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REVIEW

Tibolone in postmenopausal women: a review based on recent randomised controlled clinical trials

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Abstract
Aim. To critically discuss the use of tibolone (T), in light of a series of very recent double-blind placebo (PL) controlled trials (LISA, LIFT, OPAL, THEBES, LIBERATE) conducted worldwide in a large number of postmenopausal women (PMW).
Methods. The most relevant publications on T therapy in PMW were considered with emphasis on menopausal symptoms, quality of life, sexuality, bone, cardiovascular system (CVS) and oncologic risk.
Results. T significantly relieves climacteric symptoms and improves mood and sexual well-being (LISA). T is as effective as estrogen–progestin therapy in preventing bone loss and reducing the relative risk of vertebral and non-vertebral fractures (LIFT). By using surrogate endpoints of the individual risks for the CVS, studies show mixed results, but a favourable effect on acute miocardial infarction and thromboembolism has been documented (THEBES, LIFT, OPAL). Although findings about endometrial and colon cancer are reassuring, conclusive data on breast cancer risk with T are not available and an increased risk of recurrence in women with previous breast cancer emerged (LIBERATE).
Conclusions. T is effective in treating menopausal syndrome with a good tolerability profile. In spite of some unsolved issues in term of safety, T is still a good treatment option for early PMW.

Keywords: *Brain, bone, breast, endometrium, cardio-vascular system, urogenital tract, sexual function, well-being, STEAR*

Introduction

Tibolone (T) is a synthetic steroid available for prescription in postmenopausal women (PMW) in a variety of countries worldwide since 1988 and it has been used in over 1.5 million women-years. According to recent data, T has been classified as a selective tissue estrogenic activity regulator (STEAR) by acting differently in multiple tissues and organs (brain, bone, breast, endometrium, urogenital tract, cardiovascular system, etc.). On the other hand, T combines estrogenic, progestogenic and androgenic activity in a unique molecule because of its metabolites, each of which has peculiar properties in different tissues. Indeed, T is metabolised in the gastrointestinal tract to the 3α and 3β metabolites, which circulates predominantly in their inactive sulphated form and become estrogenically active when desulphated [1,2]. The global effect of T is, therefore, estrogenic in target organs. Indeed, T increases the vaginal maturation index and enhances vaginal health [3,4] offering relief from climacteric symptoms and bone protection as it occurs with conventional estrogen–progestin therapy (EPT) [1]. However, T itself and its 3β metabolite can be converted to a Δ^4-isomer which is able to bind and transactivate the progesterone receptor with a concomitant protection of the endometrium [5]. Finally, the Δ^4-isomer displays intrinsic capacity to activate the androgen receptor in many tissues [6]. That notwithstanding, the primary metabolic product in each tissue depends on the relative concentration of the enzymes that make the conversion locally. For example, human endometrial cells primarily convert T only to the Δ^4-isomer, thus the progestational action predominates

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in the uterus, while within the breast the effect of T is primarily on local enzyme activity that inhibits the formation of active estrogens.

The consequence of these tissue-specific properties is that T can provide the beneficial effects of estrogenic activity in the required target tissues as effectively as EPT, without exerting the detrimental effect of estrogen alone which require the use of additional progestogens to prevent for example endometrial hyperplasia. In addition, the androgenic properties of T may provide additional benefits on sexual well-being and mood.

We aimed at critically discuss in here the main available clinical evidences on the use of T for the treatment of climacteric symptoms in light of a series of very recent double-blind placebo (PL) controlled trials (LISA, LIFT, OPAL, THEBES, LIBERATE) conducted worldwide in a large number of PMW (Table I). By no means is it either a systematic review or a meta-analysis of all the available evidence, but it merely reflects the expert opinion of the authors on addressing efficacy and safety issues of T use in PMW.

Tibolone, menopausal symptoms, quality of life and sexuality

In Europe, we have a long-term experience with the use of T for the treatment of climacteric symptoms, including mood and sexual dysfunction. Indeed, besides the mild androgenic capacity of the Δ^4-isomer, it has been demonstrated that T reduces sex-hormone binding globulin (SHBG) and, hence, increases bioavailable testosterone, estradiol (E2) and dehydroephiandrosterone-sulphate (DHEA-S) [12]. T exerts also positive neuroendocrine effects by improving the opioidergic and serotoninergic tone to the same extent observed with EPT [13] and significantly increases allopregnanolone, a steroid with sedative and anxiolytic properties, without reducing, unlike estrogen-based therapy, the adrenal function in the menopause [14]. The net result is to maintain a hormonal milieu which is favourable to sexual and mental well-being.

Some years ago, Modelska and Cummings [15] reviewed extensively the clinical effects of T (2.5 mg/ day) in PMW demonstrating a significant reduction in hot flushes and sweating in women taking T in comparison with PL. In addition, when the effects of T on hot flushes were compared with the effects of EPT, the reduction of hot flushes was similar. Many trials reported a beneficial effect of T also on fatigability, frequency of headaches, psychological instability and insomnia. Interestingly, in postmenopausal headache sufferers, analgesics were more effective in alleviating severe head pain when women were treated with T in comparison with low-dose EPT for climacteric complaints [16]. Another comprehensive review by Davis [13] indicated that

T has positive effects on mood compared with PL and alleviates several adverse mood parameters to a similar extent as EPT. With respect to cognition, T seems to improve semantic memory but does not significantly improve recognition memory. More recently, a multicentre, randomised, double-blind, PL-controlled study demonstrated the safety and efficacy of two doses of T (1.25 and 2.5 mg) in the treatment of moderate to severe vasomotor symptoms and symptoms associated with vaginal atrophy confirming the usefulness even of low dose [17].

As far as the effect of T on sexual functioning after menopause is concerned, in randomised studies against PL [18] or oral E2 (2 mg/day) plus NETA (1 mg/day) [19] T treatment (2.5 mg/day) alleviates vaginal dryness and dyspareunia, ameliorating sexual desire, arousal and sexual satisfaction significantly more than EPT. Moreover, T shows a positive effect on sexuality which is superimposable to that observed with estro–androgenic preparations [20]. This data, together with the observation that 6 month of T treatment significantly increased vaginal pulse amplitude at baseline and following erotic stimulation against PL [21] and modulated clitoral circulation in PMW with desire and arousal disorders improving sexual function [4], further supports the notion that such tissue-specific compound may be consider a good therapeutic option to relief female sexual dysfunction (FSD) in naturally PMW, due to both its estrogenic and androgenic properties. In addition, T may be even useful in surgical menopause by improving mood, sexual desire and somatic symptoms to a greater extent than estrogen therapy (ET) alone [22] and its progestogenic activity may be useful when surgical menopause is consequent to estrogen-dependent conditions to avoid the risk of recurrence or malignant transformation related to the use of unopposed estrogens [23].

Even in older PMW, half dose T (1.25 mg/day) treatment has shown a trend towards an improvement in quality of life (QoL) and sexuality when compared to raloxifene (RLX, 60 mg/day) in a double-blind, randomised study conducted in osteopenic, but otherwise healthy subjects (mean age 66 years) treated for 2 years. No difference could be assessed between the T and RLX group in mean total score and separate domains' scores of the McCoy Female Sexual Questionnaire (MFSQ), except for the vaginal lubrication domain [24]. Very recently, a multicentre, double-blind, randomised, clinical trial was performed to compare the efficacy on sexual function of T (2.5 mg) to continuous combined transdermal E2/NETA (50 mcg/140 mcg) in naturally PMW with FSD (*N*: 403; mean age: 56 years) (LISA study) [7]. Both treatments resulted to improved overall sexual function, as determined by scores on the Female Sexual Function Index (FSFI), an increase in the frequency of sexual events, and a

Table I. Double-blind placebo (PL) controlled trials (LISA, LIFT, OPAL, THEBES, LIBERATE) recently conducted worldwide in PMW.

	Study design	Population	Study endpoints	Results
LISA study Nijland et al., 2008 [7]	Double blind randomised Treatment: 1. Tibolone 2.5 mg/day 2. Transdermal E2/NETA (50 μg/140 μg) Duration 24 weeks (June 2004–Nov2005)	403 naturally postmenopausal Women with sexual dysfunction Mean age 56 A total of 29 study centres in US, Australia, 6 in Europe	FSFI assessment at baseline, week 12 and week 24 To compare the efficacy on sexual function	Both therapies improved sexual function The increase in the FSFI scores was significantly larger in the tibolone group at week 24 The incidence of adverse events was comparable between the two groups; bleeding profile resulted to be better with tibolone
OPAL study Bots et al., 2006 [8]	Three-arm randomized placebo controlled double blind to determine 1. Tibolone 2.5 mg/day 2. CEE/MPA 0.625/2.5 mg/day 3. Placebo Duration: 3 years	866 healthy post-menopausal women from 6 US and 5 European centres Age 45–79	Arterial effect of tibolone: 1. Progression of carotid intima-media thickness (CIMT) 2. Change in meanMax CIMT	In tibolone and CEE/MPA groups significantly higher then placebo HDL cholesterol increased in CEE/MPA group and decreased in the tibolone group no statistically significant differences between groups
LIFT study, Cummings et al., 2008 [9]	Randomised double blind placebo-controlled Treatment: 1. Tibolone 1.25 mg/day 2. Placebo Recruitment: July 2001–June 2003 Duration: 3 years	4538 postmenopausal women with a BMD T score of ≤ -2.5 at the hip or spine Mean age 68	1. Annual spine radiographs were used to assess for vertebral fracture 2. Rates of cardiovascular events 3. Rates of cancer events	Decreased risk of vertebral fracture Decreased risk of non-vertebral fracture Increased risk of stroke (for which the study was stopped in Feb 2006) No differences in the risk of either coronal heart disease or venous thromboembolism Decreased risk of invasive breast cancer Decreased risk of colon
THEBES study, Archer et al., 2007 [10]	Randomised double blind comparative Treatment: 1. Tibolone 1.25 mg/day 2. Tibolone 2.5mg/day 3. Combined CEE/MPA (0.625/2.5 mg/day) in a 1:1:2 ratio Duration: 2 years	3240 healthy postmenopausal women Mean age 54.5 years; BMI ≥ 18 A total of 146 centres: 73 US and 69 Europe and 4 Chile	1. Endometrial safety: incidence of hyperplasia and/or carcinoma at 1 y or 2 y endpoints 2. Vaginal bleeding pattern Additional observations:	No cases of hyperplasia or carcinoma in either tibolone group. 2 cases of endometrial hyperplasia and1 case low grade of stromal sarcoma in the CEE/MPA group Tibolone is associated with a better vaginal bleeding profile then CEE/MPA Incidence of breast pain was significantly lower in the tibolone group No stroke was reported in the tibolone group
LIBERATE study, Kenemans et al., 2009 [11]	Randomised, placebo controlled double blind parallel group Treatment: 1. Tibolone 2.5 mg/day 2. Placebo Recruitment: July 2002–Dec 2004	3098 women surgically treated for histologically confirmed breast cancer with vasomotor symptoms Mean age 52.7 years Mean time since surgery 2.1 years 245 centres in 31 countries	Safety of tibolone in: 1. Breast cancer recurrence 2. Vasomotor symptoms, BMD, HRQL	15.2% women on tibolone had cancer recurrence, compared with10.7% on placebo Study was stopped 6 months before planned NB risk of recurrence with tibolone was more evident in women with ER positive tumor status Overall significant improvement with tibolone compared with placebo Tibolone was not different from Tibolone was not different from safety outcomes

reduction in sexuality-related personal distress. Indeed, transdermal E2/NETA can be considered the best EPT to treat PMW complaining of FSD because it does not change significantly SHBG and the bio-availability of sex hormones into the general circulation [25]. However, in the per protocol analysis, but not in the intent-to-treat analysis, the change from baseline for the composite subscore of the arousal, desire and satisfaction domains was significantly larger in the T group when compared with the E2/NETA patch group at week 24 supporting previous evidence of a positive effect of T on sexual symptoms. The bleeding profile was better with T in comparison with E2/NETA [26]. That being so, Nappi and Polatti [25] recently reinforced the idea that T may be a suitable therapeutic option in those PMW specifically suffering from FSD, as already proposed by Kenemans and Speroff [1]. Indeed, few years ago an international multidisciplinary panel of experts proposed a number of subgroups of PMW with vasomotor symptoms in whom T might have added value, including not only women with sexual complaints, but also women with mood disorders, fibroids and urogenital symptoms, as well as those with breast tenderness or high mammographic breast density with EPT use [1].

Tibolone and bone

T acts as an estrogen on bone, as only an antiestrogen (not an antiandrogen nor an antiprogestogen) was shown to be able to decrease its effect in experimental model [27] and may be considered a suitable option, as effective as EPT, in preventing bone loss in healthy PMW. Indeed, at dose 2.5 mg/day, T improved bone mineral density (BMD) to a similar degree in comparison with conjugated equine estrogens (CEE) 0.625 mg/day plus medroxyprogesterone acetate (MPA) 2.5 mg/day (OPAL study) [28]. In dose-finding evaluation, T seems to be active on bone at 0.625 mg/day, 1.25 mg/day and 2.5 mg/day in a 2-years study, with a significant difference *versus* PL in increasing spine and total hip BMD and in decreasing bone markers levels (with a variation indicating overall a decreased rate of bone resorption) for all groups of active treatment from baseline [29]. Interestingly, the effect of T on bone tissue was maintained also in long-term period [30], without loss of pharmacological activity over time. At dose 1.25 mg/day, T can prevent postmenopausal bone loss in older women with a larger increase of BMD at lumbar spine and hip in comparison with RLX 60 mg/day [31]. T can even prevent bone loss due to Gonadotropin releasing hormone (GnRH)-agonist administration in young women [32]. Overall, several randomised, PL- and active-controlled studies have shown that T is effective in preserving and/or increasing BMD and preventing bone loss and osteoporosis [33,34] in early and late PMW and even

when osteoporosis is already established [35]. T (1.25 mg/day), in comparison with PL, can decrease the relative hazard of osteoporosis-related vertebral and non-vertebral fractures in older PMW during a median of 34 months of treatment (LIFT study) [9]. In particular, the extent of the reduction in relative risk of vertebral fractures was similar to those observed for therapy with estrogens, bisphosphonates, and RLX, while the magnitude of the reduction in relative risk of non-vertebral fractures was similar to that reported with ET. Such study enrolled 4538 women, who were between the ages of 60 and 85 years and had a BMD T score of −2.5 or less at the hip or spine or a T score of −2.0 or less and radiologic evidence of a vertebral fracture. Unfortunately, it was prematurely stopped due to an increase of relative hazard of stroke (2.19; 95% confidence interval: 1.14–4.23; $p = 0.02$) in the T group (mean age: 68.3 ± 5.2) in comparison with PL group (mean age: 68.2 ± 5.2). On the other hand, another study (THEBES study) [10] conducted in 3224 women treated with T 1.25 mg/day, 2.5 mg/day, or CEE 0.625 mg/day plus MPA 2.5 mg/day with the primary endpoint of demonstrating endometrial safety, did not report any stroke in the T group (1598 subjects treated with 1.25 mg/day or 2.5 mg/day for 2 years; mean age: 54.5 ± 4.4 years). These data seem to suggest a critical role for age in determining stroke relative risk similarly to EPT, since the population recruited in THEBES study was younger. Moreover, in the LIFT study the population had osteoporosis or osteopenia and vertebral fracture, well known risk factors for cardiovascular disease [36–38]. These data have to be considered in the decision-making process about the prescription of T.

Tibolone and cardiovascular system (CVS)

CRP and inflammatory markers

Conflicting data are available on the effects of T on CRP and other inflammatory markers [39–42]. In a randomised, double-blind, PL-controlled, crossover study T did not significantly increase CRP levels, unlike a conventional dose of EPT, suggesting no induction of inflammation in healthy PMW [39,40]. Recently, Sezer Ozer et al. showed a significant increase of CRP and a reduction of hepatocyte growth factor and TNF in PMW aged 47–52 years [43], while Vural et al. have previously shown that the postmenopausal increase of plasma TNFα, IL-4, IL-10, IL-12 is not reversed by T probably due to its progestogenic and androgenic properties [44].

Atherosclerosis and lipids

T showed favourable effect on atherosclerosis protection in the animal model. Indeed, cholesterol-fed

ovariectomised rabbits were protected from atherosclerosis by T supplementation which completely prevented atherogenesis in the arterial wall by reducing the accumulation of cholesterol, the fatty streak formation, the impairment of endothelium-dependent response, and the advanced lesion formation after endothelial damage. A substantial part of these beneficial effects were plasma lipid independent, because T reduces HDL cholesterol levels by about 20–30% [45]. Findings from a long-term experimental study in postmenopausal monkeys treated with T indicated that, despite reduction in plasma levels of HDL-cholesterol (at least as great as seen in PMW), there was no induction of coronary artery atherosclerosis [46]. T has some beneficial effects on lipid profile such as a reduction of total cholesterol, LDL cholesterol, and lipoprotein (a) levels. Furthermore, it has been reported that T, despite decreasing HDL cholesterol levels in healthy PMW, significantly reduced the triglyceride/HDL cholesterol ratio, which is a powerful predictor of insulin resistance and CAD risk [39]. Moreover, the lowering of HDL cholesterol by T was not associated with changes in cholesterol efflux capacity or para-oxonase activity, indicating that antiatherogenic effects of HDL remained unchanged [47]. Thus, despite the complex effects on lipid profile, T appears to exert antiatherogenic properties.

Endothelial function

Simoncini et al. showed that the Δ^4 isomer had a neutral effect on nitric oxide (NO) synthesis, which implies that the effect of T on endothelial NO production is likely to be mediated by estrogen receptors [48]. On the other hand, T active metabolites induce also a rapid nongenomic activation of NO synthase produced via MAPK pathway, as well as an upregulation of the expression of the enzyme protein [48]. Therefore, like estrogens, T was found to exert dual, genomic and nongenomic actions that influence NO synthesis. It has not been possible to determine which of these two mechanisms is responsible for T-induced increase in NO production in clinical studies. T is likely to increase NO release by means of both non-genomic and genomic effects via an estrogen receptor-dependent mechanism [49]. T and its 3α and 3β metabolites have also been shown to exert direct vascular anti-inflammatory actions and to inhibit leukocyte adhesion molecule expression in human endothelial cells [50]. Moreover, in healthy PMW T reduced serum levels of vascular cell adhesion molecules [51] and significantly decreased endothelial expression of sE-selectin, sL-selectin, and sPECAM-1 after 8 weeks of treatment [52].

Collectively, these data suggest that T might exert additional, lipid-independent, cardioprotective effects by reducing leukocyte adhesion molecule expression in endothelial cells, and by the activation of NO production.

Peripheral and coronary arteries

In clinical studies, the effects of T on peripheral and coronary arteries are controversial. Some studies confirmed that T significantly improved flow-mediated brachial artery dilator response by a magnitude similar to conventional EPT [39,53], while others did not [54,55]. The effects of T on the carotid arteries have also been investigated. In healthy PMW, 3 months of T decreased the intima-media thickness (IMT) of the carotid artery by 28% [56]. As assessed by Doppler ultrasonography, T reduced the thickness and length of carotid ather-omatous plaques and the degree of vascular stenosis [57]. However, the OPAL study showed increased progression of common carotid intima-media thickness (CIMT) [8]. This study enrolled 866 healthy postmenopausal women from six US and five European centres into one of three arms: tibolone 2.5 mg/day, conventional EPT (CEE/MPA) or PL for 3 years. The primary outcome was change in CIMT; mean maximum CIMT progression was a secondary outcome. Annual common CIMT rates were significantly higher in the T and EPT groups as compared to PL, but there were no significant differences between all three groups in mean maximum CIMT progression rates. Thus, neither CEE/MPA nor T favourably affected atherosclerosis in healthy PMW. However, differences in annual common CIMT progression translate into a relative risk of CAD of 1.47% per year, which is less than that observed in the WHI study with EPT (average annual increased risk of 4.6%). Furthermore, different outcomes were observed between US and European women enrolled in this trial; indeed, no changes in CIMT were found vs. PL and EPT in the US women [58]. There was, however, evidence that T may possess anti-ischemic effects. Indeed, a prospective randomised open-label pilot study performed in PMW with ischemic heart disease demonstrated that 6 months of T significantly improved stress myocardial perfusion defects, as well as the 'amount of ischemia' as assessed by SPECT imaging [59]. Thus, T may exert a favourable effect on CV secondary prevention by improving myocardial perfusion in PMW with cardiac perfusion defect.

Coagulatory system

Even data of the effects of T on the coagulatory system are not univocal [60]. The potential benefits were related to a decrease in fibrinogen, Factor VII, plasminogen activator inhibitor 1 (PAI-1) and tissue plasminogen activator. Such tendency towards fibrinolytic activity in the haemostatic system seemed

to be related to the androgenic effect of T [61,62]. On the other hand, the potential procoagulant effects were related to a decrease in antithrombin III and an increase in fibrin degradation products (D-dimer) [1,63]. However, no change in antithrombin III has been also documented [39], as well as an increase of tissue-type plasminogen activator activity and a parallel decrease of plasminogen activator inhibitor activity after 1 year T [64].

Nevertheless, it is important to underline that T does not increase the risk of venous thromboembolism, as confirmed from the more recent randomised controlled trials (LIFT study and THEBES study) [9,10].

Acute myocardial infarction and stroke

In a National cohort study, it has been confirmed that regimen and route of administration could modify the influence of hormone therapy (HT) on the risk of acute myocardial infarction (AMI). No increased risk was found with unopposed oestrogen, cyclic combined therapy, or T [65]. The difference in risk between continuous combined therapy *vs.* cyclic combined therapy, and *vs.* T was significant ($p < 0.001$ and < 0.007, respectively) [66]. Moreover, in a population-based cohort and case–control study, nested within a cohort of EPT and T users, results were consistent in supporting the hypothesis that the use of HT was associated with a decrease in risk of AMI. Case fatality differed between EPT users and non-users, suggesting a protective effect of EPT. The use of EPT was associated with a statistically significant decrease in risk for AMI in PMW. This association was seen for both oral and transdermal EPT and for all regimens, although this was not significant for combined–continuous EPT or T [67].

The THEBES study considered cardiovascular events (myocardial infarction, stroke, venous thromboembolism and pulmonary embolism) as secondary endpoints. In total, two adjudicated cardiovascular events have been observed in the combined T groups *vs.* eight in the CEE/MPA group. These findings regarding cardiovascular events are reassuring, but no statistical analysis was performed because these events were rare and the study was not designed to evaluate adverse outcomes between groups [10]. However, it is important to remark that no venous, pulmonary thromboembolism and stroke events were recorded in this study. Absence of thromboembolism (no cases with T *vs.* three in CEE/MPA) may distinguish between estrogen-based compounds and T, supporting the different effects of these compounds on the haemostatic system [67]. In the LIFT study, it was also planned to assess the risks of breast cancer, cardiovascular disease and endometrial cancer after 5 years of treatment with 1.25 mg/day of T. As reported above, during treatment period, the T

group, as compared with the PL group, had an increased risk of stroke (relative hazard, 2.19; 95% CI, 1.14–4.23; $p = 0.02$), for which the study was stopped in February 2006 [9]. In this study, women between the ages of 60 and 85 years were randomly assigned to receive either 1.25 mg of T or an indistinguishable PL once daily (2249 in the T group and 2257 in the PL group). Among patients 70 years of age or older, the risk of stroke was 6.6 per 1000 person-years for T and 3.4 per 1000 person-years for PL (difference in absolute risk, 3.1 per 1000 person-years), while among those between the ages of 60 and 69 years, the risks were 2.8 and 1.0 per 1000 person-years, respectively (difference in absolute risk, 1.8 per 1000 person-years). The increased risk of stroke appeared to be greater in the first year (relative hazard, 4.1) than in later years (relative hazard, 1.6), but the treatment-by-time interaction was not significant ($p = 0.23$). Overall, the number of adverse events was small and there was no increased risk of venous thromboembolism, as it has been seen with EPT and SERMs, nor an increased risk of coronary events, as it has been seen with CEE combined with MPA [10,68].

Similarly to the WHI [69], the women population enrolled was old and therefore at a major risk of ischemic events. Nonetheless, in contrast with the WHI, no increase of thromboembolic events and AMI has been found. However, T is associated with an increased risk of stroke in elderly women and therefore should not be used in older women with risk factors for stroke.

A more recent case–control study has been conducted within the cohort of eligible women in the UK General Practice Research Database consisting of all women aged 50–79 between 1 January 1987 and 31 October 2006 without history of stroke prior to cohort entry. All cases of stroke, ischemic or haemorrhagic, occurring during the study period were identified using diagnostic codes referring to these events and 15,710 cases and 59,958 randomly selected matched controls were studied in the analysis. The mean age of cases and controls at the index date was 70 years. The mean duration of follow-up in the up-to-standard practice was 6.7 years for the cases and 6.6 years for the controls. All CV risk factors were more frequent in case patients than in control subjects. Interestingly enough, it has been found no evidence of an elevated risk of stroke associated with T, although the low number of subjects using T did not permit to rule out a small risk [70].

Tibolone and oncologic risk

Breast cancer

Results from several epidemiological studies as the Women's Health Initiative (WHI) [69,71] and the

Million Women Study (MWS) [72] have raised concerns regarding safety and adverse effects of conventional EPT on breast cancer risk [73]. A significant decline in HT use following the publication of these studies was reported worldwide [74,75].

In breast tissue, the 3β metabolites of T strongly inhibits the enzyme sulphatase, blocking the conversion of estrone sulphate to estrone [76]. The reduction of bioactive estrogen induces inhibition of proliferation and stimulates apoptosis and differentiation in breast cancer cells [77]. These data support a potential lower risk of breast cancer with T, as compared to conventional EPT [15]. Indeed, T has little influence on mammographic density, probably due to lower plasma estrogen levels [78,79]. An increase of breast density may cause diagnostic difficulties and delay in detecting early breast cancer. Moreover, incidence of breast tenderness and mastalgia with T is significantly lower than in EPT users [1,80].

However, data on breast cancer risk in PMW treated with T are not univocal. Between 1996 and 2001, 1,084,110 postmenopausal women were enrolled in the MWS in the UK. This cohort study found a relative risk (RR) for breast cancer of 1.45 (1.25–1.68, $p < 0.0001$) in women treated with T; this association was similar to that seen for unopposed ET (RR 1.3), but significantly less than that noted with EPT (RR 2.0) [72]. Many criticisms followed the publication of the MWS, because the findings were at variance with most of the studies comparing the risk of breast cancer in HRT users. MWS reported a significantly higher RR in EPT group as compared with other trials results; moreover, it showed an increase in the RR for breast cancer in women exposed to T and ET alone, in contrast to subsequent studies, which demonstrated no increase in the risk. These differences could be attributed to changing from prior EPT: the increased RR seen in the MWS among users of T or ET was probably the result of previous EPT exposure, since 30% of the enrolled women had used more than one formulation of EPT [81,82]. Notelovitz suggested other limitations of MWS which could have affected outcomes: preferential prescribing of T to higher-risk patients, because T is regarded to be a safer alternative (Danish Nurse Cohort Study), inadequacy in assessing breast cancer presence at baseline or in defining genetic predisposition of women prior to initiating therapy [78]. Data from MWS were also in contrast with findings of a large case–control study, based on the UK General Practice Research Database (GPRD). Matching 6347 cases with 31,516 controls, the authors reported no increased risk with T (RR 0.86; 95% CI 0.65–1.13) or ET (RR 0.97; 95% CI 0.86–1.09), while an increased rate of breast cancer was confirmed for sequential EPT (1.33; 95% CI 1.23–1.44) [73]. Such a result is consistent with

that suggested in the LIFT study [9]. The primary outcome of the LIFT was to assess the effect of T in reducing risk of vertebral and clinical fractures in more than 4500 PMW (60–85 years) with poor bone mass density. Secondary endpoints were to determine the risks of breast cancer, cardiovascular disease and endometrial cancer after 5 years of therapy. The T group had a decreased risk of invasive breast cancer (relative hazard, 0.32; 95% CI, 0.13–0.80; $p = 0.02$) and colon cancer (relative hazard, 0.31; 95% CI, 0.10–0.96; $p = 0.04$).

Endometrial cancer

The effect of T on human endometrial tissue was well explained by its intrinsic progestogenic properties. In addition, T is locally converted into the Δ^4-isomer by 3β-OH steroid dehydrogenase isomerase, which prevents endometrial proliferation and hyperplasia; finally, it stimulates sulphotransferase enzymes and induces the inhibition of sulphatase, causing a further reduction in estrogenic activity in the endometrium [5,83]. The International Tibolone Consensus Group highlighted the good profile of tolerability which is associated with a better vaginal bleeding control as compared to EPT, especially in the first 6 months of therapy [1].

A multicentre randomised trial conducted by Hammar et al. [84] on 572 healthy symptomatic PMW confirmed a significant lower incidence of bleeding with T in comparison with low-dose continuous combined EPT (18.3 *versus* 33.1%), which partially explained the higher adherence of women to T therapy.

Conflicting data about endometrial cancer are reported in the published studies.

In the MWS, authors observed 1320 cases of invasive endometrial cancer after a mean follow up of 3.4 years in 716,738 postmenopausal women treated with different EPT formulations. A significant increased RR of developing endometrial cancer in T group was seen (RR = 1.79; 95% CI: 1.43–2.25). This unexpected finding must be carefully interpreted because T was selectively prescribed to women with a prior history of unopposed ET use and with an increased risk of endometrial cancer, when compared to EPT group [81,82].

Strikingly different data on endometrial safety of T and vaginal bleeding profile were reported in the THEBES study [10]. Endometrial pattern and thickness of 3240 PMW enrolled in this study were assessed by biopsy and transvaginal ultrasonography (TVUS) at baseline and after 2 years of treatment with T or EPT. Endometrial hyperplasia occurred in two women receiving EPT and did not occur in those given T. No cases of endometrial cancer were reported in both groups; one woman assigned to EPT group developed an endometrial stromal

sarcoma during treatment. T users did not show a significant increase in double-wall endometrial thickness and a better tolerability of T compared to EPT was confirmed. These findings were consistent with the results of another randomised, PL-controlled clinical trial (OPAL study) [85], whose secondary objective was to assess the effects of T, continuous combined EPT and PL on the endometrium. The incidence of endometrial proliferation was 1.4%, 4.8%, 0%, for T, EPT and PL group, respectively, while cancer was assessed in 1 case for T and 1 in PL.

Colon cancer

Promising data about colon cancer risk and T came from the LIFT study. It demonstrated in 4538 elderly postmenopausal women that the use of T for 5 years was associated with a decreased risk of colon cancer (relative hazard, 0.31; 95% CI, 0.10 to 0.96; $p = 0.04$) [9]. This positive effect could be explained with the lower blood levels of insulin and insulin-like growth factor-1, the decreased production of potentially carcinogenic bile acids and proliferation of intestinal epithelial cells due to T use [86]. Similar results were reported in the WHI study for EPT users but not for unopposed ET [71]. However, the reduction of colon cancer risk with T needs to be widely assessed in other future studies.

Breast cancer survivors

To test T safety in women with history of breast cancer has been an intriguing research topic since more than 10 years. Many of breast cancer survivors suffer from climacteric symptoms, such as hot flushes and sweats, which result directly from the use of chemotherapy or hormone therapy with tamoxifen and GnRH agonists. Conventional ERT is considered to be contraindicated because of the risk of recurrence [87]. The HABITS (Hormonal replacement therapy After Breast cancer – is IT Safe?), a randomised trial to evaluate whether HRT was safe for women with previous breast cancer, was prematurely stopped: the risk of recurrence was significantly higher amongst women receiving HRT than amongst those with no therapy for climacteric symptoms (relative hazard 3.3; 95% CI 1.5–7.4) [88]. Antidepressants, including venlafaxine or mirtazapine, and gabapentin have been used for the relief of hot flushes, but there are no data on the long-term use of these drugs [89].

T has been considered as a good alternative for breast cancer women, due to the promising results of several small studies [90,91]. A prospective, randomised, PL-controlled trial was planned (LIBERATE) [92] to establish the safety of T in women treated for breast cancer with climacteric complaints; secondary endpoints were mortality, vasomotor symptoms, BMD and health-related quality of life. Unfortunately, the LIBERATE trial was stopped prematurely because of an increased risk of recurrence with T use [relative hazard 1.40 (1.14–1.70; $p = 0.001$)] [11]. The risk for recurrence with T was more evident in women with ER-positive tumour status than in women with an ER-negative tumour status and in women receiving aromatase inhibitors as compared to women treated with tamoxifen.

Conclusions

In conclusion, T significantly relieves climacteric symptoms and improves mood and sexual well-being (LISA study) with a good tolerability profile in PMW. T is as effective as EPT in preventing bone loss and reducing the relative risk of vertebral and non-vertebral fractures (LIFT study). It is not recommended to start T in older PMW (> 60 years of age) to prevent or treat osteopenia/osteoporosis because of the small but significant risk of stroke. Further studies on the risk of stroke are, however, needed in younger PMW.

Experimental and clinical studies have been conducted with the aim of assessing whether T might be beneficial for the CVS. Some surrogate endpoints of the individual risks have been considered with mixed results. However, it is worth to mention that clinical endpoint data collected in a high number of PMW treated with T (THEBES, LIFT, OPAL studies) are currently available and confirm a favourable effect on AMI and thromboembolism.

Conclusive data on breast cancer risk with T are not available, while an increased risk of recurrence in patients with previous breast cancer emerged from the LIBERATE study. Findings about endometrial and colon cancer are reassuring.

Collectively, we believe that, even though there are still some unsolved issues in term of safety, the recent randomised clinical trials confirm T as still a good treatment option for early PMW.

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