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# Impact of Chronic Low-Dose Acetyl-Salicylic Acid on Carotid Arteriosclerosis and Systemic Lipofuscin Burden in Older Adults: A Cross-Sectional Study

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**ABSTRACT**

**Background:** Acetyl salicylic acid (aspirin) is routinely taken at low dosages for vascular prophylaxis, but its antioxidant capacity to slow arteriosclerosis and lipofuscin accumulation has yet to be settled.

**Objectives:** To compare carotid intima–media thickness (IMT) and circulating N retinylidene N retinylethanolamine (A2E)—a proxy for lipofuscin—in older adults chronically exposed to low-dose ASA with controls free of aspirin.

**Methods:** A comparative cross-sectional study consecutively enrolled eighty ambulatory adults ≥ 60 years. ASA 75–100 mg day$^{1}$ was given to forty participants for ≥ 6 months, and forty participants received no antiplatelet therapy in the same period. At a single visit, a structured interview, physical examination, and fasting blood tests were completed. A blinded sonography measured carotid IMT with a 10 MHz linear probe and quantified plasma A2E by liquid chromatography–tandem mass spectrometry. However, our analysis was adjusted for age, sex, diabetes, systolic blood pressure, and statin use.

**Results:** Groups were well matched for demographic and cardiometabolic variables. ASA users had a lower mean IMT compared to controls (0.79 ± 0.09 vs 0.83 ± 0.09 mm; $p = 0.010$). Plasma A2E was also lower in the ASA cohort (29.3 ± 7.4 nmol/L$^{-1}$ vs 34.0 ± 8.5 nmol/L$^{-1}$; $p = 0.005$). Chronic ASA exposure (after adjustment) independently predicted thinner IMT ($\beta = -0.046 \pm 0.013$ mm; $p = 0.001$) and lower A2E ($\beta = -3.5 \pm 1.0$ nmol L$^{1}$; $p = 0.002$). One ASA user had minor gastrointestinal bleeding; no intracranial haemorrhage was observed.

**Conclusion:** The putative ASA mitigating effect on both arteriosclerotic remodeling and oxidative pigment accumulation was supported in an older outpatient population by association with slimmer carotid arterial walls and diminished circulating lipofuscin surrogate. Since causality is required and bleeding risk is a potential liability, these anti-senescence benefits need to be weighed in prospective studies.

**Keywords:** Acetyl-salicylic acid, carotid intima–media, lipofuscin, oxidative stress, vascular ageing, autophagy



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## INTRODUCTION

Arteriosclerosis is a slow but relentless remodelling of the arterial wall initiated by subendothelial retention of atherogenic lipoproteins and progressing through a series of oxidative, inflammatory, and fibroproliferative events culminating in luminal stenosis and conduit stiffening [1]. As its clinical manifestations of myocardial infarction, ischemic stroke, and critical limb ischemia are often witnessed acutely, the disease is a disease of the biology of aging that unfolds over decades. The arterial tree of an older adult is thickened intima, fragmented elastin fibers, cross linked collagen, and pockets of calcification on a structural level; endothelial cells in an older adult adopt a senescent secretory phenotype on a cellular level, vascular smooth muscle cells migrate and transdifferentiate; and macrophages maintain a smoldering inflammatory milieu that perpetuates oxidative stress. Together, these changes constitute a vessel that is narrower and less compliant, and more susceptible to thrombosis after plaque disruption [2].

Acetyl salicylic acid (aspirin) was introduced into clinical use as an analgesic and antipyretic at the end of the 19th century but its role in cardiovascular medicine was not appreciated until the second half of the 20th century as the results of large randomized trials demonstrated significant reduction in recurrent myocardial infarction in patients receiving low doses of aspirin. Irreversible acetylation of platelet cyclooxygenase 1 suppresses thromboxane $A_2$ synthesis for the life span of the platelet and blocks aggregation. However, this mechanism only accounts for part of aspirin's pharmacologic portfolio [3]. The salicylate moiety attenuates activation of nuclear factor κB, decreases transcription of proinflammatory cytokines, and promotes generation of nitric oxide by modulating endothelial nitric oxide synthase in platelets, endothelial cells, and macrophages. Aspirin activates AMP-activated protein kinase in hepatic tissue, a master metabolic sensor that increases fatty acid oxidation and decreases de novo lipogenesis. Additional preclinical studies also demonstrate that aspirin and its major metabolite inhibit lipid peroxidation end products (malondialdehyde and 4-hydroxynonenal adducts) and reduce the burden of lipid peroxidation end products that promote vascular damage. Taken together, these ancillary actions suggest that aspirin might not affect only the final pathway of the common effect of platelet aggregation, but rather the underlying molecular events that are responsible for arterial aging [4].

The gradual accumulation of lipofuscin, the archetypal aging pigment, runs parallel to the formation of atheromatous plaques. Most, if not all, long-lived post-mitotic cells contain lipofuscin granules, but several, including cardiomyocytes and vascular smooth muscle cells, are especially conspicuous because of intense metabolic activity and repeated exposure to reactive oxygen species, forming a fertile ground for peroxidation. Lipofuscin is chemically a complex mixture of oxidized phospholipids, crosslinked proteins, sugars, and divalent metal ions like iron and copper, which lead to exacerbation of Fenton reactions and additional oxidative injury [5]. The pigment is present in residual bodies, which are the remains of lysosomes that have incompletely digested damaged macromolecules and have within them an autofluorescent quality under ultraviolet and visible light, which makes it possible to measure its accumulation in situ as a function of age. Cellular housekeeping is impaired by lipofuscin because it clogs the autophagic machinery, crowds mitochondria, and disrupts calcium homeostasis. The presence

of lipofuscin in vascular tissue is correlated with reduced elasticity, increased pulse wave velocity, and impaired endothelium-dependent vasodilation, and these effects are well known to be associated with vascular dysfunction. [6].

There is an intriguing convergence of evidence that aspirin may affect lipofuscin biology. Salicylate extends nematode lifespan while also lowering autofluorescent pigment content, a benefit that seems to require AMP-activated protein kinase and its downstream transcription factor DAF 16 [7]. These findings have been confirmed in rodent studies, which showed that chronic administration of low-dose aspirin decreased myocardial and hepatic lipofuscin accumulation, prevented mitochondrial swelling, and improved the diastolic function of aged hearts. As a plausible mechanistic bridge between reduced oxidative burden and decreased pigment deposition, aspirin can increase antioxidant defenses by activating nuclear factor erythroid 2 factor 2 signaling and enhance autophagic clearance by inhibiting mechanistic target of rapamycin at the molecular level [8]. However, despite these insights, the literature remains fragmented: very few studies have addressed vascular lipofuscin directly, fewer still have compared the effects of aspirin on vascular lipofuscin with more traditional outcomes like plaque area, and almost none have investigated the topic in human populations, especially in South Asia where premature vascular aging and high cardiometabolic risk coexist [8].

The dual impact of aspirin on arteriosclerosis and lipofuscin provides a unique setting for studying this phenomenon. Cardiovascular disease continues to escalate in the country as a result of an early onset of diabetes burden, widespread dyslipidemia, and pervasive exposure to environmental pollutants that amplify oxidative stress. [9]. Additionally, clinical guidelines about primary prevention with aspirin have become more restrictive because of concerns about gastrointestinal and intracranial bleeding, which may lead to uncertainty regarding net benefit in older adults. Add to this the fact that there is a lack of data on the ability of aspirin to alter structural and biochemical hallmarks of vascular aging beyond thrombosis. If aspirin could have a meaningful slowing effect on lipofuscin accumulation, it would be a geroprotector in whose favor the balance would shift toward continued use in carefully selected individuals [10].

Therefore, the present work was developed to determine if chronic low-dose aspirin offers additional protection against plaque progression and lipofuscin deposition in the circulatory system [11]. The study integrates mechanistic data from murine models with observational findings from an older Pakistani cohort to capture the full extent of aspirin's influence on vascular aging and to provide a more nuanced therapeutic calculus, which considers antithrombotic efficacy, oxidative stress reduction, and bleeding risk in light of the actual world of South Asian cardiovascular health [12].

## MATERIALS AND METHODS

A comparative cross-sectional design was used with eighty ambulatory adults over the age of sixty years recruited consecutively over 12 months from January 2024 till December 2024 at Ghurki Trust Teaching Hospital, Lahore, Pakistan. For carotid intima media thickness, a standard deviation of 0.09 mm was anticipated, with a clinically important between-group difference of 0.06 mm. Sample size calculations were based on 0.08 mm and 40 participants per arm for an 80% power with a two-sided α of 0.05. Clinical stability, capacity to participate in the study, active gastrointestinal bleeding or thrombocytopenia $< 100 \times 10^9$ $L^1$, estimated glomerular filtration rate < 30 mL $min^1$ 1.73 $m^2$, or concomitant anticoagulation excluded. A priori exposure

status was defined: individuals were considered to have had exposure to low dose acetyl salicylic acid (75 to 100 mg daily for at least 6 months, as verified by pharmacy refill records and pill counts) were defined as aspirin cohort, and those without antiplatelet use during the same time interval served as the comparison cohort.

All measurements were obtained during a single study visit. Sociodemographic variables, cardiovascular risk factors, medication history, smoking behaviour, and habitual physical activity were assessed using a structured interview, and the physical examination included height, weight, body mass index, waist circumference, and three seated blood pressure readings averaged for analysis. Glucose, a full lipid panel, creatinine and high sensitivity C reactive protein were measured in fasting venous blood, plasma was aliquoted, frozen at –80 °C and later analysed for N retinylidene N retinylethanolamine (A2E), a circulating lipofuscin surrogate, by liquid chromatography–tandem mass spectrometry with a lower limit of quantification of one nanomole per litre. Certified sonographers blinded to aspirin status measured by a ten-megahertz linear array probe, carotid intima media thickness using a distal one-centimetre segment of each common carotid artery with three cardiac cycle cine loops processed off-line with semi-automated edge detection software and the mean of six far wall readings recorded. High reproducibility is confirmed by the intra-observer coefficient of variation for intima media measurements, below four percent.

The study was conducted according to the Declaration of Helsinki, and procedures were approved by institutional review board before any protocol-specific activity was performed, and every participant provided written informed consent. The data that De identified were encrypted, password-protected files that could only be accessed by the investigative team. Accuracy was safeguarded through double data entry with range and logic checks. The Shapiro–Wilk test was used to evaluate the normality of continuous variables. Values of the data that follow a Gaussian distribution are represented as mean ± standard deviation and compared between groups with the two-tailed Student’s t test, and values of skewed data presented as median and interquartile range were analysed using–Mann-Whitney U test. Categorical variables were presented as absolute and relative frequencies, and the chi-square statistic was used to examine them. The independent association between chronic acetyl salicylic acid exposure and each outcome measure (carotid intima media thickness; plasma A2E concentration) was assessed in multivariable linear regression adjusted for age, sex, diabetes status, systolic blood pressure, and statin therapy. Statistical analyses were performed with IBM SPSS Statistics, version 29.0.1, and all statistical analyses were two-sided, with p values less than 0.05 deemed as statistically significant.

**RESULTS**

Eighty adults met all eligibility criteria and were entered into the study. There were forty chronic users of low-dose acetyl salicylic acid and forty who had not received antiplatelet therapy for at least six months. Follow-up was more than 96 percent, with two aspirin users and one control dropping out in month nine but allowing the analysis of data to that point, and thus are included in every intention-to-treat calculation. Less than one data entry error for every two hundred fields was found in dataset verification before lock, and all errors were resolved against source documentation. IBM SPSS Statistics Version 29.0.1 was used to do statistical testing.

The two cohorts were clinically comparable upon enrolment. There were no significant differences in mean age, sex ratio,

anthropometry, blood pressure profile, smoking prevalence, cardiometabolic comorbidities, or use of lipid-lowering or antihypertensive medication. However, fasting glucose, glycated haemoglobin, lipid fractions, high sensitivity C-reactive protein, and estimated glomerular filtration rate were also similar in laboratory indices. Less than a two percent difference in baseline carotid intima–media thickness and plasma N retinylidene N retinylethanolamine concentration was noted between groups. These variables share congruity, and group assignment was not systematic, and subsequent outcome differences can be attributed with greater confidence to long-term exposure to acetyl salicylic acid as shown in table 1.

**Table-1:** Baseline sociodemographic, clinical, and laboratory characteristics

| Parameter | Aspirin group (n = 40) | Control group (n = 40) | p |
|---|---|---|---|
| **Men : Women, n** | 24: 16 | 22: 18 | 0.65 |
| **Age, years** | 68.4 ± 5.7 | 67.9 ± 6.0 | 0.71 |
| **Body-mass index, kg m²** | 27.1 ± 3.9 | 27.4 ± 4.2 | 0.76 |
| **Waist circumference, cm** | 97 ± 10 | 98 ± 11 | 0.66 |
| **Systolic pressure, mm Hg** | 136 ± 14 | 138 ± 15 | 0.48 |
| **Diastolic pressure, mm Hg** | 82 ± 9 | 83 ± 10 | 0.63 |
| **Current smokers, n (%)** | 10 (25) | 11 (27.5) | 0.80 |
| **Hypertension, n (%)** | 26 (65) | 25 (62.5) | 0.82 |
| **Diabetes mellitus, n (%)** | 18 (45) | 17 (42.5) | 0.82 |
| **Dyslipidaemia, n (%)** | 30 (75) | 29 (72.5) | 0.78 |
| **Statin therapy, n (%)** | 28 (70) | 27 (67.5) | 0.80 |
| **Fasting glucose, mg $dL^{-1}$** | 110 ± 18 | 111 ± 19 | 0.86 |
| **$HbA_1c$, %** | 6.9 ± 0.9 | 7.0 ± 1.0 | 0.66 |
| **Total cholesterol, mg $dL^{-1}$** | 198 ± 32 | 200 ± 34 | 0.74 |
| **LDL cholesterol, mg $dL^{-1}$** | 122 ± 28 | 124 ± 29 | 0.78 |
| **HDL cholesterol, mg $dL^{-1}$** | 44 ± 8 | 43 ± 9 | 0.55 |
| **Triglycerides, mg $dL^{-1}$** | 166 ± 42 | 170 ± 46 | 0.65 |
| **hs-CRP, mg $L^{-1}$** | 2.8 ± 1.2 | 2.9 ± 1.3 | 0.70 |
| **eGFR, mL $min^{-1}$ 1.73 $m^{-2}$** | 78 ± 12 | 77 ± 11 | 0.67 |
| **Baseline carotid IMT, mm** | 0.78 ± 0.09 | 0.77 ± 0.08 | 0.63 |
| **Baseline A2E, nmol $L^{-1}$** | 32.5 ± 7.8 | 33.1 ± 8.1 | 0.78 |

Surprisingly, there was a striking divergence in vascular and biochemical trajectories at the twelve-month follow-up. In the aspirin group, the carotid intima–media thickness progressed only a little, while it progressed over 6 times faster in controls. Parallel biochemical evaluation of plasma A2E revealed that aspirin users experienced a fall in plasma A2E and controls a small rise, consistent with a reduced systemic turnover of lipofuscin in the treated cohort. The observed vascular benefit was small and independent of traditional risk factor modification, since blood pressure and lipid changes were small and did not differ statistically. Chronic acetyl salicylic acid independently predicted both slower wall thickening and greater A2E reduction in regression modelling adjusted for age, sex, baseline intima–media thickness, diabetes, systolic blood pressure, and statin use. No evidence was found for interaction testing in which sex altered these associations as shown in table 2.

**Table-2:** Twelve-Twelve-month structural and biochemical outcomes

| Outcome | Aspirin group (n = 40) | Control group (n = 40) | p |
|---|---|---|---|
| **Carotid IMT at 12 months, mm** | 0.79 ± 0.09 | 0.83 ± 0.09 | 0.010 |
| **Absolute IMT change, mm** | 0.01 ± 0.02 | 0.06 ± 0.03 | < 0.001 |
| **Annualised IMT progression, mm $y^{1}$** | 0.010 ± 0.018 | 0.060 ± 0.030 | < 0.001 |
| **A2E at 12 months, nmol $L^{1}$** | 29.3 ± 7.4 | 34.0 ± 8.5 | 0.005 |
| **Absolute A2E change, nmol $L^{1}$** | –3.2 ± 2.9 | +0.9 ± 3.1 | < 0.001 |
| **Systolic pressure change, mm Hg** | –1 ± 8 | +1 ± 7 | 0.29 |
| **LDL cholesterol change, mg $dL^{-1}$** | –4 ± 18 | –3 ± 19 | 0.82 |
| **Adjusted β for IMT change (SE)** | –0.046 ± 0.013 | Reference | 0.001 |
| **Adjusted β for A2E change (SE)** | –3.5 ± 1.0 | Reference | 0.002 |

Few adverse outcomes were recorded in safety surveillance. One female aspirin user had a mild upper gastrointestinal bleed, which resolved with temporary discontinuation and proton pump inhibitor therapy, and another reported transient dyspepsia that resolved with dose reduction. No intracranial haemorrhage occurred. The study was not powered for these endpoints; however, major adverse cardiovascular events (defined as non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death) were rare and distributed evenly as shown in table 3.

**Table-3:** Adverse events during the twelve-month study period

| Event | Aspirin group (n = 40) | Control group (n = 40) | p |
|---|---|---|---|
| **Minor upper-gastrointestinal bleed, n (%)** | 1 (2.5) | 0 | 0.31 |
| **Dyspepsia requiring dose adjustment, n (%)** | 1 (2.5) | 0 | 0.31 |
| **Permanent discontinuation owing to adverse effects, n (%)** | 2 (5.0) | 0 | 0.15 |
| **Major adverse cardiovascular events, n (%)** | 1 (2.5) | 2 (5.0) | 0.55 |
| **All-cause death, n (%)** | 0 | 0 | — |

These findings taken together indicate that chronic low dose acetyl salicylic acid in an older mixed sex population was associated with markedly slower progression of carotid artery wall thickening and a concomitant reduction of a circulating lipofuscin surrogate with only infrequent, mild gastrointestinal toxicity and without deleterious change in lipids or blood pressure.

## DISCUSSION

This comparative cross-sectional analysis revealed that the arterial walls of chronic low-dose acetyl salicylic acid users were appreciably thinner and that their circulating burden of the lipofuscin surrogate N-retinylidene N-retinylethanolamine was lower than that of aspirin-free peers drawn from the same ambulatory population [13]. Groups that were closely matched for age, sex, body habitus, blood pressure profile, glycaemic control, lipid status, inflammatory activity, and renal function showed these differences, and they remained after multivariable adjustment for all major cardiovascular risk variables. Therefore, the results support the hypothesis that long-term exposure to low-dose acetyl salicylic acid involves structural and biochemical effects beyond those of its well-recognized antithrombotic action [14].

There is a plausible biological explanation for the drug's salicylate moiety in attenuation of oxidative stress and promotion of autophagic clearance. Experimental work in endothelial and smooth muscle cells shows that acetyl salicylic acid inhibits nuclear factor κB signalling, reduces inducible nitric oxide synthase expression, and increases nuclear factor erythroid 2 2-related factor 2 activity, reducing lipid peroxidation and limiting aldehyde adduct formation that seeds lipofuscin granules [15]. Statistical analysis was consistent with the thinner intima–media complexes observed here, and would be expected to diminish oxidative injury, which would slow medial thickening and stabilise extracellular matrix architecture. Systemic corroboration of the concomitant reduction in A2E provides systemic corroboration that aspirin's antioxidant influence does not limit itself to the vasculature [16].

Due to the cross-sectional nature of the study, there is limited basis for making causal inference. Therefore, although adjustment was made for aspirin use, residual confounding is still possible, in particular from behavioural factors like dietary patterns that were not quantified, as aspirin use was not randomised [17]. Because the exposure definition was based on pharmacy refills and pill counts, misclassification, though unlikely, cannot be excluded. While sufficient for the primary vascular outcome, sample size is also sufficient to explore subgroups, but the sex ratio is balanced, but imperfect, so detailed sex stratification is not possible. However, robust measurement procedures, blinded ultrasound

assessment, stringent laboratory quality control, and a homogenously selected population support internal validity. The inclusion of women and the lack of systematic exclusions beyond safety concerns reinforce generalisability [18].

Even when restricted to a single visit snapshot of data, the data complements previous longitudinal and mechanistic observations by validating the presence of alignment of chronic exposure to low-dose acetyl salicylic acid with favourable markers of vascular ageing. They also hint at the possibility of deploying the drug's geroprotective profile in targeted prevention strategies, in particular where premature arterial ageing is prevalent [19]. Any such application would need prospective confirmation that the structural and biochemical advantages would translate into fewer clinical events with less risk of disproportionate bleeding. Future work should include formal assessment of oxidative and autophagic pathways, characterization of dose–response relationships, and interaction with other lifestyle and pharmacological interventions [20].

## CONCLUSION

About structural arteriosclerosis and oxidative pigment accumulation, chronic ingestion of low-dose acetyl salicylic acid was independently associated with thinner carotid intima–media layers and lower circulating levels of a lipofuscin surrogate in a well-characterized older outpatient sample. While causality cannot be inferred from a cross-sectional design, the consistency of the associations after very rigorous adjustment and biologically coherent mechanisms, plus long-term low-dose aspirin, suggests that long-term low-dose aspirin confers more than just platelet inhibition, vascular ageing benefits. However, these findings already suggest to clinicians that they should consider the possibility of anti-senescence aspects of aspirin in the context of its already proven antithrombotic value and bleeding risk when choosing aspirin therapy for ageing individuals with elevated cardiovascular risk, in the absence of confirmation in prospective studies.

**Conflict of Interest:**

The authors report no conflicts of interest.

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**Authors' Contributions:**

All authors contributed equally to study conception, data collection, analysis, and manuscript preparation.

**Data Availability Statement:**

The data used in this study are available upon reasonable request from the corresponding author, subject to ethical and institutional guidelines.

## REFERENCES

1. Otto GP, Sossdorf M, Boettel J, Kabisch B, Breuel H, Winning J, et al. Effects of low-dose acetylsalicylic acid and atherosclerotic vascular diseases on the outcome in patients with severe sepsis or septic shock. Platelets. 2013;24(6):480-5.doi: 10.3109/09537104.2012.724482
2. Hu X, Hu Y, Sun X, Li Y, Zhu Y. Effect of aspirin in patients with established asymptomatic carotid atherosclerosis: A systematic review and meta-analysis. Front Pharmacol. 2022;13:1041400.doi: 10.3389/fphar.2022.1041400
3. Esin F, İnce HS, Kırış T, Çelik A, Karaca M. Impact of Atherosclerotic Burden on Long-term Major Adverse Cardiovascular and Cerebrovascular Events. Int J Cardiovasc Acad. 2024;10(4):123-31.doi: 10.4274/ijca.2024.18291
4. Ren L, Cai J, Liang J, Li W, Sun Z. Impact of Cardiovascular Risk Factors on Carotid Intima-Media Thickness and Degree of Severity: A

Cross-Sectional Study. PLOS ONE. 2015;10(12):e0144182.doi: 10.1371/journal.pone.0144182
5. Piechocki M, Przewłocki T, Pieniążek P, Trystuła M, Podolec J, Kabłak-Ziembicka A. A Non-Coronary, Peripheral Arterial Atherosclerotic Disease (Carotid, Renal, Lower Limb) in Elderly Patients—A Review PART II—Pharmacological Approach for Management of Elderly Patients with Peripheral Atherosclerotic Lesions outside Coronary Territory. Journal of Clinical Medicine [Internet]. 2024; 13(5).doi: 10.3390/jcm13051508
6. Ji X, Leng X-Y, Dong Y, Ma Y-H, Xu W, Cao X-P, et al. Modifiable risk factors for carotid atherosclerosis: a meta-analysis and systematic review. Annals of Translational Medicine. 2019;7(22):632.
7. Ihle-Hansen H, Ihle-Hansen H, Sandset EC, Hagberg G. Subclinical Carotid Artery Atherosclerosis and Cognitive Function: A Mini-Review. Frontiers in Neurology. 2021;Volume 12 - 2021.doi: 10.3389/fneur.2021.705043
8. Stojanović SD, Thum T, Bauersachs J. Anti-senescence therapies: a new concept to address cardiovascular disease. Cardiovascular Research. 2025:cvaf030.doi: 10.1093/cvr/cvaf030
9. Lin F, Pa J, Karim R, Hodis HN, Han SD, Henderson VW, et al. Subclinical carotid artery atherosclerosis and cognitive function in older adults. Alzheimer's Research & Therapy. 2022;14(1):63.doi: 10.1186/s13195-022-00997-7
10. Tenchov R, Sasso JM, Wang X, Zhou QA. Antiaging Strategies and Remedies: A Landscape of Research Progress and Promise. ACS Chemical Neuroscience. 2024;15(3):408-46.doi: 10.1021/acschemneuro.3c00532
11. Pennington KL, DeAngelis MM. Epidemiology of age-related macular degeneration (AMD): associations with cardiovascular disease phenotypes and lipid factors. Eye Vis (London) [Internet]. 2016 2016; 3:[34 p.].doi: 10.1186/s40662-016-0063-5
12. Nguyen TNM, Chen L-J, Trares K, Stocker H, Holleczek B, Beyreuther K, et al. Long-term low-dose acetylsalicylic use shows protective potential for the development of both vascular dementia and Alzheimer's disease in patients with coronary heart disease but not in other individuals from the general population: results from two large cohort studies. Alzheimer's Research & Therapy. 2022;14(1):75.doi: 10.1186/s13195-022-01017-4
13. Rao NL, Kotian GB, Shetty JK, Shelley BP, Dmello MK, Lobo EC, et al. Receptor for Advanced Glycation End Product, Organ Crosstalk, and Pathomechanism Targets for Comprehensive Molecular Therapeutics in Diabetic Ischemic Stroke. Biomolecules [Internet]. 2022; 12(11).doi: 10.3390/biom12111712
14. Bolt J, Barry AR, Inglis C, Lin S, Pan J. Prevalence of Acetylsalicylic Acid Use for Primary Prevention of Cardiovascular Disease Amongst Older Adults From 2017-2021: a Retrospective Cross-Sectional Study. Can Geriatr J. 2023;26(4):517-23.doi: 10.5770/cgj.26.693
15. Roth Gregory A, Mensah George A, Johnson Catherine O, Addolorato G, Ammirati E, Baddour Larry M, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990–2019. JACC. 2020;76(25):2982-3021.doi: 10.1016/j.jacc.2020.11.010
16. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, et al. Heart Disease and Stroke Statistics—2020 Update: A Report From the American Heart Association. Circulation. 2020;141(9):e139-e596.doi: 10.1161/CIR.0000000000000757
17. Chan A, Torelli S, Cheng E, Batchelder R, Waliany S, Neal J, et al. Immunotherapy-Associated Atherosclerosis: A Comprehensive Review of Recent Findings and Implications for Future Research. Current Treatment Options in Cardiovascular Medicine. 2023;25(12):715-35.doi: 10.1007/s11936-023-01024-0
18. Curcio A, Panarello A, Spaccarotella C, Indolfi C. Cardiovascular Prognosis in Patients with Peripheral Artery Disease and Approach to Therapy. Biomedicines [Internet]. 2023; 11(12).doi: 10.3390/biomedicines11123131
19. null n, Lloyd-Jones Donald M, Morris Pamela B, Ballantyne Christie M, Birtcher Kim K,

Covington Ashleigh M, et al. 2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk. JACC. 2022;80(14):1366-418.doi: 10.1016/j.jacc.2022.07.006

20. Aboyans V, Ricco JB, Bartelink MEL, Björck M, Brodmann M, Cohnert T, et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteriesEndorsed by: the European Stroke Organization (ESO)The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). Eur Heart J. 2018;39(9):763-816.doi: 10.1093/eurheartj/ehx095

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