Systematic Review and Meta-Analysis of the Effect of Statins on Circulating E-Selectin, L-Selectin, and P-Selectin

Angelo Zinellu 1 and Arduino A. Mangoni 2,3,*

1 Department of Biomedical Sciences, University of Sassari, 07100 Sassari, Italy; azinellu@uniss.it
2 Discipline of Clinical Pharmacology, College of Medicine and Public Health, Flinders University, Bedford Park, SA 5042, Australia
3 Department of Clinical Pharmacology, Flinders Medical Centre, Southern Adelaide Local Health Network, Bedford Park, SA 5042, Australia
* Correspondence: arduino.mangoni@flinders.edu.au

Abstract: The pleiotropic effects of statins might involve preventing inflammatory cell adhesion to the endothelium, which is a critical step in the pathogenesis of atherosclerosis. We conducted a systematic review and meta-analysis of the effects of statins on the circulating cell adhesion molecules E-Selectin, L-Selectin, and P-Selectin. A literature search was conducted in PubMed, Web of Science, and Scopus, from inception to July 2021. Risk of bias and certainty of evidence were assessed using the Joanna Briggs Institute Critical Appraisal Checklist and GRADE, respectively. In 61 studies, statins significantly reduced P-selectin (standard mean difference, SMD = −0.39, 95% CI −0.55 to −0.22, p < 0.001; moderate certainty of evidence), L-selectin (SMD = −0.49, 95% CI −0.89 to −0.10, p = 0.014; very low certainty of evidence), and E-Selectin (SMD = −0.73, 95% CI −1.02 to −0.43, p < 0.001; moderate certainty of evidence), independently of baseline lipid profile and other study and patient characteristics. The corresponding pooled SMD values in sensitivity analysis were not substantially altered when individual studies were sequentially removed. Simvastatin had a significant lowering effect on both P-selectin and E-selectin. Therefore, statins significantly reduce circulating selectins. Further studies are required to investigate whether selectin lowering mediates cardiovascular risk reduction with these agents. (PROSPERO registration number: CRD42021282778).

Keywords: statins; E-Selectin; L-Selectin; P-Selectin; atherosclerosis

1. Introduction

A critical step in the pathophysiology of atherosclerosis involves the adhesion of inflammatory cell types to the endothelium. This process is facilitated by several cell adhesion molecules [1]. The selectins are a key family of cell adhesion molecules that includes the C-type lectins P-selectin, stored in platelets and endothelial cells [2]; L-selectin, expressed in leukocytes [3]; and E-selectin, expressed in the endothelium [2,4]. L-selectin mediates lymphocyte rolling, whereas P-selectin and E-selectin are primarily expressed in states of endothelial inflammation and facilitate monocyte, neutrophil, and lymphocyte rolling [4]. E-Selectin, L-Selectin, and P-Selectin also exist in soluble forms and can be measured in blood to characterize the state of endothelial and platelet activation in atherosclerosis [4–6].

The pathophysiological role of selectins, particularly P-Selectin and E-selectin, in atherosclerotic cardiovascular disease is supported both by experimental and human studies [7]. In particular, epidemiological studies have reported significant and positive associations between the concentration of soluble selectins and adverse cardiovascular outcomes. For example, higher soluble P-selectin concentrations have been shown to be significantly associated with incident cardiovascular events in women [8]. Similar associations between P-selectin and cardiovascular events have been reported in other studies [9,10]. Soluble E-selectin has also shown significant associations with incident cardiovascular disease in patients with renal failure [11] and atrial fibrillation [12].
Therefore, the available evidence suggests that soluble selectins play a critical role in the pathophysiology of atherosclerosis and endothelial dysfunction and as markers of cardiovascular risk [7], and that interventions targeting this family of cell adhesion molecules might exert atheroprotective effects [13].

Treatment with statins, the leading class of lipid-lowering agents for cardiovascular prevention [14,15], has been shown to exert beneficial effects on endothelial and vascular homeostasis independently of their primary target, inhibition of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase [16]. These so-called pleiotropic effects of statins include the suppression of specific pro-inflammatory cytokines with consequent reduced activation of selectins [17–19]. As human studies have investigated the effects of treatment with statins on soluble concentrations of selectins, we sought to critically appraise this evidence by conducting a systematic review and meta-analysis of the effects of statins on circulating E-Selectin, L-Selectin, and P-Selectin. Meta-regression and subgroup analyses were also conducted to investigate associations between effect size and specific study and patient characteristics.

2. Materials and Methods

A systematic literature search was conducted in the electronic databases PubMed, Web of Science, and Scopus, from inception to July 2021, using the following terms and their combination: “Selectin” or “P-Selectin” or “L-Selectin” or “E-Selectin” and “Statin”. Abstracts were independently screened by two investigators. If relevant, the full-text articles were reviewed according to the following eligibility criteria: (1) assessment of soluble P-Selectin and/or L-Selectin and/or E-Selectin in plasma or serum at baseline and after statin treatment; (2) ≥10 adult participants; (3) English language; and (4) full-text available. The references of the retrieved articles were also searched to identify additional studies. Any disagreement between reviewers was resolved by a third investigator. Data extracted from each study included the year of publication; the continent where the study was conducted; age; the proportion of males; the concentrations of P-Selectin, L-Selectin, and E-Selectin before and after treatment; the primary condition studied; baseline lipid profile; statin and daily dose used; and treatment duration.

The risk of bias was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for analytical studies. A score of ≥5, 4, and <4 indicated low, moderate, and high risk, respectively [20]. The certainty of evidence was assessed using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) Working Group system. GRADE considers the study design (randomized vs. observational), the risk of bias (JBI checklist), the presence of unexplained heterogeneity, the indirectness of evidence, the imprecision of results (sample size, 95% confidence interval width and threshold crossing), the effect size (small, SMD < 0.5, moderate, SMD 0.5–0.8, and large, SMD >0.8) [21], and the probability of publication bias [22–24]. The study complied with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 statement (Supplementary Materials, Tables S1 and S2) [25]. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO registration number: CRD42021282778).

Statistical Analysis

Standardized mean differences (SMDs) were calculated to generate forest plots of continuous data and to evaluate differences in selectin serum concentrations before and after statin treatment. If necessary, means and standard deviations were extrapolated from medians and interquartile ranges [26], or from graphs using the Graph Data Extractor software. Heterogeneity of SMD across studies was assessed using the Q-statistic (significance level set at \( p < 0.10 \)) and \( I^2 \)-statistic (<25%, no heterogeneity; between 25–50%, moderate heterogeneity; between 50–75%, large heterogeneity; and >75%, extreme heterogeneity) [27,28]. Random-effects models were used in the presence of significant heterogeneity (\( I^2 \geq 50\% \)). Sensitivity analysis was conducted to investigate the influence of each study on the over-
all risk estimate [29]. The presence of publication bias was assessed using the Begg’s and Egger’s tests (significance level set at $p < 0.05$) [30,31], and the Duval and Tweedie “trim-and-fill” method [32].

Univariate meta-regression analyses were conducted to investigate associations between effect size and the following study and patient characteristics: age; proportion of males; body mass index; baseline total cholesterol, low-density lipoproteins (LDL)-cholesterol, high-density lipoproteins (HDL)-cholesterol, and triglycerides; year of publication; sample size; continent where the study was conducted; specific statin and class used (lipophilic: atorvastatin, simvastatin, lovastatin, fluvastatin, cerivastatin, and pitavastatin; hydrophilic: rosuvastatin, pravastatin); and treatment duration. Pre-planned subgroup analyses investigated the effects of specific statins, statin classes, and continent where the study was conducted. Statistical analyses were performed using Stata 14 (STATA Corp., College Station, TX, USA).

3. Results
3.1. Systematic Research

A flow chart describing the screening process is presented in Figure 1. We initially identified 1698 articles. A total of 1613 were excluded after the first screening because they were either duplicates or irrelevant. After a full-text review of the remaining 85 articles, 24 were further excluded due to missing data ($n = 7$) or because they did not fulfill the inclusion criteria ($n = 1$, age $< 18$ years; $n = 4$, participants already on lipid-lowering treatment; $n = 3$, sample size $< 10$; $n = 9$ measurement of cell surface selectin). Thus, 61 studies published between 1999 and 2018 were included in the final analysis (Table 1) [33–93].

![Figure 1. PRISMA 2020 flow chart.](image-url)
Table 1. Study characteristics.

| First Author, Year, Country [Reference] | N  | Age (Years) | Males (%) | P-Selectin before Mean ± SD (ng/mL) | P-Selectin after Mean ± SD (ng/mL) | L-Selectin before Mean ± SD (ng/mL) | L-Selectin after Mean ± SD (ng/mL) | E-Selectin before Mean ± SD (ng/mL) | E-Selectin after Mean ± SD (ng/mL) | Primary Condition | Statin and Daily Dose | Treatment Duration |
|----------------------------------------|----|-------------|-----------|------------------------------------|------------------------------------|-------------------------------------|-------------------------------------|-----------------------------------|-----------------------------------|------------------|------------------------|---------------------|
| Koh KK, 1999, USA [33]                 | 28 | 57          | 0         | -                                  | -                                  | 49 ± 18                             | 51 ± 19                             | Hypercholesterolaemia            | Simvastatin 10 mg  | 6 weeks               |
| Rauch U (a), 2000, USA [34]           | 24 | 62          | NR        | 130 ± 30                           | 129 ± 22                           | 753 ± 30                            | 738 ± 31                            | Hypercholesterolaemia            | Pravastatin 40 mg  | 12 weeks              |
| Rauch U (b), 2000, USA [34]           | 26 | 58          | NR        | 105 ± 17                           | 115 ± 15                           | 834 ± 42                            | 778 ± 32                            | Hypercholesterolaemia            | Simvastatin 20 mg  | 12 weeks              |
| Romano M, 2000, Italy [35]            | 13 | 59          | 23        | 118 ± 63                           | 81 ± 36                            | -                                   | -                                  | Hypercholesterolaemia            | Fluvastatin 80 mg  | 12 weeks              |
| Sbarouni E, 2000, Greece [36]         | 16 | 66          | 0         | -                                  | -                                  | -                                   | -                                  | Ischaemic heart disease          | Simvastatin 20 mg  | 8 weeks               |
| Alonso R, 2001, Spain [37]            | 25 | 48          | 44        | -                                  | -                                  | -                                   | -                                  | Familial hypercholesterolaemia  | Simvastatin 40–80 mg | 52 weeks              |
| Blann AD, 2001, UK [38]               | 17 | 65          | 59        | 30 ± 9                             | 26 ± 10                            | -                                   | -                                  | Peripheral artery disease        | Pravastatin 40 mg  | 4 weeks               |
| Sardo MA, 2001, Italy [39]            | 20 | 45          | 45        | -                                  | -                                  | -                                   | -                                  | Hypercholesterolaemia            | Simvastatin 20 mg  | 24 weeks              |
| Solheim S, 2001, Norway [40]          | 40 | 54          | 100       | 54 ± 13                            | 52 ± 13                            | -                                   | -                                  | Hypercholesterolaemia            | Pravastatin 40 mg  | 8 weeks               |
| van Haelst PL, 2001, The Netherlands [41] | 10 | 52          | 90        | -                                  | -                                  | -                                   | -                                  | Ischaemic heart disease          | Fluvastatin 80 mg  | 48 weeks              |
| Atalar E, 2002, Turkey [42]           | 36 | 53          | 61        | -                                  | -                                  | 666 ± 201                           | 584 ± 162                          | Hypercholesterolaemia            | Atorvastatin 10 mg  | 12 weeks              |
Table 1. Cont.

| First Author, Year, Country [Reference] | N  | Age (Years) | Males (%) | P-Selectinbefore Mean ± SD (ng/mL) | P-Selectinafter Mean ± SD (ng/mL) | L-Selectinbefore Mean ± SD (ng/mL) | L-Selectinafter Mean ± SD (ng/mL) | E-Selectinbefore Mean ± SD (ng/mL) | E-Selectinafter Mean ± SD (ng/mL) | Primary Condition | Statin and Daily Dose | Treatment Duration |
|-----------------------------------------|----|-------------|-----------|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|-------------------|---------------------|---------------------|
| Seljeflot I (a), 2002, Norway [43]      | 28 | NR          | 79        | 99 ± 30                           | 86 ± 21                           | -                                 | -                                 | 43 ± 19                           | 42 ± 19                           | Ischaemic heart disease | Atorvastatin 20 mg | 12 weeks            |
| Seljeflot I (b), 2002, Norway [43]      | 30 | NR          | 93        | 106 ± 30                          | 96 ± 36                           | -                                 | -                                 | 49 ± 19                           | 47 ± 21                           | Ischaemic heart disease | Simvastatin 20 mg  | 12 weeks            |
| Bogaty P, 2003, Canada [44]              | 17 | 60          | 6         | 56 ± 20                           | 58 ± 23                           | -                                 | -                                 | 74 ± 18                           | 54 ± 14                           | Ischaemic heart disease | Atorvastatin 10–80 mg | 11 weeks            |
| Dalla Nora I, 2003, Italy [45]           | 13 | 66          | 54        | -                                 | -                                 | -                                 | -                                 | 16 ± 3                            | 8 ± 1                             | Type 2 diabetes     | Atorvastatin 10 mg  | 12 weeks            |
| Empen K, 2003, Germany [46]              | 11 | 62          | 55        | -                                 | -                                 | -                                 | -                                 | 70 ± 37                           | 67 ± 40                           | Type 2 diabetes     | Atorvastatin 10 mg  | 6 weeks             |
| Ferroni P, 2003, Italy [47]              | 25 | 54          | 36        | 70 ± 20                           | 52 ± 18                           | -                                 | -                                 | -                                 | -                                 | Hypercholesterolaemia | Simvastatin 20 mg  | 8 weeks             |
| Hernández C, 2003, Spain [48]            | 44 | 50          | 100       | -                                 | -                                 | -                                 | -                                 | 36 ± 4                            | 33 ± 4                            | Hypercholesterolaemia | Various statins and doses | 16 weeks            |
| Homma Y, 2003, Japan [49]                | 30 | 67          | 13        | 250 ± 103                         | 196 ± 81                          | -                                 | -                                 | -                                 | -                                 | Type 2 hyperlipoproteinemia | Fluvastatin 20–40 mg | 24 weeks            |
| Malyszko J, 2003, Poland [50]            | 12 | NR          | 58        | 115 ± 52                          | 84 ± 13                           | -                                 | -                                 | -                                 | -                                 | Kidney transplant   | Fluvastatin 20 mg  | 12 weeks            |
| Nawawi H (a), 2003, Malaysia [51]        | 27 | 42          | 41        | -                                 | -                                 | -                                 | -                                 | 209 ± 18                          | 35 ± 11                           | Familial hypercholesterolaemia | Atorvastatin 80 mg  | 9 weeks             |
| Nawawi H (b), 2003, Malaysia [51]        | 47 | 48          | 55        | -                                 | -                                 | -                                 | -                                 | 246 ± 14                          | 144 ± 11                          | Familial hypercholesterolaemia | Atorvastatin 10 mg  | 9 weeks             |
Table 1. Cont.

| First Author, Year, Country [Reference] | N  | Age (Years) | Males (%) | P-Selectinbefore Mean ± SD (ng/mL) | P-Selectinafter Mean ± SD (ng/mL) | L-Selectinbefore Mean ± SD (ng/mL) | L-Selectinafter Mean ± SD (ng/mL) | E-Selectinbefore Mean ± SD (ng/mL) | E-Selectinafter Mean ± SD (ng/mL) | Primary Condition Statin and Daily Dose Treatment Duration |
|----------------------------------------|----|-------------|-----------|------------------------------------|-----------------------------------|------------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|----------------------------------------------------------------------------------|
| Puccetti L, 2003, Italy [52]           | 14 | 50          | 57        | 23 ± 4                             | 10 ± 2                            | -                                  | -                                 | -                                 | -                                 | Hypercholesterolaemia Simvastatin 20 mg                                      |
| van Haelst PL, 2003, The Netherlands [53] | 35 | 42          | 60        | -                                  | -                                 | -                                  | -                                 | -                                 | 69 ± 27                           | 62 ± 27                                                                           |
| Brown SL, 2004, South Africa [54]      | 23 | 36          | 70        | -                                  | -                                 | -                                  | -                                 | -                                 | 61 ± 58                           | 61 ± 55                                                                           |
| Ceriello A, 2004, Italy [55]           | 30 | 54          | 73        | -                                  | -                                 | -                                  | -                                 | -                                 | 79 ± 73                           | 46 ± 55                                                                           |
| Cha JK, 2004, Korea [56]               | 32 | 60          | 87        | 97 ± 12                            | 87 ± 8                            | -                                  | -                                 | -                                 | -                                 | Ischaemic stroke Simvastatin 20 mg                                          |
| Koh KK, 2004, Korea [57]               | 32 | 62          | 41        | -                                  | -                                 | -                                  | -                                 | -                                 | 44 ± 17                           | 45 ± 20                                                                           |
| Malyszko J, 2004, Poland [58]          | 15 | 50          | NR        | 103 ± 46                           | 94 ± 36                           | -                                  | -                                 | -                                 | 64 ± 26                           | Peritoneal dialysis Simvastatin 10 mg                                         |
| Nomura S (a), 2004, Japan [59]         | 30 | 67          | 37        | 190 ± 23                           | 164 ± 23                          | -                                  | -                                 | -                                 | -                                 | Hypertension and diabetes Simvastatin 10 mg                                  |
| Nomura S (b), 2004, Japan [59]         | 18 | 64          | 56        | 108 ± 15                           | 107 ± 15                          | -                                  | -                                 | -                                 | -                                 | Hypertension Simvastatin 10 mg                                               |
| Skhra J, 2004, Czech Republic [60]     | 20 | 57          | 60        | 190 ± 54                           | 199 ± 55                          | -                                  | -                                 | -                                 | 65 ± 19                           | 70 ± 19                                                                            |
| Akçay MN, 2005, Turkey [61]            | 10 | 41          | 40        | -                                  | -                                 | -                                  | -                                 | -                                 | 24 ± 3                            | 11 ± 1                                                                            |
Table 1. Cont.

| First Author, Year, Country [Reference] | N  | Age (Years) | Males (%) | P-Selectinbefore Mean ± SD (ng/mL) | P-Selectinafter Mean ± SD (ng/mL) | L-Selectinbefore Mean ± SD (ng/mL) | L-Selectinafter Mean ± SD (ng/mL) | E-Selectinbefore Mean ± SD (ng/mL) | E-Selectinafter Mean ± SD (ng/mL) | Primary Condition | Statin and Daily Dose | Treatment Duration |
|----------------------------------------|----|-------------|-----------|------------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|-------------------|------------------------|---------------------|
| Undas A, 2005, Poland [62]             | 20 | 56          | 70        | 118 ± 54                           | 100 ± 45                           | -                                 | -                                 | -                                 | -                                 | Hypercholesterolaemia | Simvastatin 40 mg    | 4 weeks             |
| Bleske BE, 2006, USA [63]              | 15 | 56          | 60        | 30 ± 19                            | 23 ± 20                            | -                                 | -                                 | -                                 | -                                 | Non-ischaemic cardiomyopathy | Atorvastatin 80 mg  | 12 weeks            |
| Marschang P, 2006, Austria [64]        | 47 | 59          | 64        | 92 ± 75                            | 52 ± 27                            | -                                 | -                                 | 55 ± 27                           | 60 ± 27                           | Ischaemic heart disease | Various statins and doses | 12 weeks            |
| Peverill RE, 2006, Australia [65]      | 24 | 59          | 0         | 43 ± 11                            | 34 ± 9                             | -                                 | -                                 | -                                 | -                                 | Hypercholesterolaemia | Pravastatin 20 mg   | 24 weeks            |
| Potaczek PD (a), 2006, Poland [66]     | 10 | 54          | NR        | 135 ± 63                           | 129 ± 66                           | -                                 | -                                 | -                                 | -                                 | Hypercholesterolaemia | Simvastatin 40 mg    | 4 weeks             |
| Potaczek PD (b), 2006, Poland [66]     | 10 | 54          | NR        | 118 ± 54                           | 91 ± 41                            | -                                 | -                                 | -                                 | -                                 | Hypercholesterolaemia | Simvastatin 40 mg    | 4 weeks             |
| Alber HF, 2007, Austria [67]           | 15 | 57          | NR        | -                                  | -                                 | -                                 | -                                 | 56 ± 23                           | 52 ± 25                           | Ischaemic heart disease | Atorvastatin 20 mg  | 12 weeks            |
| Inami N (a), 2007, Japan [68]          | 65 | 65          | 35        | 177 ± 226                          | 203 ± 282                          | -                                 | -                                 | -                                 | -                                 | Hypercholesterolaemia | without diabetes    | 24 weeks            |
| Inami N (b), 2007, Japan [68]          | 52 | 62          | 46        | 238 ± 260                          | 200 ± 296                          | -                                 | -                                 | -                                 | -                                 | Hypercholesterolaemia | and diabetes         | 24 weeks            |
| Jeffs LS, 2007, Australia [69]         | 25 | 57          | 64        | -                                  | -                                 | -                                 | -                                 | 3.6 ± 1.5                         | 3.9 ± 1.6                         | End-stage renal disease | Pravastatin 10–40 mg | 20 weeks            |
| Souza-Costa DC (a), 2007, Brazil [70]  | 15 | 28          | 100       | 30 ± 16                            | 29 ± 15                            | -                                 | -                                 | -                                 | -                                 | Healthy              | Atorvastatin 10 mg  | 2 weeks             |
| First Author, Year, Country [Reference] | N  | Age (Years) | Males (%) | P-Selectinbefore Mean ± SD (ng/mL) | P-Selectinafter Mean ± SD (ng/mL) | L-Selectinbefore Mean ± SD (ng/mL) | L-Selectinafter Mean ± SD (ng/mL) | E-Selectinbefore Mean ± SD (ng/mL) | E-Selectinafter Mean ± SD (ng/mL) | Primary Condition | Statin and Daily Dose | Treatment Duration |
|----------------------------------------|----|-------------|-----------|----------------------------------|----------------------------------|-----------------------------------|-----------------------------------|----------------------------------|----------------------------------|----------------|---------------------|-----------------|
| Souza-Costa DC (b), 2007, Brazil [70] | 15 | 31          | 100       | 42 ± 18                          | 31 ± 21                          | -                                 | -                                 | -                                | -                                | Healthy        | Atorvastatin 10 mg  | 2 weeks         |
| Barreto AC, 2008, Brazil [71]         | 30 | 35          | 40        | 40 ± 22                          | 35 ± 16                          | -                                 | -                                 | -                                | -                                | Pulmonary arterial hypertension | Rosuvastatin 10 mg  | 24 weeks          |
| Bolewski A, 2008, France [72]        | 26 | 57          | 62        | 55 ± 26                          | 54 ± 20                          | -                                 | -                                 | 36 ± 20                          | 38 ± 20                          | Hypercholesterolaemia | Atorvastatin 20 mg  | 12 weeks         |
| Del Papa N, 2008, Italy [73]          | 20 | 59          | 0         | -                                | -                                | -                                 | -                                 | 52 ± 89                          | 38 ± 45                          | Systemic sclerosis | Simvastatin 20 mg  | 12 weeks         |
| Forst T, 2008, Germany [74]           | 80 | 62          | 48        | 277 ± 125                        | 291 ± 161                        | -                                 | -                                 | -                                | -                                | High cardiovascular risk | Atorvastatin 40 mg  | 24 weeks          |
| Hogue JC, 2008, Canada [75]           | 15 | 55          | 84        | -                                | -                                | -                                 | -                                 | 50 ± 28                          | 48 ± 22                          | Type 2 diabetes   | Atorvastatin 20 mg  | 6 weeks         |
| Nomura S (a), 2008, Japan [76]        | 30 | 60          | 43        | 136 ± 33                         | 128 ± 62                         | 784 ± 121                         | 769 ± 114                         | 52 ± 10                          | 42 ± 11                          | Hypercholesterolaemia | Pitavastatin 2 mg  | 24 weeks         |
| Nomura S (b), 2008, Japan [76]        | 45 | 62          | 44        | 238 ± 64                         | 223 ± 33                         | 896 ± 141                         | 814 ± 129                         | 74 ± 21                          | 51 ± 10                          | Hypercholesterolaemia | Pitavastatin 2 mg  | 24 weeks         |
| Stule T, 2008, Czech Republic [77]    | 27 | 52          | 30        | -                                | -                                | -                                 | -                                 | 58 ± 38                          | 59 ± 35                          | Hypercholesterolemia | Atorvastatin 20 mg  | 12 weeks         |
| Wang L, 2008, USA [78]                | 25 | NR          | NR        | 111 ± 36                         | 119 ± 71                         | -                                 | -                                 | -                                | -                                | Metabolic syndrome | Simvastatin 40 mg  | 8 weeks         |
| Baldassarre D, 2009, Italy [79]       | 85 | 58          | 85        | -                                | -                                | -                                 | -                                 | 32 ± 15                          | 22 ± 10                          | Ischaemic heart disease | Atorvastatin 20 mg  | 12 weeks         |
Table 1. Cont.

| First Author, Year, Country [Reference] | N  | Age (Years) | Males (%) | P-Selectin before Mean ± SD (ng/mL) | P-Selectin after Mean ± SD (ng/mL) | L-Selectin before Mean ± SD (ng/mL) | L-Selectin after Mean ± SD (ng/mL) | E-Selectin before Mean ± SD (ng/mL) | E-Selectin after Mean ± SD (ng/mL) | Primary Condition | Statin and Daily Dose | Treatment Duration |
|----------------------------------------|----|-------------|-----------|-----------------------------------|-----------------------------------|------------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|-------------------|-----------------------|----------------------|
| Grip O, 2009, Sweden [80]              | 10 | 32          | 50        | 255 ± 105                         | 222 ± 41                          | -                                  | -                                 | 18 ± 9                           | 15 ± 9                           | Crohn’s disease     | Atorvastatin 80 mg    | 12 weeks             |
| Nomura S (a), 2009, Japan [81]         | 63 | 61          | NR        | 188 ± 50                           | 182 ± 48                          | -                                  | -                                 | -                                | -                                | Hypercholesterolaemia | Simvastatin 10 mg    | 24 weeks             |
| Nomura S (b), 2009, Japan [81]         | 72 | 61          | NR        | 184 ± 47                           | 175 ± 51                          | -                                  | -                                 | -                                | -                                | Hypercholesterolaemia | Pitavastatin 2 mg   | 24 weeks             |
| Prázný M, 2009, Czech Republic [82]    | 20 | 57          | 50        | 203 ± 64                           | 178 ± 51                          | -                                  | -                                 | 66 ± 27                          | 33 ± 10                          | Type 2 diabetes      | Simvastatin 20 mg    | 12 weeks             |
| Serrano CV, 2009, Brazil [83]          | 23 | 63          | 56        | -                                 | -                                 | -                                  | -                                 | 46 ± 17                          | 59 ± 24                          | Hypercholesterolaemia | Simvastatin 40 mg    | 12 weeks             |
| Fichtenbaum CJ, 2010, USA [84]         | 37 | NR          | 92        | 61 ± 21                           | 57 ± 13                           | -                                  | -                                 | -                                | -                                | Hypercholesterolaemia | Pravastatin 40 mg    | 12 weeks             |
| Kater AL, 2010, Brazil [85]            | 25 | 53          | 76        | -                                 | -                                 | -                                  | -                                 | 44 ± 20                          | 40 ± 15                          | Pre-diabetes         | Simvastatin 20 mg    | 12 weeks             |
| Kirmizis K, 2010, Greece [86]          | 25 | 63          | 48        | -                                 | -                                 | -                                  | -                                 | 77 ± 31                          | 69 ± 31                          | Haemodialysis        | Simvastatin 10 mg    | 24 weeks             |
| Xu DY, 2010, China [87]                | 79 | 64          | 59        | 101 ± 19                          | 73 ± 15                           | -                                  | -                                 | -                                | -                                | High cardiovascular risk | Atorvastatin 10 mg | 8 weeks               |
| Wu YW, 2012, Taiwan [88]               | 34 | 54          | 71        | -                                 | -                                 | -                                  | -                                 | 44 ± 50                          | 42 ± 50                          | Ischaemic heart disease | Atorvastatin 40 mg | 12 weeks             |
| Altun I, 2014, Turkey [89]             | 30 | 53          | 100       | -                                 | -                                 | -                                  | -                                 | 100 ± 35                         | 89 ± 31                          | Acute coronary syndrome | Atorvastatin 40 mg | 12 weeks             |
| First Author, Year, Country [Reference] | N    | Age (Years) | Males (%) | P-Selectinbefore Mean ± SD (ng/mL) | P-Selectinafter Mean ± SD (ng/mL) | L-Selectinbefore Mean ± SD (ng/mL) | L-Selectinafter Mean ± SD (ng/mL) | E-Selectinbefore Mean ± SD (ng/mL) | E-Selectinafter Mean ± SD (ng/mL) | Primary Condition               | Statin and Daily Dose | Treatment Duration |
|----------------------------------------|------|-------------|-----------|-----------------------------------|---------------------------------|----------------------------------|---------------------------------|---------------------------------|---------------------------------|-------------------------|---------------------|------------------|
| Pawelczyk M, 2015, Poland [90]         | 31   | 62          | 57        | 124 ± 60                          | 78 ± 38                        | -                                | -                               | -                               | -                               | Ischaemic stroke,       | Simvastatin 20 mg   | 24 weeks         |
| Hernandez-Mijares A, 2016, Spain [91]  | 20   | 58          | 33        | -                                 | -                              | -                                | -                               | 45 ± 31                         | 39 ± 20                         | Hypercholesterolaemia,  | Simvastatin 40 mg   | 4 weeks          |
| Barale C, 2018, Italy [92]             | 25   | 59          | 44        | -                                 | -                              | -                                | -                               | 44 ± 15                         | 25 ± 8                          | Hypercholesterolaemia   | Simvastatin 40 mg   | 8 weeks          |
| Kotyla PJ, 2018, Poland [93]           | 25   | 55          | 12        | 67 ± 41                           | 66 ± 26                        | 887 ± 222                        | 927 ± 385                       | 276 ± 122                       | 253 ± 125                       | Systemic sclerosis      | Simvastatin 20 mg   | 4 weeks          |

Legend: NR, not reported.
3.2. Meta-Analysis of Soluble P-Selectin

3.2.1. Study Characteristics

Thirty-three studies reported 41 treatment arms in 1238 participants (mean age 59 years, 55% males) [34,35,38,40,43,44,47,49,50,52,56,58–60,62–66,68,70–72,74,76,78,80–82,84,87,90,93]. Simvastatin was used in 17 arms [47,52,56,58–60,62,66,78,81,82,90,93], atorvastatin in 9 [43,44,63,70,72,74,80,87], pravastatin in 7 [34,38,40,65,84], fluvastatin in 3 [35,49,50], pitavastatin in 3 [68,76], and rosuvastatin [71] and combination of various statins [64] in 1, respectively. Treatment duration ranged between 2 and 24 weeks (Table 1).

3.2.2. Risk of Bias

The risk of bias was low in all studies [34,35,38,40,43,44,47,49,50,52,56,58–60,62–66,68,70–72,74,76,78,80–82,84,87,90,93] (Table 2).
Table 2. The Joanna Briggs Institute critical appraisal checklist.

| Study            | Were the Criteria for Inclusion in the Sample Clearly Defined? | Were the Study Subjects and the Setting Described in Detail? | Was the Exposure Measured in a Valid and Reliable Way? | Were Objective, Standard Criteria Used for Measurement of the Condition? | Were Confounding Factors Identified? | Were Strategies to Deal with Confounding Factors Stated? | Were the Outcomes Measured in a Valid and Reliable Way? | Was Appropriate Statistical Analysis Used? | Risk of Bias |
|------------------|---------------------------------------------------------------|---------------------------------------------------------------|--------------------------------------------------------|------------------------------------------------------------------------|-------------------------------------|----------------------------------------------------------|----------------------------------------------------------|------------------------------------------|--------------|
| Koh KK [33]      | Yes                                                           | Yes                                                           | Yes                                                    | Yes                                                                    | Yes                                                | Yes                                                      | Yes                                                      | Yes                                                     | Low          |
| Rauch U [34]     | Yes                                                           | Yes                                                           | Yes                                                    | Yes                                                                    | No                                                 | No                                                       | Yes                                                      | No                                                      | Low          |
| Romano M [35]    | Yes                                                           | Yes                                                           | Yes                                                    | Yes                                                                    | No                                                 | No                                                       | Yes                                                      | No                                                      | Low          |
| Sbarouni E [36]  | Yes                                                           | Yes                                                           | Yes                                                    | Yes                                                                    | No                                                 | No                                                       | Yes                                                      | Yes                                                     | Low          |
| Alonso R [37]    | Yes                                                           | Yes                                                           | Yes                                                    | Yes                                                                    | No                                                 | No                                                       | Yes                                                      | No                                                      | Low          |
| Blann AD [38]    | Yes                                                           | Yes                                                           | Yes                                                    | Yes                                                                    | No                                                 | No                                                       | Yes                                                      | No                                                      | Low          |
| Sardo MA [39]    | Yes                                                           | Yes                                                           | Yes                                                    | Yes                                                                    | No                                                 | No                                                       | Yes                                                      | Yes                                                     | Low          |
| Solheim S [40]   | Yes                                                           | Yes                                                           | Yes                                                    | Yes                                                                    | Yes                                                | Yes                                                      | Yes                                                      | Yes                                                     | Low          |
| van Haelst PL [41]| Yes                                                           | Yes                                                           | Yes                                                    | Yes                                                                    | No                                                 | No                                                       | Yes                                                      | No                                                      | Low          |
| Atalar E [42]    | Yes                                                           | Yes                                                           | Yes                                                    | Yes                                                                    | No                                                 | No                                                       | Yes                                                      | No                                                      | Low          |
| Seljeflot I [43] | Yes                                                           | Yes                                                           | Yes                                                    | Yes                                                                    | No                                                 | No                                                       | Yes                                                      | Yes                                                     | Low          |
| Bogaty P [44]    | Yes                                                           | Yes                                                           | Yes                                                    | Yes                                                                    | No                                                 | No                                                       | Yes                                                      | Yes                                                     | Low          |
| Dalla Nora [45]  | Yes                                                           | Yes                                                           | Yes                                                    | Yes                                                                    | Yes                                                | Yes                                                      | Yes                                                      | Yes                                                     | Low          |
| Empen K [46]     | Yes                                                           | Yes                                                           | Yes                                                    | Yes                                                                    | Yes                                                | Yes                                                      | Yes                                                      | Yes                                                     | Low          |
| Ferroni P [47]   | Yes                                                           | Yes                                                           | Yes                                                    | Yes                                                                    | No                                                 | No                                                       | Yes                                                      | No                                                      | Low          |
| Hernández C [48] | Yes                                                           | Yes                                                           | Yes                                                    | Yes                                                                    | No                                                 | No                                                       | Yes                                                      | No                                                      | Low          |
| Homma Y [49]     | Yes                                                           | Yes                                                           | Yes                                                    | Yes                                                                    | No                                                 | No                                                       | Yes                                                      | No                                                      | Low          |
| Malyszko J [50]  | Yes                                                           | Yes                                                           | Yes                                                    | Yes                                                                    | No                                                 | No                                                       | Yes                                                      | No                                                      | Low          |
| Nawawi H [51]    | Yes                                                           | Yes                                                           | Yes                                                    | Yes                                                                    | No                                                 | No                                                       | Yes                                                      | No                                                      | Low          |
| Puccetti L [52]  | Yes                                                           | Yes                                                           | Yes                                                    | Yes                                                                    | No                                                 | No                                                       | Yes                                                      | No                                                      | Low          |
| van Haelst PL [53]| Yes                                                           | Yes                                                           | Yes                                                    | Yes                                                                    | No                                                 | No                                                       | Yes                                                      | No                                                      | Low          |
| Brown SL [54]    | Yes                                                           | Yes                                                           | Yes                                                    | Yes                                                                    | No                                                 | No                                                       | Yes                                                      | No                                                      | Low          |
| Ceriello A [55]  | Yes                                                           | Yes                                                           | Yes                                                    | Yes                                                                    | Yes                                                | Yes                                                      | Yes                                                      | Yes                                                     | Low          |
| Cha JK [56]      | Yes                                                           | Yes                                                           | Yes                                                    | Yes                                                                    | Yes                                                | Yes                                                      | Yes                                                      | Yes                                                     | Low          |
| Koh KK [57]      | Yes                                                           | Yes                                                           | Yes                                                    | Yes                                                                    | No                                                 | No                                                       | Yes                                                      | Yes                                                     | Low          |
| Malyszko J [58]  | Yes                                                           | Yes                                                           | Yes                                                    | Yes                                                                    | No                                                 | No                                                       | Yes                                                      | No                                                      | Low          |
Table 2. Cont.

| Study          | Were the Criteria for Inclusion in the Sample Clearly Defined? | Were the Study Subjects and the Setting Described in Detail? | Was the Exposure Measured in a Valid and Reliable Way? | Were Objective, Standard Criteria Used for Measurement of the Condition? | Were Confounding Factors Identified? | Were Strategies to Deal with Confounding Factors Stated? | Were the Outcomes Measured in a Valid and Reliable Way? | Was Appropriate Statistical Analysis Used? | Risk of Bias |
|----------------|---------------------------------------------------------------|---------------------------------------------------------------|--------------------------------------------------------|------------------------------------------------------------------------|-------------------------------------|--------------------------------------------------------|--------------------------------------------------------|-----------------------------------------------|----------------|
| Nomura S [59]  | Yes                                                           | Yes                                                           | Yes                                                    | Yes                                                                     | No                                  | No                                                    | Yes                                                   | No                                            | Low            |
| Skrha J [60]   | Yes                                                           | Yes                                                           | Yes                                                    | Yes                                                                     | No                                  | No                                                    | Yes                                                   | No                                            | Low            |
| Akçay MN [61]  | Yes                                                           | Yes                                                           | Yes                                                    | Yes                                                                     | No                                  | No                                                    | Yes                                                   | No                                            | Low            |
| Undas A [62]   | Yes                                                           | Yes                                                           | Yes                                                    | Yes                                                                     | No                                  | No                                                    | Yes                                                   | No                                            | Low            |
| Bleske BE [63] | Yes                                                           | Yes                                                           | Yes                                                    | Yes                                                                     | Yes                                 | Yes                                                   | Yes                                                   | Yes                                           | Low            |
| Marschang P [64]| Yes                                                           | Yes                                                           | Yes                                                    | Yes                                                                     | No                                  | No                                                    | Yes                                                   | No                                            | Low            |
| Peverill RE [65]| Yes                                                           | Yes                                                           | Yes                                                    | Yes                                                                     | No                                  | No                                                    | Yes                                                   | No                                            | Low            |
| Potaczek PD [66]| Yes                                                           | Yes                                                           | Yes                                                    | Yes                                                                     | No                                  | No                                                    | Yes                                                   | No                                            | Low            |
| Alber HF [67]  | Yes                                                           | Yes                                                           | Yes                                                    | Yes                                                                     | No                                  | No                                                    | Yes                                                   | No                                            | Low            |
| Inami N [68]   | Yes                                                           | Yes                                                           | Yes                                                    | Yes                                                                     | No                                  | No                                                    | Yes                                                   | No                                            | Low            |
| Jeff LS [69]   | Yes                                                           | Yes                                                           | Yes                                                    | Yes                                                                     | No                                  | No                                                    | Yes                                                   | No                                            | Low            |
| Souza-Costa DC [70]| Yes                                                          | Yes                                                           | Yes                                                    | Yes                                                                     | No                                  | No                                                    | Yes                                                   | No                                            | Low            |
| Barreto AC [71]| Yes                                                           | Yes                                                           | Yes                                                    | Yes                                                                     | No                                  | No                                                    | Yes                                                   | No                                            | Low            |
| Bolewski A [72]| Yes                                                           | Yes                                                           | Yes                                                    | Yes                                                                     | No                                  | No                                                    | Yes                                                   | No                                            | Low            |
| Del Papa N [73]| Yes                                                           | Yes                                                           | Yes                                                    | Yes                                                                     | No                                  | No                                                    | Yes                                                   | No                                            | Low            |
| Forst T [74]   | Yes                                                           | Yes                                                           | Yes                                                    | Yes                                                                     | No                                  | No                                                    | Yes                                                   | No                                            | Low            |
| Hogue JC [75]  | Yes                                                           | Yes                                                           | Yes                                                    | Yes                                                                     | No                                  | No                                                    | Yes                                                   | No                                            | Low            |
| Nomura S [76]  | Yes                                                           | Yes                                                           | Yes                                                    | Yes                                                                     | Yes                                 | Yes                                                   | Yes                                                   | No                                            | Low            |
| Stuc T [77]    | Yes                                                           | Yes                                                           | Yes                                                    | Yes                                                                     | No                                  | No                                                    | Yes                                                   | No                                            | Low            |
| Wang L [78]    | Yes                                                           | Yes                                                           | Yes                                                    | Yes                                                                     | No                                  | No                                                    | Yes                                                   | No                                            | Low            |
| Baldassarre D [79]| Yes                                                          | Yes                                                           | Yes                                                    | Yes                                                                     | No                                  | No                                                    | Yes                                                   | No                                            | Low            |
| Grip O [80]    | Yes                                                           | Yes                                                           | Yes                                                    | Yes                                                                     | No                                  | No                                                    | Yes                                                   | No                                            | Low            |
| Nomura S [81]  | Yes                                                           | Yes                                                           | Yes                                                    | Yes                                                                     | Yes                                 | Yes                                                   | Yes                                                   | No                                            | Low            |
| Prázný M [82]  | Yes                                                           | Yes                                                           | Yes                                                    | Yes                                                                     | No                                  | No                                                    | Yes                                                   | No                                            | Low            |
| Serrano CV [83]| Yes                                                           | Yes                                                           | Yes                                                    | Yes                                                                     | No                                  | No                                                    | Yes                                                   | No                                            | Low            |
| Fichtenbaum CJ [84]| Yes                                                         | Yes                                                           | Yes                                                    | Yes                                                                     | No                                  | No                                                    | Yes                                                   | No                                            | Low            |
Table 2. Cont.

| Study           | Were the Criteria for Inclusion in the Sample Clearly Defined? | Were the Study Subjects and the Setting Described in Detail? | Was the Exposure Measured in a Valid and Reliable Way? | Were Objective, Standard Criteria Used for Measurement of the Condition? | Were Confounding Factors Identified? | Were Strategies to Deal with Confounding Factors Stated? | Were the Outcomes Measured in a Valid and Reliable Way? | Was Appropriate Statistical Analysis Used? | Risk of Bias |
|-----------------|---------------------------------------------------------------|---------------------------------------------------------------|--------------------------------------------------------|------------------------------------------------------------------------|--------------------------------------|--------------------------------------------------------|--------------------------------------------------------|-------------------------------------------|-------------|
| Kater AL [85]   | Yes                                                          | Yes                                                          | Yes                                                   | Yes                                                                     | No                                   | No                                                    | Yes                                                    | Yes                                                      | Low          |
| Kirmizis K [86] | Yes                                                          | Yes                                                          | Yes                                                   | Yes                                                                     | No                                   | No                                                    | Yes                                                    | Yes                                                      | Low          |
| Xu DY [87]      | Yes                                                          | Yes                                                          | Yes                                                   | Yes                                                                     | No                                   | No                                                    | Yes                                                    | No                                                       | Low          |
| Wu YW [88]      | Yes                                                          | Yes                                                          | Yes                                                   | Yes                                                                     | No                                   | No                                                    | Yes                                                    | No                                                       | Low          |
| Altun I [89]    | Yes                                                          | Yes                                                          | Yes                                                   | Yes                                                                     | No                                   | No                                                    | Yes                                                    | No                                                       | Low          |
| Pawelczyk M [90]| Yes                                                          | Yes                                                          | Yes                                                   | Yes                                                                     | No                                   | No                                                    | Yes                                                    | No                                                       | Low          |
| Hernandez-Mijares A [91]| Yes                      | Yes                                                          | Yes                                                   | Yes                                                                     | No                                   | No                                                    | Yes                                                    | No                                                       | Low          |
| Barale C [92]   | Yes                                                          | Yes                                                          | Yes                                                   | Yes                                                                     | No                                   | No                                                    | Yes                                                    | No                                                       | Low          |
| Kotyla PJ [93]  | Yes                                                          | Yes                                                          | Yes                                                   | Yes                                                                     | No                                   | No                                                    | Yes                                                    | No                                                       | Low          |
3.2.3. Results of Individual Studies and Syntheses

The forest plot for circulating P-Selectin concentrations before and after statin treatment is shown in Figure 2. In six arms [34,44,60,68,74,78], concentrations were higher after treatment (mean difference range, 0.10 to 0.62); however, the difference was statistically significant only in one [34]. In the remaining arms [35,38,40,43,47,49,50,52,56,58,62–66,70–72,76,80–82,84,87,90,93], P-Selectin concentrations were lower after treatment (mean difference range, −0.03 to −4.11) with a significant difference reported in nine [47,49,52,56,59,64,65,87,90]. The large between-study heterogeneity observed (I² = 74.1%, p < 0.001) prompted the use of random-effects models. Pooled results showed that P-Selectin concentrations were significantly lower after statin treatment (SMD = −0.39, 95% CI −0.55 to −0.22, p < 0.001).

Figure 2. Forest plot of circulating P-Selectin concentrations before and after statin treatment.

In sensitivity analysis, the corresponding pooled SMD values were not substantially altered when individual studies were sequentially removed (effect size range, between −0.41 and −0.33, Figure 3A). However, the funnel plot analysis, reported in Figure 3B, detected a distortive effect of one study [52]. Removing this study mildly attenuated both the effect size (SMD = −0.35, 95% CI −0.50 to −0.20, p < 0.001) and the heterogeneity (I² = 68.5%, p < 0.001).

3.2.4. Publication Bias

The analysis of the remaining 40 arms, after removing the previously described study [52], did not show significant publication bias (Begg’s test, p = 0.12; Egger’s test, p = 0.57). The “trim-and-fill” method identified one potential missing study to be added to the left side of the funnel plot to ensure symmetry (adjusted SMD = −0.37, 95% CI −0.52 to −0.22, p < 0.001; Figure 4).
3.2.4. Publication Bias
The analysis of the remaining 40 arms, after removing the previously described study [52], did not show significant publication bias (Begg's test, \( p = 0.12 \); Egger's test, \( p = 0.57 \)). The “trim-and-fill” method identified one potential missing study to be added to the left side of the funnel plot to ensure symmetry (adjusted SMD = \(-0.37\), 95% CI \(-0.52\) to \(-0.22\), \( p < 0.001 \); Figure 4).

3.2.5. Meta-Regression and Subgroup Analysis
In univariate meta-regression, there were no significant associations between effect size and age (\( t = -0.61, p = 0.55 \)); proportion of males (\( t = 0.03, p = 0.98 \)); body mass index (\( t = 0.43, p = 0.67 \)); publication year (\( t = -0.37, p = 0.71 \)); sample size (\( t = -0.23, p = 0.81 \)); baseline total cholesterol (\( t = 0.80, p = 0.43 \)), LDL-cholesterol (\( t = 0.95, p = 0.35 \)), HDL-cholesterol (\( t = 0.36, p = 0.72 \)), and triglycerides (\( t = 0.79, p = 0.44 \)); and treatment duration (\( t = 0.19, p = 0.85 \)). In subgroup analysis, the P-Selectin-lowering effect with lipophilic statins (SMD = \(-0.37\), 95% CI \(-0.55\) to \(-0.18\), \( p < 0.001 \); \( I^2 = 72.2\%, p < 0.001 \)) was relatively larger than that with hydrophilic statins (SMD = \(-0.19\), 95% CI \(-0.38\) to \(-0.004\), \( p = 0.046 \); \( I^2 = 22.7\%, p = 0.25 \), Figure 5); however, this difference was not statistically significant (\( p = 0.45 \)).

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**Figure 3.** (A) Sensitivity analysis of the association between P-Selectin and statin treatment. The influence of individual studies on the overall standardized mean difference (SMD) is shown. The middle vertical axis indicates the overall SMD, and the two vertical axes indicate the 95% confidence intervals (CIs). The hollow circles represent the pooled SMD when the remaining study is omitted from the meta-analysis. The two ends of each broken line represent the 95% CIs. (B) Funnel plot of studies investigating P-Selectin concentrations before and after statin treatment.

**Figure 4.** Funnel plot of P-Selectin concentrations before and after statin treatment after “trimming-and-filling”. Dummy studies and genuine studies are represented by enclosed circles and free circles, respectively.
3.2.5. Meta-Regression and Subgroup Analysis

In univariate meta-regression, there were no significant associations between effect size (t = −0.61, p = 0.55); proportion of males (t = 0.03, p = 0.98); body mass index (t = 0.43, p = 0.67); publication year (t = −0.37, p = 0.71); sample size (t = −0.23, p = 0.81); baseline total cholesterol (t = 0.80, p = 0.43); LDL-cholesterol (t = 0.95, p = 0.35); HDL-cholesterol (t = 0.36, p = 0.72), and triglycerides (t = 0.79, p = 0.44); and treatment duration (t = 0.19, p = 0.85). In sub-group analysis, the P-Selectin-lowering effect with lipophilic statins (SMD = −0.37, 95% CI −0.55 to −0.18, p < 0.001; I² = 72.2%, p < 0.001) was relatively larger than that with hydrophilic statins (SMD = −0.19, 95% CI −0.38 to −0.004, p = 0.046; I² = 22.7%, p = 0.25, Figure 3); however, this difference was not statistically significant (p = 0.45).

When considering individual agents, a significant lowering effect was observed with simvastatin (SMD = −0.32, 95% CI −0.57 to −0.08, p = 0.005; I² = 64.5%, p < 0.001) and fluvastatin (SMD = −0.67, 95% CI −1.05 to −0.28, p = 0.001; I² = 0.0%, p = 0.89), but not with atorvastatin (SMD = −0.39, 95% CI −0.88 to 0.11, p = 0.12; I² = 86.5%, p < 0.001), pravastatin (SMD = −0.19, 95% CI −0.41 to 0.02, p = 0.06; I² = 32.9%, p = 0.18), or pitavastatin (SMD = −0.21, 95% CI −0.44 to 0.02, p = 0.07; I² = 0.0%, p = 0.98) (Figure 6). As reported in Figure 7, a significant P-Selectin-lowering effect was reported in studies conducted in Asia (SMD = −0.47, 95% CI −0.82 to −0.12, p = 0.008; I² = 86.3%, p < 0.001) and Europe (SMD = −0.35, 95% CI −0.51 to −0.18, p < 0.001; I² = 32.9%, p = 0.08) but not America (SMD = −0.05, 95% CI −0.28 to 0.17, p = 0.63; I² = 20.7%, p = 0.26).

Figure 5. Forest plot of P-Selectin concentrations before and after statin treatment according to statin class (hydrophilic or lipophilic).
Figure 6. Forest plot of P-Selectin concentrations before and after statin treatment according to individual agents.

Figure 7. Forest plot of P-Selectin concentrations before and after statin treatment according to continent where the study was conducted.
We further sought to identify more homogeneous study sub-groups according to statin used and continent. In a sub-group of nine studies (10 treatment arms) conducted in Europe using atorvastatin [43,47,58,60,62,66,82,90,93], the significant reduction in P-Selectin concentrations (SMD = −0.37, 95% CI −0.60 to −0.14, p = 0.002) was associated with a markedly lower heterogeneity (I² = 24.1%, p = 0.22) (Figure 8).

![Forest plot of a sub-group of 10 studies examining P-Selectin concentrations, homogeneous for statin used and continent.](image)

Figure 8. Forest plot of a sub-group of 10 studies examining P-Selectin concentrations, homogeneous for statin used and continent.

### 3.2.6. Certainty of Evidence

The initial level of certainty for P-Selectin SMD values was considered moderate because of the interventional nature of the studies (rating 3, ⊕⊕⊕⊖). After considering the low risk of bias in all studies (upgrade one level), generally large heterogeneity was partially explained by the specific statin used and the continent where the study was conducted (no rating change required), the lack of indirectness (no rating change required), the relatively low imprecision (relatively narrow confidence intervals without threshold crossing, no rating change required), the relatively small effect size (SMD = −0.39, downgrade one level), and the absence of publication bias (no rating change required); the overall level of certainty remained moderate (rating 3, ⊕⊕⊕⊖).

### 3.3. Meta-Analysis of Soluble L-Selectin

#### 3.3.1. Study Characteristics

Four studies reported six treatment arms in 186 participants (mean age 55 years, 59% males) [34,42,76,93]. The statin used was simvastatin in two arms [34,93], pitavastatin in two [76], and atorvastatin [42] and pravastatin [34] in one, respectively. Duration of therapy ranged between 4 and 24 weeks (Table 1).

#### 3.3.2. Risk of Bias

The risk of bias was low in all studies [34,42,76,93] (Table 2).

#### 3.3.3. Results of Individual Studies and Syntheses

The forest plot for circulating L-Selectin concentrations before and after statin treatment is shown in Figure 9. In five arms [34,42,76], concentrations were lower after treatment (mean difference range, −1.50 to −0.13), and the difference was statistically significant in two [34,76]. In the remaining arm [93], L-Selectin concentrations were non-significantly higher after treatment. Random-effects models were used in view of the large heterogeneity observed (I² = 71.1%, p = 0.004). Pooled results showed that L-Selectin concentrations were
significantly lower after treatment (SMD = −0.49, 95% CI −0.89 to −0.10, p = 0.014). In sensitivity analysis, the corresponding pooled SMD values were not substantially altered when individual studies were sequentially removed (effect size range, between −0.61 and −0.33, Figure 10).

| Study            | Year | TREATED SMD (95% CI) | N. mean (SD) | N. mean (SD) | Weight |
|------------------|------|----------------------|--------------|--------------|--------|
| Rauch U et al. (a) | 2009 | -1.50 (-2.12, -0.88) | 28,778 (32)  | 28,834 (42)  | 14.93  |
| Rauch U et al. (b)| 2009 | -0.49 (-1.07, 0.09)  | 24,738 (31)  | 24,733 (30)  | 15.71  |
| Atalar E et al.  | 2002 | -0.41 (-1.03, 0.21)  | 45,814 (120) | 45,596 (141) | 15.58  |
| Nomura S et al. (a) | 2006 | -0.13 (-0.32, 0.07)  | 29,769 (114) | 29,742 (121) | 15.99  |
| Nomura S et al. (a) | 2006 | -0.12 (-0.53, 0.38)  | 30,704 (114) | 29,742 (121) | 15.99  |
| Kotify PJ et al.  | 2010 | 0.13 (-0.43, 0.68)   | 25,927 (205) | 25,607 (222) | 16.06  |
| Overall (I² = 71.1%, p < 0.004) | | -0.49 (-0.89, -0.10) | 186 | 186 | 100.00 |

NOTE: Weights are from random effects analysis.

Figure 9. Forest plot of L-Selectin concentrations before and after statin treatment.

Figure 10. Sensitivity analysis of the association between L-Selectin and statin treatment. The influence of individual studies on the overall standardized mean difference (SMD) is shown. The middle vertical axis indicates the overall SMD, and the two vertical axes indicate the 95% confidence intervals (CIs). The hollow circles represent the pooled SMD when the remaining study is omitted from the meta-analysis. The two ends of each broken line represent the 95% CIs.

3.3.4. Publication Bias

Assessment of publication bias was not possible because of the small number of studies.

3.3.5. Meta-Regression and Subgroup Analysis

Meta-regression and sub-group analysis were not possible because of the small number of studies.
3.3.6. Certainty of Evidence

The initial level of certainty for L-Selectin SMD values was considered moderate because of the interventional nature of the studies (rating 3, ⊕⊕⊕⊖). After considering the low risk of bias in all studies (upgrade one level), a large unexplained heterogeneity (downgrade one level), the lack of indirectness (no rating change required), the relatively low imprecision (relatively narrow confidence intervals without threshold crossing, no rating change required), the relatively small effect size (SMD = −0.49, downgrade one level), and the lack of assessment of publication bias (downgrade one level), the overall level of certainty was considered very low (rating 1, ⊕⊖⊖⊖).

3.4. Meta-Analysis of Soluble E-Selectin

3.4.1. Study Characteristics

Thirty-eight studies reported 41 treatment arms in 1097 patients (mean age 55 years, 60% males) [33,36,37,39–41,43–46,48,51,53–55,57,58,60,61,64,67,69,72,73,75–77,79,80,82,83,85,86,88,89,91–93]. Simvastatin was used in 19 arms [33,36,37,39,43,53–55,57,58,60,61,73,82,83,85,86,91–93], atorvastatin in 15 [43–46,51,67,72,75,77,79,80,88,89], pravastatin in 2 [40,69], pitavastatin in 2 [76], various combination of statins in 2 [48,64], and fluvastatin in 1 [41]. Duration of therapy ranged between 4 and 52 weeks (Table 1).

3.4.2. Risk of Bias

The risk of bias was low in all studies [33,36,37,39–41,43–46,48,51,53–55,57,58,60,61,64,67,69,72,73,75–77,79,80,82,83,85,86,88,89,91–93] (Table 2).

3.4.3. Results of Individual Studies and Syntheses

The forest plot for circulating E-Selectin concentrations before and after statin treatment is shown in Figure 11. In nine arms [43,49,67,70,74,79,82,87,93], concentrations were higher after treatment (mean difference range, 0.03 to 0.63); however, a significant difference was reported only in one [83]. Virtually identical pre- and post-treatment concentrations were reported in two arms [36,54]. In the remaining arms [37,40,41,43–46,48,51,53,55,58,61,67,73,75,76,79,80,82,85,86,88,89,91–93], E-Selectin concentrations were lower after treatment (mean difference range, −0.04 to −11.66), with a significant difference reported in 13 [37,41,44,45,48,51,61,76,79,82,92]. Extreme heterogeneity between studies was observed (I² = 90.4%, p < 0.001), requiring the use of random-effects models. Pooled results showed that circulating E-Selectin concentrations were significantly lower after treatment (SMD = −0.73, 95% CI −1.02 to −0.43, p < 0.001). In sensitivity analysis, the corresponding pooled SMD values were not substantially altered when individual studies were sequentially removed (effect size range, between −0.76 and −0.53, Figure 12A). However, the funnel plot analysis, reported in Figure 12B, detected a distortive effect of three studies (four treatment arms) [45,51,61]. Their removal attenuated both the effect size (SMD = −0.33, 95% CI −0.50 to −0.16, p < 0.001) and the magnitude of the heterogeneity (I² = 71.4%, p < 0.001).
Figure 11. Forest plot of E-Selectin concentrations before and after statin treatment.

Figure 12. (A) Sensitivity analysis of the association between E-Selectin and statin treatment. The influence of individual studies on the overall standardized mean difference (SMD) is shown. The middle vertical axis indicates the overall SMD, and the two vertical axes indicate the 95% confidence intervals (CIs). The hollow circles represent the pooled SMD when the remaining study is omitted from the meta-analysis. The two ends of each broken line represent the 95% CIs. (B) Funnel plot of studies investigating E-Selectin concentrations before and after statin treatment.
3.4.4. Publication Bias

The analysis of the remaining 37 treatment arms did not show publication bias (Begg’s test, \( p = 0.57 \); Egger’s test, \( p = 0.90 \)). However, the “trim-and-fill” method identified four potential missing studies to be added to the left side of the funnel plot to ensure symmetry (adjusted SMD = \(-0.41\), 95% CI \(-0.58\) to \(-0.24\), \( p < 0.001 \); Figure 13).

Figure 12. (A) Sensitivity analysis of the association between E-Selectin and statin treatment. The influence of individual studies on the overall standardized mean difference (SMD) is shown. The middle vertical axis indicates the overall SMD, and the two vertical axes indicate the 95% confidence intervals (CIs). The hollow circles represent the pooled SMD when the remaining study is omitted from the meta-analysis. The two ends of each broken line represent the 95% CIs. (B) Funnel plot of studies investigating E-Selectin concentrations before and after statin treatment.

Figure 13. Funnel plot of studies investigating E-Selectin concentrations before and after statin treatment after “trimming-and-filling”. Dummy studies and genuine studies are represented by enclosed circles and free circles, respectively.
3.4.5. Meta-Regression and Subgroup Analysis

In univariate meta-regression, there were no significant associations between effect size and age ($t = -0.23, p = 0.82$), proportion of males ($t = -0.58, p = 0.57$), body mass index ($t = 0.43, p = 0.67$), publication year ($t = -0.87, p = 0.31$), sample size ($t = -0.90, p = 0.38$), baseline total cholesterol ($t = -0.37, p = 0.71$), LDL-cholesterol ($t = -0.30, p = 0.77$), HDL-cholesterol ($t = 0.91, p = 0.37$), and triglycerides ($t = 0.94, p = 0.36$), and treatment duration ($t = -1.44, p = 0.16$). In sub-group analysis, a significant lowering effect was observed with lipophilic (SMD = $-0.35, 95\% CI -0.54$ to $-0.17, p < 0.001; I^2 = 71.4\%, p < 0.001$) but not hydrophilic statins (SMD = $-0.06, 95\% CI -0.49$ to $0.37, p = 0.65; I^2 = 33.5\%, p = 0.22$) (Figure 14). When assessing individual agents, a significant lowering effect was observed with simvastatin (SMD = $-0.28, 95\% CI -0.52$ to $-0.03, p = 0.03; I^2 = 70.2\%, p < 0.001$), atorvastatin (SMD = $-0.27, 95\% CI -0.53$ to $-0.02, p = 0.035; I^2 = 54.1\%, p = 0.016$), and pitavastatin (SMD = $-1.20, 95\% CI -1.63$ to $-0.76, p < 0.001; I^2 = 35.0\%, p = 0.22$), but not pravastatin (SMD = $-0.06, 95\% CI -0.49$ to $0.37, p = 0.65; I^2 = 33.5\%, p = 0.22$) (Figure 15). Moreover, as reported in Figure 16, a significant decrease in E-Selectin concentrations was reported in studies conducted in Europe (SMD = $-0.36, 95\% CI -0.55$ to $-0.16, p < 0.001; I^2 = 66.7\%, p < 0.001$) but not America (SMD = $-0.13, 95\% CI -0.67$ to $0.40 p = 0.62; I^2 = 20.7\%, p = 0.26$) or Asia (SMD = $-0.53, 95\% CI -1.10$ to $0.03, p = 0.06; I^2 = 84.7\%, p < 0.001$).

3.4.6. Certainty of Evidence

The initial level of certainty for E-Selectin SMD values was considered moderate because of the interventional nature of the studies (rating 3, ⊕⊕⊕⊖). After considering the low risk of bias in all studies (upgrade one level), a large heterogeneity that was only partially attenuated after removing three studies (downgrade one level); the lack of indirectness (no rating change required); the relatively low imprecision (relatively narrow confidence intervals without threshold crossing, no rating change required); the relatively moderate effect size (SMD = $-0.73$, no rating change required); and the lack of publication bias (no rating change required), the overall level of certainty remained moderate (rating 3, ⊕⊕⊕⊖).

![Figure 14](image-url) Forest plot of E-Selectin concentrations before and after statin treatment according to statin class (hydrophilic or lipophilic).
3.4.6. Certainty of Evidence

The initial level of certainty for E-Selectin SMD values was considered moderate because of the interventional nature of the studies (rating 3, ⊕⊕⊕⊝). After considering the low risk of bias in all studies (upgrade one level), a large heterogeneity that was only partially attenuated after removing three studies (downgrade one level); the lack of indirectness (no rating change required); the relatively low imprecision (relatively narrow confidence intervals without threshold crossing, no rating change required); the relatively moderate effect size (SMD = −0.73, no rating change required); and the lack of publication bias (no rating change required), the overall level of certainty remained moderate (rating 3, ⊕⊕⊕⊝).

4. Discussion

In this systematic review and meta-analysis, statin treatment significantly reduced the concentrations of soluble E-Selectin, L-Selectin, and P-Selectin in participants with a range of cardiovascular risk profiles. In sensitivity analysis, the pooled SMD values were not substantially altered when individual studies were sequentially removed. In meta-regression, no significant associations were observed between effect size and various patient and study characteristics, including baseline lipids. The absence of significant associations with treatment duration, ranging between 2 and 52 weeks, suggests that the selectin-lowering effects of statins are evident relatively early during treatment and are maintained for up to 1 year.

The activation of selectins, particularly P-Selectin and E-Selectin, has an established role in the pathogenesis of atherosclerosis and its clinical manifestations [94]. The results of several observational studies further support this proposition. In the Women's Health Study, participants with baseline soluble P-selectin concentrations in the highest quartile had a relative risk of suffering a cardiovascular event during a 3.5-year follow up period 2.2 times higher than those in the lowest quartile (95% CI 1.2 to 4.2). Notably, this...
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In subgroup analysis, lipophilic, but not hydrophilic, statins significantly reduced soluble E-Selectin concentrations. However, these results need to be interpreted with cau-
tion because of the extremely low number of treatment arms, two, involving hydrophilic statins. Significant differences were also observed with individual statins, with simvastatin and fluvastatin being particularly effective against P-Selectin, and simvastatin, atorvastatin, and pitavastatin against E-Selectin. Further research is warranted to investigate whether specific statin classes and individual agents have superior capacity to reduce soluble selectin concentrations and whether this effect might be particularly beneficial in specific patient groups. Another interesting observation, in subgroup analysis, was the difference in selectin-lowering according to specific continent, with studies conducted in Europe showing a particular efficacy against P-Selectin and E-Selectin. Previous studies have investigated the concentrations of soluble selectins in different ethnic groups. In the Multi-Ethnic Study of Atherosclerosis, no significant differences in soluble E-Selectin concentrations were observed between white, black, Hispanic, and Chinese participants [105]. Other studies have also failed to detect significant differences in soluble E-Selectin and P-Selectin across ethnic groups [106–108]. It remains to be established whether potential ethnic-related differences in statin-mediated selectin-lowering effects might translate into different effects on surrogate markers and/or clinical endpoints in intervention trials.

The strengths of our study include the relatively large number of treatment arms analysed (41 for P-Selectin, five for L-Selectin, and 41 for E-Selectin), the assessment of possible associations between effect size and a comprehensive range of study and patient characteristics by means of meta-regression and/or subgroup analysis, and a robust assessment of the certainty of evidence according to GRADE. One significant limitation is the large-to-extreme between-study heterogeneity, which limits the generalizability of our results. However, particularly in studies investigating P-selectin, this heterogeneity was substantially attenuated in a sub-group of studies performed in Europe using atorvastatin.

5. Conclusions

In this systematic review and meta-analysis, treatment with statins was associated with a significant reduction in the concentrations of soluble P-Selectin, L-Selectin, and E-Selectin, a critical family of cell adhesion molecules that is involved in the pathogenesis of atherosclerosis. The selectin-lowering effect was independent of various patient and study characteristics, particularly baseline lipid profile and treatment duration, and was more prominent with specific agents, i.e., simvastatin, in studies conducted in Europe. These results warrant adequately designed intervention trials to determine whether selectin-lowering can mediate the atheroprotective effects of these agents and whether specific patient groups are more likely to benefit from this phenomenon. In particular, the reported differences in effect size according to the continent where the study was conducted require further research to determine whether ethnicity is an important mediator of the effects of statin treatment on circulating soluble selectins.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/biomedicines9111707/s1, Table S1: PRISMA 2020 abstract checklist; Table S2: PRISMA 2020 checklist and search strategy.

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References

1. Price, D.T.; Loscalzo, J. Cellular adhesion molecules and atherogenesis. Am. J. Med. 1999, 107, 85–97. [CrossRef]
2. McEver, R.P. Selectins: Lectins that initiate cell adhesion under flow. Curr. Opin. Cell Biol. 2002, 14, 581–586. [CrossRef]
3. Eriksson, E.E.; Xie, X.; Werr, J.; Thoren, P.; Lindbom, L. Importance of primary capture and L-selectin-dependent secondary capture in leukocyte accumulation in inflammation and atherosclerosis in vivo. J. Exp. Med. 2001, 194, 205–218. [CrossRef] [PubMed]
4. Balko, A.; Bode, B.; Aromataris, E., Munn, Z., Eds.; Johanna Briggs Institute: Adelaide, SA, Australia, 2017.
5. Balshem, H.; Helfand, M.; Schunemann, H.J.; Oxman, A.D.; Kunz, R.; Brozek, J.; Vist, G.E.; Falck-Ytter, Y.; Meerpohl, J.; Norris, S.; et al. GRADE guidelines: 3. Rating the quality of evidence. J. Clin. Epidemio. 2011, 64, 401–406. [CrossRef]
6. Hozo, S.P.; Djulbegovic, B.; Hozo, I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med. Res. Methodol. 2005, 5, 13. [CrossRef]
27. Bowden, J.; Tierney, J.F.; Copas, A.J.; Burdett, S. Quantifying, displaying and accounting for heterogeneity in the meta-analysis of RC Ts using standard and generalised Q statistics. *BMC Med. Res. Methodol.* 2011, 11, 41. [CrossRef]
28. Higgins, J.P.; Thompson, S.G. Quantifying heterogeneity in a meta-analysis. *Stat. Med.* 2002, 21, 1539–1558. [CrossRef]
29. Tobias, A. Assessing the influence of a single study in the meta-analysis estimate. *Stat. Tech. Bull.* 1999, 47, 15–17.
30. Begg, C.B.; Mazumdar, M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994, 50, 1088–1101. [CrossRef]
31. Sterne, J.A.; Egger, M. Funnel plots for detecting bias in meta-analysis: Guidelines on choice of axis. *J. Clin. Epidemiol.* 2001, 54, 1046–1055. [CrossRef]
32. Duval, S.; Tweedie, R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 2000, 56, 455–463. [CrossRef]
33. Koh, K.K.; Cardillo, C.; Bui, M.N.; Hathaway, L.; Csako, G.; Wclawiw, M.A.; Panza, J.A.; Cannon, R.O., 3rd. Vascular effects of estrogen and cholesterol-lowering therapies in hypercholesterolemic postmenopausal women. *Circulation* 1999, 99, 354–360. [CrossRef][PubMed]
34. Rauch, U.; Osende, J.I.; Chesebro, J.H.; Fuster, V.; Vorchoheimer, D.A.; Harris, K.; Harris, P.; Sandler, D.A.; Fallon, J.T.; Jayaraman, S.; et al. Statins and cardiovascular diseases: The multiple effects of lipid-lowering therapy by statins. *Atherosclerosis* 2000, 153, 181–189. [CrossRef]
35. Romano, M.; Mezzetti, A.; Marulli, C.; Ciabattoni, G.; Febo, F.; Di Lenno, S.; Roccaforte, S.; Vigneri, S.; Nubile, G.; Milani, M.; et al. Fluvastatin reduces soluble P-selectin and ICAM-1 levels in hypercholesterolemic patients: Role of nitric oxide. *J. Investig. Med.* 2000, 48, 183–189. [PubMed]
36. Sbarouni, E.; Kroupis, C.; Kyriakides, Z.S.; Koniavitou, K.; Kremastinos, D.T. Cell adhesion molecules in relation to simvastatin and hormone replacement therapy in coronary artery disease. *Eur. Heart J.* 2000, 21, 975–980. [CrossRef]
37. Alonso, R.; Mata, P.; De Andres, R.; Villacastin, B.P.; Martinez-Gonzalez, J.; Badimon, L. Sustained long-term improvement of arterial endothelial function in heterozygous familial hypercholesterolaemia patients treated with simvastatin. *Atherosclerosis* 2001, 157, 423–429. [CrossRef]
38. Blann, A.D.; Gurney, D.; Hughes, E.; Buggins, P.; Silverman, S.H.; Lip, G.Y.H. Influence of Pravastatin on Lipoproteins, and on Endothelial, Platelet, and Inflammatory Markers in Subjects With Peripheral Artery Disease. *Am. J. Cardiol.* 2001, 88, 89–92. [CrossRef]
39. Sardo, M.A.; Castaldo, M.; Cinquegrani, M.; Bonaito, M.; Maesano, A.; Schepis, F.; Zema, M.C.; Campo, G.M.; Squadrito, F.; Saitia, A. Effects of simvastatin treatment on sICAM-1 and e-selectin levels in hypercholesterolemic subjects. *Atherosclerosis* 2001, 155, 143–147. [CrossRef]
40. Solheim, S.; Seljeflot, I.; Arnesen, H.; Eritsland, J.; Eikvar, L. Reduced levels of TNF alpha in hypercholesterolemic individuals after treatment with pravastatin for 8 weeks. *Atherosclerosis* 2001, 157, 411–415. [CrossRef]
41. van Haelst, P.L.; van Doormaal, J.J.; May, J.F.; Gans, R.O.; Crijns, H.J.; Tervaat, J.W. Secondary prevention with fluvastatin decreases levels of adhesion molecules, neopterin and C-reactive protein. *Eur. J. Intern. Med.* 2001, 12, 503–509. [CrossRef]
42. Atalar, E.; Ozmen, F.; Haznedaroglu, I.; Acil, T.; Ozer, N.; Ovunc, K.; Aksoyek, S.; Kes, S. Effects of short-term atorvastatin treatment on global fibrinogen capacity, and s-selectin and sFas levels in hyperlipidemic patients with coronary artery disease. *Int. J. Cardiol.* 2002, 84, 227–231. [CrossRef]
43. Seljeflot, I.; Tonstad, S.; Hjermann, I.; Arnesen, H. Reduced expression of endothelial cell markers after 1 year treatment with simvastatin and atorvastatin in coronary patients with heart disease. *Atherosclerosis* 2002, 162, 179–185. [CrossRef]
44. Bogaty, P.; Dagenais, G.R.; Poirier, P.; Boyer, L.; Auclair, L.; Pepin, G.; Jobin, J.; Arenaault, M. Effect of atorvastatin on exercise-induced myocardial ischemia in patients with stable angina pectoris. *Am. J. Cardiol.* 2003, 92, 1192–1195. [CrossRef]
45. Dalla Nora, E.; Passaro, A.; Calzoni, F.; Fellin, R.; Solini, A. Atorvastatin improves metabolic control and endothelial function in type 2 diabetic patients: A placebo-controlled study. *J. Endocrinal. Invest.* 2003, 26, 73–78. [CrossRef]
46. Empen, K.; Frost, R.J.; Geiss, H.C.; Otto, C.; Parhofer, K.G. Differential effects of fenofibrate versus atorvastatin on the concentrations of e-selectin and vascular cellular adhesion molecule-1 in patients with type 2 diabetes mellitus and mixed hyperlipoproteinemia: A randomized cross-over trial. *Cardiovasc. Diabetol.* 2003, 2, 17. [CrossRef]
47. Ferroni, P.; Martin, F.; Cardarello, C.M.; Gazzaniga, P.P.; Davi, G.; Basili, S. Enhanced interleukin-Ibeta in hypercholesterolemia: Effects of simvastatin and low-dose aspirin. *Circulation* 2003, 108, 1673–1675. [CrossRef]
48. Hernandez, C.; Recube, A.; Barbera, G.; Chacon, P.; Lima, J.; Simo, R. Effects of hypolipidemic treatment on serum markers of vascular inflammation in dyslipidemic men. *Med. Sci. Monit.* 2003, 9, CR114–CR119.
49. Homma, Y.; Homma, K.; Iizuka, S.; Iigaya, K. Effects of Fluvastatin on Plasma Levels of Low-Density Lipoprotein Subfractions, Oxidized Low-Density Lipoprotein, and Soluble Adhesion Molecules: A Twenty-Four–Week, Open-Label, Dose-Increasing Study. *Curr. Ther. Res.* 2003, 64, 236–247. [CrossRef]
50. Malyszko, J.; Malyszko, J.S.; Myśliwiec, M. Fluvastin therapy affects TAFI concentration in kidney transplant recipients. *Transpl. Int.* 2003, 16, 53–57. [CrossRef]
51. Nawawi, H.; Osman, N.S.; Annuar, R.; Khalid, B.A.K.; Yusoff, K. Soluble intercellular adhesion molecule-1 and interleukin-6 levels reflect endothelial dysfunction in patients with primary hypercholesterolaemia treated with atorvastatin. *Atherosclerosis* 2003, 169, 283–291. [CrossRef]
52. Puccetti, L.; Pasqui, A.L.; Pastorelli, M.; Bova, G.; Di Renzo, M.; Leo, A.; Cercignani, M.; Palazzuoli, A.; Auteri, A.; Bruni, F. Platelet hyperactivity after statin treatment discontinuation. *Thromb. Haemost.* 2003, 90, 476–482. [CrossRef]

53. Van Haelst, P.L.; van Doormal, J.J.; Asselbergs, F.W.; van Roon, A.M.; Veeger, N.J.; Hennemann, M.M.; Smit, A.J.; Tervaert, J.W.; May, J.F.; Gans, R.O. Correlates of endothelial function and their relationship with inflammation in patients with familial hypercholesterolaemia. *Clin. Sci.* 2003, 104, 627–632. [CrossRef]

54. Brown, S.L.; Raal, F.J.; Panz, V.R.; Stevens, B.A.; Veller, M.G. High-dose atorvastatin therapy is required for significant improvement of endothelial function in heterozygous familial hypercholesterolemia patients. *Cardiovasc. J. S. Afr.* 2004, 15, 70–75.

55. Ceriello, A.; Quagliaro, L.; Piconi, L.; Assaloni, R.; Da Ros, R.; Maior, A.; Esposito, K.; Giugliano, D. Effect of postprandial hypertriglyceridemia and hyperglycemia on circulating adhesion molecules and oxidative stress generation and the possible role of simvastatin treatment. *Diabetes* 2004, 53, 701–710. [CrossRef]

56. Cha, J.K.; Jeong, M.H.; Kim, J.W. Statin reduces the platelet P-selectin expression in atherosclerotic ischemic stroke. *J. Thromb. Thrombolysis* 2004, 18, 39–42. [CrossRef]

57. Koh, K.K.; Son, J.W.; Ahn, J.Y.; Jin, D.K.; Kim, H.S.; Choi, Y.M.; Ahn, T.H.; Kim, D.S.; Shin, E.K. Vascular effects of diet and statin in hypercholesterolemic patients. *Int. J. Cardiol.* 2004, 95, 185–191. [CrossRef]

58. Malyszko, J.; Malyszko, J.S.; Hryszyko, T.; Mysliwiec, M. Increased soluble CD40L levels are reduced by long-term simvastatin treatment in peritoneally dialyzed patients. *Blood Cogul. Fibrinolysis* 2004, 15, 463–467. [CrossRef]

59. Nomura, S.; Shouzu, A.; Omoto, S.; Nishikawa, M.; Iwasaka, T. Effects of losartan and simvastatin on monocyte-derived microparticles in hypertensive patients with and without type 2 diabetes mellitus. *Clin. Appl. Thromb. Hemost.* 2004, 10, 133–141. [CrossRef]

60. Skrha, J.; Stulc, T.; Hilgertova, J.; Weisrnerova, H.; Kvasnicka, J.; Ceska, R. Effect of simvastatin and fenofibrate on endothelium in Type 2 diabetes. *Eur. J. Pharmacol.* 2004, 493, 183–189. [CrossRef]

61. Akcay, M.N.; Akcay, G.; Kiziltunc, A.; Ozturk, G.; Aydini, B. The effect of short-term treatment with atorvastatin on E-selectin levels in severely burned patients. *Int. J. Clin. Pharmacol. Res.* 2005, 25, 65–69.

62. Undas, A.; Celinska-Lowenhoff, M.; Domagala, T.B.; Iwaniec, T.; Dropinski, J.; Lowenhoff, T.; Lowenhoff, T.; Szczeklik, A. Early antithrombotic and anti-inflammatory effects of simvastatin versus fenofibrate in patients with hypercholesterolemia. *Thromb. Haemost.* 2005, 94, 193–199. [CrossRef]

63. Bleske, B.E.; Nicklas, J.M.; Bard, R.L.; Brook, R.D.; Gurbel, P.A.; Bliden, K.P.; Rajagopalan, S.; Pitt, B. Neutral effect on markers of heart failure, inflammation, endothelial activation and function, and vagal tone after high-dose HMG-CoA reductase inhibition in non-diabetic patients with non-ischemic cardiomyopathy and average low-density lipoprotein level. *J. Am. Coll. Cardiol.* 2006, 47, 338–42. [CrossRef] [PubMed]

64. Marsch, C.R.; Friedrich, G.; Ditlbacher, H.; Stoeger, A.; Nedden, D.Z.; Kirchmair, R.; Dienstl, A.; Pachinger, O.; Patsch, J.R. Reduction of soluble P-selectin by statins is inversely correlated with the progression of coronary artery disease. *Int. J. Cardiol.* 2006, 106, 183–190. [CrossRef] [PubMed]

65. Peverill, R.E.; Smolich, J.J.; Malan, E.; Goldstal, R.; Davis, S.R. Comparison of effects of pravastatin and hormone therapy on soluble P-selectin and platelet P-selectin expression in postmenopausal hypercholesterolemic women. *Maturitas* 2006, 53, 158–165. [CrossRef] [PubMed]

66. Potaczek, D.P.; Undas, A.; Celinska-Lowenhoff, M.; Szczeklik, A. Interleukin-6 -174 G/C promoter polymorphism and effects of fenofibrate and simvastatin on inflammatory markers in hypercholesterolemic patients. *Blood Cogul. Fibrinolysis* 2006, 17, 35–38. [CrossRef] [PubMed]

67. Alber, H.F.; Frick, M.;ussenbacher, A.; Dorler, J.; Dichtl, W.; Stocker, E.M.; Pachinger, O.; Weidinger, F. Effect of atorvastatin on peripheral endothelial function and systemic inflammatory markers in patients with stable coronary artery disease. *Wien. Med. Wochenschr.* 2007, 157, 73–78. [CrossRef] [PubMed]

68. Inami, N.; Nomura, S.; Shouzu, A.; Omoto, S.; Kimura, Y.; Takahashi, N.; Tanaka, A.; Namba, M.; Shouda, Y.; Iwasa, T. Effects of pitavastatin on adiponectin in patients with hyperlipidemia. *Pathophysiol. Thromb. Haemost.* 2007, 36, 1–8. [CrossRef] [PubMed]

69. Jeffs, L.S.; Skilton, F.; Nitschke, J.; Bannister, K.M.; Faull, R.J. Effect of pravastatin on markers of endothelial activation in dialysis patients. *Nephrology* 2007, 12, 234–238. [CrossRef] [PubMed]

70. Souza-Costa, D.C.; Sandrim, V.C.; Lopes, L.F.; Gerlach, R.F.; Rego, E.M.; Tanus-Santos, J.E. Anti-inflammatory effects of atorvastatin: Modulation of the T-876C polymorphism in the endothelial nitric oxide synthase gene. *Atherosclerosis* 2007, 193, 438–444. [CrossRef] [PubMed]

71. Barreto, A.C.; Maeda, N.Y.; Soares, R.P.; Cicero, L.; Lopes, A.A. Rosuvastatin and vascular dysfunction markers in pulmonary arterial hypertension: A placebo-controlled study. *Braz. J. Med. Biol. Res.* 2008, 41, 657–663. [CrossRef]

72. Bolewski, A.; Lipiecki, J.; Plewa, R.; Burchardt, P.; Siminiak, T. The effect of atorvastatin treatment on lipid profile and adhesion molecule levels in hypercholesterolemic patients: Relation to low-density lipoprotein receptor gene polymorphism. *Cardiology* 2008, 111, 140–146. [CrossRef]

73. Del Papa, N.; Cortiana, M.; Vitali, C.; Silvestris, I.; Maglione, W.; Comina, D.P.; Lucchi, T.; Corteletti, A. Simvastatin reduces endothelial activation and damage but is partially ineffective in inducing endothelial repair in systemic sclerosis. *J. Rheumatol.* 2008, 35, 1323–1328.
Biomedicines 2021, 9, 1707

74. Forst, T.; Wilhelm, B.; Pfutzner, A.; Fuchs, W.; Lehmann, U.; Schaper, F.; Weber, M.; Muller, J.; Konrad, T.; Hanefeld, M. Investigation of the vascular and pleiotropic effects of atorvastatin and pioglitazone in a population at high cardiovascular risk. Diabetes Vasc. Dis. Res. 2008, 5, 298–303. [CrossRef]

75. Hogue, J.C.; Lamarche, B.; Tremblay, A.J.; Bergeron, J.; Gagne, C.; Couture, P. Differential effect of atorvastatin and fenofibrate on plasma oxidized low-density lipoprotein, inflammation markers, and cell adhesion molecules in patients with type 2 diabetes mellitus. Metabolism 2008, 57, 380–386. [CrossRef]

76. Nomura, S.; Shouzu, A.; Omoto, S.; Inami, N.; Tanaka, A.; Nanba, M.; Shouda, Y.; Takahashi, N.; Kimura, Y.; Iwasaka, T. Correlation between adiponectin and reduction of cell adhesion molecules after pitavastatin treatment in hyperlipidemic patients with type 2 diabetes mellitus. Thromb. Res. 2009, 122, 39–45. [CrossRef]

77. Stulc, T.; Vrablik, M.; Kasalova, Z.; Marinov, I.; Svozil, H.; Ceska, R. Leukocyte and endothelial adhesion molecules in patients with hypercholesterolemia: The effect of atorvastatin treatment. Physiol. Res. 2008, 57, 185–194. [CrossRef]

78. Wang, L.; Rockwood, J.; Zak, D.; Devaraj, S.; Jialal, I. Simvastatin reduces circulating plasminogen activator inhibitor 1 activity in volunteers with the metabolic syndrome. Metab. Syndr. Relat. Disord. 2008, 6, 149–152. [CrossRef]

79. Prazny, M.; Kasalova, Z.; Mazoch, J.; Kvasnicka, J.; Skrha, J. Microvascular Reactivity and Endothelial Function in Type 2 Diabetic Patients with Hyperlipidemia Treated with Simvastatin: 3-year Follow-up. Prague Med. Rep. 2009, 110, 290–300.

80. Grip, O.; Janciauskiene, S. Atorvastatin reduces plasma levels of chemokine (CXCL10) in patients with Crohn’s disease. Nutr. Metab. Cardiovasc. Dis. 2009, 19, 481–490. [CrossRef]

81. Nomura, S.; Shouzu, A.; Omoto, S.; Inami, N.; Tanaka, A.; Nanba, M.; Shouda, Y.; Takahashi, N.; Kimura, Y.; Iwasaka, T. Effects of simvastatin on monocyte chemoattractant protein-1 in hyperlipidemic patients. Blood Coagul. Fibrinolysis 2009, 20, 440–447. [CrossRef] [PubMed]

82. Kater, A.L.; Batista, M.C.; Ferreira, S.R. Improved endothelial function with simvastatin but unchanged insulin sensitivity with simvastatin or ezetimibe. Metabolism 2010, 59, 921–926. [CrossRef] [PubMed]

83. Ferrer, S.R. Improved endothelial function with simvastatin but unchanged insulin sensitivity with simvastatin or ezetimibe. Metabolism 2010, 59, 921–926. [CrossRef] [PubMed]

84. Fichtenbaum, C.J.; Yeh, T.M.; Evans, S.R.; Aberg, J.A. Treatment with pravastatin and fenofibrate improves atherogenic lipid profiles but not inflammatory markers in ACTG 5087. J. Clin. Lipidol. 2010, 4, 279–287. [CrossRef] [PubMed]

85. Kirmizis, D.; Papagianni, A.; Dogrammatzi, F.; Skoura, L.; Belechri, A.M.; Alexopoulos, E.; Efstratiadis, G.; Memmos, D. Effects of simvastatin on markers of inflammation, oxidative stress and endothelial cell apoptosis in patients on chronic hemodialysis. J. Atheroscler. Thromb. 2010, 17, 1256–1265. [CrossRef]

86. Xu, D.Y.; Shu, J.; Huang, Q.Y.; Wasti, B.; Chen, C.; Liu, L.; Zhao, S.P. Evaluation of the lipid lowering ability, anti-inflammatory effects and clinical safety of intensive therapy with Zhibai, a Chinese traditional medicine. Atherosclerosis 2010, 211, 237–241. [CrossRef]

87. Wu, Y.W.; Kao, H.L.; Huang, C.L.; Chen, M.F.; Lin, L.Y.; Wang, Y.C.; Lin, Y.H.; Lin, H.J.; Tzen, K.Y.; Yen, R.F.; et al. The effects of 3-month atorvastatin therapy on arterial inflammation, calcification, abdominal adipose tissue and circulating biomarkers. Eur. J. Nucl. Med. Mol. Imaging 2012, 39, 399–407. [CrossRef]

88. Altun, I.; Oz, F.; Arkaya, S.C.; Altun, I.; Bilge, A.K.; Umman, B.; Turkoglu, U.M. Effect of statins on endothelial function in patients with acute coronary syndrome: A prospective study using adhesion molecules and flow-mediated dilatation. J. Clin. Med. Res. 2014, 6, 354–361. [CrossRef] [PubMed]

89. Paweleczyk, M.; Chmielewski, H.; Kaczorowska, B.; Przybyla, M.; Baj, Z. The influence of statin therapy on platelet activity markers in hyperlipidemic patients after ischemic stroke. Arch. Med. Sci. 2015, 11, 115–121. [CrossRef]

90. Hernandez-Mijares, A.; Banuls, C.; Rovira-Llopis, S.; Diaz-Morales, N.; Escribano-Lopez, I.; de Pablo, C.; Alvarez, A.; Veses, S.; Rocha, M.; Victor, V.M. Effects of simvastatin, ezetimibe and simvastatin/ezetimibe on mitochondrial function and leukoocyte/endothelial cell interactions in patients with hypercholesterolemia. Atherosclerosis 2016, 247, 40–47. [CrossRef]

91. Barale, C.; Frascaroli, C.; Senkeev, R.; Cavalot, F.; Russo, I. Simvastatin Effects on Inflammation and Platelet Activation Markers in Hypercholesterolemia. Biomed. Res. Int. 2018, 2018, 6508709. [CrossRef]

92. Kotyla, P.J. Short course of simvastatin has no effect on markers of endothelial activation in normolipemic patients with systemic sclerosis. J. Int. Course Res. Med. 2018, 46, 1893–1901. [CrossRef] [PubMed]

93. Dong, Z.M.; Chapman, S.M.; Brown, A.A.; Frenette, P.S.; Hynes, R.O.; Wagner, D.D. The combined role of P- and E-selectins in atherosclerosis. J. Clin. Invest. 1998, 102, 145–152. [CrossRef] [PubMed]

94. Tardif, J.C.; Tanguay, J.F.; Wright, S.R.; Duchatelle, V.; Petroni, T.; Gregoire, J.C.; Ibrahim, R.; Heinonen, T.M.; Robb, S.; Bertrand, O.F.; et al. Effects of the P-selectin antagonist inclacumab on myocardial damage after percutaneous coronary intervention for non-ST-segment elevation myocardial infarction: Results of the SELECT-ACS trial. J. Am. Coll. Cardiol. 2013, 61, 2048–2055. [CrossRef] [PubMed]
96. Stahli, B.E.; Gebhard, C.; Duchatelle, V.; Cournoyer, D.; Petroni, T.; Tanguay, J.F.; Robb, S.; Mann, J.; Guertin, M.C.; Wright, R.S.; et al. Effects of the P-Selectin Antagonist Inclacumab on Myocardial Damage After Percutaneous Coronary Intervention According to Timing of Infusion: Insights From the SELECT-ACS Trial. *J. Am. Heart Assoc.* 2016, 5. [CrossRef]

97. Cai, T.; Abel, L.; Langford, O.; Monaghan, G.; Arorson, J.K.; Stevens, R.J.; Lay-Flurrie, S.; Koshiaris, C.; McManus, R.J.; Hobbs, F.D.R.; et al. Associations between statins and adverse events in primary prevention of cardiovascular disease: Systematic review with pairwise, network, and dose-response meta-analyses. *BMJ* 2021, 374, n1537. [CrossRef]

98. Blais, J.E.; Wei, Y.; Yap, K.K.W.; Alwafi, H.; Ma, T.T.; Brauer, R.; Lau, W.C.Y.; Man, K.K.C.; Siu, C.W.; Tan, K.C.B.; et al. Trends in lipid-modifying agent use in 83 countries. *Atherosclerosis* 2021, 328, 44–51. [CrossRef]

99. Salami, J.A.; Warraich, H.; Valero-Elizondo, J.; Spatz, E.S.; Desai, N.R.; Rana, J.S.; Virani, S.S.; Blankstein, R.; Khera, A.; Blaha, M.J.; et al. National Trends in Statin Use and Expenditures in the US Adult Population From 2002 to 2013: Insights From the Medical Expenditure Panel Survey. *JAMA Cardiol.* 2017, 2, 56–65. [CrossRef]

100. Wang, H.; Yin, J.; Guo, Y. Atorvastatin might resist tobacco smoking-induced endothelial inflammation through the inhibition of NF-kappaB signal pathway. *Clin. Exp. Hypertens.* 2019, 41, 1–4. [CrossRef]

101. Liu, T.; Zhang, L.; Joo, D.; Sun, S.C. NF-kappaB signaling in inflammation. *Signal Transduct. Target. Ther.* 2017, 2. [CrossRef]

102. Sun, P.; Hernandez-Guillamon, M.; Campos-Martorell, M.; Simats, A.; Montaner, J.; Unzeta, M.; Sole, M. Simvastatin blocks soluble SSAO/VAP-1 release in experimental models of cerebral ischemia: Possible benefits for stroke-induced inflammation control. *Biochim. Biophys. Acta Mol. Basis Dis.* 2018, 1864, 542–553. [CrossRef]

103. Steffen, B.T.; Steffen, L.M.; Tracy, R.; Siscovick, D.; Jacobs, D.; Liu, K.; He, K.; Hanson, N.Q.; Nettleton, J.A.; Tsai, M.Y. Ethnicity, plasma phospholipid fatty acid composition and inflammatory/endothelial activation biomarkers in the Multi-Ethnic Study of Atherosclerosis (MESA). *Eur. J. Clin. Nutr.* 2012, 66, 600–605. [CrossRef]

104. Stepanikova, I.; Bateman, L.B.; Oates, G.R. Systemic Inflammation in Midlife: Race, Socioeconomic Status, and Perceived Discrimination. *Am. J. Prev. Med.* 2017, 52, S63–S76. [CrossRef]

105. Makin, A.J.; Chung, N.A.; Silverman, S.H.; Lip, G.Y. Thrombogenesis and endothelial damage/dysfunction in peripheral artery disease. Relationship to ethnicity and disease severity. *Thromb. Res.* 2003, 111, 221–226. [CrossRef]

106. Jaumdally, R.J.; Varma, C.; Blann, A.D.; Macfadyen, R.J.; Lip, G.Y. Indices of angiogenesis, platelet activation, and endothelial damage/dysfunction in relation to ethnicity and coronary artery disease: Differences in central versus peripheral levels. *Ann. Med.* 2007, 39, 628–633. [CrossRef]