Tibolone Decreases Lipoprotein(a) levels in Postmenopausal Women:  
A Systematic Review and Meta-Analysis of 12 studies with 1009 patients

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ABSTRACT

INTRODUCTION: Circulating lipoprotein (a) (Lp(a)) is a recognized risk factor for cardiovascular disease (CVD). Tibolone, a synthetic steroid, may lower Lp(a) levels; however, evidence of the effects of tibolone on Lp(a) still remain to be defined. Therefore, we investigated the effects of tibolone treatment on circulating Lp(a) levels in postmenopausal women.

METHODS: The search included PUBMED, Web of Science, Scopus, and Google Scholar (up to January 31st, 2015) to identify controlled clinical studies investigating the effects of oral tibolone treatment on Lp(a) levels in postmenopausal women. Random-effects meta-regression was performed using unrestricted maximum likelihood method for the association between calculated weighted mean difference (WMD) and potential moderators.

RESULTS: Meta-analysis of data from 12 trials (16 treatment arms) suggested a significant reduction of Lp(a) levels following tibolone treatment (WMD: -25.28%, 95% confidence interval [CI]: -36.50, -14.06; \( p < 0.001 \)). This result was robust in the sensitivity analysis and its significance was not influenced after omitting each of the included studies from the meta-analysis. When the studies were categorized according to the tibolone dose, there were consistent significant reductions of Lp(a) in the subsets of studies with doses <2.5 mg/day (WMD: -17.00%, 95%CI: -30.22, -3.77; \( p < 0.012 \)) and 2.5 mg/day (WMD: -29.18%, 95%CI: -45.02, -13.33; \( p < 0.001 \)). Likewise, there were similar reductions in the subsets of trials with follow-up either <24 months (WMD: -26.79%, 95%CI: -38.40, -15.17; \( p < 0.001 \)) or \( \geq 24 \) months (WMD: -23.10%, 95%CI: -40.17, -6.03; \( p = 0.008 \)).

CONCLUSIONS: This meta-analysis shows that oral tibolone treatment significantly lowers circulating Lp(a) levels in postmenopausal women. Further studies are warranted to explore the mechanism of this effect and the potential value and place of tibolone or its analogues in the treatment of elevated Lp(a) in individuals at risk of CVD.

Keywords: cardiovascular disease, cardiovascular risk, lipoprotein(a), tibolone.
INTRODUCTION

Lipoprotein(a) (Lp(a)) is a unique lipoprotein particle, which consists of an apolipoprotein B containing lipoprotein moiety very similar to low-density lipoprotein (LDL) covalently linked to the glycoprotein component apoprotein(a) [apo(a)]\(^1\). Apo(a) is exclusively produced in the liver, and its secretions highly correlated with circulating Lp(a) levels\(^2\). Clinical and epidemiological evidence reveals an increased level of Lp(a) to be a causal, independent risk factor for cardiovascular disease (CVD)\(^3-6\). The atherogenic properties of Lp(a) are associated with several mechanisms, including the inhibition of the fibrinolitic system by homologous structure of apo(a) with plasminogen\(^7\), the interaction with extracellular matrix conjugates such as glycoproteins\(^8\), the binding to scavenger receptors on macrophages\(^9,10\), and the induction of inflammatory molecules\(^11\).

Given the above, there has been an interest in Lp(a) as a target for residual risk therapy\(^12-14\). In general, circulating Lp(a) levels are genetically determined\(^15\), while the levels can change in certain circumstances, such as under acute vascular and inflammatory pathologies\(^16-18\). The European Atherosclerosis Society (EAS) Consensus Panel recommends screening for elevated Lp(a) in those at intermediate or high CVD/coronary heart disease (CHD) risk, a desirable level <50 mg/dL as a function of global CV risk, and use of niacin for Lp(a) and CVD/CHD risk reduction\(^19\). Since currently available LDL cholesterol-lowering drugs, such as statins, have little effects of Lp(a), and other, such as niacin is poorly tolerated and is not available in many countries, there has been a continuous search for effective agents for lowering circulating Lp(a) levels\(^20\).

Tibolone (Livial, Org OD 14) is a synthetic steroid with estrogenic, androgenic and progestogenetic properties, and used orally for the prevention of osteoporotic bone loss and
hormonal replacement treatment on climacteric symptoms in postmenopausal women. Tibolone itself has no activities, but two estrogenic metabolites (3α- and 3β-hydroxy [OH] tibolone) and the third metabolite (Δ4-tibolone) exert the effects on climacteric symptoms, and the third metabolite also exerts additional progestogenic effects in endometrium. Tibolone treatment can modulate the lipid profile and its possible reduction of Lp(a) has been observed, although the effects of tibolone on Lp(a) were not previously analysed within systematic review and meta-analysis. Therefore, we performed a meta-analysis to evaluate the efficacy of tibolone treatment on circulating Lp(a) levels in postmenopausal women.

MATERIAL AND METHODS

Search Strategy

This study was designed according to the guidelines of the 2009 preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement. PubMed (http://www.ncbi.nlm.nih.gov/pubmed), Web of Science (http://apps.webofknowledge.com), SCOPUS (http://www.scopus.com), and Google Scholar (http://www.scholar.google.com) databases were searched and the search was limited to the controlled studies (mainly randomized controlled trials [RCTs], as well as controlled clinical trials, perspective and open-label studies) carried out up to January 31, 2014, investigating the potential effects of tibolone treatment on Lp(a) concentrations in the group of postmenopausal women. The databases were searched using the following search terms in titles and abstracts (also in the combination with MESH terms): (tibolone OR OrgOD14 OR “Org OD14” OR livial OR livial®) AND (lipoprotein(a) OR “lipoprotein (a)” OR Lp(a) OR “Lp(a)”). The wild-card term “*” was used to increase the sensitivity of the search strategy. No language restriction was used in the literature search. The
search was limited to studies in humans. Selected articles were searched to identify further relevant studies. Two reviewers (KK and AS) evaluated each article separately. Disagreements were resolved by agreement and discussion with a third party (MB).

**Study Selection**

Original studies (all in postmenopausal women) were included if they met the following inclusion criteria: (i) being a controlled clinical study (RCT, controlled perspective or open-label study), (ii) investigating the impact of tibolone on plasma/serum concentrations of Lp(a), (iii) presentation of sufficient information on Lp(a) concentrations at baseline and at the end of follow-up in each group or providing the net change values.

Exclusion criteria were: (i) lack of a an appropriate control group in the study design, (ii) non-clinical observational studies with case-control, cross-sectional or cohort design, (iii) lack of sufficient information on baseline or follow-up Lp(a) concentrations, (iv) inability to obtain adequate details of study methodology or results from the article or the investigators, and, (v) the study was ongoing.

**Data extraction**

Eligible studies were reviewed and the following data were abstracted: 1) first author's name; 2) year of publication; 3) study location; 4) study design; 5) tibolone dose and the route of administration; 6) number of participants in the tibolone and control groups; 7) inclusion and exclusion criteria; 8) age, gender and body mass index (BMI) of study participants; 9) prevalence of diabetes mellitus; and 10) baseline and follow-up plasma concentrations of Lp(a).
Quality assessment

A systematic assessment of bias in the included studies was performed using the Cochrane criteria. The items used for the assessment of each study were as follows: adequacy of sequence generation, allocation concealment, blinding, addressing of dropouts (incomplete outcome data), selective outcome reporting, and other potential sources of bias. According to the recommendations of the Cochrane Handbook, a judgment of “yes” indicated low risk of bias, while “no” indicated high risk of bias. Labeling an item as “unclear” indicated an unclear or unknown risk of bias.

Quantitative Data Synthesis

Meta-analysis was conducted using Comprehensive Meta-Analysis (CMA) V2 software (Biostat, NJ). Net changes in measurements (change scores) were calculated as follows: measure at end of follow-up – measure at baseline. For cross-over trials, net change in plasma concentrations of Lp(a) were calculated by subtracting the value after control intervention from that reported after treatment. All values were collated in percentage changes from baseline levels. Standard deviations (SDs) of the mean difference were calculated using the following formula: 

\[ SD = \text{square root} \left[ (SD_{\text{pre-treatment}})^2 + (SD_{\text{post-treatment}})^2 - (2R \times SD_{\text{pre-treatment}} \times SD_{\text{post-treatment}}) \right], \]

assuming a correlation coefficient (R) = 0.5. If the outcome measures were reported in median and inter-quartile range, mean and standard SD values were estimated using the method described by Hozo et al. Where standard error of the mean (SEM) was only reported, standard deviation (SD) was estimated using the following formula: 

\[ SD = \text{SEM} \times \text{square root} (n), \]

where \( n \) is the number of subjects. When the results were presented in multiple time points, only data relating to the longest duration of treatment were considered.
A random-effects model (using DerSimonian-Laird method) and the generic inverse variance method were used to compensate for the heterogeneity of studies in terms of demographic characteristics of populations being studied and also differences in study design. Heterogeneity was quantitatively assessed using $I^2$ index. Effect sizes were expressed as weighted mean difference (WMD) and 95% confidence interval (CI). In order to evaluate the influence of each study on the overall effect size, sensitivity analysis was conducted using leave-one-out method, i.e. removing one study each time and repeating the analysis \(^{30, 31}\).

**Meta-regression**

Random-effects meta-regression was performed using unrestricted maximum likelihood method to evaluate the association between calculated WMD and potential moderators including duration of treatment with tibolone.

**Publication bias**

Potential publication bias was explored using visual inspection of Begg’s funnel plot asymmetry, fail-safe N test, and Begg’s rank correlation and Egger’s weighted regression tests. Duval & Tweedie “trim and fill” method was used to adjust the analysis for the effects of publication bias \(^{32}\).

**RESULTS**

The search provided 82 articles excluding duplicates. Of those, 67 were excluded after initial screening and the remaining 15 full text papers were reviewed. Finally 12 were scrutinized as full texts and were selected to be included in the analysis \(^{33-44}\). The reasons for excluding the
removing 3 articles were: not controlled for tibolone \((n=2)\) and no tibolone treatment arm \((n=1)\) (Figure 1). In total, 1009 participants were randomized, of whom 634 were allocated to tibolone supplementation group and 375 to control group in the selected studies. The number of participants in these studies ranged from 6 to 136. They were published between 1996 and 2009, and were conducted in USA, Greece, Ireland, the Netherlands (3 trials), Italy (2 trials), UK, Serbia and Turkey. A range of tibolone doses from 0.3 to 2.5 mg/day was administered in the included trials. Duration of supplementation with tibolone ranged between 3 and 60 months. Tibolone was safe and well-tolerated in all included studies with no report of any drug-related adverse events. Baseline parameters of the included studies are shown in Table 1.

**Risk of bias assessment**

According to the Cochrane Collaboration \(^{45}\), a specific tool for assessing risk of bias in each involved study comprises judgment of specific features of the study. This involves evaluating the risk of bias as ‘low risk’, ‘high risk’ or ‘unclear risk’. The last category shows either lack of information or uncertainty over the potential for bias. There are seven analyzed domains comprising: sequence generation (selection bias), allocation sequence concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other potential sources of bias (Table 2).

**Effect of tibolone on plasma Lp(a) concentrations**

Overall, the impact of tibolone on plasma Lp(a) concentrations were reported in 12 trials comprising 16 treatment arms with 1009 women-patients. The results suggested a significant
reduction of Lp(a) levels following treatment with tibolone (WMD: -25.28%, 95%CI: -36.50, -14.06; \( p < 0.001 \)), which are robust in the sensitivity analysis, and their significance was not influenced after omitting each of the included studies from meta-analysis (Figure 2). When the studies were categorized according to the dose of treatment, there was consistent significant reduction in Lp(a) concentrations in the subsets of trials with doses <2.5 mg/day (WMD: -17.00%, 95%CI: -30.22, -3.77; \( p < 0.012 \)) and \( \geq 2.5 \) mg/day (WMD: -29.18%, 95%CI: -45.02, -13.33; \( p < 0.001 \)) (Figure 3). Likewise, there were similar reductions in the subsets of trials lasting either <24 months (WMD: -26.79%, 95%CI: -38.40, -15.17; \( p < 0.001 \)) or \( \geq 24 \) months (WMD: -23.10%, 95%CI: -40.17, -6.03; \( p = 0.008 \)) (Figure 4).

**Meta-regression**

Random-effects meta-regression was performed to assess if the Lp(a) response to tibolone is associated with administered dose and duration of treatment. The results did not suggest any significant association between the changes in plasma concentrations of Lp(a) with dose (slope: -6.07; 95%CI: -20.16, 8.02; \( p = 0.399 \)) and duration of treatment (slope: 0.27; 95%CI: -0.53, 1.08; \( p = 0.505 \)).

**Publication bias**

The funnel plot of the study standard error by effect size (WMD) was symmetric, suggesting lack of publication bias in the analysis of the effect tibolone on plasma Lp(a) concentrations. This finding was confirmed by the results of Egger’s linear regression (intercept = -3.04, standard error = 1.72; 95%CI: -6.73, 0.65, \( t = 1.77 \), df = 14, two-tailed \( p = 0.099 \)) and Begg’s rank correlation tests (Kendall’s Tau with continuity correction = -0.24, \( z = 1.31 \), two-tailed
\( p\text{-value} = 0.192 \) (Figure 5). The “fail-safe N” test suggested that 523 studies would be needed to bring the effect size down to a non-significant \( (p > 0.05) \) value.

**DISCUSSION**

The present meta-analysis of data from 12 trials comprising 16 treatment arms revealed that oral tibolone treatment significantly reduced circulating Lp(a) levels in postmenopausal women. These results are of high importance because Lp(a) is an independent risk factor for CVD, there are no effective and safe treatments for high Lp(a) levels, and postmenopausal women are at higher CVD risk \(^{3-5}\).

Tibolone treatment can reduce circulating Lp(a) levels by 25\% \((42-44)\). More recently, significant reductions of Lp(a) have been shown with a range of new therapies, including cholesteryl ester transfer protein (CETP) inhibitors, sequence-specific antisense oligonucleotides against apoB, inhibitory monoclonal antibodies to proprotein convertase subtilisin/kexin type-9 (PCSK9), thyroid hormone analogues, and synthetic inhibitors of microsomal triglyceride transfer protein \(^{46-51}\). The magnitude of reductions of Lp(a) by these drugs appears to be similar to the ones with tibolone, while the overall magnitude of these recent drugs is still not established \(^{46-48, 52}\). The magnitude of reduction of Lp(a) with tibolone is similar to that of niacin. The influences of the dose and duration of used drugs on Lp(a) is also of concern \(^{25}\). Niacin can reduce Lp(a) in a dose-dependent manner \(^{53}\). Whereas, the present meta-analysis did not find a dose- or duration-dependent manner of tibolone treatment on Lp(a). This may be an advantage in using tibolone to decrease Lp(a) levels.

The reduction of circulating Lp(a) by tibolone is still incompletely explained. The estrogenic property of tibolone is a possible explanation of the reduction of Lp(a) \(^{25}\); however, the details in...
the involvement of estrogens in the Lp(a) regulation still remain to be fully clarified. One of the mechanism potentially responsible might be the fact that Lp(a) gene has an estrogen response element and tibolone may active this and reduce hepatic output of Apo(a). Lp(a) is also decreased by testosterone and the androgenic component of tibolone may have a dual effect. However, further studies of the mechanism of action of tibolone on Lp(a) metabolism are still required.

The present meta-analysis has limitations. First, the studies included in the present meta-analysis were not always interventional studies focused on the Lp(a) levels, as a main endpoint, therefore well-designed interventional trials specific for Lp(a) are still necessary. Next, the included studies did not evaluate the long-term CVD outcomes associated with Lp(a) reduction. The reduction of Lp(a) is theoretically thought to be favorable for the prevention of the events, but whether the reduction of Lp(a) with Lp(a)-targeted therapies can lead to the favorable outcomes still needs to be proven, especially that available long-term controlled studies with a Lp(a)-lowering drug (nicotinic acid plus laropiprant) have failed to find a positive impact of the Lp(a) reduction on CV events. Some studies have also indicated that very low Lp(a) levels might be harmful, however Mendelian randomization studies did not confirm that low Lp(a) increases the risk of diabetes. However, tibolone can improve not only Lp(a) level but also vascular functions (e.g. vasodilation) with its estrogenic property. Additionally, tibolone is reported to modulate other lipoprotein factors, i.e. the drug with its androgenic properties can reduce high-density lipoprotein cholesterol (HDL-C) as an unfavorable change. However, there are findings that the change of HDL-C is usually transient; on the other hand there are more and more data that we should not focus on HDL-C as it is not main target of the lipid-lowering therapy, also due to the lasting debate on HDL functionality in different patients’
groups \cite{42,60,61}. It should be emphasized that data on circulating Lp(a) levels were obtained from studies using different assays for Lp(a). It would be also necessary to look at the tibolone effects in general, including the influence on inflammatory markers, and other risk factors of CVD (e.g. blood pressure) \cite{62}, in order to finally confirm the possible benefits of its therapy. Finally, the included studies did not particularly focus on tibolone therapy-related side effects. One should notice that the side effects after tibolone therapy with doses \( \leq 2.5 \) mg/day are uncommon \cite{63}. In the Long-Term Intervention on Fractures with Tibolone (LIFT) trial \cite{64} in older postmenopausal women (aged 60-85 years) tibolone therapy (in comparison to placebo) significantly reduced the risk of vertebral and nonvertebral fractures, invasive breast cancer and colon cancer, however, increased of the stroke risk. There were also no significant differences in the risk of either CHD or venous thromboembolism \cite{64}. However the above mentioned stroke risk was not observed in other studies with younger postmenopausal women \cite{65,66}.

In conclusion, the present meta-analysis revealed that oral tibolone treatment significantly reduced circulating Lp(a) levels in postmenopausal women. The significance of this metabolic effect for the prevention of CVD needs to be weighed against other effects of tibolone and requires further investigations. Large-scale, well-designed studies may then be justified to explore the value of tibolone treatment in high risk subjects with elevated plasma Lp(a) levels \cite{19}.
DECLARATION OF INTEREST

This meta-analysis was written independently; no company or institution supported it financially. No authors have any conflict of interest concerning the preparation of this analysis. Some of the authors have given talks, attended conferences and participated in trials and advisory boards sponsored by various pharmaceutical companies. No professional writer was involved in the preparation of this meta-analysis.
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### TABLES

#### Table 1. Demographic characteristics of the included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Bjarnason et al. 33</th>
<th>Gallagher et al. 34</th>
<th>Kalogeropoulos et al. 35</th>
<th>Kroiss et al. 36</th>
<th>Lloyd et al. 37</th>
<th>Milner et al. 38</th>
<th>Ostberg et al. 39</th>
<th>Perrone et al. 40</th>
<th>Von Eckardstein et al. 41</th>
<th>Von Eckardstein et al. 42</th>
<th>Amedda et al. 43</th>
<th>Dimroth et al. 44</th>
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<tr>
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<td>Design</td>
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<td>Randomized double-blind, placebo controlled study</td>
<td>Clinical controlled trial</td>
<td>Randomized double-blind, placebo controlled study</td>
<td>Randomized double-blind, placebo controlled study</td>
<td>Randomized placebo-controlled, pilot study</td>
<td>One-year open-label controlled study</td>
<td>Prospective controlled study</td>
<td>Randomized double-blind, placebo controlled study</td>
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<td>Duration of study</td>
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<td>24 month</td>
<td>60 month</td>
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<td>Inclusion criteria</td>
<td>Healthy women not being treated with any medication known to affect coagulation on fibrinolysis is lipid or bone metabolism and with more than 10 years of spontaneous menopause</td>
<td>Healthy Caucasian or Asian women 45 years of age or older, with body weight &gt;80–130% ideal body weight, 1 year or more but 4 years or less past natural menopause</td>
<td>Postmenopausal women (≥75 years old; BMI 18–30 kg/m²) with newly diagnosed and histologically confirmed invasive or non-invasive early stage breast cancer, with surgical treatment</td>
<td>Postmenopausal women with antihypertensive treatment</td>
<td>Patients at least 45 years of age, postmenopausal for 12 months or more, with 1% ideal body weight or height and had intact uteri and ovaries</td>
<td>Postmenopausal women undergoing chronic hemodialysis, with at least 6 months of amenorrhea, age less than 65 years, and serum FSH &gt;20 mIU/L</td>
<td>Postmenopausal women (absence of any menstrual bleeding for 12 months and FSH &gt; 50 IU/l and estradiol &lt;20 pg/ml), 45 to 60 years of age with BMI ranging between 20 and 28 kg/m²</td>
<td>Healthy postmenopausal women with previous oophorectomy or 12 months passed after the last menstrual bleed, FSH &gt; 50 IU/l and serum levels of estradiol &lt; 70 pmol, aged 45–60</td>
<td>Healthy menopausal women 50–50 years of age who had undergone hysterectomy and bilateral salpingooophorectomy as a result of benign diseases</td>
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<td>Route of administration</td>
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<p>| Participants            | Case | 29&lt;sup&gt;a&lt;/sup&gt; 132&lt;sup&gt;b&lt;/sup&gt; 136&lt;sup&gt;c&lt;/sup&gt; | 53 35&lt;sup&gt;e&lt;/sup&gt; 19 31&lt;sup&gt;f&lt;/sup&gt; 13 20&lt;sup&gt;g&lt;/sup&gt; 12 34 11 | 28&lt;sup&gt;h&lt;/sup&gt; |
|                         | 28&lt;sup&gt;a&lt;/sup&gt; 127&lt;sup&gt;d&lt;/sup&gt; 131&lt;sup&gt;e&lt;/sup&gt; | 32&lt;sup&gt;f&lt;/sup&gt; 21&lt;sup&gt;g&lt;/sup&gt; | 28&lt;sup&gt;h&lt;/sup&gt; |
|                         | Contr | 13 130 | 29 35 11 | 50 13 19 | 6 31 11 | 27 |
| Age (years)             | Case | 66.4 (7.0)&lt;sup&gt;a&lt;/sup&gt; | 52.3 (2.9)&lt;sup&gt;b&lt;/sup&gt; | 52.4 (0.74)&lt;sup&gt;c&lt;/sup&gt; | 54.5 (4.6) | 51.1 ± 4.1&lt;sup&gt;f&lt;/sup&gt; | 45 - 60 | 54.5 ± 3.7 | 51.6±0.49 | 48±0.6&lt;sup&gt;c&lt;/sup&gt; |
|                         | Contr | 68.4 (6.1)&lt;sup&gt;a&lt;/sup&gt; | 52.6 (3.4) | 48.4±4 | 59 (5.5) | 62.73 (1.79) | 55.6±0.61 | 56.0 (7.4) | 52.7 ± 3.3 | 45 - 60 | 53.5 ± 3.7 | 52.1±0.44 | 47± 0.6 |
| Male (%)                | Case | 0&lt;sup&gt;a&lt;/sup&gt; 0&lt;sup&gt;b&lt;/sup&gt; 0&lt;sup&gt;c&lt;/sup&gt; | 0&lt;sup&gt;d&lt;/sup&gt; 0&lt;sup&gt;e&lt;/sup&gt; 0&lt;sup&gt;f&lt;/sup&gt; | 0&lt;sup&gt;g&lt;/sup&gt; 0&lt;sup&gt;h&lt;/sup&gt; 0&lt;sup&gt;i&lt;/sup&gt; 0&lt;sup&gt;j&lt;/sup&gt; | 0&lt;sup&gt;k&lt;/sup&gt; |
|                         | Contr | 0 0 | 0 0 | 0 0 | 0 0 | 0 0 | 0 0 |
| BMI (kg/m²)             | Case | 24.5 (3.4)&lt;sup&gt;a&lt;/sup&gt; | 24.8 (3.8)&lt;sup&gt;b&lt;/sup&gt; | 22–26 | 24.8 (3.2)&lt;sup&gt;c&lt;/sup&gt; | 33.90 (5.99) | 41.1± 0.6&lt;sup&gt;d&lt;/sup&gt; | 23.9 (4.0) | 24 ± 2.7&lt;sup&gt;e&lt;/sup&gt; | 20-28 | 24.5 ± 2.5 | 21.2±0.32 | 25.4± 0.3&lt;sup&gt;b&lt;/sup&gt; |</p>
<table>
<thead>
<tr>
<th></th>
<th>Contr</th>
<th>23.1 (2.8)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>25.5 (3.5)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>39.6±0.7&lt;sup&gt;b&lt;/sup&gt;</th>
<th>25.2 ± 2.6&lt;sup&gt;b&lt;/sup&gt;</th>
<th>24.4±0.7&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lp(a)</strong></td>
<td>Contr</td>
<td>24.7 (3.2)</td>
<td>25.4 (3.8)</td>
<td>22–25</td>
<td>25.4 (3.7)</td>
<td>29.60 (1.30)</td>
</tr>
<tr>
<td><strong>prevalence of diabetes mellitus (%)</strong></td>
<td>Case</td>
<td>NS&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NS&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NS&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NS&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>Contr</td>
<td>NS</td>
<td>0</td>
<td>NS&lt;sup&gt;c&lt;/sup&gt;</td>
<td>NS&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Lp(a)</strong></td>
<td>Case</td>
<td>23.1 (12.6–44.9)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>25±4 (25.1)&lt;sup&gt;**&lt;/sup&gt;</td>
<td>20.4 (10.7–23)</td>
<td>14.1 (0.9–106.1)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>19 (8–117)</td>
</tr>
<tr>
<td></td>
<td>Contr</td>
<td>24.3 (16.6–51.2)</td>
<td>26±5</td>
<td>17.8 (14.5–66)</td>
<td>12.6 (0.6–87.5)</td>
<td>16 (8–84)</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD or median (25–75 percentiles).

**ABBREVIATIONS:** BMI: body mass index; BP: blood pressure; NS: not stated; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; DM: diabetes mellitus; FSH: serum levels of follicle stimulating hormone; HRT: hormonal replacement therapy; <sup>a</sup> denotes 1.25 mg/day tibolone; <sup>b</sup> denotes 2.5 mg/day tibolone; <sup>c</sup> denotes 0.3 mg/day tibolone; <sup>d</sup> denotes 0.625 mg/day tibolone; <sup>e</sup> denotes 20 mg/day oral tamoxifen (Nolvadex-D; Astra-Zeneca) plus either 2.5 mg/ day oral tibolone (Livial; NVOrganon), <sup>f</sup> denotes a combined estrogen (0.625 mg/day) – progestin (0.15 mg for 12 days in 28) preparation; <sup>g</sup> denotes oral medroxyprogesterone acetate (MPA; 10 mg/day for 12 days); <sup>h</sup> denotes conjugated ET (Premarin, 0.625 mg/d oral tablets; Wyeth, Istanbul, Turkey); <sup>i</sup> denotes patients belonging to tibolone group n = 34; <sup>**</sup> denotes patients belonging to tibolone group or placebo group n = 29.
Table 2. Risk of bias assessment in the studies considered for meta-analysis.

<table>
<thead>
<tr>
<th>Study</th>
<th>Ref</th>
<th>SEQUENCE GENERATION</th>
<th>ALLOCATION CONCEALMENT</th>
<th>BLINDING OF PARTICIPANTS AND PERSONNEL</th>
<th>BLINDING OF OUTCOME ASSESSMENT</th>
<th>INCOMPLETE OUTCOME DATA</th>
<th>SELECTIVE OUTCOME REPORTING</th>
<th>OTHER POTENTIAL THREATS TO VALIDITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bjarnason et al.</td>
<td>33</td>
<td>U</td>
<td>U</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
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<tr>
<td>Gallagher et al.</td>
<td>34</td>
<td>U</td>
<td>H</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
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<tr>
<td>Kalogeropoulos et al.</td>
<td>35</td>
<td>U</td>
<td>U</td>
<td>U</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
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<tr>
<td>Kroiss et al.</td>
<td>36</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>Lloyd et al.</td>
<td>37</td>
<td>U</td>
<td>U</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>Müllner et al.</td>
<td>38</td>
<td>L</td>
<td>U</td>
<td>U</td>
<td>U</td>
<td>L</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>Ostberg et al.</td>
<td>39</td>
<td>U</td>
<td>U</td>
<td>U</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
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<tr>
<td>Perrone et al.</td>
<td>40</td>
<td>U</td>
<td>U</td>
<td>U</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
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<tr>
<td>von Eckardstein et al.</td>
<td>41</td>
<td>U</td>
<td>U</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>von Eckardstein et al.</td>
<td>42</td>
<td>U</td>
<td>U</td>
<td>L</td>
<td>L</td>
<td>L</td>
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<tr>
<td>Anedda et al.</td>
<td>43</td>
<td>U</td>
<td>U</td>
<td>L</td>
<td>L</td>
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<tr>
<td>Demiroglu et al.</td>
<td>44</td>
<td>U</td>
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<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
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</tr>
</tbody>
</table>

L: low risk of bias; H: high risk of bias; U: unclear risk of bias
FIGURE LEGENDS

**Figure 1.** Flow chart of the number of studies included to the meta-analysis.

**Figure 2.** Forest plot displaying weighted mean difference and 95% confidence intervals for the impact of tibolone on circulating Lp(a) levels. Lower plot shows leave-one-out sensitivity analysis.

**Figure 3.** Forest plot displaying weighted mean difference and 95% confidence intervals for the impact of tibolone on circulating Lp(a) levels in trials administering doses < 2.5 mg/day (upper plot) and ≥ 2.5 mg/day (lower plot).

**Figure 4.** Forest plot displaying weighted mean difference and 95% confidence intervals for the impact of tibolone on circulating Lp(a) levels in trials lasting < 24 months (upper plot) and ≥ 24 months (lower plot).

**Figure 5.** Meta-regression plots of the association between mean changes in circulating Lp(a) levels and dose and duration of treatment with tibolone. The size of each circle is inversely proportional to the variance of change.

**Figure 6.** Funnel plot detailing publication bias in the studies reporting the impact of tibolone on circulating Lp(a) levels. Open diamond represents observed effect size; closed diamond represents imputed effect size.
### Study Name: **Favours Tibolone Favours Control**

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Difference in Means</th>
<th>Standard Error</th>
<th>Variance</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
<th>Z-Value</th>
<th>p-Value</th>
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</thead>
<tbody>
<tr>
<td>Kimura et al., 2003</td>
<td>-2.562</td>
<td>9.048</td>
<td>81.647</td>
<td>-15.494</td>
<td>10.369</td>
<td>-0.576</td>
<td>0.561</td>
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<tr>
<td>Lloyd et al., 2000</td>
<td>-4.362</td>
<td>10.112</td>
<td>105.362</td>
<td>-16.634</td>
<td>7.910</td>
<td>-2.317</td>
<td>0.021</td>
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<tr>
<td>Oberg et al., 2003</td>
<td>-5.000</td>
<td>10.99</td>
<td>110.99</td>
<td>-17.090</td>
<td>7.090</td>
<td>-1.910</td>
<td>0.058</td>
</tr>
<tr>
<td>von Eschenbach et al., 2001</td>
<td>-10.600</td>
<td>11.123</td>
<td>123.96</td>
<td>-20.924</td>
<td>-0.720</td>
<td>-0.072</td>
<td>0.940</td>
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<tr>
<td>von Eschenbach et al., 2002</td>
<td>5.225</td>
<td>7.323</td>
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<td>-9.422</td>
<td>2.755</td>
<td>2.755</td>
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<tr>
<td>Dorn et al., 2007</td>
<td>5.535</td>
<td>6.093</td>
<td>36.521</td>
<td>-19.893</td>
<td>1.993</td>
<td>2.668</td>
<td>0.008</td>
</tr>
</tbody>
</table>

### Study Name: **Favours Tibolone Favours Control**

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Difference in Means</th>
<th>Standard Error</th>
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<th>Lower Limit</th>
<th>Upper Limit</th>
<th>Z-Value</th>
<th>p-Value</th>
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<tbody>
<tr>
<td>Birmingham et al., 2001</td>
<td>1.000</td>
<td>4.102</td>
<td>95.407</td>
<td>-14.392</td>
<td>16.392</td>
<td>0.026</td>
<td>0.980</td>
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<td>Barracan et al., 2002</td>
<td>0.580</td>
<td>5.330</td>
<td>28.508</td>
<td>-9.947</td>
<td>10.047</td>
<td>0.094</td>
<td>0.925</td>
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<tr>
<td>Gallagher et al., 2003</td>
<td>-12.000</td>
<td>6.450</td>
<td>42.190</td>
<td>-29.328</td>
<td>-5.100</td>
<td>-2.065</td>
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<td>Gallagher et al., 2004</td>
<td>1.600</td>
<td>6.536</td>
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<td>-9.614</td>
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<td>Gallagher et al., 2005</td>
<td>-7.600</td>
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<td>Kallergitsidis et al., 2003</td>
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<td>Milner et al., 1996</td>
<td>-1.190</td>
<td>8.448</td>
<td>77.873</td>
<td>-10.173</td>
<td>6.020</td>
<td>2.668</td>
<td>0.008</td>
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</table>
HIGHLIGHTS:

- Circulating Lp(a) is a recognized risk factor for cardiovascular disease (CVD).
- Tibolone may lower Lp(a), however, evidence of this effect remains to be confirmed.
- Meta-analysis suggests a significant Lp(a) reduction following tibolone (by 25.28%).
- Further studies are warranted to explore the mechanism of this effect.
- A place of tibolone in individuals at CVD risk needs to be further investigated.