal inverse allocation of elevated and dyslipidemic levels with normal lipid levels at age 17 years attenuated the associations of cumulative elevated TC, non–HDL-C, LDL-C, and low HDL-C with cIMT progression. Cumulative elevated lipids or dyslipidemia were not associated with cfPWV progression.

Simulated treatment intervention at age 17 years neutralizes the effect of dyslipidemia on atherosclerosis progression. Optimal timing for reversing dyslipidemia-related atherosclerosis progression in asymptomatic youths is late adolescence. A universal pediatric lipid screening is highly recommended for the primary prevention of subclinical atherosclerosis.

How does cholesterol burden change the case for investing in familial hypercholesterolaemia? A cost-effectiveness analysis

There is widespread consensus that early diagnosis and treatment of familial hypercholesterolaemia (FH) are effective, safe, cost-effective, and inexpensive. Nonetheless, little is known about the magnitude of health losses and costs due to underdiagnosis and the benefits from diagnosis and treatment. Furthermore, in individuals with FH, the duration of exposure to high LDL-C is an important determinant of cardiovascular disease risk (CVD) – termed “cholesterol burden”. However, cost-effectiveness studies have not examined the impact of cholesterol burden on their results. Faria et al. aimed to assess how the long-term benefits and costs of diagnosis and treatment of FH vary by prognostic factors and cholesterol burden.

A new cost-effectiveness model was developed from the perspective of the UK National Health Service (NHS), informed by routine data from individuals with FH. The primary outcome was net health gain (i.e., health benefits net of the losses due to costs), expressed in quality-adjusted life years (QALYs) at the £15,000/QALY threshold. Prognostic factors included pre-treatment LDL-C, age, gender, and CVD history.

If cholesterol burden is considered, diagnosis resulted in positive net health gain in all individuals with pre-treatment LDL-C ≥ 4 mmol/L, and in those with pre-treatment LDL-C ≥ 2 mmol/L aged ≥50 years or who have CVD history. If cholesterol burden is not considered, diagnosis resulted in lower net health gain, but still positive in children aged 10 years with pre-treatment LDL-C ≥ 6 mmol/L and adults aged 30 years with pre-treatment LDL-C ≥ 4 mmol/L.

Diagnosis and treatment of most people with FH results in large net health gains, particularly in those with higher pre-treatment LDL-C. Economic evaluations of FH interventions should consider the sensitivity of the study conclusions to cholesterol burden, particularly where interventions target younger patients, and explicitly consider prognostic factors such as pre-treatment LDL-C, age, and CVD history.

Cardiovascular disease onset in old people with severe hypercholesterolemia

People with severe hypercholesterolemia, usually defined by low-density lipoprotein cholesterol (LDL-C) concentrations ≥ 190 mg/dL, are considered at high risk for development of atherosclerotic cardiovascular disease (ASCVD). FH variants are associated with higher atherosclerotic cardiovascular disease risk (ASCVD) even when compared with other forms of severe hypercholesterolemia, especially in young people. Lipid lowering therapies (LLT) may change hypercholesterolemia natural history. Coutinho et al. evaluated the factors associated with occurrence of ASCVD in old severe hypercholesterolemics diagnosed or not with FH and undergoing LLT.

Hypercholesterolemic individuals ≥60 years participating on a genetic cascade screening for FH were divided in 4 groups (2 × 2) according to the presence (variant+) or not (variant-) of FH genetic variants and previous ASCVD (ASCVD+ and ASCVD-). Biomarkers associated with new incident ASCVD events were tested using Cox models.

From 4,111 genotyped individuals, 377 (9.1%) were elderly, 28.9% males, 42.7% variant+, 32.1% with previous ASCVD, LLT duration 9 years, and on treatment LDL-cholesterol 144 mg/dL. After 4.8 years of follow up there were 47 incident events. The annualized event rates were 0.8%, 2.3%, 5.2% and 6.3%, respectively for groups variant-/ASCVD-, variant+/ASCVD-, variant-/ASCVD+ and, variant+/ASCVD+. Only presence of previous ASCVD was independently associated with incident ASCVD. No interaction was found for previous ASCVD and variants.

In old severe hypercholesterolemic patients, FH variants were not associated with new ASCVD disease onset. Previous cardiovascular disease was independently associated with new ASCVD onset.

Long-term persistence with evolocumab treatment and sustained reductions in LDL-cholesterol levels over 30 months: Final results from the European observational HEYMANS study

Variability in low-density lipoprotein-cholesterol (LDL-C) level control at a population level is associated with poor cardiovascular outcomes. Limited data exist on LDL-C level variability or long-term persistence with the monoclonal antibody evolocumab in routine clinical practice. Using data from the HEYMANS registry, Ray et al. aimed to assess evolocumab persistence and discontinuation over 30 months of evolocumab treatment and to evaluate at a population level the variability in LDL-C level reductions during the study period.

HEYMANS is a prospective registry of adults initiating evolocumab in routine clinical practice in 12 European countries. Data were collected for up to, and including, 6 months before evolocumab initiation and up to 30 months after. Evolocumab discontinuation was analysed for two time periods: 0–12 months and 12–30 months.

In total, 1951 patients were included in the study. The median reduction in LDL-C levels was 58% within 3 months after evolocumab initiation; this reduction was maintained over 30 months. More than 90% of patients continued receiving evolocumab at 12 months and 30 months of follow-up. Of patients with an LDL-C level measurement during follow-up, approximately 85% achieved a ≥30% reduction from baseline at each follow-up visit and approximately 60% achieved a ≥50% reduction.

Evolocumab therapy was associated with sustained LDL-C level reductions up to 30 months, and persistence with evolocumab remained high, both at 12 and 30 months. Expanding the use of monoclonal antibodies such as evolocumab could provide improvements in LDL-C level control at a population level in European clinical practice.

Efficacy, safety, adherence and persistence of PCSK9 inhibitors in clinical practice: A single country, multicenter, observational study (AT-TARGET-IT)

Hypercholesterolaemia is a major risk factor of atherosclerotic cardiovascular disease (ASCVD), the leading cause of death worldwide. Proprotein Convertase Subtilisin/Kexin type 9 inhibitors (PCSK9i) are recommended in patients at high and very-high cardiovascular risk, with documented ASCVD, and in very-high risk patients with familial hypercholesterolaemia not achieving LDL-cholesterol (LDL-C) goal while receiving maximally tolerated dose of lipid-lowering therapy (LLT). Single country real-life data, reporting the use of PCSK9i in clinical practice, are limited. Therefore, Gargiulo et al. designed AT-TARGET-IT, an Italian, multicenter, observational registry on the use of PCSK9i in clinical practice. All data were recorded at the time of the first prescription and at the latest observation preceding inclusion in the study.

798 patients were enrolled. The median reduction in LDL-C levels was 64.9%. After stratification for CV risk, 63.8% achieved LDL-C target; of them, 83.3% took LLTs at PCSK9i initiation

and 16.7% did not. 760 patients (95.2%) showed high adherence to therapy, 13 (1.6%) partial adherence, and 25 (3.1%) poor adherence. At 6 months, 99.7% of patients enrolled in the study remained on therapy; there were 519 and 423 patients in the study with a follow-up of at least 12 and 18 months, respectively. Persistence in these groups was 98.1% and 97.5%, respectively. Overall, 3.5% of patients discontinued therapy. No differences in efficacy, adherence, and persistence were found between alirocumab and evolocumab.

PCSK9i are safe and effective in clinical practice, leading to very high adherence and persistence to therapy, and achievement of recommended LDL-C target in most patients, especially when used as combination therapy.