Repurposing antihypertensive and statin medications for spinal pain: a Mendelian randomization study

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CONFLICTS OF INTEREST AND SOURCES OF FUNDING

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Study Design: Mendelian randomization (MR) study

Objective: To examine whether antihypertensive medications (beta-blockers, calcium channel blockers, and angiotensin-converting enzyme [ACE] inhibitors) and statins can be repurposed to prevent or treat spinal pain (back or neck pain).

Summary of Background Data: Observational studies and a recent MR study have found associations between elevated blood pressure and greater risk of back pain. Observational studies have found associations between hyperlipidemia and statin use, and greater risk of back pain. No prior MR studies have examined the effects of antihypertensives or statins on spinal pain.

Methods: This was a two-sample MR study using publicly available summary statistics from large-scale genome-wide association studies (GWAS). Sample sizes in exposure GWASs were n=757,601 (systolic blood pressure) and n=173,082 (low density lipoprotein[LDL] cholesterol), and n=1,028,947 for the outcome GWAS of spinal pain defined as health care seeking for any spinal pain-related diagnosis. Genes and cis-acting variants were identified as proxies for the drug targets of interest. MR analyses used inverse-variance weighted meta-analysis. The threshold for statistical significance after correction for multiple testing was $p < 0.0125$.

Results: No statistically significant associations of these medications with spinal pain were found. However, findings were suggestive of a protective effect of beta blockers on spinal pain risk (odds ratio [OR] 0.84, 95% confidence interval [CI] 0.72 to 0.98; $p = 0.03$), and calcium channel blockers on greater spinal pain risk (OR 1.12, 95% CI 1.02 to 1.24; $p = 0.02$).

Conclusions: A protective effect of beta-blockers on spinal pain was suggested in the current study, consistent with findings from observational studies of various other pain phenotypes. The detrimental effect of calcium channel blockers on spinal pain suggested in the current study must be interpreted in the context of conflicting directions of effect on non-spinal pain phenotypes in other observational studies.

Key Points (3-5 main points of the article)

Drug Repurposing for Spinal Pain

This Mendelian randomization study examined whether antihypertensive medications (beta-blockers, calcium channel blockers, and angiotensin-converting enzyme inhibitors) and statins can be repurposed to prevent or treat spinal.

This was a two-sample MR study using publicly available summary statistics from large-scale genome-wide association studies ranging size from 173,082 to 1,028,947 adults.

While no statistically significant associations were found, a protective effect of beta-blockers on spinal pain was suggested (odds ratio [OR] 0.84, 95% confidence interval [CI] 0.72 to 0.98; p= 0.03), as was a detrimental effect of calcium channel blockers on spinal pain (OR 1.12, 95% CI 1.02 to 1.24; p= 0.02).

Mini Abstract (50 words)

Drug Repurposing for Spinal Pain

This Mendelian randomization study examined whether antihypertensive medications and statins can be repurposed to prevent or treat spinal pain. While no statistically significant associations with spinal pain were found, suggestive signals were found for beta blockers and decreased spinal pain risk, and calcium channel blockers and increased spinal pain risk.

Introduction

Back and neck pain (spinal pain) are prevalent in all countries and the leading cause of health care spending in the United States.[21] Accordingly, the development of novel pharmacologic treatments for pain conditions, such as spinal pain, is a research priority.[11] However, such development requires considerable investment, with average costs of $1.3 billion per new medication.[51] Once a medication is brought to market, prices remain high until patent expiry.[47] Even after regulatory approval, nearly 1/3 of new medications are found to have unanticipated safety events.[16]

A less costly and safer alternative to novel medication development for pain conditions is to "repurpose" existing medications developed for other purposes. When repurposing a medication already in common use, safety profiles are known and costs mitigated due to competition from generic medications.[47] There are many examples of medications originally developed for other purposes that are now used for analgesia or prophylaxis of pain conditions, such as amitriptyline[46] and duloxetine for back pain;[48] gabapentin and pregabalin for radicular pain;[37] beta-blockers for headache;[26] etc. Yet, previously the discovery of these medications' potential roles in pain occurred largely through observations during clinical use or marketing efforts by manufacturers[13] and not through deliberate, prospective scientific inquiry.

Contemporary genomics methods such as Mendelian randomization (MR) allow the exploration of a medication's potential effectiveness for preventing or treating a health condition in situations where the medication's mechanism of action is known. MR uses specific genetic variants that proxy a medication's biological effect as instrumental variables to enable causal inference about the effect of a medication on an outcome.[12] The method takes advantage of the fact that genetic variants are allocated randomly prior to birth (conditional on parental genotypes), are independent of environmental factors, and precede the onset of a health condition outcome.[8] As MR studies are less prone to reverse causation and confounding, they are thought to have advantages over other methods, with a strength of evidence between that of conventional observational studies and randomized controlled trials (RCTs).[12] MR studies of antihypertensive medications have successfully replicated their effects on cardiovascular outcomes produced by RCTs, validating the method.[19]

Cardiovascular risk factors, including hypertension, are associated with back pain and lumbar spine degeneration.[28, 39] Some have suggested causal links between cardiovascular risk factors and back pain, with a possible vascular mechanism mediated through atherosclerosis of the lumbar aorta and penetrating vessels that innervate the lumbar intervertebral discs, leading to decreased disc nutrition, spinal degeneration, and consequent back pain.[28] The same links are theorized to apply to neck pain.[1] A recent MR study found significant detrimental effects of higher blood pressure on spinal pain risk,[39] raising the question of whether lowering blood pressure could decrease spinal pain risk. Hypertension is often treated using antihypertensive medications such as beta-blockers and calcium channel blockers, which have been commonly used for decades and have well-studied mechanisms of action. Beta-blockers are also effective for the prevention and treatment of chronic pain conditions such as episodic and chronic migraines[26], and have short-term effects on post-operative pain.[22] Calcium channel blockers are sometimes used in the prevention of migraine and cluster headaches.[25, 43] Separate from antihypertensives, statin medications have been found in observational studies to be associated with a greater risk of spinal pain.[30] This background suggests medications targeting cardiovascular risk factors might be potential candidates for repurposing to prevent spinal pain, or medications that could be avoided if an alternative exists.

In the current MR study, we examined whether four classes of cardiovascular medications—beta-blockers, calcium channel blockers, angiotensin-converting enzyme [ACE] inhibitors, and statins— are candidates for repurposing to prevent or treat spinal pain.

Materials and Methods

The current study emulates methods previously reported by Gill and colleagues,[19] which produced MR estimates for the effects of beta-blockers, calcium channel blockers, and ACE inhibitors on coronary heart disease (CHD) and stroke that were comparable to results from RCTs, validating their methods. We then used analogous methods to examine the effects of statin medications on spinal pain. This study used publicly available GWAS summary statistics. Research approval (1587681) was obtained at VA Puget Sound Health Care System .

Overview of Mendelian Randomization (MR) Methods

MR uses an instrumental variable approach to estimate associations of a risk factor with an outcome that can be interpreted as *causal* associations.[12] In MR, genetic variants (typically single-nucleotide variants or "SNVs") are used as instrumental variables. The major assumptions required with instrumental variable approaches are that the instruments used (1) are associated with the risk factor under study; (2) are not associated with potential confounders; and (3) do not affect the outcome except through the risk factor of interest. Using genetic variants as instrumental variables leverages the facts that variants undergo random assortment during gamete formation and this precedes the onset of disease, assuring temporal ordering whereby the exposure precedes the outcome. Additionally, genetic instrumental variables identified from genome-wide association studies (GWAS) are independent of confounding factors provided that the rigorous methods used in contemporary GWAS studies have fully accounted for population stratification. Although residual confounding may affect variants associated with complex traits that have strong social determinants,[23] recent work has shown that such confounding largely does not apply to genetic variants predictive of molecular phenotypes such as those targeted in drug repurposing MR studies.[24]

Study samples and phenotypes

Two-sample MR studies using summary data require an exposure GWAS and an outcome GWAS. Participants in the included GWAS studies completed written informed consent.[2, 17, 49] For estimating the effects of antihypertensive medications on spinal pain we used an exposure GWAS examining genetic associations with systolic blood pressure, as used previously in work by Gill and colleagues. This GWAS was a meta-analysis of 757,601 individuals of European ancestry from studies comprising the International Consortium of Blood Pressure GWAS meta-analysis and the UK Biobank.[17] For estimating the effects of statin medications on spinal pain we used an exposure GWAS examining genetic associations with LDL cholesterol comprised of 173,082 individuals of European ancestry from the GLGC consortium.[49]

The outcome GWAS for all analyses was comprised of 1,028,947 adults of European ancestry (119,100 cases and 909,847 controls) from the FinnGen biobank, cohorts from Denmark and Iceland, and UK Biobank.[2] It is the largest published GWAS of any spinal pain phenotype conducted to date. This study identified spinal pain cases using electronic health record (EHR)-based phenotyping and the "dorsalgia" code group (M54) from the International Classification of Diseases, 10th Revision (ICD-10). The M54 code group includes back pain-associated diagnostic codes as well as neck pain-associated codes. Similar EHR-based spinal pain phenotypes have been used extensively in large-scale back pain research [6, 14, 15, 31], and we have previously shown that they are robust to changes in the diagnostic codes used while yielding replicable GWAS findings across different health care systems and countries.[40] This spinal pain phenotype is expected to capture pain presentations of a severity to have warranted health care use, including predominantly chronic or recurrent pain, but also including cases of acute pain.[4, 27, 32] Summary-level data were transferred from the GRCh38 to GRCh37 human genome assembly using the liftOver tool (https://github.com/broadinstitute/liftover/).

Genetic instrumental variable selection

Initial steps in MR studies of drug repurposing include identifying genes corresponding to the drug target of interest and selecting genetic variants as instrumental variables.[20] As our interest in the analysis of antihypertensives was specifically in estimating the effects of altering drug targets with existing indications for treating hypertension, we wished to identify instruments located at the gene or its regulatory region ("cis-acting" variants) corresponding to the respective drug target that *also* predicted higher blood pressure. Accordingly, we used the same genetic instruments for the analysis of effects of antihypertensives as selected previously by Gill and colleagues.[19] Those authors identified genes encoding the targets of the effects of beta-blockers (the *ADRB1* gene), calcium channel blockers (11 genes), and ACE inhibitors (the *ACE* gene) on blood pressure using the DrugBank database.[50] The location of each gene and its regulatory regions were identified using the GeneCards platform v5.4 and the GeneHancer database,[18] with the resulting selection of 6 genetic instruments for beta-blockers, 24 instruments for calcium channel blockers, and 1 instrument for ACE inhibitors. These instruments had F-statistics between 54 and 534. Further details of genetic variant selection by Gill and colleagues are available elsewhere.[19] We followed these same steps to identify genes encoding the targets of the effects of statin medications on low-density lipoprotein (LDL) cholesterol and instrumental variables to proxy the effect of LDL lowering through statins. SNVs from the gene and corresponding regulatory regions were selected as potential instruments and clumped using PLINK v1.90b6.24.[5, 36] Clumping was performed using the 1000G p3 v5 reference panel for Europeans (N = 503) at genome-wide significance ($p < 5*10^{-8}$) with linkage disequilibrium threshold of $r^2 > 0.1$ and genomic distance of ±10 Mb.

Methods for validation of genetic instruments by replicating expected effects on cardiovascular phenotypes.

The instrumental variables selected to proxy the effects of antihypertensives were previously validated using MR by Gill and colleagues by reproducing "on-target" effects on CHD and stroke.[19] In this earlier work, there were

significant protective effects of beta-blockers on CHD risk, and of calcium channel blockers on CHD and stroke risk, that were consistent in direction and magnitude with the effect estimates obtained from meta-analyses of RCTs.[25] Additionally, even when effects of antihypertensives on CHD and stroke were not statistically significant, they were consistent in direction and magnitude with estimates from RCTs. As a preparatory step in the current analyses, we ensured fidelity to the methods of Gill and colleagues by repeating the same MR analyses and successfully replicating their results (data not shown). To validate the instruments we selected as a genetic proxy for statins, we performed an MR analysis of the instrument's effect on CHD, using summary statistics from a GWAS of CHD by the CARDIOGRAM & CD4 Consortium (n=184,306).[34] GWAS were unified and quality-controlled using the GWAS-MAP database.[38]

Statistical analysis

All MR analyses were carried out using the inverse-variance weighted (IVW) method in the TwoSampleMR package v0.5.5. Exposure and outcome data were harmonized using the harmonise_data function. MR effect estimates were scaled to account for each drug effect on the exposure phenotype by multiplying them by the drug effect size evaluated from RCTs.[7, 52] The MR estimates were transformed to odds ratios (ORs) using the generate_odds_ratios() function and 95% confidence intervals (95% CIs) were calculated. The threshold for statistical significance was $p < 0.0125 = 0.05/4$, where 4 reflects the number of analyzed drug classes. First, we estimated "on-target" effects on CHD. Next, we estimated effects on spinal pain. *Post hoc* power calculations were conducted to estimate the magnitude of detectable effects of each medication class on spinal pain, assuming 80% power and $p < 0.0125$ (Supplemental Digital Content)

Results

Validation of genetic instruments

As described above, the genetic instruments selected for antihypertensive medications were previously validated with regards to effects on CHD and stroke.[19] Using the DrugBank database, we identified a single target gene coding 3-Hydroxy-3-Methylglutaryl-CoA Reductase (*HMGCR*). Using the GWAS of LDL cholesterol, 99 cis-acting SNVs were identified in *HMGCR*, but there was only 1 independent IV after clumping, rs3846663 (F-statistic = 380.78, Supplemental Table S1) . In IVW MR analyses this variant had a protective on-target effect on CHD of OR = 0.63 (0.48, 0.83) with p-value = 1.02e-03, consistent with the beneficial effect of statins from RCTs.[41]

Drug repurposing MR results (Table 1)

Point estimates for the MR analyses of beta-blockers suggested a protective effect on spinal pain (OR = 0.84 [95% CI 0.72-0.98], p=0.026), but this was not statistically significant after accounting for multiple statistical testing ($p< 0.0125$). Point estimates for the MR analyses of calcium channel blocks suggested a detrimental effect on spinal pain (OR=1.12 [95% CI 1.02-1.24], p=0.020) that was not statistically significant after accounting for multiple statistical testing ($p<0.0125$). MR analyses of ACE inhibitors and statins showed wide 95% CIs reflecting imprecise estimates and were not significantly associated with spinal pain.

Power calculations

In *post hoc* analyses, expected detectable effects for beta-blockers, calcium channel blockers, ACE inhibitors, and statins were estimated to be OR = 0.81, OR = 0.90, OR = 0.37, and OR = 0.80 respectively.

Discussion

To our knowledge, this is the first Mendelian randomization (MR) study attempting to repurpose medications for the prevention and/or treatment of spinal pain. We studied antihypertensives and statins due to their widespread use, known side effect profiles, and because of the potential for concurrent improvement in cardiovascular risk factor profiles as a (beneficial) side effect while using these medications to treat pain, or *vice versa*. No statistically significant effects of these medications on spinal pain were found. However, two medications showed suggestive associations with spinal pain: beta-blockers, which had a tendency towards a protective effect (OR = 0.84); and calcium-channel blockers, which had a tendency towards a detrimental effect (OR = 1.12).

This work was prompted by a recent MR study by our group indicating detrimental effects of higher systolic and diastolic blood pressure on spinal pain, and earlier laboratory-based studies which demonstrated context-specific

relationships between blood pressure and hypoanalgesia in the setting of acute pain, and between blood pressure and hyperalgesia in the setting of chronic back pain. [3, 9, 10] The findings of the current study, in the context of the methods we used, imply that the mechanism of beta-blocker action on the prevention and/or treatment of spinal pain is mediated through decreases in blood pressure. Beta-blockers are used clinically in pain conditions primarily related to headache or migraine.[26] An RCT of the beta-blocker propranolol also showed improvements in some pain outcomes.[42] Recently, beta-blockers have been found to be significantly associated with better outcomes in limb osteoarthritis and pain.[33] One other study found evidence supporting this relationship,[45] yet another did not.[53] Overall, current evidence from observational studies and trials suggests a potential small yet beneficial effect of beta-blockers on pain conditions, consistent with the non-significant yet suggestive causal association with spinal pain in the current study; our MR findings strengthen the case for an overlooked yet potentially useful adjunctive use for beta-blockers in spinal pain conditions. We suggest that future trials of beta-blockers (for any health condition) should include back pain as a secondary outcome.

While calcium channel blockers have biological reasons for being linked to pain conditions,[35] and are sometimes used for migraine, there is much less consistent evidence for connections with pain from large studies of humans than exists for beta-blockers.[25, 26] A systematic review did not find associations between calcium channel blocker use and migraine outcomes.[25] However, a multicenter cohort study of people with knee osteoarthritis found associations between calcium channel blocker use and worse pain outcomes,[29] consistent with the current study. In contrast, an unpublished agnostic drug repurposing MR study of pain intensity irrespective of pain location suggested potential analgesic effects of calcium channel blockers.[44] This lack of clear triangulation with evidence from observational studies and trials mirrors the complexity of calcium channel modulators affecting the pain neuraxis, and reminds that various calcium channel blockers showed early promise in preclinical studies yet disappointed in later RCTs.[43] Calcium channel blockers may be a more challenging repurposing target for spinal pain, but further study may still be useful in separating out the beneficial vs. detrimental aspects of calcium channel blockade.

While MR studies are sometimes considered to have a strength of evidence between that produced by cohort studies and RCTs, the design has limitations.[12] MR studies proxy the effect of an exposure over the lifetime and produce larger effects than expected with a change in the exposure during adulthood. For this and other reasons, the *magnitude* of MR effects should be viewed cautiously, whereas their *direction* is more trustworthy. In the current study, there was a degree of overlap between the two samples studied, due to UK Biobank participants included in both the exposure and outcome GWAS, which might have biased associations towards the conventional observational estimate.[12] Future studies of completely independent samples are warranted. Additionally, the current study was underpowered for examination of ACE inhibitors, so type II error is possible for this medication class. Last, the current study examined a general spinal pain phenotype which largely reflects back pain yet also includes neck pain. As spinal pain is often an episodic or recurrent condition, the outcome used in the current study included both chronic and acute cases, and thus the results pertain to spinal pain treatment, prevention, or both.

In summary, this was the first MR study of medication repurposing for any spinal pain condition. While no statistically significant effects of antihypertensives or statins were found, suggestive findings of a protective effect of beta-blockers on spinal pain, and a detrimental effect of calcium channel blockers on spinal pain, warrant further study.

Introduction

Back and neck pain (spinal pain) are prevalent in all countries and the leading cause of health care spending in the United States.[21] Accordingly, the development of novel pharmacologic treatments for pain conditions, such as spinal pain, is a research priority.[11] However, such development requires considerable investment, with average costs of $1.3 billion per new medication.[51] Once a medication is brought to market, prices remain high until patent expiry.[47] Even after regulatory approval, nearly 1/3 of new medications are found to have unanticipated safety events.[16]

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Power calculations

In *post hoc* analyses, expected detectable effects for beta-blockers, calcium channel blockers, ACE inhibitors, and statins were estimated to be OR = 0.81, OR = 0.90, OR = 0.37, and OR = 0.80 respectively.

Discussion

To our knowledge, this is the first Mendelian randomization (MR) study attempting to repurpose medications for the prevention and/or treatment of spinal pain. We studied antihypertensives and statins due to their widespread use, known side effect profiles, and because of the potential for concurrent improvement in cardiovascular risk factor profiles as a (beneficial) side effect while using these medications to treat pain, or *vice versa*. No statistically significant effects of these medications on spinal pain were found. However, two medications showed suggestive associations with spinal pain: beta-blockers, which had a tendency towards a protective effect (OR = 0.84); and calcium-channel blockers, which had a tendency towards a detrimental effect (OR = 1.12).

This work was prompted by a recent MR study by our group indicating detrimental effects of higher systolic and diastolic blood pressure on spinal pain, and earlier laboratory-based studies which demonstrated context-specific

relationships between blood pressure and hypoanalgesia in the setting of acute pain, and between blood pressure and hyperalgesia in the setting of chronic back pain. [3, 9, 10] The findings of the current study, in the context of the methods we used, imply that the mechanism of beta-blocker action on the prevention and/or treatment of spinal pain is mediated through decreases in blood pressure. Beta-blockers are used clinically in pain conditions primarily related to headache or migraine.[26] An RCT of the beta-blocker propranolol also showed improvements in some pain outcomes.[42] Recently, beta-blockers have been found to be significantly associated with better outcomes in limb osteoarthritis and pain.[33] One other study found evidence supporting this relationship,[45] yet another did not.[53] Overall, current evidence from observational studies and trials suggests a potential small yet beneficial effect of beta-blockers on pain conditions, consistent with the non-significant yet suggestive causal association with spinal pain in the current study; our MR findings strengthen the case for an overlooked yet potentially useful adjunctive use for beta-blockers in spinal pain conditions. We suggest that future trials of beta-blockers (for any health condition) should include back pain as a secondary outcome.

While calcium channel blockers have biological reasons for being linked to pain conditions,[35] and are sometimes used for migraine, there is much less consistent evidence for connections with pain from large studies of humans than exists for beta-blockers.[25, 26] A systematic review did not find associations between calcium channel blocker use and migraine outcomes.[25] However, a multicenter cohort study of people with knee osteoarthritis found associations between calcium channel blocker use and worse pain outcomes,[29] consistent with the current study. In contrast, an unpublished agnostic drug repurposing MR study of pain intensity irrespective of pain location suggested potential analgesic effects of calcium channel blockers.[44] This lack of clear triangulation with evidence from observational studies and trials mirrors the complexity of calcium channel modulators affecting the pain neuraxis, and reminds that various calcium channel blockers showed early promise in preclinical studies yet disappointed in later RCTs.[43] Calcium channel blockers may be a more challenging repurposing target for spinal pain, but further study may still be useful in separating out the beneficial vs. detrimental aspects of calcium channel blockade.

While MR studies are sometimes considered to have a strength of evidence between that produced by cohort studies and RCTs, the design has limitations.[12] MR studies proxy the effect of an exposure over the lifetime and produce larger effects than expected with a change in the exposure during adulthood. For this and other reasons, the *magnitude* of MR effects should be viewed cautiously, whereas their *direction* is more trustworthy. In the current study, there was a degree of overlap between the two samples studied, due to UK Biobank participants included in both the exposure and outcome GWAS, which might have biased associations towards the conventional observational estimate.[12] Future studies of completely independent samples are warranted. Additionally, the current study was underpowered for examination of ACE inhibitors, so type II error is possible for this medication class. Last, the current study examined a general spinal pain phenotype which largely reflects back pain yet also includes neck pain. As spinal pain is often an episodic or recurrent condition, the outcome used in the current study included both chronic and acute cases, and thus the results pertain to spinal pain treatment, prevention, or both.

In summary, this was the first MR study of medication repurposing for any spinal pain condition. While no statistically significant effects of antihypertensives or statins were found, suggestive findings of a protective effect of beta-blockers on spinal pain, and a detrimental effect of calcium channel blockers on spinal pain, warrant further study.

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Tables

Table 1. Causal effects of antihypertensive and statin medications on spinal pain*

Risk factor	Gene[a]	# of SNVs	Beta	SE	p-value	Coefficient	Beta (scaled)	SE (scaled)	OR (95% CI) for effect on spinal pain[a]
Antihypertensive medications									
Beta-blockers[b]	*ADRB1*	5	0.019	0.0084	0.026	-9.5[c]	-0.18	0.080	0.84 (0.72-0.98)
Calcium channel blockers[b]	11 genes	18	-0.13	0.0057	0.020	-8.9[c]	0.12	0.050	1.12 (1.02-1.24)
ACE inhibitors[b]	*ACE*	1	0.0042	0.015	0.78	-21.1[c]	-0.089	0.32	0.91 (0.49-1.71)
Statin medications									
Statins[d]	*HMGCR*	1	-0.096	0.068	0.16	-1.1[e]	0.10	0.072	1.11 (0.96-1.27)

*IVW analysis, significance threshold set at 0.0125 = 0.05/4 (where 4 is the number of medication classes examined)

[a]Cis-acting instrumental variables were selected from these genes

[b]Summary statistics and instruments selected taken from Gill et al.[19]

[c]coefficients taking from Wright et al.[52]

[d]GWAS summary statistic data taken from Nikpay et al.[34] and Willer et al.[49]

[e]average effect size of 42.0 (from Cheung et al.)[7] divided by standard deviation of 39.9 (from largest cohort in Willer et al.)[49]

LDL=low-density lipoprotein