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**Abstract**

Hormone therapy (HT) is the most effective treatment for correcting menopausal symptoms after menopause. HT initially consisted of estrogens alone and progestogens were secondly added to estrogens for preventing the risk of endometrial cancer associated to estrogens use. Venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism, is a major harmful effect of HT. It is now well known that oral and transdermal estrogens are differentially associated with VTE risk but progestogens may be another important determinant of the thrombotic risk among HT users. Both randomized controlled trials and meta-analysis of observational studies suggested that the VTE risk was higher among users of estrogens plus progestogens than among users of estrogens alone. With respect to the different pharmacological classes of progestogens, there is evidence for a deleterious effect of medroxyprogesterone acetate on VTE risk. In addition, observational studies showed that norpregnane derivatives were significantly associated with an increased VTE risk whereas micronized progesterone could be safe with respect to thrombotic risk. The effect of tibolone on VTE risk remains uncertain. In conclusion, progestogens may have differential effects on VTE risk according to the molecules and therefore represent an important potential determinant of the thrombotic risk among postmenopausal women using estrogens.

## Introduction

After menopause, many women suffer from postmenopausal symptoms associated with the decline of endogenous estrogens levels due to the cessation of ovary activity. Postmenopausal hormone therapy (HT) has been introduced in the 50' for correcting climacteric symptoms, vaginal dryness and depression. Initially, HT exclusively consisted of an estrogenic compound and in 70', progestogens were added to estrogens to reduce the increased risk of endometrial hyperplasia and cancer associated with estrogens therapy (ET) [1]. Currently, women may be prescribed several molecules including natural progesterone and synthetic compounds which have very different pharmacological effects.

Venous thromboembolism (VTE), either deep vein thrombosis or pulmonary embolism, is a main harmful effect of HT among postmenopausal women [2-4]. For about 10 years, epidemiological data have shown a differential association of oral and transdermal estrogens with the VTE risk among postmenopausal women [5-8]. Indeed, oral estrogens increase the VTE risk while transdermal estrogens appear to be safe with respect to thrombotic risk [4, 9]. More recently, the type of progestogens has also emerged as another important determinant of the thrombotic risk among HT users [6, 7, 9-11].

This review focuses on the different progestogens pharmacological classes in relation to VTE risk among postmenopausal women, including the current knowledge regarding the effect of progestogens on relevant haemostatic variables (prothrombin fragment 1+2 (F1+2) and Ddimers) as well as on activated protein C resistance (APCr), a validated surrogate marker of VTE.

**Different pharmacological classes of progestogens**

Progestogens include both progesterone, the physiological molecule synthesized and secreted by ovary, and synthetic compounds named progestins which derived from either progesterone (pregnanes and 19-norpregnanes) or testosterone (19-nortestosterone) [1]. Pregnanes derivatives consist of several molecules including dydrogesterone, medrogestone, chlormadinone acetate, cyproterone acetate and medroxyprogesterone acetate (MPA). Norpregnane derivatives include nomegestrol acetate, promegestone, trimegestone and nestorone. Finally, nortestosterone derivatives consist of ethinylated derivatives, non ethinylated derivatives, spironolactone derivatives and tibolone. Nortestosterone ethinylated derivatives are composed of estranes, including especially norethisterone acetate (NETA) and of gonanes which are preferentially used in contraceptive pills [1]. Nortestosterone non ethinylated derivative is dienogest and the spironolactone derivative is drospirenone. In European countries and especially in France, women are prescribed a wide variety of progestogens while MPA and some specific testosterone derivatives are the almost exclusive progestogens used in Anglo-Saxon countries [12].

Progestins have different pharmacological properties depending upon the parent molecules which they are derived and the metabolites they product (especially for nortestosterone derivatives). In addition, changes in progestogen effect occur according to the administered daily dose. Very small structural changes may induce considerable differences in the progestin activity (Table 1). The effects of progestins are related to interactions with the progesterone receptors but also with other steroid hormone receptors such as estrogens receptors, androgens receptors, glucocorticoid and mineralocorticoid receptors [13, 14]. These interactions may either induce or prevent the transactivation of steroid receptors. Therefore, the balance between the receptor coactivators and corepressors recruited by a progestin determines whether the overall effect of a molecule will be agonistic or antagonistic for each hormonal effect [15]. For example, some of progestins have a high antiandronegic activity and others possess progestogenic effect with antiestrogenic actions.

**Progestogens and venous thromboembolism: clinical data**

*Estrogens alone versus Estrogens plus progestogens*

Since 1996, several observational studies have separately assessed the impact of unopposed estrogens and estrogen-progestogen therapy (EPT) on VTE risk among postmenopausal women. In these analyses, women used oral estrogens and no distinction was made between the different types of progestogens [5, 8, 16-19]. Using a random-effect model meta-analysis as previously described [4, 9], the overall VTE risk was 1.7 (95% Confidence Interval (CI):1.3-2.2) for ET use and 2.3 (95%CI: 1.7-3.2) for EPT use (figure 1). Despites a non significant difference between these two overall risk ratios (p=0.15), this result showed that the VTE risk would be more elevated among EPT users as compared to ET users, suggesting a thrombogenic tendency of progestogens when associated to estrogens. However, no attempt was made in these studies to distinguish whether the different progestogens had the same influence on VTE risk.

*Different types of progestogens*

For many years, the association of VTE risk with the different pharmacological classes of progestogens has not been a mainstream topic for clinical investigations. Analysis of two randomized controlled trials allowed assessing the effect of MPA on VTE risk. On one hand, an indirect comparison of the Women's Health Initiative (WHI) clinical trials showed that the association of estrogens plus progestogens was more thrombogenic than unopposed estrogens [10, 20]. Indeed, compared to placebo, the VTE risk was 2.09 (95% CI: 1.59-2.74) and 1.34 (95% CI: 1.01-1.77) among HT users in the Estrogen plus Progestogen clinical trial and in the Estrogen alone clinical trial, respectively and this difference in VTE risk was statistically significant (CEE/CEE+MPA: 0.59; 95%CI: 0.37-0.94; p=0.03) [10]. On the other hand, the Women's International Study of long Duration Oestrogen after Menopause (WISDOM) trial has recently provided a direct comparison of the effect of conjugated equine estrogens (CEE) alone and CEE plus MPA on VTE risk among postmenopausal hysterectomised women [11]. Results showed that users of CEE plus MPA had a higher thrombotic risk than did women treated by CEE alone but this

difference in VTE risk did not reach the signification (Hazard ratio=2.39, 95%CI: 0.62-9.24, p=0.19).

With regard to the other progestogens, the ESTHER (EStrogen and THromboEmbolism Risk) Study, a French case/control study of VTE among postmenopausal women, was the first to establish a differential association of VTE risk with the different progestogen subgroups irrespective of the route of estrogens administration [6]. Results showed that micronized progesterone and pregnane derivatives might be safe with respect to thrombotic risk (OR=0.7; 95%CI: 0.3-1.9 and OR=0.9; 95%CI: 0.4-2.3, respectively) while norpregnane derivatives were associated with a significant increase in VTE risk (OR=3.9; 95%CI: 1.5-10.0). This study was the first to suggest that the type of progestogens could be a determinant of VTE risk as important as the route of estrogens administration among postmenopausal HT users. Few years later, the VTE risk by route of estrogens administration and type of progestogens among postmenopausal women has been further assessed in the E3N study (Etude Epidémiologique de l'Education Nationale), a large prospective French cohort study [7]. These results confirmed that the impact of progestogens on VTE risk was different according to the pharmacological classes. In this study, micronized progesterone was not associated with an increased VTE risk (OR=0.9; 95%CI: 0.6-1.5) while norpregnane derivatives could be thrombogenic (OR=1.8; 95%CI: 1.2-2.7). Nevertheless, uncertainty remained regarding the impact of pregnane and nortestosterone derivatives on VTE risk (OR=1.3; 95%CI: 0.9-2.0 and OR=1.4; 95%CI: 0.7-2.4, respectively), in part due to the lack of statistical power for subgroups analysis.

Despite their unquestionable interest, these results have to be cautiously interpreted since they have been obtained in observational studies which were subject to bias. In particular, a selection bias might have occurred due to the differential prescription of progestogens according to the estrogenic status of women using HT. Norpregnane derivatives are potent progestogens with antiestrogenic activity. Women with moderate to severe hyperestrogenic symptoms, such as breast tenderness or endometrial diseases, may be more likely to be prescribed these types of progestogens [21, 22]. Because there is evidence that lifetime estrogen exposure is positively related to VTE in postmenopausal women [23], this prescription bias could partly explain the increase in thrombotic risk among women using such antiestrogenic progestogens.

All together, results from both ESTHER and E3N studies suggest that the safest option for correcting menopausal women may be transdermal estrogens combined with micronized progesterone. However, randomized controlled trials are needed to confirm this result.

*Tibolone*

Tibolone, a testosterone derived progestin, has estrogenic, progestogenic and androgenic properties [24]. Tibolone can be used alone as treatment of climacteric symptoms among postmenopausal women [25, 26]. It is administrated at low dose and its effect is partly mediated by its metabolites. The association of VTE with tibolone use among postmenopausal women has been so far only investigated in one case/control study [16], one cohort study [8] and two randomized controlled trials [25, 26]. All the studies showed that tibolone use was not associated with the risk of VTE. Using a random-effect model meta-analysis as previously described [4, 9], the overall VTE risk was 0.5 (95%CI: 0.1-2.0) among postmenopausal women using tibolone as compared to non users or placebo users (figure 2). However, the wide confidence interval did not allow concluding regarding the impact of tibolone on VTE risk and we cannot exclude an increase in the VTE risk of 100% among users of tibolone. Further data are therefore needed to clarify the effect of tibolone on VTE risk, especially among healthy postmenopausal women.

**Progestogens and haemostatis: biological studies**

For many years, the effect of HT on haemostatis has been largely investigated in observational studies as well as in high evidence level studies among users of oral and transdermal estrogens [27-52]. However, few studies, which most of them were randomized controlled trials, were adequately designed for assessing the effect of progestogens or for comparing the effect of a specific progestogen to each other on APCr, a validated surrogate marker of VTE and on F1+2 or Ddimers, first-generation biomarkers of coagulation and fibrinolysis [29, 33, 40, 41, 43, 47-51, 53] (table 2). In addition, because postmenopausal women using progestogens are also prescribed estrogens, it is important to note that the influence of progestogens on haemostasis among postmenopausal women has been only investigated in a context of estrogens use.

On one hand, some data allowed assessing the main effect of some progestogens by comparing the changes in haemostasis between users of oral estrogens alone or combined with either micronized progesterone [51], dydrogesterone [33, 40] , MPA [29, 47, 51], trimegestone [33, 40] or gestodene [43]. Micronized progesterone, dydrogesterone, MPA and trimegestone may not induce significant changes in F1+2, DDimers and APCr related to oral estrogens use. As part of the investigation regarding MPA, these biological data are not in accordance with the clinical results which show an increased VTE risk among users of CEE+MPA as compared with CEE alone users. However, since oral estrogens activate blood coagulation and induce APCr, a potential influence of progestogen on haemostasis could be diluted by oral estrogens effect and partly explain why little or no variation was detected. With regard to gestodene, data remained inconclusive with a higher increase in DDimers but a lower one in APCr among gestodene users [43].

On the other hand, some studies compared the effect of two different progestogens on haemostasis in the context of either oral estrogen users [29, 33, 40, 48, 49, 51, 54] or transdermal estrogens users [53]. Among oral estrogens users, no clear differences have been highlighted. While a randomized controlled trials showed no significant difference in blood coagulation activation and APCr between trimegestone and dydrogesterone [33, 40], another study showed that trimegestone was associated with a significantly higher increase in DDimers concentration as compared

to dydrogesterone [49]. When compared to other progestogen, MPA could have similar [51] or more deleterious effect [41, 50] on haemostasis, suggesting a potential detrimental impact of progestogens with androgenic properties on coagulation. Because transdermal estrogens, contrary to oral estrogens, have little or no effect on blood coagulation activation [43], studying the impact of progestogens on haemostasis seems to be more relevant among postmenopausal women using transdermal ET. The Study of NorpregnAnes of Coagulation (SNAC) provided the only data comparing the impact of micronised progesterone and norpregnane derivatives on haemostasis among transdermal estrogens users [53]. In the study, norpregnane derivatives, but not micronized progesterone, were associated with an increase in F1+2 concentrations and an APCr induction. These results were concordant with clinical data showing an association between norpregnane derivatives but not micronized progesterone with the VTE risk. However, the SNAC study was a cross-sectional study and a selection bias might have occurred, as described in the clinical data.

In conclusion, no clear evidence for a differential effect of progestogens on haemostasis has been highlighted but norpregnane derivatives could activate blood coagulation and induce APCr [53], providing a biological support to the clinical results [6, 7].

*Tibolone*

Data regarding the effect of tibolone on haemostasis are scarce [55-62]. Only one study provided a direct assessment of the tibolone effect on F1+2, DDimers and APCr and showed that compared to placebo treatment, tibolone would not significantly induce a higher APCr [62] (table 3). However, this study included a low number of subjects and the lach of statistical power did not allow clearly concluding. Two studies consistently showed that tibolone would have the same or a less deleterious effect on F1+2 and DDimers than did CEE or E2 combined with NETA [55, 56, 59-61]. By contrast, data were more controversial regarding the comparison of the effects of tibolone and estrogens combined with NETA on APCr. While tibolone might more induced APCr than did estradiol and estriol, it could have less effect on haemostasis than did CEE [55, 59-61]. With regards to other progestogens, one study has investigated the differential effect of tibolone and CEE combined with micronized progesterone on haemostasis and showed that increase in F1+2 was

more pronounced among HT users compared to tibolone ones [57]. Overall, data on the effect of tibolone on haemostasis remain conflicting and further investigations are needed to clarify this effect.

## Conclusion

In conclusion, progestogens, as part of a HT compound for postmenopausal women, may have differential effects on VTE risk according to the molecules and therefore recently emerge as an important determinant of the thrombotic risk. While MPA has a thrombogenic effect among postmenopausal women using estrogens, micronized progesterone could be safe with respect to thrombotic risk. However, the effects of the different types of progestogens on VTE risk has to be further investigated in high evidence level studies performed among postmenopausal women using estrogens.

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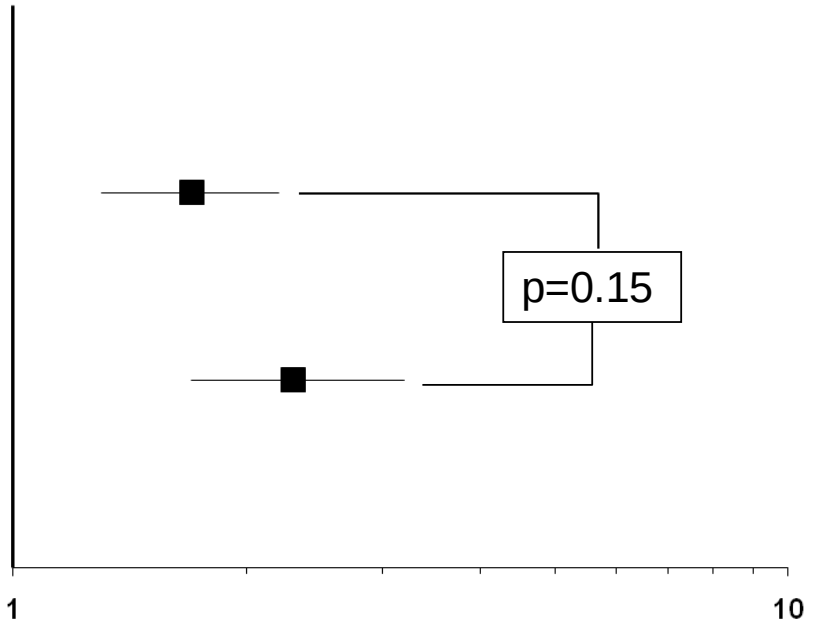
Table 1. Hormonal effect of the different progestogens used among postmenopausal women

| Pharmacological class | Molecules | Progestogenic activity | Estrogenic activity | Androgenic activity | Anti-androgenic activity | Gluco-corticoid activity | Anti Mineralo-corticoid |
|---|---|---|---|---|---|---|---|
| ***Micronised progesterone*** | Micronised progesterone | + | - | - | +/- | +/- | + |
| ***Pregnanes*** | Dydrogesterone | + | - | - | - | - | - |
| | Medrogestone | + | - | - | - | - | - |
| | Chlormadinone acetate | ++ | - | - | + | + | - |
| | Cyproterone acetate | ++ | - | - | +++ | + | - |
| | Medroxyprogesterone acetate | + | - | + | - | + | - |
| ***Norpregnanes*** | Nomegestrol acetate | + | - | - | + | - | - |
| | Promegestone | + | - | - | - | + | - |
| | Trimegestone | + | - | - | +/- | - | - |
| | Nestorone | + | - | - | - | - | - |
| ***19 Nortestosterone ethinylated*** | | | | | | | |
| Estranes | Norethisterone acetate | ++ | + | + | - | - | - |
| Gonanes | Levonorgestrel | ++ | - | + | - | +/- | - |
| | Gestodene | ++ | - | + | - | +/- | - |
| ***19 Nortestosterone non ethinylated*** | Dienogest | ++ | - | - | + | - | - |
| ***Spironolactone derivatives*** | Drospirenone | + | - | - | + | - | ++ |
| ***Tibolone*** | Tibolone | + | + | ++ | - | - | - |

Figure 1: Risk of venous thromboembolism among users of oral estrogens alone or oral estrogens combined with progestogens in observational studies

| Characteristics of HT | OR (95% CI) |
|---|---|
| Current use of E alone | 1.7 (1.3-2.2)* |
| *Test for homogeneity: $\chi^2$=10.3 (p=0.11), $I^2$=42 %* | |
| Current use of E+P | 2.3 (1.7-3.2)* |
| *Test for homogeneity: $\chi^2$=20.3 (p<0.01), $I^2$=70 %* | |

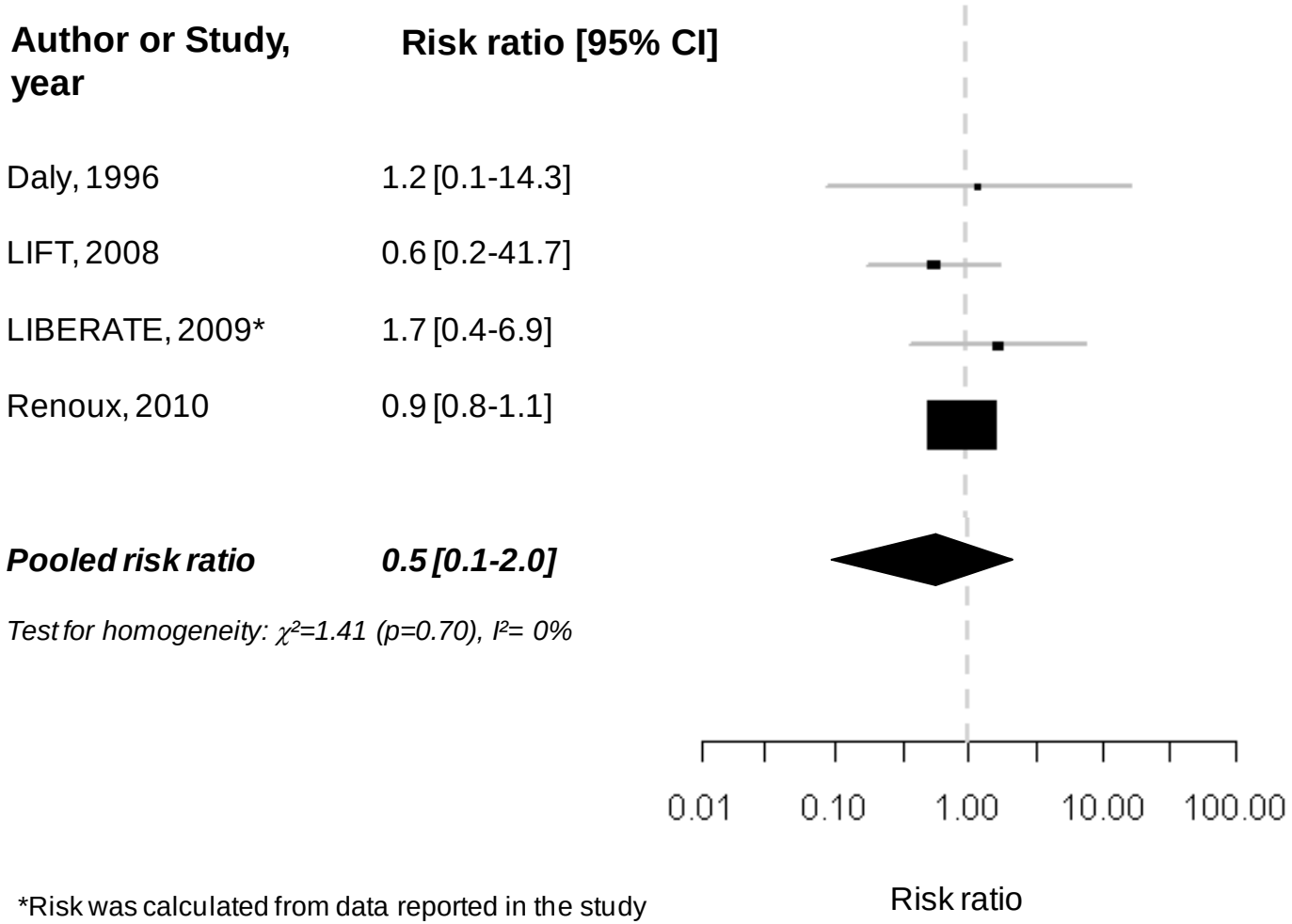



* Derived from 6 observational studies [5, 8, 12-15]

E: Estrogens

E+P: Estrogens combined with progestogens

Figure 2: Risk of venous thromboembolism among postmenopausal women using tibolone




*Risk was calculated from data reported in the study

Table 2. Impact of progestogens on haemostasis among postmenopausal women from randomized controlled trials

| Authors, years of publication | Number of women | Groups of treatment | Assessed effect | | Haemostasis | | |
|---|---|---|---|---|---|---|---|
| | | | Progestogens | Route of estrogen administration | F1+2 | Ddimers | APCr |
| Koh et al, 1997 | 50 | O CEE alone | MPA | Oral | NA | NS | NA |
| | | O CEE + MPA | | | | | |
| | | T E2 alone | MPA | Transdermal | NA | NA | NA |
| | | T E2 + MPA | | | | | |
| Van Baal et al, 2000 and Post et al, 2002 | 60 | O E2 alone | Trimegestone | Oral | NS | NS | NS |
| | | O E2 + Trimegestone | Dydrogesterone | | NS | NS | NS |
| | | O E2 + Dydrogesterone | Trimegestone *versus* Dydrogesterone | | NS | NS | NS |
| | | Placebo | | | | | |
| Skouby et al, 2002 | 149 | O E2 cycl + CPA | CPA *versus* NOR | Oral | NS | NS | NS |
| | | O E2 cont + CPA | | | | | |
| | | O E2 cont + NETA | CPA *versus* MPA | | ↗ in MPA | NS | NS |
| | | O E2 + MPA | | | | | |
| | | O E2 + IUD LVN | MPA *versus* NETA | | ↗ in MPA | NS | NS |
| | | No Treatment | | | | | |
| Post et al, 2003 | 152 | O E2 alone | Gestodene | Oral | NS | ↗ superior with Gestodene | ↗ inferior with Gestodene |
| | | O E2 + Gestodene | | | | | |
| | | T E2 alone | | | | | |
| | | Placebo | | | | | |
| Bonduki et al, 2007 | 45 | O CEE alone | MPA | Oral | NS | NA | NS |
| | | O CEE + MPA | | | | | |
| | | T E2 + MPA | | | | | |
| Endrikat et al, 2008 | 315 | O E2 + Dienogest | Dienogest *versus* NETA | Oral | NS | NS | |
| | | O E2 + NETA | | | | | |
| Smith et al, 2008 | 288 | O CEE alone | MP | Oral | NS | NS | NS |
| | | O CEE + MP | | | | | |
| | | O CEE + MPA Cycl | MPA | | NS | NS | NS |
| | | O CEE + MPA cont | | | | | |
| | | Placebo | MP *versus* MPA | | NS | NS | NS |
| Norris et al, 2008 | 186 | O E2 + Trimegestone | Trimegestone *versus* dydrogesterone | Oral | NS | ↗ in Trimegestone | NS |
| | | O E2 + Dydrogesterone | | | | | |

RCT: Randomised Controlled Trial

NA: Not Applicable; NS: Not Significant difference in haemostatic parameters changes between progestins

O: Oral; T: Transdermal

CEE: Conjugated Equin Estrogens; E2: Estradiol

MP: Micronised Progesterone; MPA: MedroxyProgesterone Acetate; CPA: CyProterone Acetate; LVN: LeVoNorgestrel; NETA: NorEthisTerone Acetate

Cont: continu; Cycl: Cyclic

IUD: Intra Uterin Device

Table 3. Impact of tibolone on haemostasis among postmenopausal women

| Authors, years of publication | Study design | Number of women | Groups of treatment | Assessed effect | Haemostasis | | |
|---|---|---|---|---|---|---|---|
| | | | | | F1+2 | Ddimers | APCr |
| Winkler et al, 2000 | RT | 60 | Tibolone | Tibolone *versus* O E2 + E3 + NETA | ↗ superior with HT | ↗ superior with HT | ↗ superior with Tibolone |
| | | | O E2 + O E3 + NETA | | | | |
| Norris et al, 2002 | RT | 80 | O E2 + NETA | Tibolone *versus* O E2 + NETA | NA | ↗ superior with HT | NA |
| | | | Tibolone | | | | |
| Koh et al, 2003 and 2005 | RT | 53 | O CEE + MP | Tibolone *versus* O CEE + MP | ↗ superior with Tibolone | NA | NA |
| | | | Tibolone | | | | |
| Eilersten et al, 2006 and 2007 | RT | 202 | Low dose O E2 + NETA | Tibolone *versus* high dose of O E2 + NETA | ↗ superior with HT | ↗ superior with HT | ↗ superior with HT |
| | | | High dose O E2 + NETA | | | | |
| | | | Tibolone | Tibolone *versus* low dose of O E2 + NETA | NS | NS | ↗ superior with HT |
| | | | Raloxifene | Tibolone *versus* Raloxifene | NS | ↗ with Tibolone ↘ with raloxifene | NA |
| Demirol et al, 2007 | RCT | 90 | O CEE | Tibolone *versus* O CEE | NA | NA | NS |
| | | | Tibolone | | | | |
| | | | Placebo | Tibolone *versus* placebo | NA | NA | NS |

RT: Randomised Trial; RCT: Randomised Controlled Trial

NA: Not Applicable; NS: Not Significant difference

O: Oral;

CEE: Conjugated Equin Estrogens; E2: Estradiol; E3: Estriol

MP: Micronised Progesterone; NETA: Norethisterone Acetate