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The Effects of Tamoxifen on Plasma Lipoprotein(a) Concentrations: Systematic Review and Meta-Analysis

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Published online: 1 June 2017

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Abstract

Introduction Tamoxifen is a selective estrogen receptor modulator widely used in the treatment of breast cancer. Tamoxifen therapy is associated with lower circulating low-density lipoprotein cholesterol and increased triglycerides, but its effects on other lipids are less well studied. **Aims** We aimed to investigate the effect of tamoxifen on circulating concentrations of lipoprotein(a) [Lp(a)] through a meta-analysis of available randomized controlled trials (RCTs) and observational studies. **Methods** This study was registered in the PROSPERO database (CRD42016036890). Scopus, MEDLINE and

EMBASE were searched from inception until 22 March 2016 to identify studies investigating the effect of tamoxifen on Lp(a) values in humans. Meta-analysis was performed using an inverse variance-weighted, random-effects model with standardized mean difference (SMD) as the effect size estimate.

Results Meta-analysis of five studies with 215 participants suggested a statistically significant reduction of Lp(a) levels following tamoxifen treatment (SMD -0.41 , 95% confidence interval -0.68 to -0.14 , $p = 0.003$). This effect was robust in the sensitivity analysis.

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Conclusions Meta-analysis suggested a statistically significant reduction of Lp(a) levels following tamoxifen treatment. Further well-designed trials are required to validate these results.

Key Points

Lipoprotein(a) [Lp(a)] is an emerging risk factor for cardiovascular disease; it is relatively resistant to reduction by dietary and pharmacological methods.

Tamoxifen, a selective estrogen receptor modulator, is widely used in the treatment of breast cancer.

This meta-analysis demonstrates a significant reduction of Lp(a) levels after tamoxifen treatment.

1 Introduction

Lipoprotein(a) [Lp(a)], first discovered by Kare Berg in 1963, is a low-density lipoprotein (LDL)-like particle containing apolipoprotein(a) [apo(a)] and apolipoprotein B-100 (apo-B100) linked through a disulfide bond [1]. It has been shown that Lp(a) contributes to atherosclerosis through accelerated transport of oxidized phospholipids [2] and inhibition of fibrinolysis [3]. Plasma Lp(a) levels are influenced by several factors such as genetic polymorphisms of apo(a) [4], sex, age, race [5, 6], smoking, alcohol consumption, dietary habits, intense exercise, thyroid function [7] and hormonal factors. However, Lp(a) appears to be more resistant to drug and lifestyle interventions than any other lipoprotein [8]. A continuous and independent association between enhanced Lp(a) levels and risk of coronary heart disease [9], ischemic stroke [10], venous thromboembolism [11], aortic valve stenosis and aortic valve calcification [12] has been observed. Many strategies designed to target Lp(a) have been tested, including nicotinic acid [13–15], apheresis [16], the apo-B synthesis inhibitor mipomersen [17, 18], inhibitors of proprotein convertase subtilisin/kexin type 9 (PCSK9), coenzyme Q10 [19], cholesteryl ester transfer protein (CETP) inhibitors, aspirin, the thyroid hormone analog eprotirome [20], and synthetic inhibitors of microsomal triglyceride transfer protein [21]. However, the benefit of these strategies in clinical trials seems to be derived from effects on other lipids [22].

Tamoxifen is a selective estrogen receptor modulator (SERM), which has been used since 1977 for the treatment of women with early or advanced stages of breast

tumors [23]. SERMS act as agonists of estrogen receptors in some tissues and as antagonists in others [24], hence their designation as “modulators” of estrogen receptors rather than as “agonists” or “antagonists.” In addition to its beneficial effects on cancer, it has been suggested that tamoxifen may decrease the risk of cardiovascular disease (CVD) and associated mortality by modulating lipid metabolism [25–27]. In particular, tamoxifen has been associated with a reduction in circulating low-density lipoprotein-cholesterol (LDL-C) [28]. However, tamoxifen was not shown to have any benefit on cardiovascular risk in the Breast Cancer Prevention trial [29]. Moreover, the Heart and Estrogen/Progestin Replacement Study (HERS) showed that treatment with estrogen plus progestin led to greater CVD risk than placebo in a randomized controlled trial (RCT) in high-risk patients [30]. It is thus important that the effects of individual SERMS and estrogen receptor ligands on lipid profiles and cardiovascular risk are thoughtfully explored, rather than assuming a class effect for these drugs [29].

Some experimental and clinical trials have reported an important role of tamoxifen in decreasing lipids and Lp(a) levels; however, the available evidence is controversial and mostly inconclusive. Therefore, we aimed to assess the impact of tamoxifen on plasma Lp(a) concentrations through a meta-analysis of available RCTs and observational studies.

2 Methods

This study was designed according to the guidelines of the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [31] and was registered in the Prospero database (CRD42016036890).

2.1 Search Strategy

Scopus (<http://www.scopus.com>), EMBASE (<http://www.embase.com>) and MEDLINE (<http://www.ncbi.nlm.nih.gov/pubmed>) databases were searched using the following search terms in titles and abstracts: (“Lp(a)” OR “LP (a)” OR “lipoprotein(a)” OR “lipoprotein (a)”) AND (tamoxifen). 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. The literature was searched from inception until 22 March 2016. Two reviewers (MCS and PP) evaluated each article independently. Disagreements were resolved by discussion with a third party (MB).

2.2 Study Selection

Original studies were included if they met the following inclusion criteria: (1) interventional studies (either with a parallel or cross-over design), post hoc analyses and observational studies (either with a prospective or retrospective design); (2) inclusion of a control group; (3) investigating the impact of tamoxifen on plasma/serum concentrations of Lp(a); and (4) 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 (1) lack of an appropriate control group in the study design and (2) lack of sufficient information on baseline or follow-up Lp(a) concentrations.

2.3 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) inclusion criteria and underlying disease; (6) number of participants in the statin and control (in case of randomized design) groups; (7) age, gender and body mass index (BMI) of study participants; and (8) baseline, follow-up and change values of plasma Lp(a) concentrations. Data extraction was performed independently by two reviewers; disagreements were resolved by a third reviewer. Risk of bias in non-randomized and observational studies was assessed using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool [32]. This tool evaluates the risk of bias across seven domains, including confounding, selection of participants, classification of interventions, deviation from intended interventions, missing data, measurement of outcomes or interventions, and selection of reported results.

2.4 Quality Assessment

A systematic assessment of bias in the included studies was performed using the Cochrane criteria [33]. The items used for the assessment of each study were as follows: adequacy of sequence generation, allocation concealment, blinding, dropouts addressed (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. Risk-of-bias assessment was performed independently by two reviewers; disagreements were resolved by a third reviewer.

2.5 Quantitative Data Synthesis

Meta-analysis was conducted using Comprehensive Meta-Analysis (CMA) V2 software (Biostat, NJ) [34]. 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 the control intervention from that reported after treatment. All values were collated in mg/dL. Standard deviations (SDs) of the mean difference were calculated using the following formula: $SD = \text{square root} [(SD_{\text{pre-treatment}})^2 + (SD_{\text{post-treatment}})^2 - (2R \times SD_{\text{pre-treatment}} \times SD_{\text{post-treatment}})]$, assuming a correlation coefficient (R) = 0.5. If the outcome measures were reported in median and interquartile range, mean and SD values were estimated using the method described by Hozo et al. [35]. To convert interquartile range into minimum–maximum range, the following equations were used: $A = \text{median} + 2 \times (Q_3 - \text{median})$ and $B = \text{median} - 2 \times (\text{median} - Q_1)$, where A , B , Q_1 and Q_3 are upper and lower ends of the range and upper and lower ends of the interquartile range, respectively. Where only standard error of the mean (SEM) was reported, 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. In order to avoid the double-counting problem in trials comparing multiple treatment arms versus a single control group, the number of subjects in the control group was divided by the number of treatment arms. When no SD was provided for plasma Lp(a) concentrations in a study, the pooled SD of other studies was used as the substitute. When the data were not tabulated, but presented only as graphs, the software GetData Graph Digitizer 2.24 (<http://getdata-graph-digitizer.com/>) was applied to digitize and extract the data.

A random-effects model (using the 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 designs. Heterogeneity was quantitatively assessed using the I^2 index. Effect sizes were expressed as standardized mean difference (SMD) and 95% confidence interval (CI). In order to evaluate the influence of each study on the overall effect size, sensitivity analysis was conducted using the leave-one-out method, i.e., removing one study each time and repeating the analysis [36–38].

3 Results

3.1 Flow and Characteristics of Included Studies

The initial screening for potential relevance removed the articles whose titles and/or abstracts were obviously irrelevant. Among the 11 full-text articles assessed for eligibility, six studies were excluded because of the following reasons: study was not controlled for tamoxifen ($n = 1$), duplicate data report ($n = 3$), incomplete data ($n = 1$), not measuring Lp(a) ($n = 1$) (Fig. 1). After assessment, five studies met the inclusion criteria and were included in the meta-analysis [28, 39–42]. In total, 104 participants were allocated to the tamoxifen group and 111 to the control group in the selected studies. The number of participants in these studies ranged from 17 to 68. Included studies were published between 1994 and 2003, and were conducted in USA (two studies), Italy, Turkey and the UK. All studies used tamoxifen tablets, and the administered dosage ranged from 10 mg administered on alternate days to 40 mg/day. The duration of tamoxifen therapy ranged between 56 days and 14 months. Five studies were designed as randomized parallel-group trials and one as an observational study. Demographic and baseline parameters of the included studies are shown in Table 1. The assessment of risk of bias in the included studies using Cochrane criteria is shown in Table 2. Most of the included studies had a low risk of bias with respect to different criteria specified for the quality assessment. However, the studies by Decensi et al. [43] and Love et al. [44] were identified as having a high risk regarding blinding of participants and personnel and outcome assessment.

3.2 Effect of Tamoxifen on Plasma Lp(a) Concentrations

The impact of tamoxifen on plasma Lp(a) concentrations was reported in seven treatment arms. Meta-analysis suggested a significant reduction of Lp(a) levels following tamoxifen treatment (SMD -0.41 , 95% CI -0.68 to -0.14 , $p = 0.003$; $I^2 = 0\%$; $Q = 1.97$) (Fig. 2). This result was robust in the sensitivity analysis (Fig. 3). Likewise, when the studies with higher risk of bias were removed from the meta-analysis, the effect size remained statistically significant (SMD -0.49 , 95% CI -0.92 to -0.05 , $p = 0.027$; $I^2 = 0\%$; $Q = 1.44$).

4 Discussion

To our knowledge, this meta-analysis is the first to collate the evidence obtained from RCTs and observational studies on the efficacy of supplementation with tamoxifen on

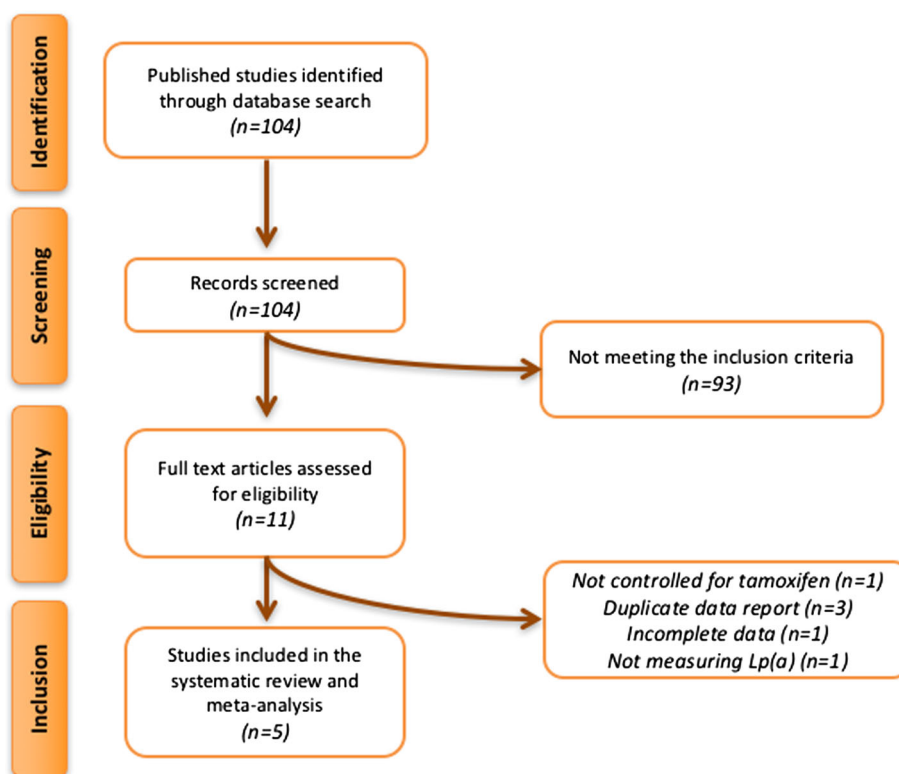
plasma Lp(a) concentrations. The results suggested a statistically significant reduction of circulating Lp(a) concentrations following tamoxifen treatment. Based on a general rule of thumb, our estimated effect size could be regarded as a small to medium effect.

Our results are in agreement with the findings of other studies whose design did not make them eligible for inclusion in this study. For example, in a study that included 38 tamoxifen-treated (20 mg/day) postmenopausal women with breast cancer, Elisaf et al. observed a statistically significant reduction in median circulating concentrations of Lp(a) [45]. These methods and results were very similar to those of a small study performed by Shewmon et al., where a stable reduction in Lp(a) was observed after 1 month of tamoxifen therapy in five out of six study participants with breast cancer [46].

Similar effects have been observed with other SERMS. In a recent systematic review and meta-analysis of 12 studies with 1009 patients, tibolone was shown to be effective in decreasing Lp(a) levels in postmenopausal women [47]. Tibolone has estrogenic, progestogenic, and weak androgenic actions, and together, the results of these two meta-analysis suggest that further investigation of estrogen receptor ligands may be fruitful in the treatment of elevated Lp(a).

The effects of tamoxifen on lipid metabolism have been researched in several experimental and clinical studies, but the exact mechanisms responsible for tamoxifen-lowering effects on Lp(a) levels are not fully understood. Because tamoxifen acts as an agonist of estrogen receptors in some tissues [48, 49], we can look to the effects of estrogen on the liver and on lipoprotein metabolism to help us understand the effects of tamoxifen. Barton has extensively reviewed the effects of estrogen on cholesterol and atherosclerosis [50]. With respect to Lp(a), it has been demonstrated that hormone replacement therapy (HRT) with estrogen leads to lower circulating Lp(a) concentrations [51] and that letrozole, an aromatase inhibitor that reduces endogenous production of estrogen, has the opposite effect on Lp(a) [52]. Estrogen may mediate its effects by altering the biosynthesis of Lp(a) and thus reducing the availability of precursors and component molecules, in particular apoB-100 and apo(a). Circulating concentrations of Lp(a) levels are determined to a greater extent by genetically defined hepatic biosynthesis than by catabolism [53]; estrogens are known to enhance hepatic very low-density lipoprotein (VLDL) synthesis and excretion [4], thus leaving less apoB-100 available for the biosynthesis of Lp(a). Apo(a) has an interleukin-6 (IL-6) responsive element in its gene promoter region [54], and estrogens may regulate apo(a) levels indirectly through their impact on IL-6 [55], despite the fact that tamoxifen

Fig. 1 Flow chart of the number of studies identified and included into the meta-analysis



was found to be associated with increased apo(a) in one clinical study [28].

Recent *in vitro* studies have shed light on potential mechanisms by which the effect of tamoxifen may be mediated. Experiments employing primary hepatocytes [56] and HepG2 hepatocytes [57] supported evidence for a role of LDL receptors (LDLRs) in the catabolism of Lp(a). In the same cell type, the SERMS tamoxifen, raloxifene and toremifene have been shown to up-regulate LDLR activity [58]. Similar effects of estradiol have been observed in the rat, leading to up-regulation of hepatic LDLR and a reduction of LDL [59]. It is not clear whether the same effects would occur in humans *in vivo* at clinically relevant doses of SERMS; however, these experimental results highlight plausible mechanisms by which tamoxifen may reduce circulating concentrations of Lp(a).

Although tamoxifen has a generally favorable safety profile, long-term use of tamoxifen is associated with serious side effects, including menopause symptoms, endometrial cancer, and thromboembolism, which have all led to controversy regarding its use [60]. Of particular concern with respect to lipid profiles, tamoxifen has been shown to increase circulating concentrations of triglycerides [61, 62], which can cause life-threatening acute pancreatitis [63, 64]. These limitations in the overall risk:benefit ratio of tamoxifen, in addition to the potential development of drug resistance and problems associated

with patient compliance, have led to the development of better tolerated and more effective endocrine agents.

The adverse effects described above are likely to limit the usefulness of tamoxifen as a clinical modulator of Lp(a). Nevertheless, the results of this meta-analysis are important because tamoxifen has been shown to reduce plasma concentrations of Lp(a), despite the fact that this lipoprotein is relatively resistant to treatment with other drugs and diet [8]. Furthermore, Lp(a) may partially account for residual cardiovascular risk after optimal LDL reduction with statins [65, 66]. Thus, Lp(a) should be regarded as a crucial clinical target, and the results of the present study suggest that estrogen receptor ligands show promise in this respect. Finally, the widespread use of tamoxifen and especially its use in the prophylaxis of breast cancer [67] makes it important that clinicians understand the cardiovascular effects of such treatment. The present study adds to our understanding of this issue.

The present meta-analysis has some limitations. There were only a few eligible RCTs, and most of them had a modest number of participants. Administered tamoxifen dose in the included studies was mainly fixed at 20 mg/day, and this hindered assessment of any dose–response association for the Lp(a)-lowering activity of the drug. Furthermore, the included studies were heterogeneous concerning the characteristics of patients, study design, duration and the methods of Lp(a) quantification. Finally, it remains somewhat unclear whether the calculated Lp(a)-

Table 1 Demographic and baseline parameters and characteristics of the included studies

	Decensi et al. [39]	Clarke et al. [40]	Love et al. [28]	Genç et al. [41]	Shewmon et al. [42]
Year	1998	2001	1994	2003	1994
Location	Italy	UK	USA	Turkey	USA
Design	Randomized, placebo-controlled, parallel-group trial	Randomized, single-blind, placebo-controlled, parallel-group trial	Randomized, placebo-controlled, parallel-group trial	Observational study	Randomized, double-blind, placebo-controlled, parallel-group trial
Duration of trial	6 months	56 days	5 years	12 ± 2 months	3 months
Inclusion criteria	Premenopausal and postmenopausal healthy women aged 35–70 years who had undergone a hysterectomy procedure previously for nonmalignant conditions and who were negative for breast cancer	One group of male patients, who had a reduction of ≥75% in the intraluminal diameter of all three coronary arteries, defined as the TVD patients. Another group of male patients with a history of chest pain suggestive of angina pectoris but with NCA	Postmenopausal women with breast cancer and histologically negative axillary lymph nodes	One group breast cancer patients Another operated breast cancer patients, who either completed the chemotherapy and or radiotherapy protocols at least a year ago, or new patients operated 1 month ago	Healthy postmenopausal women recruited from the community
Tamoxifen form	10 mg tablets	40 mg tablets	10 mg tablets	20 mg tablets	20 mg tablets
Tamoxifen intervention	20 mg/day	40 mg/day	10 mg every 2nd day	20 mg/day	20 mg/day
Participants					
Case	31	16	30	19	8
Control	37	10	32	18	9
Age (years)					
Case	51.4 ± 4.5	61.1 ± 2.1 ^{a***} 51.2 ± 4.0 ^{b**}	NS	55 (35–74)	55.6 ± 3.3 ^{**}
Control	52.1 ± 4.6	64.3 ± 2.6 ^{**}	NS	54 (36–73)	64.6 ± 1.8 ^{**}
Male (%)					
Case	0.0	100.0 ^a	0.0	0.0	0.0
Control	0.0	100.0 ^b	0.0	0.0	0.0
BMI (kg/m ²)					
Case	24.7 ± 4.5	28.9 ± 1.0 ^{a***} 27.0 ± 1.1 ^{b**}	NS	NS	NS
Control	24.0 ± 3.0	30.0 ± 0.9 ^{**}	NS	NS	NS

Table 1 continued

	Decensi et al. [39]	Clarke et al. [40]	Love et al. [28]	Genç et al. [41]	Shewmon et al. [42]
Total cholesterol (mg/dL)					
Case	NS	177.56 ± 7.72 ^{a**} 212.3 ± 7.72 ^{b***}	220 ± 5 ^{**}	NS	236.23 ± 8.49 ^{**}
Control	NS	181.42 ± 7.72 ^{**}	217 ± 6 ^{**}	NS	246.27 ± 10.80 ^{**}
LDL-C (mg/dL)					
Case	149 ± 32	100.36 ± 7.72 ^{a**} 131.24 ± 7.72 ^{b**}	142 ± 5 ^{**}	NS	163.66 ± 9.26 ^{**}
Control	160 ± 29	100.36 ± 7.72 ^{**}	137 ± 6 ^{**}	NS	167.52 ± 9.65 ^{**}
HDL-C (mg/dL)					
Case	52 ± 13	38.6 ± 1.54 ^{a***} 39.76 ± 2.70 ^{b***}	57 ± 2 ^{**}	NS	52.88 ± 3.47 ^{**}
Control	55 ± 13	42.46 ± 2.70 ^{**}	59 ± 3 ^{**}	NS	58.67 ± 3.86 ^{**}
Triglycerides (mg/dL)					
Case	NS	194.7 ± 26.55 ^{a**} 194.7 ± 26.55 ^{b**}	106 ± 8 ^{**}	NS	130.98 ± 27.43 ^{**}
Control	NS	203.55 ± 26.55 ^{**}	107 ± 8 ^{**}	NS	106.2 ± 11.50 ^{**}
Lipoprotein(a) (mg/dL)					
Case	25.9 ± 26.3	42.2 ± 6.2 ^{a**} 35.2 ± 10.3 ^{b***}	7.5 [*]	NS	8.9 ± 1.4 ^{**}
Control	22.7 ± 15.1	30.7 ± 6.6 ^{**}	15 [*]	NS	11.2 ± 1.4 ^{**}

Values are expressed as mean ± SD or mean (range)

BMI body mass index, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol, NCA normal coronary angiograms, NS not stated, SD standard deviation, SEM standard error of the mean, TVD triple-vessel disease

* Median value; ** values are expressed as mean ± SEM

^a Denotes TVD group

^b Denotes NCA group

Table 2 Assessment of risk of bias in the included studies using Cochrane criteria

Study	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other potential threats to validity
Decensi et al. 1998 [39]	U	U	H	H	L	L	L
Clarke et al. 2001 [40]	L	L	L	L	L	L	L
Love et al. 1994 [28]	L	L	H	H	L	L	L
Shewmon et al. 1994 [42]	U Bias due to confounding	U Bias in participant selection	L Bias in classification of interventions	L Bias due to departures from intended interventions	L Bias due to missing data	L Bias in measurement of outcomes	L Bias in selection of the reported result
Genç et al. 2003 [41] ^a	L	L	L	L	L	L	L

Risk of bias assessment according to the Cochrane Collaboration’s tool for randomized controlled trials and ROBINS-I tool for non-randomized and observational studies

H high risk of bias, *L* low risk of bias, ROBINS-I Risk Of Bias In Non-randomized Studies of Interventions, *U* unclear risk of bias

^a Study had an observational design

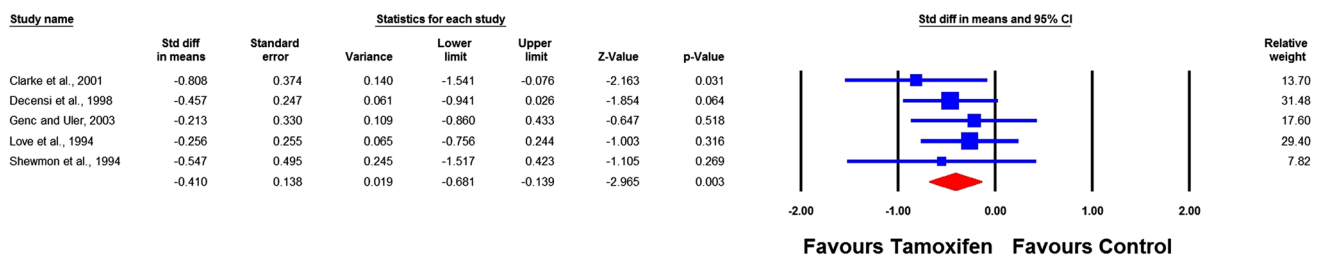


Fig. 2 Forest plot detailing standardized mean difference and 95% confidence intervals (CIs) for the impact of tamoxifen on plasma lipoprotein(a) concentrations ($I^2 = 0\%$; $Q = 1.97$, $p = 0.741$)

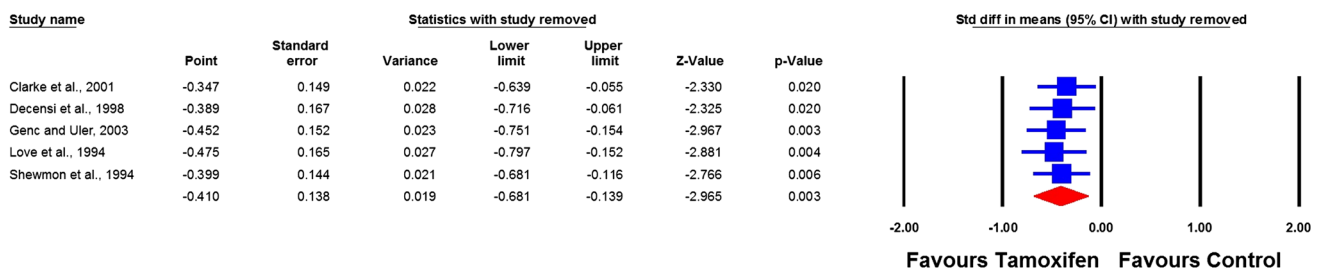


Fig. 3 Leave-one-out sensitivity analysis of the meta-analysis of tamoxifen’s effects on plasma lipoprotein(a) concentrations. Sensitivity analysis was performed by iterative removal of each study and repeating the analysis. *CI* confidence interval

lowering effect of tamoxifen can be translated to a clinically relevant cardiovascular risk reduction. Addressing this uncertainty necessitates additional evidence from large-scale trials, particularly those performed in subjects with elevated plasma Lp(a) concentrations at baseline.

5 Conclusion

This meta-analysis suggests a statistically significant reduction of Lp(a) levels after tamoxifen treatment. Further well-designed trials are required to validate these results.

Author contributions Maciej Banach, Maria-Corina Serban, Camelia Gurban, Sorin Ursoniu and Amirhossein Sahebkar conceived and designed the work, and contributed to the drafting of the manuscript. Maria-Corina Serban, Peter Penson and Sorin Ursoniu performed the searches and extracted data. Amirhossein Sahebkar performed the statistical analysis. Peter Penson, Peter P. Toth, Steven R. Jones, Giuseppe Lippi, Kazuhiko Kotani, Karam Kostner, Manfredi Rizzo, Jacek Rysz and Maciej Banach contributed to the interpretation of the work and revised the manuscript critically for important intellectual content. All authors have approved the final manuscript and agree to be held accountable for all aspects of the work.

Compliance with ethical standards

Conflicts of interest This meta-analysis was written independently; no company or institution supported it financially. Dr. Penson owns four shares in AstraZeneca PLC, which he inherited during 2015. Dr. Toth is a member of the speakers' bureau for Amarin, Amgen, Merck, and Regeneron-Sanofi; and a consultant to Amarin, Amgen, AstraZeneca, Kowa, Merck, and Regeneron-Sanofi. No professional writer was involved in the preparation of this meta-analysis.

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