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# Menopause symptom management in women with dyslipidemias: An EMAS clinical guide

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ABSTRACT

*Introduction:* Dyslipidemias are common and increase the risk of cardiovascular disease. The menopause transition is associated with an atherogenic lipid profile, with an increase in the concentrations of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), apolipoprotein B (apoB) and potentially lipoprotein (a) [Lp(a)], and a decrease in the concentration of high-density lipoprotein cholesterol (HDL-C).
*Aim:* The aim of this clinical guide is to provide an evidence-based approach to management of menopausal symptoms and dyslipidemia in postmenopausal women. The guide evaluates the effects on the lipid profile both of menopausal hormone therapy and of non-estrogen-based treatments for menopausal symptoms.
*Materials and methods:* Literature review and consensus of expert opinion.
*Summary recommendations:* Initial management depends on whether the dyslipidemia is primary or secondary. An assessment of the 10-year risk of fatal cardiovascular disease, based on the Systematic Coronary Risk Estimation (SCORE) system, should be used to set the optimal LDL-C target. Dietary changes and pharmacological management of dyslipidemias should be tailored to the type of dyslipidemia, with statins constituting the mainstay of treatment.

With regard to menopausal hormone therapy, systemic estrogens induce a dose-dependent reduction in TC, LDL-C and Lp(a), as well as an increase in HDL-C concentrations; these effects are more prominent with oral administration. Transdermal rather than oral estrogens should be used in women with hypertriglyceridemia. Micronized progesterone or dydrogesterone are the preferred progestogens due to their neutral effect on the lipid profile. Tibolone may decrease TC, LDL-C, TG and Lp(a), but also HDL-C concentrations. Low-dose vaginal estrogen and ospemifene exert a favorable effect on the lipid profile, but data are scant regarding dehy-

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droepiandrosterone (DHEA). Non-estrogen-based therapies, such as fluoxetine and citalopram, exert a more favorable effect on the lipid profile than do sertraline, paroxetine and venlafaxine. Non-oral testosterone, used for the treatment of hypoactive sexual desire disorder/dysfunction, has little or no effect on the lipid profile.

## 1. Introduction

Worldwide, dyslipidemias are one of the leading causes of cardiovascular disease, mainly coronary heart disease [1]. Dyslipidemias are also associated with an increased risk of ischemic stroke [2]. Dyslipidemias embrace a wide constellation of lipid and lipoprotein abnormalities. Lipoproteins bind lipids and are involved in their transport. Lipid abnormalities include high serum concentrations of low-density lipoprotein (LDL) cholesterol (LDL-C) and/or triglycerides and/or low concentrations of high-density lipoprotein (HDL) cholesterol (HDL-C). High LDL-C and lipoprotein (a) [Lp(a)] concentrations, as well as low HDL-C concentrations, are associated with an increased risk of cardiovascular disease [3,4]. Hypertriglyceridemia is also associated with a greater risk of atherosclerotic cardiovascular disease, but this effect is mediated by changes in triglyceride-rich lipoproteins, as estimated by non-HDL-C levels (calculated by subtracting HDL-C from TC concentrations), which reflects the total concentrations of all lipoproteins containing apolipoprotein-B [3]. Dyslipidemias may be either inherited (primary) or acquired (secondary). Secondary causes encompass endocrinopathies (such as diabetes and hypothyroidism), chronic kidney disease, nephrotic syndrome, infections (human immunodeficiency virus), cirrhosis, alcohol abuse, smoking and drugs (such as β-blockers and thiazide diuretics) [3].

Dyslipidemias are common. The estimated prevalence of high LDL-C in US adults aged 20 years or over, according to the definition in the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) [5], is 33.5 % overall (31 % in women and 36 % in men) [6]. It increases with age, from 11.7 % at 20–39 years to 41.2 % at 40–64 years and 58.2 % at ≥65 years [6]. The European Study on Cardiovascular Risk Prevention and Management in Usual Daily Practice EURIKA studied 7641 people aged over 50 with at least one cardiovascular risk factor but no history of cardiovascular disease 51.6 % women and 95.6 % White/Caucasian). It found that over 20 % of the EURIKA population had either triglyceride or HDL-C levels characteristic of atherogenic dyslipidemia. Furthermore, the proportion of hypertriglyceridemia patients who were male was greater than the proportion who were female, whereas the reverse was true of patients with low HDL-C levels [7].

The menopause results in estrogen-deficiency symptoms, such as hot flushes and night sweats and those related to vulvo-vaginal atrophy. In women without dyslipidemia, administration of systemic estrogen-based menopausal hormone therapy (MHT) for menopausal symptoms has a favorable risk–benefit profile for those under the age of 60 years or up to 10 years after menopause [8,9]. Systemic MHT can be taken orally or transdermally. Estrogen alone is given to women who have undergone hysterectomy. Progestogens and the selective estrogen receptor modulator bazedoxifene are added in regimens for women with an intact uterus to reduce the risk of endometrial hyperplasia and carcinoma which occurs with unopposed estrogen [8,9]. Tibolone is a synthetic steroid compound that is, in itself, inert, but whose metabolites have estrogenic, progestogenic and androgenic actions. It is classified as MHT [10]. Availability of different MHT preparations varies worldwide. For vasomotor symptoms, the non-hormonal pharmacological options include selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs), clonidine and gabapentin. Symptoms due to vulvo-vaginal atrophy can be managed with low-dose topical estrogen, ospemifene or dehydroepiandrosterone (DHEA) as well as non-hormonal lubricants [11,12].

The purpose of this clinical guide is to provide an evidence-based individualized approach to menopause symptom management in women with dyslipidemias, as well as to the management of dyslipidemia in menopausal women. Diet, lifestyle, hormonal and non-hormonal pharmacological strategies will be discussed. Treatment of dyslipidemias *per se* should be undertaken in accordance with individual/national healthcare pathways and guidelines using the available specialist resources. This clinical guide will not consider herbal supplements and botanicals as there is a lack of data regarding their safety and efficacy [13]. In addition, some products contain compounds which may interact with lipid-lowering therapies.

## 2. Methods

We searched PubMed for English-language publications through to 15 November 2019, under the following terms: (“menopause” OR “post-menopausal” OR “postmenopausal” OR “ovarian insufficiency” OR “ovarian failure” OR “hormone replacement therapy” OR “hormone therapy” OR “menopausal hormone therapy” OR “menopausal hormonal therapy” OR “estrogen*” OR “estrone*” OR “estradiol” OR “oestradiol” OR “tibolone”) AND (“dyslipidemia” OR “dyslipidemias” OR “hyperlipidaemia” OR “hyperlipidaemias” OR “hypercholesterolaemia” OR “hypertriglyceridaemia” OR “dyslipidemia” OR “dyslipidemias” OR “hyperlipidemia” OR “hyperlipidemias” OR “hypercholesterolemia” OR “hypertriglyceridemia” OR “lipoprotein(a)” OR “Lp(a)”). Further references, after a manual search in key journals in the fields of endocrinology and lipidology, were also included in this clinical guide.

## 3. Lipid changes with age and menopause

The menopause transition has been associated with increased risk of cardiovascular events, although it is unclear whether this is the consequence of the aging process or menopause *per se* [14]. Menopause-associated cardiovascular risk appears to be the corollary of a composite of risk factors, such as abdominal obesity, insulin resistance, hyperglycemia and atherogenic dyslipidemia [15–17]. Both estrogen deficiency and the increase in levels of free androgens at the menopause may also be associated with increased cardiovascular risk [18]. The association between menopause and cardiovascular risk is more evident in women with premature or early ovarian failure (menopause before age 40 or 45 respectively). These women have a higher risk of all-cause mortality, as well as of cardiovascular disease morbidity and mortality, compared with women of normal age at menopause (i.e. 51 years) [19–22].

Menopause-associated cardiovascular risk is largely attributed to the change towards an atherogenic lipid profile, characterized by an increase in the concentrations of TC, LDL-C and triglycerides and a decrease in HDL-C concentration. The latter mostly refers to $HDL_2$-C rather than $HDL_3$-C subfractions [15,23,24]. These alterations in the lipid profile seem to be independent of age, body mass index (BMI) and time since the final menstrual period [25]. With respect to HDL-C changes, it is not clear if these are attributed to age [25] or the menopause transition [26]. The greater average levels of triglycerides among postmenopausal women seems to be the consequence of a higher prevalence of the metabolic syndrome in this group compared with premenopausal women [27].

Other lipid parameters affected by the menopause transition which may independently predict cardiovascular disease risk are apolipoproteins B (apoB), A-I (apo A-I) and apo A-I I (apo A-I I) [3]. In particular, apoB, which is the main apolipoprotein of LDL and very low-density (VDL) particles, as well as apo A-I and apo A-I I concentrations, which

constitute the main apolipoproteins of HDL particles, increase during menopause [16,28,29]. Most important are the alterations of cholesterol content in LDL and HDL particles, as indicated by the increase in apoB/apo A-I, LDL-C/apoB, HDL-C/apo A-I and HDL-C/apo A-I I ratios. These contribute to the menopause-induced atherosclerotic risk [16]. Thus, low HDL-C and apo A-I concentrations are associated with high risk of cardiovascular disease (mainly coronary heart disease and not stroke) in women aged over 45 years. However, this inverse association between HDL-C and apo A-I concentrations and cardiovascular disease does not apply in women with low apoB-100 levels (< 90 mg/dL) [30]. Of note, the rise in apoB and apo A-I concentrations after the age of 60 years is more prominent in women than in men [16].

High levels of Lp(a) are attracting increasing attention as a cardiovascular risk factor. Thus, Lp(a) measurement is currently recommended at least once in an adult's life [3], especially in those with a personal or family history of premature atherosclerotic cardiovascular disease or with a first-degree relative with high Lp(a) concentrations or with a family history of hypercholesterolemia or calcific aortic valve stenosis, or with a borderline (< 15 %) 10-year risk of a cardiovascular event [4]. However, whether transition to menopause leads to an increase in Lp(a) concentrations needs to be elucidated. More specifically, epidemiological evidence suggests that serum Lp(a) concentrations > 55 mg/dL (131 nmol/L) after the menopause are associated with increased risk of cardiovascular disease events compared with concentrations < 25 mg/dL (60 nmol/L) (HR 1.54, 95 % CI 0.99–2.39) [31].

## 4. Screening for dyslipidemia

Healthcare systems differ worldwide and thus screening for dyslipidemias depends on local guidelines and resources. The 2019 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines recommend the following: the first step is to estimate the 10-year risk of fatal cardiovascular disease, according to the Systematic Coronary Risk Estimation (SCORE) system [3]. LDL-C target levels should be based on the SCORE risk categories.

The risk categories are: very high risk, high risk, moderate risk or low risk. These depend on the presence and severity of (i) documented atherosclerotic cardiovascular disease; (ii) diabetes; (iii) chronic kidney disease; (iv) heterozygous familial hypercholesterolemia; and (v) calculated SCORE [3]. The LDL-C target is set at < 55 mg/dL (1.4 mmol/L) for those at very high risk, < 70 mg/dL (1.8 mmol/L) for those at high risk, < 100 mg/dL (2.6 mmol/L) for those at moderate risk and < 116 mg/dL (3 mmol/L) for those at low risk [3]. Notably, the 2018 American College of Cardiology/American Heart Association guidelines consider premature ovarian insufficiency as a risk factor for cardiovascular disease, which necessitates statin therapy in adults aged 40–75 years without diabetes and a 10-year cardiovascular risk of 7.5–19.9 % [32].

Beyond LDL-C, non-HDL-C and apoB concentrations may be considered for more accurate cardiovascular risk stratification, especially in people with hypertriglyceridemia, diabetes, obesity or very low LDL-C [3]. Although their targets have not been tested in randomized trials, recent guidelines recommend a specific value for non-HDL-C of 30 mg/dL (0.8 mmol/L) above the calculated LDL-C goal. For apoB, the recommended targets are < 65 mg/dL, < 80 mg/dL and < 100 mg/dL for patients at very high, high and moderate total cardiovascular risk, respectively. Regarding triglycerides, a level under 150 mg/dL (1.7 mmol/L) indicates low risk [3]. Lp(a) assessment should also be considered at least once in every postmenopausal woman [3] as it may identify patients at high cardiovascular risk, i.e. if Lp(a) concentrations exceed 180 mg/dL (> 430 nmol/L), which confers a risk of atherosclerotic cardiovascular events equivalent to that associated with familial hypercholesterolemia [3].

## 5. Interventions

### 5.1. Lifestyle changes and lipid-lowering medication according to the type of dyslipidemia

#### 5.1.1. Management of hypercholesterolemia

The dietary strategy for hypercholesterolemia includes reduced consumption of saturated and trans fatty acids (< 1 % of total daily intake), increased dietary fiber (whole-grain) intake and supplementation with food components such as phytosterols (≥ 2 g/day), soy isoflavones and red yeast rice [33]. Before administration of a lipid-lowering medication, exclusion or management of secondary dyslipidemias (i.e. deprescribing beta-blockers or diuretics, treating hypothyroidism etc.) is recommended. Statins are the cornerstone of medical management (LDL-C reduction 30–50 %) [3], and are of comparable cardiovascular benefit in both genders [34]. Statins are generally well tolerated; their relatively rare side-effects include an increase in transaminase concentrations, new-onset diabetes and myalgias. Myalgias, though, can also be simply a symptom of advanced aging [3]. In cases of suboptimal LDL-C lowering or intolerance to statins, ezetimibe (which gives an LDL-C reduction of 18–20 %) or bile acid sequestrants (colesevelam, colestipol or cholestyramine, which give an LDL-C reduction of 10–20 %) may also be considered [3]. For cases not adequately managed with a maximum tolerated dose of statin and/or ezetimibe, especially those at high or very high cardiovascular risk, combination with a proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitor is recommended (which gives an LDL-C decrease of 50–70 %) [3].

#### 5.1.2. Management of hypertriglyceridemia

Weight-loss strategies (5–10 % reduction in body weight), increased physical activity (> 150 min/week), reduced alcohol consumption and a low-carbohydrate diet (45–50 % of total daily intake, of foods with a low glycemic index) that is low in mono- and disaccharides and rich in omega-3 fatty acids and, to a lesser extent, in mono-unsaturated and poly-unsaturated fatty acids (rather than rich in saturated fatty acids) are recommended for persons with hypertriglyceridemia [33]. If triglyceride concentrations remain high [135–499 mg/dL (1.5–5.6) mmol/L] despite statin treatment, high doses of omega-3 fatty acids (icosapent ethyl 2 × 2 g/day) [35] or fibrate (fenofibrate or bezafibrate) may be considered [3]. For people with markedly elevated triglyceride concentrations [ > 500 mg/dL (5.6 mmol/L) and especially > 880 mg/dL (> 10 mmol/L)], fibrates should be prescribed in the primary-care setting due to increased risk of pancreatitis [36]. New agents, such as pemafibrate, apolipoprotein C-III inhibitors, angiopoietin-like 3 inhibitors, alipogene tiparvovec and pradigastat, provide further options [37].

#### 5.1.3. Management of low HDL-C concentrations

General measures include increasing physical activity, smoking cessation, reduced intake of trans fatty acids, low-carbohydrate diet and substitution of dietary carbohydrates with poly-unsaturated, mono-unsaturated and saturated fatty acids. Alcohol consumption in moderation and in the context of a balanced healthy diet may reduce both triglycerides and HDL-C, but excess consumption causes hypertriglyceridemia. These interventions may increase HDL-C by 7–12 % [33]. Fibrates, niacin and, to a lesser extent, statins may increase HDL-C concentrations, but the cardiovascular benefit of these medical interventions has not yet been proven [3].

#### 5.1.4. Management of high Lp(a) concentrations

Effective Lp(a)-lowering treatments are currently unavailable. However, estrogens, tibolone, PCSK-9 inhibitors and niacin may decrease Lp(a) by 25–30 % [4,38,39]. Of note, the cardiovascular benefit of Lp(a)-lowering alone in terms of cardiovascular risk reduction has not yet been proven, except for PCSK-9 inhibitors in relation to

coronary heart disease [40].

### 5.2. Systemic MHT

A personalized approach to MHT is required in women with dyslipidemia, as individual hormones have different effects on lipids, which may also vary with dose and route of administration.

#### 5.2.1. Estrogens

In general, estrogens exert a beneficial dose-dependent effect on lipid profile, reflected in a decrease in TC and LDL-C and an increase in HDL-C concentrations [41–43]. The effect of estrogen on triglycerides depends on the route of administration: oral estrogen may raise triglyceride concentrations, whereas a null effect or a slight decrease is observed after transdermal administration [41,43,44]. The greatest changes in TC, LDL-C, HDL-C and triglyceride concentrations are seen with conjugated equine estrogen (CEE) (the highest ones with the dose of 1.25 mg/day) [41,43]. More subtle, but dose-dependent, changes are observed with 17β-estradiol and even smaller ones with transdermal 17β-estradiol, but with no effect on triglycerides [41,43]. It should be noted that the effect of MHT on total cholesterol is more pronounced in patients with high baseline concentrations [45]. A meta-analysis of randomized controlled trials showed a small but significant reduction in TC and LDL-C concentrations [−12 mg/dL (−0.3 mmol/L)] even with low doses of estrogen and changes in triglyceride and HDL-C concentrations comparable to those achieved with standard doses [42].

MHT reduces Lp(a) concentrations by a mean of 20.4 % (95 % CI 25.3%–15.4%) compared with placebo or no treatment, according to a recent meta-analysis of randomized controlled trials [46]. The reduction in Lp(a) appears to be greater with oral than with transdermal estrogen (mean relative difference: −37.7 %, 95 % CI −16.8 % to −58.45 %). The mode of MHT administration (continuous *vs.* cyclical), estrogen dose or the combination with progestogen do not seem to modify the Lp(a)-lowering effect [46]. It must be highlighted that, according to a post-hoc analysis of the Heart and Estrogen/Progestin Replacement Study (HERS), a greater reduction in cardiovascular risk with MHT was seen in postmenopausal women with high [ > 55 mg/dL (131.2 nmol/L)] compared with low [ < 25 mg/dL (59.1 nmol/L)] baseline Lp(a) concentrations [31].

These effects of estrogen on the lipid profile are presented in Table 1. An algorithm for managing postmenopausal women with dyslipidemia is detailed in Fig. 1.

#### 5.2.2. Progestogens

Progestogens seem to have little effect on the estrogen-induced decrease in TC and LDL-C concentrations. In contrast, they can modulate the effect of estrogen on triglyceride and HDL-C concentrations, the degree of which depends on the type, being mild or neutral with micronized progesterone and dydrogesterone [44,47,48]. Norethisterone acetate may also decrease HDL-C, but may have a favorable effect on triglyceride and LDL-C concentrations. The effect of medroxyprogesterone is unclear and may depend on estrogen regimen [49]. Intra-uterine levonorgestrel has no effect on triglyceride and LDL-C concentrations [50–52]. Marginal decreases in TC (4.6–8 %) and HDL-C (6–15 %) are seen after six months, but levels revert to normal by 12 months after insertion [50–52].

#### 5.2.3. Tibolone

Tibolone may result in a reduction in Lp(a) [38], TC and triglyceride concentrations [41]. However, it can also decrease HDL-C concentrations [41].

#### 5.2.4. Conjugated estrogen/bazedoxifene

Bazedoxifene addition to MHT regimens affects lipid levels. In a pooled analysis of the effects of conjugated equine estrogens (CEE)/bazedoxifene (BZA) in the Selective Estrogens, Menopause, and Response to Therapy (SMART) Trials, the administration of CEE 0.45 mg/BZA 20 mg and CEE 0.625 mg/BZA 20 mg was associated with reductions from baseline in TC (−4.2 % and −4.4 %, respectively), LDL-C (−9.3 % and −10.7 %, respectively) and the LDL-C/HDL-C ratio (−11.6 % and −14 %, respectively) and increases in HDL-C (4.6 % and 6.2 %, respectively). All were significantly (P < 0.001) greater than results with placebo at 12 and 24 months (−0.9 %, −1.1 %, −0.8 % and +1.3 %, respectively). Both treatments were associated with significant increases (P < 0.001) from baseline in triglyceride levels compared with those for placebo at 12 and 24 months (15.1 % and 15.7 % vs 4.43 %, at 12 months; and 18.87 % and 18.82 % vs 6.49 % at 24 months, respectively) [53].

### 5.3. Vaginal estrogens

Topical estrogens have been used for many years to improve symptoms due to vaginal atrophy. Preparations include: estradiol-containing tablets, rings and capsules; estriol pessaries, creams, gels and ovules; promestriene and conjugated estrogens [54–56]. They can be used alone or combined with systemic MHT. The dose of estrogen in most current licensed vaginal preparations is very low, leading to minimal systemic absorption, with circulating estrogen levels remaining in the postmenopausal range. With regard to its effect on lipid profile, vaginal estrogen (in particular, a vaginal ring delivering estradiol 7.5 μg/24 h) may decrease TC, LDL-C, apoB and the LDL-C/HDL-C ratio by 4 %, 7 %, 4 % and 7 %, after 12 months of therapy. It has no impact on serum HDL-C and triglyceride levels, whereas HDL-triglyceride levels may increase by up to 25 % [57].

### 5.4. Non-estrogen-based treatments for vulvo-vaginal atrophy

These treatments include the selective estrogen receptor modulator ospemifene and DHEA. Ospemifene is an oral selective estrogen receptor modulator (SERM) licensed in both the USA and Europe for the treatment of moderate to severe symptomatic vulvo-vaginal atrophy in postmenopausal women who are not candidates for vaginal estrogen therapy [11,58]. A pooled analysis of five randomized controlled trials n = 2,166 postmenopausal women found that the mean percentage changes in TC, LDL-C and HDL-C concentrations at 6 months were −1.8 %, −6.7 %, +5.1 % vs +1.6 %, +2.4 % and +1.5 % respectively, compared with placebo (P < 0.05 for all comparisons). These remained significant at 12 months. In contrast, the changes in triglyceride levels were comparable to those with placebo [58].

Vaginal DHEA is licensed in both the USA and Europe for the treatment of vulvo-vaginal atrophy in postmenopausal women with moderate to severe symptoms [12]. There is a paucity of data with regard to its effect on the lipid profile. In a small randomized controlled trial with 13 premenopausal participants with systemic lupus erythematosus, DHEA induced significant decreases in TC (−13.5 %) and HDL-C (−7.8 %) compared with placebo. No difference in LDL-C and

**Table 1**
Effect of menopause and menopausal hormone therapy on cardiovascular risk factors.

| Risk factor | Effect of menopause | Effect of menopausal hormone therapy |
|---|---|---|
| Total cholesterol | ↑ | ↓ (greater with oral estrogen) |
| LDL-C | ↑ | ↓ (greater with oral estrogen) |
| Triglycerides | ↑ | ↓ or ↔with transdermal estrogen<br>↑ with oral estrogen |
| HDL-C | ↓ | ↑ (greater with oral estrogen) |
| Lipoprotein (a) | ↑ or ↔ | ↓ (greater with oral estrogen) |
| Apolipoprotein B | ↑ | ↔ |
| Apolipoprotein A–I | ↑ | ↑ |

Abbreviations: LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol.

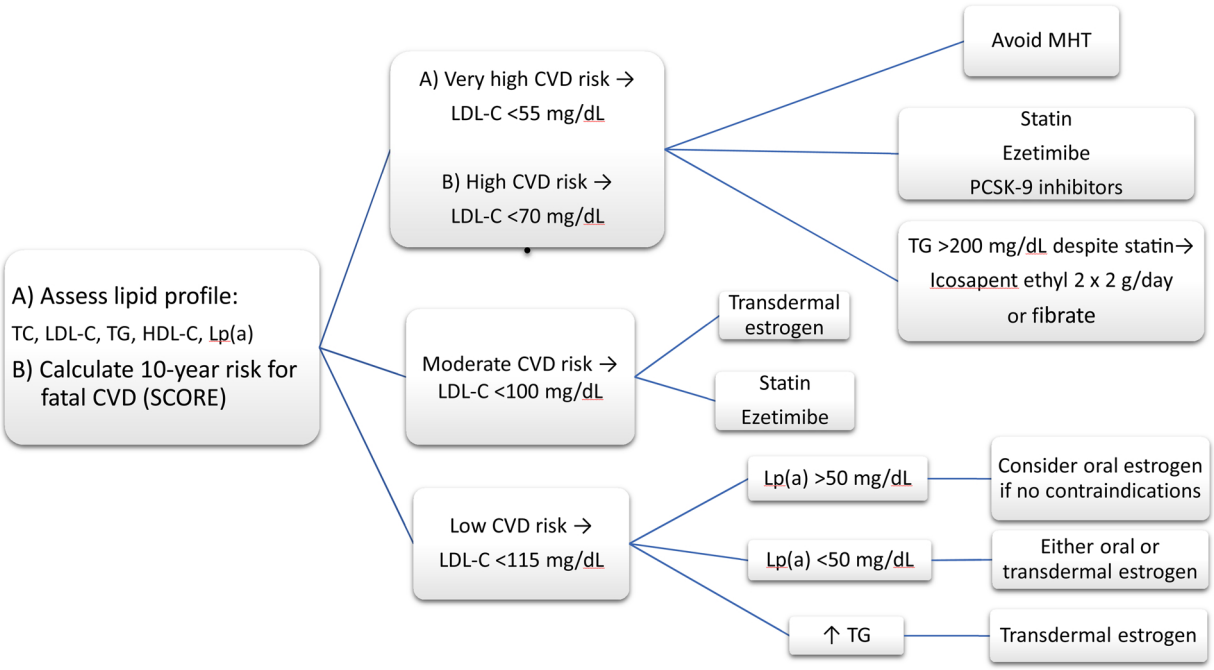


**Fig. 1.** Algorithm managing dyslipidemia in postmenopausal women (Abbreviations: apoB: apolipoprotein B; CVD: cardiovascular disease; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; Lp(a): lipoprotein (a); SCORE: Systematic Coronary Risk Estimation; TC: total cholesterol; TG: triglycerides).

triglyceride concentrations was found [59].

### 5.5. Testosterone

Recent guidelines recommend testosterone therapy for postmenopausal women diagnosed with hypoactive sexual desire disorder/dysfunction (HSDD), based on international diagnostic criteria [60]. Oral testosterone therapy increases LDL-C, decreases HDL-C levels and is not recommended for HSDD [60]. On the other hand, non-oral (percutaneous or intramuscular) testosterone administration, at doses that achieve up to premenopausal testosterone concentrations, do not have any effect on the lipid profile over the short term [60]. This is also the case with vaginal testosterone [61].

### 5.6. Non-estrogen-based treatments for vasomotor symptoms: antidepressants and gabapentin

For women for whom MHT is contraindicated, selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs) or gabapentin may be considered for the relief of vasomotor symptoms and depression [62,63]. Some of these drugs may alter the lipid profile, although to only a modest extent. It must be noted that the vast majority of the relevant studies were conducted in patients with major depression.

A 2006 systematic review on SSRIs showed that sertraline and paroxetine exhibit the most detrimental effect on the lipid profile, characterized by an increase in triglyceride levels. They also exert a neutral or pro-atherogenic effect on TC and LDL-C [64]. A more recent systematic review confirmed the pro-atherogenic effects of sertraline and paroxetine, mostly on TC and LDL-C concentrations [65]. In contrast, fluoxetine and citalopram, of all the SSRIs, have demonstrated the least detrimental impact on the lipid profile. While fluoxetine may decrease or have no effect on TC, LDL-C and triglyceride concentrations, citalopram has little or no effect [64,65]. No data are available for escitalopram [64,65]. HDL-C concentrations may be either stable or increased after treatment with SSRIs [64].

The SNRI venlafaxine (at a dose of 75 – 225 mg/day) may increase TC, LDL-C and HDL-C concentrations. In contrast, duloxetine (at a dose of 60 mg/day) has no significant effect on TC, LDL-C and triglycerides, but may decrease HDL-C levels [64]. It is of note that treatment for depression *per se*, such as with mirtazapine or venlafaxine, may also improve the lipid profile [66].

Finally, gabapentin may modestly raise LDL-C concentrations (by 6 % at doses of 900 mg/day), whereas its effect on other lipid parameters is negligible [67].

## 6. Summary recommendations

- Management of menopause symptoms and dyslipidemia needs to be individualized.
- Systemic estrogens induce a dose-dependent reduction in TC, LDL-C and Lp(a) concentrations, as well as an increase in HDL-C concentration, and these effects are more prominent with oral administration.
- Transdermal rather than oral estrogens should be used in women with hypertriglyceridemia.
- Micronized progesterone and dydrogesterone have little or no effect on the lipid profile and may be preferred in women with dyslipidemia in need of a progestogen.
- Tibolone may decrease TC, LDL-C, TG and Lp(a) concentrations, but also the HDL-C concentration.
- Systemic MHT is not recommended as first-line therapy for dyslipidemia or for reducing the risk of cardiovascular disease.
- Low-dose vaginal estrogen and ospemifene exert a favorable effect on the lipid profile, but data are scant regarding DHEA.
- Non-oral testosterone, used for the treatment of HSDD, has little or no effect on the lipid profile.
- Fluoxetine and citalopram exert a more favorable effect on the lipid profile than sertraline, paroxetine and venlafaxine.

## Contributors

Panagiotis Anagnostis, Irene Lambrinoudaki and Margaret Rees prepared the initial draft, which was circulated to all other named

authors (EMAS board members) for comments and approval; production was coordinated by Irene Lambrinoudaki and Margaret Rees.

## Conflict of interest

Panagiotis Anagnostis: none declared.

Johannes Bitzer: In the past 3 years Prof. Bitzer has served on advisory boards of Bayer AG, Merck, MSD, Teva, Theramex, Mithra, Actavis, Ava, Natural cycles, Böhringer Ingelheim, Effik, Lilly, Exeltis, Vifor, Libbs, Gedeon Richter, HRA and has given invited lectures for and received honoraria from Bayer Pharma AG, Merck, Johnson and Johnson, Teva, Mylan, Allergan, Abbott, Lilly, Pfizer, Exeltis, Libbs, HRA, Pierre Fabre.

Antonio Cano: In the past 3 years, Dr Antonio Cano has received speakers' honoraria from Shionogi and consulting fees from Pierre-Fabre Iberica and Mitsubishi Tanabe Pharma.

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