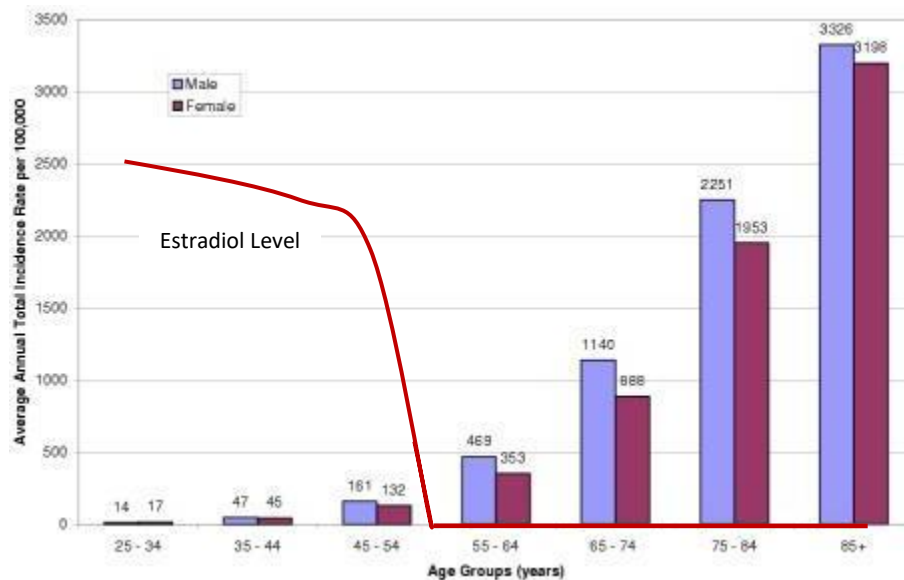


Stroke Risk with Estradiol Therapy in Menopause

Of women aged 50 to 70 years, 5 in every 1000 will have a stroke each year.
Early menopause promotes atherosclerosis and increases stroke risk later in life.
Early initiation of oral or transdermal estradiol (TE) reduces stroke risk.
Oral estradiol is associated with an increase in DVT risk; TE is not.
Low-dose TE reduces stroke risk when started at any age.
High-dose oral or TE may increase stroke risk, especially if atherosclerosis is established.
Stopping estradiol-based HT increases stroke risk in the first year.
Progesterone does not increase DVT or stroke risk, whereas some progestins do.
If a thrombophilic condition exists, low-dose transdermal estradiol is not contraindicated.
Increased fish oil intake is effective for stroke prevention and has other health benefits.

Incidence of Stroke in Women: Relation to Menopausal Status

Stroke is the fourth leading cause of death in the United States, and the leading cause of long-term severe disability. Estimates of the incidence rate for stroke vary from 3.73 for total stroke (3.29 for ischemic stroke),¹ to 5.2 per 1000 person-years (all ages combined).² According to the CDC, the lifetime



Average Annual Age-Specific Incidence Rates of Total Stroke (First-ever and Recurrent) Per 100,000 Population in the United States in 1996 by Sex. (Estradiol indicator added by author)

Williams GR. Incidence and characteristics of total stroke in the United States. BMC Neurol. 2001 Dec 18;1:2. [PubMed](#)

¹ Koton S... Stroke incidence and mortality trends in US communities, 1987 to 2011. JAMA. 2014 Jul 16;312(3):259-68. [PubMed](#)

² Carandang R... Trends in incidence, lifetime risk, severity, and 30-day mortality of stroke over the past 50 years. JAMA. 2006 Dec 27;296(24):2939-46. [PubMed](#)

prevalence of stroke in the US is 2.7%—around 3 out of every 100 living persons has experienced a stroke in their lifetime.³ Stroke is rare before age 50 and the incidence rises rapidly with age in both sexes after that. (See figure.) One should expect 3.5 out of 1000 women aged 55 to 64 to have a stroke each year. Between the ages of 65 and 74 years, the rate is 9 per 1000 per year, and between the ages of 75 and 84, it is 20 per 1000 per year. So if estradiol replacement is neutral with regard to stroke risk, one must still expect 0.5% of younger women, and up to 2 percent of older women to have a stroke each year. I have been treating women with estradiol-progesterone-testosterone therapy (EPTT) for 12 years. For the last 5 yrs. I have had around 1000 women on this therapy. Most of the women are 50 to 70 years old. In the last 5 years I should have seen 5 strokes for every 1000 patients per year, or 25 strokes. I am aware of only one case of stroke. Granted, it's possible that I did not learn of some cases. However, it seems that the stroke rate in my EPT-treated patients is much lower than expected. I will discuss my approach to menopausal hormone replacement below, and will discuss a dietary supplement that I recommend to all patients they has been shown to reduce stroke risk.

With aging, both male and female estradiol levels fall. Male estradiol levels decline gradually with age. At menopause, whether natural or surgical, women have a nearly complete loss of estradiol. Studies show that the earlier the onset of menopause the worse the consequences for a woman's

Estradiol vs. Cardiovascular Disease

Prevents the oxidation of LDL
Improves lipid profile
Reduces lipoprotein (a)
Reduces blood pressure
Improves endothelial function
Dilates arteries
Lowers blood pressure
Reduces plaque formation
Improves insulin sensitivity

health. Women who suffer ovarian failure before age 45, naturally or surgically, have higher incidences of cardiovascular (CV) events, CV and stroke mortality (but not stroke), and overall mortality—they are more likely to die at a younger age.⁴ Oophorectomy is associated with an increase in stroke risk (RR 1.42).⁵ Oophorectomy before age 45 is associated with a higher stroke risk (RR 2.29).⁶ Therefore, the risk of stroke is inversely correlated with long-term estradiol levels in men and women—loss of estradiol is associated with stroke risk. This is most likely

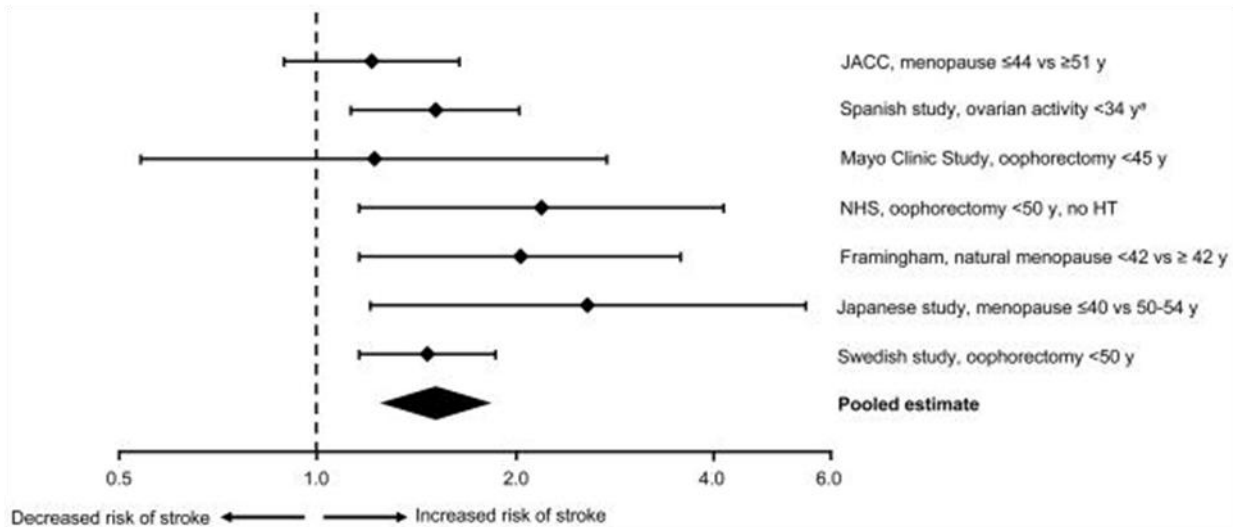
due to estradiol's known anti-atherosclerotic effects. (See inset.) It should be expected that the physiological hormone replacement, begun at the onset of ovarian failure, should reduce stroke risk. Since the ovaries produce estradiol, progesterone and testosterone, menopausal hormone therapy should include all three hormones.

³ CDC, Prevalence of Stroke — United States, 2006–2010, May 25, 2012/61(20);379-382. [Link](#)

⁴ Muka T... Association of Age at Onset of Menopause and Time Since Onset of Menopause With Cardiovascular Outcomes, Intermediate Vascular Traits, and All-Cause Mortality: A Systematic Review and Meta-analysis. JAMA Cardiol. 2016 Sep 14. [PubMed](#)

⁵ Poorthuis MH... Female- and Male-Specific Risk Factors for Stroke: A Systematic Review and Meta-analysis. JAMA Neurol. 2016 Nov 14. [PubMed](#)

⁶ Yeh JS... Hysterectomy in young women associates with higher risk of stroke: a nationwide cohort study. Int J Cardiol. 2013 Oct 3;168(3):2616-21. [PubMed](#)



Increased risk of all types of stroke in women who underwent bilateral oophorectomy compared with women who conserved their ovaries before age 50 years.

Rocca WA... Premature menopause or early menopause and risk of ischemic stroke. *Menopause*. 2012 Mar;19(3):272-7. [PubMed](#)

Oral or Transdermal Estradiol Therapies Reduce Stroke Risk

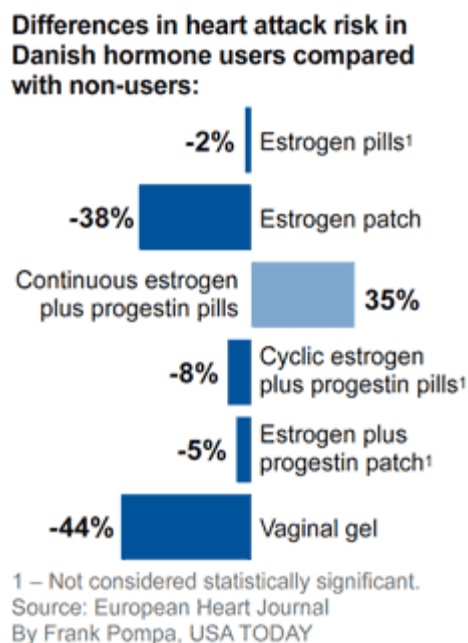
To address the question of estradiol replacement therapy and stroke risk, we must make several determinations:

1. Whether oral or transdermal estradiol (TE) has been shown to increase stroke risk at any age.
2. If TE increases stroke risk, whether the many benefits of TE outweigh the risk of stroke.
3. Whether TE increases stroke risk in those with inherited thrombophilias.
4. If TE increases stroke risk in those with thrombophilia, whether the benefits prophylactic antithrombotic treatment will outweigh the risks.

It is well-established that oral Premarin, Prempro and contraceptive pills containing ethinyl estradiol (EE) increase deep vein thrombosis (DVT) and stroke risk, especially in the first year of treatment. In premenopausal women, oral EE-progestin contraception increases the risk of myocardial infarction (RR 1.6) and stroke (RR 1.7).⁷ Here we will discuss only the evidence pertaining to the dominant human estrogen: estradiol (17-β estradiol).

⁷ Roach RE... Combined oral contraceptives: the risk of myocardial infarction and ischemic stroke. *Cochrane Database Syst Rev*. 2015 Aug 27;(8):CD011054. [PubMed](#)

A large body of research has shown that oral estrogens, including oral estradiol, increase the risk of DVT in women, whereas transdermal estradiol does not.⁸ Adding progesterone to transdermal estradiol does not increase DVT risk, whereas adding some progestins does increase risk.^{9,10} Similar results have been found with the risk of myocardial infarction with transdermal vs. oral estrogens. The key to any estrogen's thrombotic risk is the amount of estrogenic effect in the liver. Estradiol stimulates hepatic protein synthesis, and this includes clotting factors. Swallowed estrogens have a disproportionately strong effect on the liver due to the first-pass effect.



Transdermal estradiol reduced risk of MI in large Danish cohort study.

Løkkegaard E... Hormone therapy and risk of myocardial infarction: a national register study. *Eur Heart J.* 2008 Nov;29(21):2660-8. [PubMed](#)

Even so, many studies have found that oral estradiol therapy reduces the risk of myocardial infarction, heart failure, stroke and mortality. In Scandinavia, oral estradiol-based HRT has been the norm, with 1 to 2mg of estradiol daily. After 10 years of randomized treatment women receiving oral estradiol and cyclical norethisterone, started within 10 yrs of menopause, had significantly reduced risks of mortality, heart failure and myocardial infarction; without any increase in risk of breast cancer, venous thromboembolism, or stroke. The RR for stroke was 0.77 compared to controls.¹¹ The exposure to oral estradiol-based therapy (with or without a progestin) ≤ 1 year was associated with a 22% reduced risk of stroke death. Exposure to oral estradiol for 1-8 years was associated with a 40% reduced risk.¹²

⁸ Canonico M... Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis. *BMJ.* 2008 May 31;336(7655):1227-31. [PubMed](#)

⁹ Canonico M... Estrogen and Thromboembolism Risk (ESTHER) Study Group. Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study. *Circulation.* 2007 Feb 20;115(7):840-5. [PubMed](#)

¹⁰ Simon JA... Venous thromboembolism and cardiovascular disease complications in menopausal women using transdermal versus oral estrogen therapy. *Menopause.* 2016 Jun;23(6):600-10. [PubMed](#)

¹¹ Schierbeck LL... Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomised trial. *BMJ.* 2012 Oct 9;345:e6409. [PubMed](#)

¹² Tuomikoski P... The risk of fatal stroke in Finnish postmenopausal hormone therapy users before and after the Women's Health Initiative: A cohort study. *Maturitas.* 2015 Jul;81(3):384-8. [PubMed](#)

In a Finnish study of 489,105 women who used oral estradiol-based HT from 1994 to 2009, the risk of CHD death was significantly reduced by 18% to 54% and was positively related to HT exposure time. The risk of stroke death was reduced by 18% to 39%, but this reduction was not clearly related to HT exposure time. Risk of all-cause mortality was reduced in HT users by 12% to 38%, almost in linear relationship with duration of exposure. Surprisingly, all these risk reductions were comparable in women initiating HT before age 60 years and women initiating HT at age 60 years or older. In absolute terms, the risk reductions mean 19 fewer CHD deaths and 7 fewer stroke deaths per 1,000 women using any HT for at least 10 years.¹³ Later, I will discuss a possible cause for the relative lack of thrombotic events in Scandinavian oral estradiol studies.

In the wake of the report of the results of the Women's Health Initiative study, many women stopped taking menopausal hormone therapy (MHT). Researchers discovered that in the first year after discontinuing estradiol-based HT, the risk of stroke death increased (RR 1.63) relative to controls, but was lower after 1 year (RR 0.89), consistent with a longer-lasting benefit—probably less atherosclerosis. The cardiac and stroke death risk elevations with stopping HT were even higher when compared with continuing HT users as opposed to controls (RR 2.30 and RR 2.52 respectively). In women who discontinued HT at age younger than 60 years, but not in women aged 60 years or older, the cardiac mortality risk was elevated (RR 1.94).¹⁴ The increase in CHD and stroke death with stopping estradiol is most likely due to the sudden worsening of endothelial function.

One would expect better results with transdermally-applied estradiol as it avoids the first-pass effect on the liver. TE enters the venous circulation and is diluted in a large volume of blood before reaching the liver. It better mimics the natural secretion. TE affects the liver only to the same extent as a similar amount of estradiol produced endogenously. We should expect TE to have the same benefits and risks as a woman's own pre-menopausal hormone production—with a lower risk of thrombosis due to the lower serum levels obtained. Transdermal estradiol does produce a less thrombogenic milieu than oral estradiol.¹⁵ This was demonstrated in a direct comparison of oral estradiol (E2 valerate 2mg/d) and progesterone with transdermal estradiol (2.5mg in a gel) and progesterone. Oral estradiol increased several pro-thrombotic hemostatic variables, whereas transdermal estradiol did not.¹⁶ In another study, transdermal estradiol patches (50mcg/day) raised serum estradiol levels from 11 to 45 (low follicular phase levels) but produced no change in protein C or protein S activity, plasminogen, or antithrombin III levels. TE actually reduced some blood biomarkers associated with coagulation activity and improved fibrinolytic activity.¹⁷

While there are many studies showing the TE is associated with a lower DVT risk and with lower biomarkers of coagulation activity, there are only a few long-term studies of TE and CHD or stroke risk. A large, well-designed case-control study in the UK compared oral estrogen (mostly Premarin 0.625mg) to

¹³Mikkola TS... Estradiol-based postmenopausal hormone therapy and risk of cardiovascular and all-cause mortality. *Menopause*. 2015 Sep;22(9):976-83. [PubMed](#)

¹⁴Mikkola TS... Increased Cardiovascular Mortality Risk in Women Discontinuing Postmenopausal Hormone Therapy. *J Clin Endocrinol Metab*. 2015 Dec;100(12):4588-94 [PubMed](#)

¹⁵Lowe GD... Different effects of oral and transdermal hormone replacement therapies on factor IX, APC resistance, t-PA, PAI and C-reactive protein--a cross-sectional population survey. *Thromb Haemost*. 2001 Aug;86(2):550-6. [PubMed](#)

¹⁶Scarabin PY... Effects of oral and transdermal estrogen/progesterone regimens on blood coagulation and fibrinolysis in postmenopausal women. A randomized controlled trial. *Arterioscler Thromb Vasc Biol* 1997 Nov;17(11):3071-8 [PubMed](#)

¹⁷Martínez C... Transdermal estradiol does not impair hemostatic biomarkers in postmenopausal women. *Maturitas*. 2005 Jan 10;50(1):39-43. [PubMed](#)

two different transdermal estradiol doses. Premarin increased stroke risk (RR 1.3) whereas low dose transdermal estradiol (a patch delivering ≤ 50 mcg into the circulation) reduced stroke risk (RR 0.8). High-dose transdermal estradiol (>50 mcg) increased stroke risk (RR 1.89), but the latter's sample size was small.¹⁸ The authors noted that in studies that demonstrated that transdermal HRT had no or minimal effect on cardiovascular and thromboembolic risk markers, the estradiol dose was usually ≤ 50 mcg/24hrs (by patch).

The dose of transdermal estradiol is almost certainly an important factor. High estradiol levels naturally or with transdermal delivery would have more estrogenic effect in the liver and therefore would promote thrombosis. At the extreme low end is the use of very low-dose vaginal estradiol for vulvovaginal atrophy. It produces minimal rises in serum estradiol, yet has been associated with decreased risks for CHD and stroke death. The risk reduction for CHD death was highest for >3 to ≤ 5 years exposure (RR 0.64) and for stroke for >5 to ≤ 10 years exposure (RR 0.64). The risk reductions for both CHD and stroke mortality were detected in all age groups with the highest risk reduction being in women aged 50-59 years (RRs 0.43 and 0.21, respectively). In 1000 women using very low-dose vaginal estradiol for up to 10 years, a maximum of 24 fewer CHD deaths and 18 fewer stroke deaths is likely to occur.¹⁹

Should We Screen Women for Thrombophilic Mutations Before Initiating Estradiol Replacement?

Inherited thrombophilia denotes several genetic risk factors that predispose individuals to developing venous thromboembolism. Factor V Leiden is the most common. Individuals who are heterozygous for protein C, protein S, and antithrombin deficiency have a higher thrombosis risk than heterozygous factor V Leiden. Should all persons be screened for these mutations? Should women be screened prior to initiating estradiol-progesterone replacement therapy?

UpToDate is a peer-reviewed source of medical information for physicians. It does not recommend routine, population-based screening for inherited thrombophilia for three reasons:²⁰

- The low frequency of the symptomatic condition in the general population.
- The low penetrance of the symptomatic condition among carriers of the most common thrombophilic conditions (eg, factor V Leiden and prothrombin G20210A mutations), AND
- The lack of a safe, cost-effective, long-term method of prophylaxis if an abnormality is found.

There are no data that justify the risks of long-term or permanent prophylactic anticoagulation in the asymptomatic individual (ie, an individual who has not had a thromboembolic event). For the same reasons, UpToDate does not recommend routine screening in pregnancy²¹ or before initiating oral contraceptive therapy, even though both states increase the risk of DVT in women. Because of the low frequency of thromboses due to mutations, the authors note that if all potential users of oral contraceptives were screened and then discouraged from use of the drugs if they tested positive, 333

¹⁸Renoux C... Transdermal and oral hormone replacement therapy and the risk of stroke: a nested case-control study. *BMJ*. 2010 Jun 3;340:c2519. [PubMed](#)

¹⁹Mikkola TS... Vaginal estradiol use and the risk for cardiovascular mortality. *Hum Reprod*. 2016 Apr;31(4):804-9. [PubMed](#)

²⁰Bauer KA. Screening for inherited thrombophilia in asymptomatic individuals, [UpToDate](#)

²¹Lockwood CJ... Inherited thrombophilias in pregnancy, [UpToDate](#)

women would be identified for every episode of VTE prevented. There is even less indication for screening women prior to starting transdermal estradiol therapy in menopause, as low-dose TE has not been shown to increase DVT or stroke risk. There is one study of TE in women with prothrombotic mutations. A transdermal estradiol patch dose of ≤ 50 mcg did not significantly increase the risk of venous thromboembolism (RR 1.2). However, oral estradiol at a mean dose of 1.5mg daily did increase VTE risk substantially (RR 4.3).²²

The UpToDate topic does state that screening may be justified if there is a blood relative with inherited thrombophilia and clinical thromboembolic disease. Then there is the question of what to do if a woman has thrombophilic mutations. In such women, the benefits of low-dose TE clearly outweigh the risk of DVT, stroke or MI. This is particularly true if therapy is started soon after menopause—when they have recently had higher estradiol levels naturally and atherosclerosis is not established. However, even in an older woman, should one deny TE based upon the mere presence of a thrombophilic mutation? Should one advise that TE be accompanied by some sort of anti-thrombotic therapy? The most common anti-thrombotic agent is low-dose aspirin. However aspirin increases the risk of major bleeds, GI bleeds and intracranial bleeds (RR 2.0). In large-scale primary prevention trials, aspirin has been found to reduce the risk of first MI, but not stroke or cardiovascular death. For low-risk patients (i.e. men and women whose 10-year absolute risk of a first CHD event is <10 percent), the absolute benefit of a reduction in cardiovascular events is unlikely to exceed the absolute risk of major bleeding. For moderate- and high-risk patients (i.e. men and women whose 10-year absolute risk of a first CHD event is ≥ 10 percent), randomized data on benefits and risks are sparse. Experts recommend that the decision to use aspirin for thromboprophylaxis should be individualized. I think that there is a better approach to thromboprophylaxis that is perfectly safe and can be recommended to all adults.

Fish Oil Supplementation for Stroke Prevention

The general measures that can help prevent CVD including stroke are:

- Smoking avoidance and cessation
- Weight loss—avoid overweight and obesity
- Healthy diet
- Physical activity
- Optimal lipid levels
- Lower blood pressure
- Lower blood sugar levels

In addition, all physicians should recommend that patients increase their intake of fatty fish to 3 times/week, or take fish oil. While the flesh of larger fish contains mercury and PCBs, fish oil has no detectable mercury and much lower PCB levels. Fish oil for human supplementation is gathered from small fish that have not accumulated these toxins. The primary omega-3 fatty acids in fish oils are eicosapentaenoic and docosahexaenoic acids (EPA and DHA). Omega-3 FAs are present in hunter-gatherer diets as they are found in wild animals and plants. They are

²²Straczek C... Prothrombotic mutations, hormone therapy, and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration. *Circulation*. 2005 Nov 29;112(22):3495-500. [PubMed](#)

missing from the standard American diet, yet have been shown to have many health benefits. The highest amounts of EPA and DHA are obtained from the consumption of fatty fish. Inuit people have the highest omega-3 intakes, and this is the best explanation for their lower incidences of heart attack and stroke.²³

Fatty fish intake has been repeatedly shown to reduce stroke risk. Having a fatty fish meal greater than or equal to once/week decreases stroke risk compared to less than once/month (RR 0.69).²⁴ Fatty fish consumption as seldom as 1 to 3 times per month protects against ischemic stroke (RR 0.57).^{25,26} Fatty fish intake of 1 to 4 times per week reduces stroke risk (RR 0.73), and eating fish 5 or more times per week further reduces risk (RR 0.70).²⁷ Fatty fish intake also reduces CHD mortality (RR 0.66).²⁸

Many studies have helped to illuminate the mechanism by which omega-3 FAs work to reduce thrombotic events. Dietary omega-3 FAs reduce cholesterol and triglyceride levels; they reduce platelet aggregation; they exhibit antithrombotic and fibrinolytic activities; they reduce blood viscosity and they exhibit anti-inflammatory action.²⁹ A fish diet providing 2 to 3 g of EPA per day causes bleeding time prolongation and decreased platelet aggregation similar to aspirin.^{30,31} Unlike aspirin, however, omega-3 supplementation has not been shown to increase bleeding risk.³²

Fatty fish intake may explain the lack of any increase in thrombotic effect with oral estradiol therapy in the Scandinavian studies mentioned previously. The people of Finland, Sweden, Norway and Denmark consume more fatty fish than those in other European countries or the US. Omega-3 intake may also explain the apparently low stroke and CHD incidence in the women that I treat. I provide each patient with a list of recommended supplements that include fish oil:

1. High Potency Multivitamin/Multimineral Supplement
2. Fish Oil: >2500mg/day EPA+DHA Carlson's or Vitacost Fish oil, Lemon (not fishy) 4 tbsps per week, or 3 extra-strength caps daily--Carlson's Elite, LEF Super Omega 3, Sam's Club 3x.
3. Vitamin D3: 2000 to 5000IU/day, if low, 15K/day for 1mo, then 1/day.
4. Vitamin C with bioflavonoids: 1000mg daily (Vitacost, other brands)
5. Magnesium: 250-500mg daily. Vitacost Mag Citrate tabs, LEF 500mg, Solgar
6. Iodine: Iodoral or i-Throid 12.5mg tabs, ½ to 1 tab/week

²³Dyerberg J... n-3 fatty acids and cardiovascular disease--observations generated by studies in Greenland Eskimos. *Wien Klin Wochenschr.* 1989 Apr 14;101(8):277-82. [PubMed](#)

²⁴Oudin A... Fish consumption and ischemic stroke in southern Sweden. *Nutr J.* 2011 Oct 11;10:109. doi: 10.1186/1475-2891-10-109. [PubMed](#)

²⁵He K... Fish consumption and incidence of stroke: a meta-analysis of cohort studies. *Stroke.* 2004 Jul;35(7):1538-42. [PubMed](#)

²⁶He K... Fish consumption and risk of stroke in men. *JAMA.* 2002 Dec 25;288(24):3130-6. [PubMed](#)

²⁷Mozaffarian D... Fish consumption and stroke risk in elderly individuals: the cardiovascular health study. *Arch Intern Med.* 2005 Jan 24;165(2):200-6. [PubMed](#)

²⁸Oomen CM... Fish consumption and coronary heart disease mortality in Finland, Italy, and The Netherlands. *Am J Epidemiol.* 2000 May 15;151(10):999-1006. [PubMed](#)

²⁹Demaison L... Dietary n-3 polyunsaturated fatty acids and coronary heart disease-related mortality: a possible mechanism of action. *Cell Mol Life Sci.* 2002 Mar;59(3):463-77. [PubMed](#)

³⁰Thorngren M... Effects of acetylsalicylic acid and dietary intervention on primary hemostasis. *Am J Med.* 1983 Jun 14;74(6A):66-71. [PubMed](#)

³¹Thorngren M... Effects of 11-week increases in dietary eicosapentaenoic acid on bleeding time, lipids, and platelet aggregation. *Lancet.* 1981 Nov 28;2(8257):1190-3. [PubMed](#)

³²Bays HE... Safety considerations with omega-3 fatty acid therapy. *Am J Cardiol.* 2007 Mar 19;99(6A):35C-43C. [PubMed](#)

My Approach to Estradiol-Progesterone-Testosterone Replacement in Menopause

The proper physiological treatment of ovarian failure should include all the major hormones secreted by the ovary: estradiol, progesterone and testosterone. I replace all three hormones in all women. We should expect that the restoration of the youthful female hormonal milieu, with the proper hormones given by the best routes, will have synergistic effects that improve not only well-being but also long-term health. Indeed, much evidence supports this commonsense approach. The inclusion of progesterone is medically necessary to reduce estradiol-induced proliferation in the uterus and breasts. Testosterone improves mood, muscle strength and libido. Testosterone therapy has not been shown to have any cardiovascular or breast cancer risks.³³ In fact, in a four-year study of a transdermal testosterone gel revealed a lower-than-expected cardiovascular event rate.³⁴

The typical estradiol dose I prescribe to women is 1 to 3mg applied to the skin in a compounded cream. Far less than 10% of estradiol applied to the skin is absorbed into the circulation. The amount absorbed varies greatly from woman-to-woman and depends upon many factors including the vehicle and the area of application. I adjust the estradiol dose according to symptoms and serum levels. I raise the dose if there are any symptoms of estradiol deficiency and lower the dose if there are any symptoms of estradiol excess (breast fullness/tenderness or vaginal spotting/bleeding). I check serum estradiol levels at 12 hrs post dose. If symptoms do not dictate otherwise, I raise the dose if the total serum estradiol is less than 30pg/ml and lower the dose if it is greater than 100 pg/ml. The best measure of replacement of any hormone is the free or bioavailable hormone. So I am increasingly testing for free estradiol at 12 hrs. The menstruating adult female range is 0.6 to 7.0pg/ml. I find postmenopausal women seem to get sufficient benefits when the 12 hr. level is 0.6 to 1.2pg/ml—low within the adult female range. FDA-approved estradiol patches and gels can also be used.

Progesterone replacement is far more difficult to follow with blood testing for various reasons. I typically prescribe 100mg compounded sublingual tablets, 100mg in a transdermal cream, or 200mg in an FDA-approved oral capsule. I judge progesterone to be sufficient if there is no evidence of estrogen-induced breast or uterine stimulation. I prescribe testosterone in a compounded cream—typically 2mg/0.2ml with 0.1 to 0.2ml applied to the inner genital skin or larger amounts applied to the inner thighs or the back of the knee. I adjust the dose according to 12hr. serum free testosterone levels. I lower the dose if women have bothersome androgenic effects.

³³Davis SR... Efficacy and safety of testosterone in the management of hypoactive sexual desire disorder in postmenopausal women. J Sex Med. 2012 Apr;9(4):1134-48. [PubMed](#)

³⁴Simes SM... Reaction to the recent publication by rosemary basson entitled 'testosterone therapy for reduced libido in women'. Ther Adv Endocrinol Metab. 2011 Apr;2(2):95-6. [PubMed](#)