

## SYSTEMATIC REVIEW AND META-ANALYSIS

# Meta-Analysis of Intensive Lipid-Lowering Therapy in Patients With Polyvascular Disease

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**BACKGROUND:** Polyvascular atherosclerotic disease is associated with an increased risk of future cardiovascular events. Intensive lipid-lowering therapy (ILT) may mitigate this risk. The aims of this study-level meta-analysis were to examine the effects of ILT in patients with polyvascular disease and whether baseline low-density lipoprotein cholesterol (LDL-C) may determine the level of benefit.

**METHODS AND RESULTS:** Electronic databases were searched through January 2020 to identify randomized controlled trials of treatments targeting upregulation of LDL-C receptors (ie, statins, ezetimibe, and PCSK9 [proprotein convertase subtilisin-kexin type 9] inhibitors). The primary end point was major adverse vascular events as defined by the included studies. A total of 94 362 patients (14 821 [18.6%] with polyvascular disease) from 7 studies were included. In patients with monovascular disease, ILT was associated with a 13% reduction in the primary end point (rate ratio [RR] 0.87; 95% CI, 0.81–0.93 [ $P=0.0002$ ]) (absolute RR, 1.8%) compared with less ILT, while patients with polyvascular disease had 15% relative RR (0.85; 95% CI, 0.80–0.90 [ $P<0.00001$ ]) (absolute RR, 6.5%) ( $P=0.66$  for interaction). When factoring LDL-C, unlike patients with monovascular disease, the relative benefits of ILT, compared with less ILT, in patients with polyvascular disease were comparable with LDL-C  $>100$  mg/dL (RR, 0.85; 95% CI, 0.80–0.90 [ $P<0.00001$ ]) and LDL-C  $<100$  mg/dL (RR, 0.88; 95% CI, 0.81–0.96 [ $P=0.003$ ]) ( $P=0.23$  for interaction).

**CONCLUSIONS:** Patients with polyvascular disease experienced comparable benefits to those with monovascular disease in response to ILT. The benefits of ILT in patients with polyvascular disease were not dependent on baseline LDL-C, challenging the approach of using LDL-C as a prerequisite to commence ILT for this high-risk subgroup.

**Key Words:** lipid-lowering ■ low-density lipoprotein cholesterol ■ polyvascular

**P**olyvascular disease, defined as the presence of atherosclerosis in at least 2 vascular beds, is a well-established high-risk feature for adverse cardiovascular events.<sup>1</sup> The REACH (Reduction of Atherothrombosis for Continued Health) registry demonstrated that 1 in 6 patients with stable atherosclerosis disease had clinical evidence of atherosclerosis in a second or more vascular territories.<sup>2</sup> The CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines)

registry showed the close association between ischemic events, including mortality, and the number of affected vascular beds.<sup>1</sup>

The heightened risk associated with polyvascular disease has been a target using different pharmacological modalities.<sup>3</sup> Lipid-lowering therapies modify the risk in patients with atherosclerosis and have been shown to exert larger absolute risk reductions in patients with polyvascular disease.<sup>4,5</sup> Moreover, the advent of PCSK9 (proprotein convertase subtilisin-kexin type 9) inhibitors has also allowed to further

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## CLINICAL PERSPECTIVE

### What Is New?

- Intensive lipid-lowering therapy did not result in a consistent relative risk reduction in polyvascular disease despite their heightened cardiovascular risk.
- The current meta-analysis demonstrated that larger intensive lipid-lowering therapy resulted in larger absolute benefits in patients with polyvascular disease.

### What Are the Clinical Implications?

- Patients with polyvascular disease have comparable benefits from intensive lipid-lowering therapy irrespective of their low-density lipoprotein cholesterol.

## Nonstandard Abbreviations and Acronyms

<b>CRUSADE</b>	Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines
<b>EAS</b>	European Atherosclerosis Society
<b>ESC</b>	European Society of Cardiology
<b>FOURIER</b>	Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk
<b>HPS</b>	Heart Protection Study
<b>ILT</b>	intensive lipid-lowering therapy
<b>IDEAL</b>	Incremental Decrease in End Points Through Aggressive Lipid Lowering
<b>IMPROVE-IT</b>	Improved Reduction of Outcomes: Vytorin Efficacy International Trial
<b>ODYSSEY OUTCOMES</b>	Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab
<b>PCSK9</b>	proprotein convertase subtilisin-kexin type 9
<b>REACH</b>	Reduction of Atherothrombosis for Continued Health
<b>RR</b>	rate ratio
<b>SEARCH</b>	Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine
<b>WOSCOP</b>	West of Scotland Coronary Prevention Study

mitigate the lipoprotein-related risk associated with polyvascular disease.<sup>6,7</sup> The initial Task Force of European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) recommended the addition of PCSK9 inhibitors in patients with severe polyvascular disease to reach the goal of low-density lipoprotein cholesterol (LDL-C) of <100 mg/dL.<sup>8</sup> This was recently updated and the current European guidelines recommend that the lower the LDL-C level the better.<sup>9</sup> Nonetheless, a large meta-analysis reported benefit from intensive lipid-lowering therapy (ILT) only in patients with LDL-C >100 mg/dL, with a lack of association of benefit in patients with baseline LDL-C <100 mg/dL.<sup>10</sup> Importantly, polyvascular disease was not considered in the meta-analysis.<sup>10</sup>

Therefore, the aim of this study-level meta-analysis was to determine whether intensive LDL-C reduction was associated with larger risk reduction in patients with polyvascular disease compared with monovascular disease. In addition, we sought to assess whether there was any heterogeneity between monovascular and polyvascular disease in the relative benefits of intensive lipid lowering according to baseline LDL-C.

## METHODS

The data that support the findings of this study are available from the corresponding authors on reasonable request. The MEDLINE and the Cochrane Central Register of Controlled Trials databases were searched from inception until January 2020 using the following keywords: lipid-lowering, hypercholesterolemia, low-density lipoprotein, cholesterol, randomized controlled trial, and polyvascular disease.

Studies were included if they were randomized trials that compared lipid-lowering therapies and where major cardiovascular events was the primary end point. Lipid-lowering therapies were included if their primary mechanism was targeting LDL-C via the upregulation of low-density lipoprotein receptor expression such as statins, ezetimibe, or PCSK9 inhibitors.<sup>11</sup> Data on the effects of bempedoic acid in polyvascular disease have not been reported. Studies of fibrates, niacin, and cholesteryl ester transfer protein inhibitors were excluded since these pharmacotherapies do not directly target the upregulation of low-density lipoprotein receptor expression. Additionally, studies investigating the efficacy of lipid-lowering therapy in specific cohorts, such as heart failure or end-stage renal disease, were also excluded.

All included articles had initial assessment using the prespecified inclusion criteria by 2 authors (M.A. and M.K.), neither of whom was an investigator in any of the selected studies. Any cases of disagreement were resolved by consensus. Citations were

screened at title/abstract level and full reports were retrieved when considered relevant. The search results were cross-checked by reviewing systematic reviews and meta-analyses on lipid-lowering treatments. A study was included if a specific subgroup analysis investigating patients with polyvascular disease was reported. Similarly, the literature was searched to identify dedicated studies targeting the role of lipid-lowering therapy in patients with polyvascular disease. The identified records were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.<sup>12,13</sup>

Control groups from the original trials were assigned as the less intensive lipid-lowering strategy, while the more intensive therapy was defined as the experimental group or the more intensive lipid-lowering strategy of the original studies as previously described.<sup>10</sup> Therefore, the intensity of statin treatment was not assessed in absolute terms but rather relative to the comparable group. Since simvastatin (40 mg) and pravastatin (40 mg) were compared with placebo in HPS (Heart Protection Study) and WOSCOP (West of Scotland Coronary Prevention Study), respectively, the statin arms were included in the intensive lipid-lowering group.<sup>14,15</sup>

Major adverse cardiovascular events were defined according to the reported events within the selected studies. Data on mortality according to the status of polyvascular disease were not specifically reported in the majority of the studies and, therefore, exploring their association could not be reliably executed in our analysis.

## Statistical Analysis

Continuous data are presented as mean $\pm$ SD or as median (range), while categorical variables are presented as percentages, as reported in the original studies.

Using trial-level data, treatment effect was reported as rate ratio (RR) with 95% CIs adjusted by patient-years, which was used as a unit alongside the total number of events to calculate the RR of ILT versus less ILT to account for the potential differences in study duration. Subsequently, a summary RR was calculated with the random-effects models based on the inverse variance method. We elected to use random effect to relatively weight the studies equally since all included studies were large randomized trials. The presence of heterogeneity among studies was assessed using the Cochran Q (or chi-square) test and quantified using the Higgins  $I^2$  test.<sup>12</sup>

Sensitivity analysis was performed to identify any heterogeneity in the treatment effect of lipid-lowering therapy among the studies. A cutoff value for baseline

LDL-C of 100 mg/dL was used to perform the sensitivity analysis.<sup>10</sup> Publication bias was evaluated using funnel plot methodology. The statistical analysis was performed using RevMan software version 5.3 (Cochrane Collaboration) and  $P < 0.05$  were considered statistically significant.

## RESULTS

Using our search strategy, we initially identified 3441 records. The PRISMA flow diagram of the selected studies is shown in Figure 1. Seven randomized studies met the inclusion criteria, totaling 94 362 patients, of whom 47 538 (50.4%) were in the more intensive lipid-lowering group. This included high-dose statins and PCSK9 inhibitors in 2 trials,<sup>6,7</sup> high-dose statin and ezetimibe in 1 study,<sup>5</sup> high-dose statin in 3 trials,<sup>4,14,16</sup> and moderate-dose statin in 1 study.<sup>15</sup> Six studies were excluded as ILT could not be established given the comparable or undetermined intensity of the studied lipid-lowering regimens.<sup>17–22</sup> Similarly, studies investigating the role of early administration of lipid-lowering therapy on clinical outcomes were excluded as time-based analyses.<sup>23–25</sup>

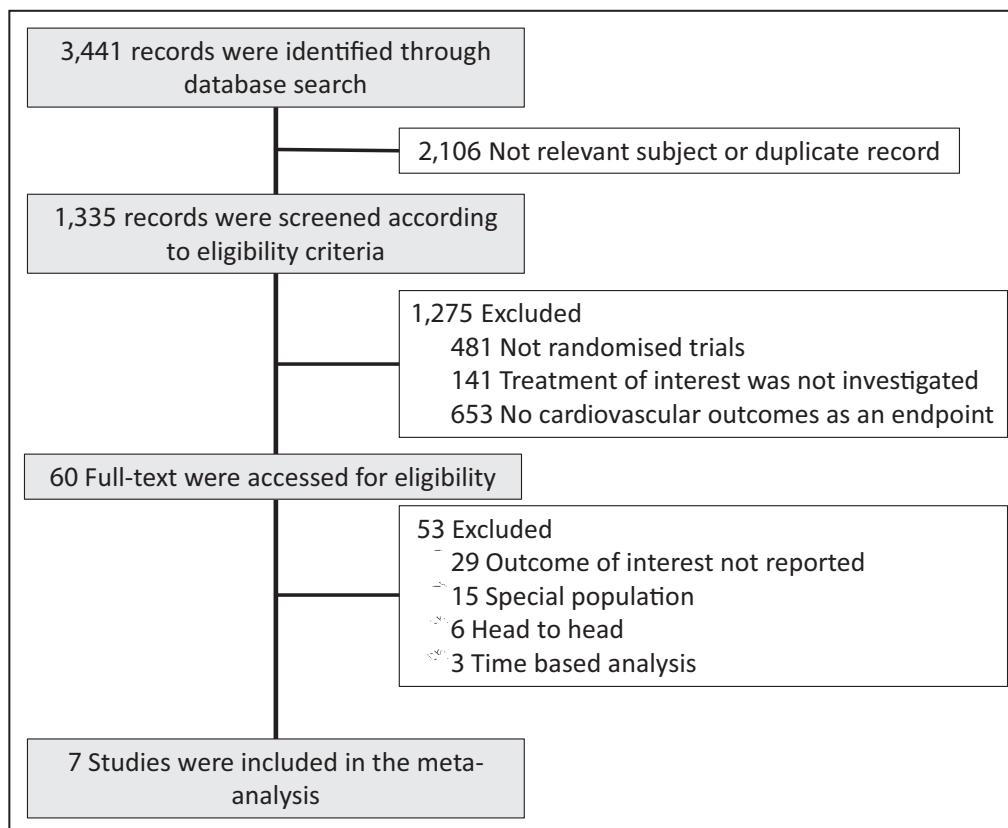
WOSCOP is considered a primary prevention study; nonetheless, data on clinical outcomes in patients with multiple risk factors including angina and claudication were reported. Therefore, this study was included in the final analysis.

The total number of patients with polyvascular disease was 14 821 (18.6%). The baseline clinical characteristics of each study are reported in the Table. The baseline LDL-C value was  $<100$  mg/dL in 4 studies. Patients with stable disease were included in 4 studies.

Risk of publication bias was assessed by visual inspection of the funnel plots for both monovascular and polyvascular disease (Figure 2). While there was no bias in reported data on polyvascular disease, studies of monovascular disease had moderate between-trial heterogeneity ( $I^2=74\%$ ,  $P=0.0009$ ).<sup>12</sup> Nonetheless, all included studies were randomized, blinded, and multicenter; and the reported data were according to the intention-to-treat analysis.

In patients with monovascular disease, the number of events in patients receiving ILT was 5919 (15%), compared with 6775 (16.9%) for those receiving less ILT. The difference between the 2 strategies was associated with a 13% reduction in major cardiovascular events (RR, 0.87; 95% CI, 0.81–0.93 [ $P=0.0002$ ]) (Figure 3). The absolute risk reduction of ILT compared with less ILT was 1.8% (95% CI, 1.3–2.3), which was translated into a number needed to treat (NNT) of 55 (95% CI, 43–76).

On the other hand, there were 2010 (24.5%) major vascular events in patients with polyvascular disease



**Figure 1.** Selection process of identified randomized controlled trials evaluating the role of intensive lipid-lowering therapy in patients with polyvascular disease.

receiving ILT compared with 2060 (31.1%) major vascular events in patients with polyvascular disease receiving less ILT. This translated into a 15% reduction in major vascular events (RR, 0.85; 95% CI, 0.80–0.90 [ $P<0.00001$ ]) (Figure 3). The absolute risk reduction of ILT versus less ILT was 6.5% (95% CI, 5.0–7.9), reflecting an NNT of 15 (95% CI, 12–19).

There was no significant heterogeneity in the relative benefits of more versus less ILT according to the number of vascular beds with atherosclerotic disease ( $P=0.66$  for subgroup differences). The lack of interaction remained evident even after excluding studies using placebo as a comparator group ( $P=0.35$  for subgroup differences).

### Role of LDL-C

When the studies were stratified according to a cutoff LDL-C value of 100 mg/dL, patients with monovascular disease with an LDL-C level  $>100$  mg/dL who were subjected to more versus less ILT had a 21% reduction in major vascular events (RR, 0.79; 95% CI, 0.68–0.92 [ $P=0.03$ ]) compared with a 9% risk reduction in those with an LDL-C level  $<100$  mg/dL (RR, 0.91; 95% CI, 0.87–0.96 [ $P=0.001$ ]) (Figure 4). The difference in treatment effect did not reach statistical significance

( $P=0.08$ ). The absolute risk reduction between ILT and less ILT was 3.2% (95% CI, 2.3–4.1) and 1.2% (95% CI, 0.6–1.8) in patients with LDL-C  $>100$  mg/dL and  $<100$  mg/dL, with corresponding NNT of 31 (95% CI, 24–43) and 81 (95% CI, 54–161), respectively.

In contrast, the relative benefits of ILT versus less ILT were consistent between patients with polyvascular disease with LDL-C  $>100$  mg/dL (RR, 0.85; 95% CI, 0.80–0.90 [ $P<0.00001$ ]) and those with LDL-C  $<100$  mg/dL (RR, 0.88; 95% CI, 0.81–0.96 [ $P=0.003$ ]) ( $P=0.23$  for interaction) (Figure 4). The absolute risk reduction of ILT compared with less ILT was higher in patients with polyvascular disease but comparable across the strata of LDL-C, 5.7% (95% CI, 3.6–7.8) in patients with polyvascular disease who had LDL-C  $>100$  mg/dL and 7.2% (95% CI 5.2–9.2) in those with LDL-C  $<100$  mg/dL. The NNT was 17.5 (95% CI, 12–27) and 14 (95% CI, 10–19), respectively. When patients with polyvascular disease were stratified according to their clinical presentation, the relative benefits of ILT was consistent in stable patients (RR, 0.83; 95% CI, 0.80–0.90 [ $P<0.001$ ]) and those with recent myocardial infarction (RR, 0.89; 95% CI, 0.79–1.00 [ $P=0.04$ ]) ( $P=0.34$  for interaction).

**Table 1. Clinical Characteristics of Patients as Reported in the Original Study**

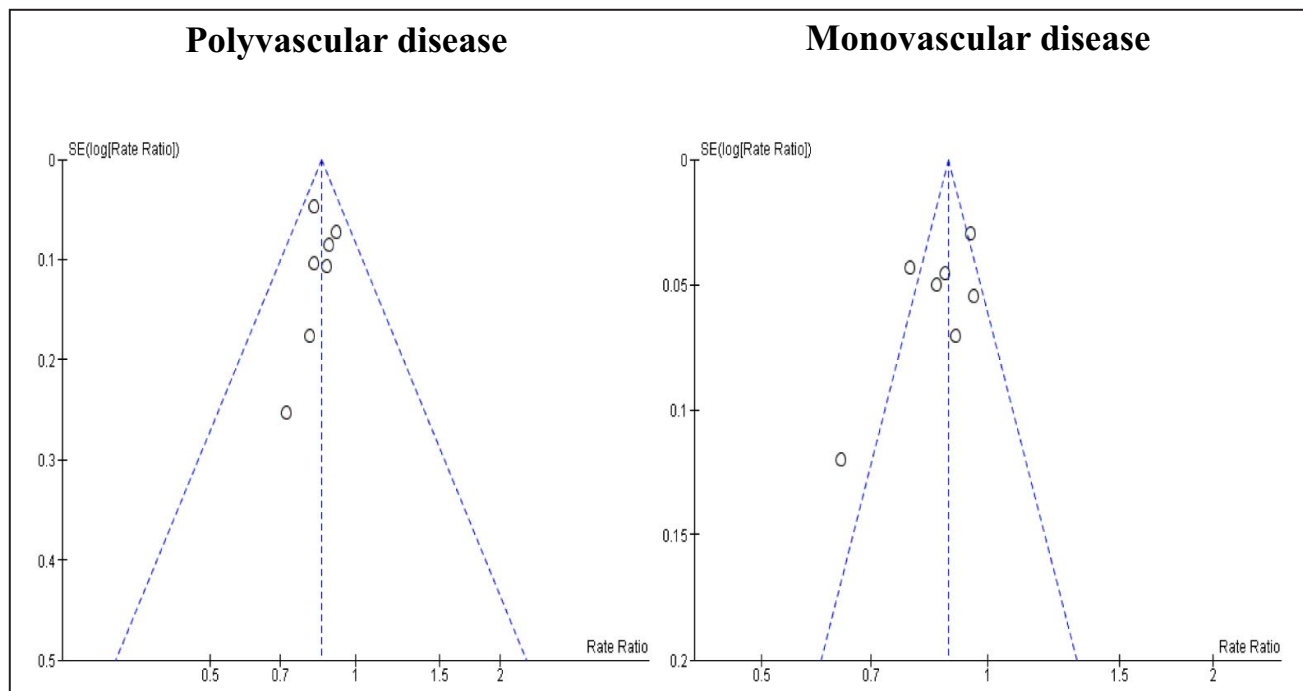
	ODYSEY OUTCOMES <sup>6</sup>	FOURIER <sup>7</sup>	IMPROVE-IT <sup>5</sup>	IDEAL <sup>4</sup>	SEARCH <sup>16</sup>	HPS <sup>14</sup>	WOSCOP <sup>15</sup>
No.	18 924	27 564	18 144	8888	12 064	20 536	6595
Monovascular	17 370	19 113*	16 204	8514	5845*	9395*	5401
Polyvascular	1554	3563	1930	374	1062	5507	1194
Studied lipid-lowering therapy	Alirocumab compared with placebo in patients receiving statin	Evolocumab compared with placebo in patients receiving statin	Ezetimibe and simvastatin compared with simvastatin (40 mg)	Atorvastatin (80 mg) compared with simvastatin (20 mg)	Simvastatin (80 mg) compared with simvastatin (20 mg)	Simvastatin (40 mg) compared with placebo	Pravastatin (40 mg) compared with placebo
Age, y	59±9	63±9	64±10	62±10	64±9	...	55±6
Women, n (%)	4762 (25)	6769 (25)	4416 (24)	1701 (19)	2052 (17)	5082 (25)	...
MI, n (%)	3633 (19)	22 351 (81)	3806 (21)	1494 (17)	12 064 (100)	8510 (41)	338† (5)
CVD, n (%)	611 (3)	5337 (19)	1071 (6)	729 (8)	837 (7)	3280 (16)	...
PVD, n (%)	759 (4)	3642 (13)	1005 (6)	377 (4)	...	6748 (33)	193 (3)
Diabetes mellitus, n (%)	5444 (29)	10 081 (37)	4933 (27)	1069 (12)	1267 (11)	5963 (29)	76 (1)
LDL-C	92±31	92 (81–108)	94	122	97±24	131±31	192±17
Clinical presentation	ACS	Stable	ACS	ACS	Stable	Stable	Stable
Major vascular events	CHD, MI, ischemic stroke, or unstable angina requiring hospitalization	CVD, MI, stroke, hospitalization for unstable angina, or coronary revascularization	CVD, MI, unstable angina requiring rehospitalization, or coronary revascularization	CHD, MI, or cardiac arrest with resuscitation	CHD, MI, stroke, or arterial revascularization	CHD, MI, strokes of any type, and coronary or noncoronary revascularizations	CHD or MI

ACS indicates acute coronary syndrome; FOURIER, Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk; HPS, Heart Protection Study; IDEAL, Incremental Decrease in End Points Through Aggressive Lipid Lowering; IMPROVE-IT, Improved Reduction of Outcomes: Vitorin Efficacy International Trial; LDL-C, low-density lipoprotein cholesterol; ODYSSEY OUTCOMES, Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab; PVD, peripheral vascular disease; SEARCH, Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine; and WOSCOP, West of Scotland Coronary Prevention Study.

\*Only patients with previous myocardial infarction were included; stroke, peripheral artery disease, or diabetes mellitus alone were not used in the analysis.

†History of angina, coronary heart death (CHD), cardiovascular death (CVD), or myocardial infarction (MI).





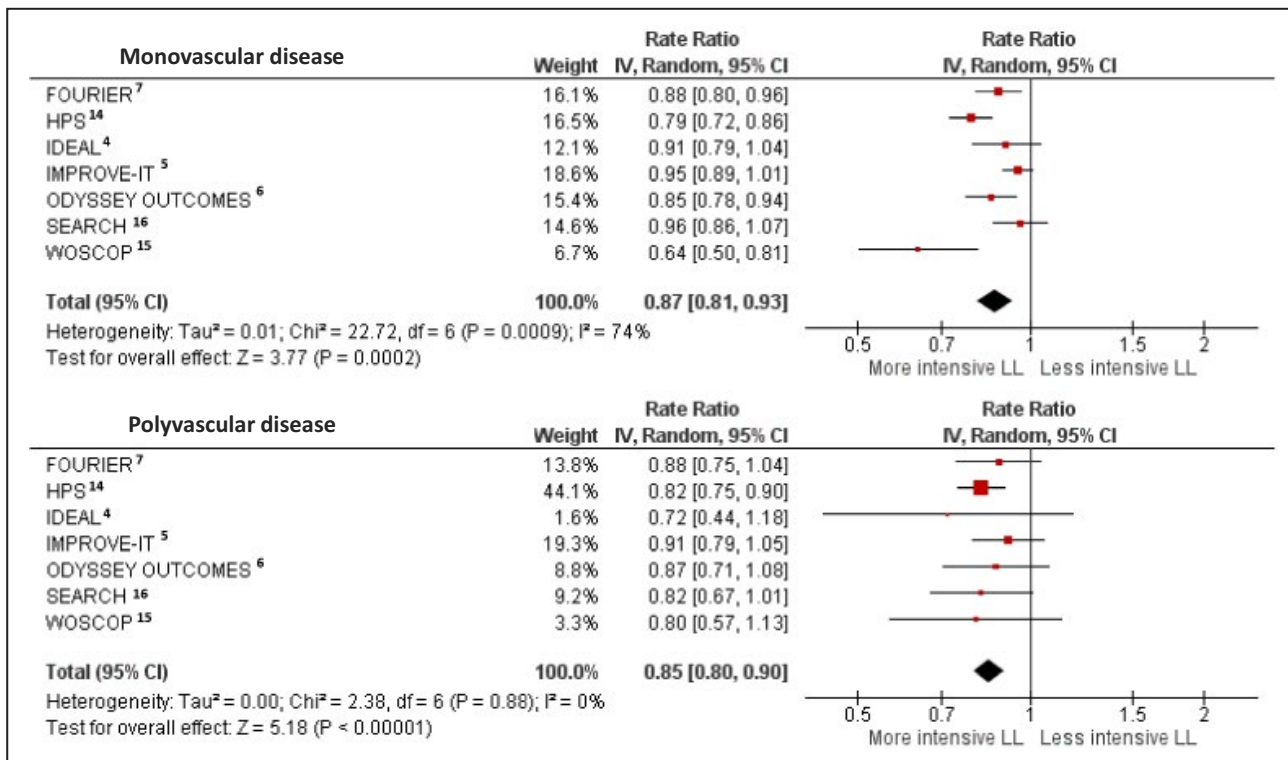
**Figure 2. Publication bias for major vascular events, stratified according to the number of atherosclerotic vascular beds.** Funnel plots of included studies in the meta-analysis. The horizontal axis represents the rate ratio (RR), while the vertical axis reflects the standard error of log RR. The vertical and sloping dotted lines represent the pooled RR and expected 95% CIs for a given standard error (SE), respectively.

## DISCUSSION

This is the first meta-analysis to investigate the role of ILT in patients with polyvascular disease. The main findings of this meta-analysis can be summarized as follows: (1) polyvascular disease is common, with almost 1 in 5 patients having atherosclerotic disease involving at least 2 vascular beds; (2) the relative benefit of ILT is evident in both patients with monovascular disease and those with polyvascular disease, although the absolute benefit is larger in those with polyvascular disease; (3) patients with monovascular disease and LDL-C >100 mg/dL may sustain a greater benefit from ILT compared with individuals with LDL-C <100 mg/dL; and (4) patients with polyvascular disease have comparable benefits irrespective of their LDL-C, reflecting the heightened risk in this group.

Atherosclerosis is a systemic disease resulting from complex and intricate processes affecting the intima of the vascular wall.<sup>26</sup> The contributing risk factors are similar across the world including hypertension, hypercholesterolemia, and diabetes mellitus.<sup>2</sup> The systemic nature of lipoprotein retention means that atherosclerotic plaques are not confined to a single vascular bed. The recognition of the heightened risk in patients with polyvascular disease have prompted few recent trials to study this subgroup specifically.<sup>5,6</sup> Both the IMPROVE-IT

(Improved Reduction of Outcomes: Vytorin Efficacy International Trial) and the ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) study reported higher risk in patients with polyvascular disease compared with those with monovascular disease.<sup>5,6</sup> Nonetheless, the relative risk reduction of ILT was comparable in patients with monovascular and polyvascular disease.<sup>5,27</sup> This is in line with the consistent decrease in major adverse events that was found to be associated with LDL-C reduction using statins among patients with different clinical characteristics.<sup>28</sup> Our data show a similar relative risk reduction in patients with polyvascular disease when compared with individuals with monovascular disease. On the other hand, patients with polyvascular disease obtained a greater absolute risk reduction (6.5% versus 1.8%) and a lower NNT (15 versus 55) compared with those with monovascular disease. Notably, the absolute risk reduction was consistent in polyvascular disease, irrespective of baseline LDL-C. In contrast, the absolute risk reduction was almost 3 times larger in those with LDL-C >100 mg/dL compared with LDL-C <100 mg/dL (3.2% versus 1.2%, respectively) in patients with monovascular disease. It is widely recognized that patients with heightened baseline lipoprotein-related risk are likely to experience more benefits when treated with more intensive therapy.<sup>26,28,29</sup> Therefore, identifying high-risk patients using different



**Figure 3. Meta-analysis of major cardiovascular events of included studies.**

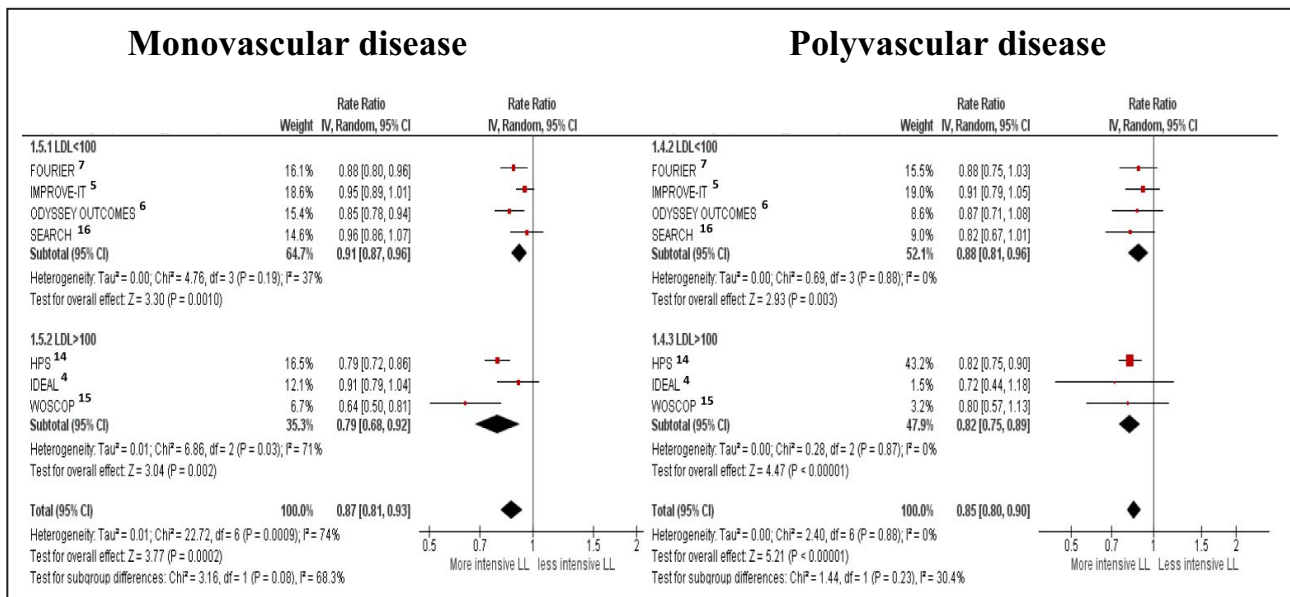
Rate ratios and 95% CIs of more intensive vs less intensive lipid-lowering therapies in patients with monovascular disease (top panel), and polyvascular disease (bottom panel). FOURIER indicates Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk; HPS, Heart Protection Study; IDEAL, Incremental Decrease in End Points Through Aggressive Lipid Lowering; IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial; LL, lipid-lowering therapy; ODYSSEY OUTCOMES, Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab; SEARCH, Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine; and WOSCOP, West of Scotland Coronary Prevention Study.

risk models, such as polyvascular disease, is of urgent need since these patients may benefit maximally from novel therapies such as PCSK9 inhibitors. Moreover, the milder regression of coronary atherosclerosis using statin in patients with polyvascular disease compared with monovascular disease provides a mechanistic indication to commence ILT, such as PCSK9 inhibitors, in this cohort.<sup>30</sup> However, the benefits of ILT was not consistently borne out in previous studies of patients with polyvascular disease.<sup>5</sup> The quantification of “polyvascular” disease as a potential substrate requires more robust evaluation. The mechanistic heterogeneity in atherosclerotic disease processes would render the use of the category of disease, such as cerebral or peripheral vascular disease, less precise in assessing future risk. Moreover, for new treatment to achieve any potential risk reduction, its therapeutic effects should target the disease processes that determine the nature of heightened risk. For lipoprotein-related risk, the benefits of LDL-C reduction are associated with a decrease in atherosclerosis burden and/ or change in plaque composition.<sup>31–33</sup> Indeed, when a category of disease reflects a large atherosclerotic burden, such as post-coronary

artery bypass surgery, the relative benefits of ILT become more sizeable.<sup>11</sup> The extended benefit of intensive lipid-lowering is even associated with a reduction in cardiovascular mortality.<sup>11</sup>

Advances in novel plaque imaging have enabled us to detect the multifocal process of atherosclerotic disease.<sup>32,34</sup> The presence of atherosclerotic plaques, even in their pre-clinical stage, is associated with increased risk of future cardiovascular events.<sup>35,36</sup> Importantly, the burden of these plaques is modifiable using lipid-lowering therapies.<sup>32</sup> The use of novel imaging techniques could serve as a risk stratification tool to identify patients with propensity to develop atherosclerotic plaques at multivascular sites.<sup>37,38</sup> This approach targets a specific process of the atherosclerotic disease, such as lipid accumulation, rather than merely a category of diagnosis and may identify those patients who may benefit maximally from ILTs.<sup>29</sup>

Our data are consistent with previous large meta-analyses highlighting that the greatest benefits of LDL-C-lowering therapy may occur for patients with baseline LDL-C >100 mg/dL.<sup>10</sup> The current meta-analysis showed that LDL-C would serve as a



**Figure 4. Meta-analysis of major cardiovascular events stratified according to baseline low-density lipoprotein cholesterol (LDL-C).**

Rate ratios and 95% CIs of more intensive vs less intensive lipid-lowering therapies in patients with monovascular disease and polyvascular disease, stratified according to baseline LDL-C >100 or <100 mg/dL. FOURIER indicates Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk; HPS, Heart Protection Study; IDEAL, Incremental Decrease in End Points Through Aggressive Lipid Lowering; IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial; LL, lipid-lowering therapy; ODYSSEY OUTCOMES, Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab; SEARCH, Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine; and WOSCOP, West of Scotland Coronary Prevention Study.

clinical discriminator in patients with monovascular disease in identifying individuals who may sustain larger benefits from intensive LDL-C reduction. On the other hand, in polyvascular disease, there is a lack of interaction between LDL-C and the magnitude of benefit of ILT. Importantly, previous studies have also demonstrated the magnitude of LDL-C reduction to be comparable irrespective of the number of diseased vascular beds.<sup>6</sup> This challenges the use of LDL-C level as a single metric in decision-making regarding the use of intensive and novel therapies. Such reasoning should not be surprising given the strong association between cardiovascular events and other blood biomarkers, such as lipoprotein (a) that has been highlighted irrespective of LDL-C.<sup>39</sup> Numerous other markers related to inflammation and platelet activation also contribute to the future risk in any individual, challenging the strategy of using only LDL-C to tailor novel therapies.<sup>26</sup> While LDL-C may be less informative as a tool for risk stratification on an individual basis, this should not overlook its established role as a risk factor in large cohort studies. The use of novel plaque imaging would provide better characterization of individual patients and could be used as a stratification tool to identify high-risk patients. Moreover, direct quantification of the burden of atherosclerotic disease would allow the effects of

standard therapies to be monitored serially and to identify patients with a lack of response as candidates for novel lipid-lowering therapies.<sup>32</sup>

We used a cutoff LDL-C level of 100 mg/dL to determine whether *baseline* LDL-C is a useful marker to aid decision-making for ILT in patients with polyvascular disease. We recognized that this cutoff was higher than recommended LDL-C targets in the current guidelines and might reflect a potential source of bias. Nonetheless, the updated European Task force acknowledged that these LDL-C targets were not examined systematically in randomized clinical trials. Moreover, a large meta-analysis suggested a lack of clinical benefits with intensive LDL-C reduction in patients with baseline LDL-C <100 mg/dL. Finally, recent studies, including those conducted on a background of high-intensity statin therapy such as the FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) and ODYSSEY OUTCOMES trials had baseline LDL-C much higher than 70 mg/dL. Therefore, our data propose the use of ILT in patients with extreme high risk, ie, polyvascular disease, irrespective of baseline LDL-C level.

Our meta-analysis includes trial-level and not individual-level data. Individual data cannot always be deduced from group-level data; nonetheless, there was a consistent favorable effect of ILT among



all included studies. Additionally, there was evidence of heterogeneity in patients with monovascular disease and this is likely to reflect the difference in the included comparator group and the definition of the primary end point.

## CONCLUSIONS

Patients with polyvascular disease experience comparable benefits to those with monovascular disease in response to ILT. While there are differential incremental benefits of ILT according to baseline LDL-C in patients with monovascular disease, patients with polyvascular disease show similar relative risk reduction irrespective of LDL-C. Considerations should be taken in using more potent therapies such as PCSK9 inhibitors to mitigate the elevated risk associated with polyvascular disease even if LDL-C is <100 mg/dL.

## ARTICLE INFORMATION

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