Female Healthy Aging

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Female Healthy Aging

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Percorsi Editoriali

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Index

Presentation

Silvia Misiti
Head of IBSA Foundation for Scientific Research

The Forum "Female Healthy Aging" was organized by IBSA Foundation for scientific research in collaboration with Prof. Imthurn, Director of Department of Reproductive Endocrinology, University Hospital Zurich.

The Forum was focused on aging, women health and menopause. Women over 50 experience daily many symptoms, as hot flashes, unstable mood, insomnia, dip in libido, and develop a higher risk of cardiovascular disease, more fragile bones, atrophy of vaginal tissue *etc*.

The aim of the Forum was to discuss this topic by different points of view: gynecology, endocrinology, psychiatry, orthopedic. Ten prominent international experts presented an overview of the remedies that are currently available and the new and most advanced therapies to overcome women's disorders and to live in good health during menopause.

Introduction

Bruno Imthurn

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Women and men are equal! Yes, they are – or at least should be – equal with respect to their human rights. However, anatomically and physiologically and with regard to their thinking and feeling they are different.

The symposium "Female Healthy Aging" was dedicated to address different health aspects exclusively of women, particularly of the aging woman.

IBSA Foundation for scientific research made this conference possible organized together with the Department of Reproductive Endocrinology at the University Hospital Zurich, Switzerland. Numerous nationally and internationally renowned speakers presented at this full day meeting their expertise in the field of Female Healthy Aging.

It could be shown that the aging process is strongly dependent on the hormonal changes in the perimenopause. These changes influence well-being, fertility, sexual life, bone health, cardiovascular health and much more. All of them were topics at this conference. However, it was demonstrated that not only the ovarian hormones have an effect on the quality of the aging process. It is also the lifestyle. That is why this subject was also an important area of interest at this event.

After the Women's Health Initiative (WHI) prospectively randomized trial was stopped in 2002 many women and physicians lost their confidence in the menopausal hormone therapy (MHT). Today we know that this was an overreaction, as the WHI study revealed only that MHT is not a candy but a medicine as any medicine. As any medicine MHT has strong benefits for the affected woman, but it has rarely also side effects and complications. However – as any medicine – also MHT needs to be improved. Therefore, in the final section of this symposium with the title "Future" the available alternatives and the substances in development were addressed.

You find now in this book the conference proceedings of this important event. We hope that this conference helped to improve the health of the aging women!

SESSION 1

DEMOGRAPHY/GLOBAL HEALTH

Demographic changes in Europe and in emerging countries. When will the age pyramid reverse?

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The focus is whether the population aging pyramid, now in Europe and in the industrialized world approaching a cylinder, will ever reverse. Nowadays the most populous countries in the world are Bangladesh, Brazil, China, India, Indonesia, Mexico, Nigeria, Pakistan, Russian Federation and USA. These ten largest countries account for 63.5% of the estimated total population of today.

The most rapidly growing continent is Africa, which is expected to account for more than a half of the world's population growth between 2015 and 2050.

To understand population dynamics, we have to start from this reality. The United Nations estimated that the world population will reach 8.5 billion by 2030, with a large proportion living in Africa, China, and India and will continue to grow over the next 50 years (• **Figure 1**).

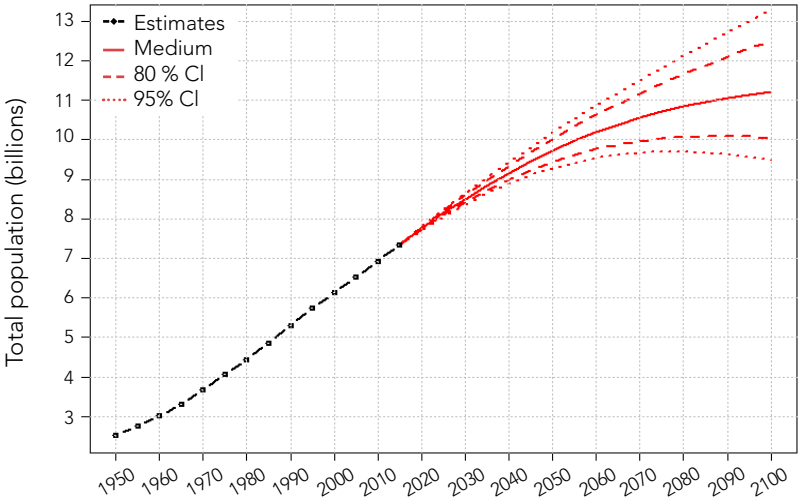
Yet projections are difficult to make and the United Nations have created four different scenarios for the world population in the year 2100; the lowest of these projections indicates that by the end of the century the population may be close to that of today. This is because fertility rates have substantially decreased almost everywhere (• **Figure 2**); this has been associated to an increase in life expectancy and a decrease in infant mortality.

In terms of fertility, in Europe age specific fertility rates have continued to decrease during the second half of the XX century and the beginning of the XXI.

Given this scenario, the answer to the question "when will the age pyramid reverse?" can only be: "never". Even in countries where fertility is still high, such as in Africa, it is projected that rates will slow down, and the pyramid will tend to become a "barrel".

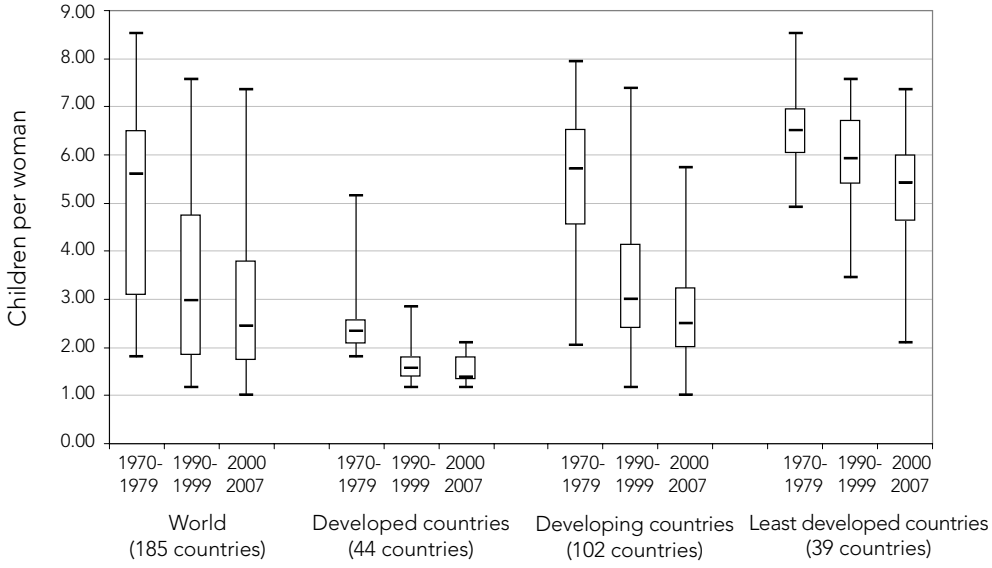
In discussing the transformation of "population pyramids" in Europe and in many other countries, it is important to reflect on the ever-increasing life expectancy that, coupled with low fertility, leads to an unprecedented ageing of European countries. This

● **Figure 1.** Population of the world: estimates, 1950-2015, medium-variant projection and 80 and 95 per cent confidence intervals, 2015-2100



Source: United Nations, Department of Economic and Social Affairs/Population Division. *World Population Prospects: The 2015 Revision*. United Nations, New York 2015.

● **Figure 2.** Distribution of total fertility, the world and the development groups



Source: United Nations, Department of Economic and Social Affairs/Population Division. *World Fertility Report: 2009*. United Nations, New York 2011.

phenomenon, per se highly positive, also carries serious consequences in a number of areas, such as the health of older people and the sustainability of the social security system.

Looking at the future of Europe, there are currently 740 million people living in it and projections indicate that in the future (not counting immigration) the population of the Northern Countries and the UK may grow, whereas that of Southern and Eastern Europe will continue to decrease. At present there is no indication that overall the indigenous population of Europe will grow.

However, trends can change. In fact, the trend in the Nordic Countries, where fertility rates were the first to decline, are changing: in 2008 live births totalled almost 300,000, 9% more than in 2001, with Iceland having the highest fertility (2.14). Total fertility rates in the other Nordic countries have also increased. Whereas this may indicate a positive trend, in absolute terms these increases are negligible for Europe's future.

What will really matter for Europe at the present moment is the unstoppable influx of migrants. This phenomenon, can by itself dramatically influence the population structure of European countries, even if the absence of regulation represents a major issue, on the one hand raising hostility against migrants and, on the other, tragically causing the death of thousands of people due to the dramatic condition of migrations.

Much more important will be how European countries will be able to regulate or control the ongoing migratory process, without doubt the most important factor in determining the future of European population.

In conclusion, the present situation in a number of European countries can be synthesized in simple terms: The demographic revolution brought with it "too many grandfathers for too few grandchildren". At the same time ageing will, hopefully, become more and more "healthy and active", although countries will have to adjust their budgets to cope with the new situation.

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Infertility and pregnancy in the menopausal transition and beyond: clinical and ethical aspects

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There are nowadays new clinical and ethical challenges concerning fertility and ageing.

We can distinguish two groups of infertility: the unspecific one, mainly represented by age, and the specific one.

Age not only affects the chance of becoming pregnant, but even more the chance to give birth, since miscarriage is influenced by the mother age. The age of mothers has grown dramatically in the last fifty years. In this time period age of menopause has sensibly shifted on in 1-2 years only, whereas life expectancy has increased in decades.

The options to overcome this gap are:

- egg donation;
- social freezing.

Egg donation is characterized by high success rates, promising results in all groups, successfulness in peri- and post-menopause women. Unfortunately, egg donation is strictly and specifically regulated by local constitution and is still banned in a couple of countries, including Switzerland. The technique is expensive, somewhat risky for the donor and increases pregnancy risks in comparison to homologous IVF, together with the risk of severe maternal and neonatal complications. In addition available eggs are limited (• Table 1).

The issue is complicated by the hypothesis that pregnancy outcomes, together with maternal and neonatal complications may somehow suffer from mother age [1]. However, recent studies have revealed that the contribution of maternal age to adverse outcomes in pregnancies without significant medical and obstetric history is modest [2]. Moreover, Steiner and Paulson conclude that there is no evidence supporting the hypothesis that mothers of advanced maternal age have reduced parenting capacity due to physical or mental disability [3]. And even Tearne *et al.* affirm that increasing maternal age was

Table 1. Egg donation: pros and cons

Advantages	• High success rates (>50% chance of delivery)
	• Promising in all age groups
	• Successful in peri- and postmenopause
Disadvantages	• Different legal regulations
	• Financially driven:
	Expensive
	Available only for wealthy recipients
	Compensation attracts donors
	Big business for infertility centers
	• Risk for harm of the donor:
	Risk of ovarian stimulation
	Risk of ovum pick-up procedure
	• Potential misuse of donors
	• Increased pregnancy risks compared to homologous IVF
	• Limited availability of eggs

found to be a protective factor for child behavior morbidity [4]. Yet, another central issue concerns the legal legislation on egg donation.

A more recently developed option is provided by social freezing. In contrast to egg donation, this technique does not present any further pregnancy risk compared to homologous IVF. In addition, donor risks are taken by the recipient, which represents an important ethical point. However this method might apply only to women in their fertile phase and chances for pregnancies are strictly dependent on the quantity and quality of the available eggs (**Table 2**).

In summary we can conclude that whereas fertility is dramatically decreasing with advancing female age, egg donation represents a reliable option for healthy women, yet social freezing may become a promising alternative.

Table 2. Social freezing: pros and cons

Advantages	• No increased pregnancy risks compared to IVF
	• No donor necessary
Disadvantages	• Longterm option / useful in the fertile phase only
	• Later pregnancy chances depending on quantity and quality of the available egg
	• Different legal regulations
	• Financially driven:
	Expensive
	Available only for wealthy women
	Big business for infertility centers
	• Potential misuse as life style technique

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Global health after menopause: which health care model?

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Health of menopausal women around the world is very different, as much as its managing. Paradoxically the average health in menopausal women is not proportioned to the number of sources in the different countries.

In 2016 we defined a model of care for healthy, menopause and ageing [1]. The need of such a model is defined by the growing number of menopausal women, which will reach 1.1 bln by 2025. Those patients need personalized approaches, based on a listening approach by the physicians, and on multidisciplinary counseling. The concept of Active and Healthy Ageing (AHA) is the one to pursue [2]. It is meant to be a process to optimize opportunities for health to increase healthy life expectancy, healthy life years and quality of life for all people as they age. AHA allows people to realize their potential for physical, social and mental well-being throughout the whole life course.

This concept has met to put into action by European Innovation Partnership, launched in 2012, and has the aim to increase the average healthy lifespan by 2 years by 2020. The project intends to enable EU citizens to:

- lead healthy, active and independent lives;
- improve the sustainability and efficiency of social and health care systems;
- boost and improve the competitiveness of the markets for innovative products and services, thus creating opportunities for business.

Health can be defined by orthogonal concept, relating diagnostic findings (x axis) and feelings (y axis). The relation between these two parameters can define the healthy, functionally healthy, sickness or disorder of a patient (• Figure 1).

Usually we operate a dynamic balance between faced demands and the individual capacity to adapt. We have to consider then that physical, mental and social functio-

ning differs between individuals and changes due to aging. In our practice, the sick people often appears as the most easy to rely to.

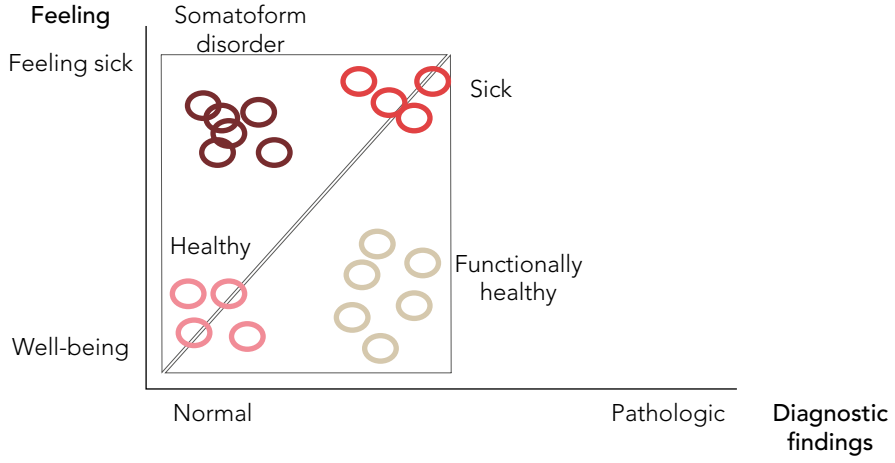
In the last century two main classifications have been created: ICD, International Classification of Disease, by the WHO in 1948; ICIDH, International Classification of Impairment, Disability and Handicap, by the WHO in 1980, further developed to ICF, International Classification of Functioning, Disability and Healthy.

Nowadays the goal is to combine the two of them, to consider the etiology, pathogenesis and organ specific manifestation, combining them with the functioning approach, considering the body structures, functions, activity and participation.

It is also important to address what is aging: the life accompanying change of structure, function and capabilities of a human being from conception till death, in health and disease. Aging can be hierarchized [3] considering the manifestation and parameters at different levels (population, individual, functional systems). The goal should be to consider ageing at a functional level. In addition we should consider that aging rate is not the same of our capabilities, but changes can be completely asynchronic and aging level is strictly dependent on what we are looking at. So when we talk about healthy ageing we should consider not only to increase life expectancy but also to improve optimal function on all levels.

Concerning healthy menopause (HM) we should consider this concept regardless when and why menopause occurs, and his should be done with a holistic model of care covering physical, psychological and social functioning (AHA). It reflects the need of midlife women to maintain or improve the quality of life. This concept incorporates disease and disability.

Figure 1. Health as orthogonal concept



This holistic model of care of healthy menopause has specific goals: health care and health promotion for midlife women and empowerment of women to make positive choices for their post-reproductive health and well-being. To put this concept into action we created a model where the woman is in the center. Usually the primary care physicians are the main actors, namely the general practitioner and general gynecologist. The gynecologist can transfer the woman to a secondary care center, a certified HM center where we have a triangle consistent of the lead clinician, the specialized nurse, and the menopausal woman. This center has also some additional duties: education and training of the professional, and to talk to authorities and the scientific world to improve the service.

The fundamental goal is to set up a personalized care plan for woman's short- , mid- and long-term goals in the context of physical, psychological and social functioning, incorporating the woman's perception of her life status within her culture and value system, expectations, concerns and opinions about endocrine and age-related physical and psychological changes related to midlife.

Clinical skills become then more complex and structured, since the practitioner should respond to many requests by the menopause woman, including medical management, comorbidities, symptoms and diagnosis in menopause, guidelines in menopause treatment, fertility and contraception, together with specific gynecological issues.

Similarly the specialist nurse should have specific skills, since she has to provide and support strategies for empowerment in relation to educational interventions, physical activity/exercise, healthy diet, stress management, healthy lifestyle, prevention of (non)-communicable disease.

The center should also cooperate with other medical experts, to build a network on the service of menopause women.

Finally, the centers should be controlled for quality, by measuring the structure or by measuring the content, the latter being more difficult. We should probably develop an ICF based assessment for measuring function.

In conclusion, the conceptual framework of the healthy menopause is a holistic model of acre covering physical, psychological and social functioning and incorporating disease and disability.

The HM healthcare model's core consists of a lead clinician, specialist nurse(s) and the woman herself, supported by an interdisciplinary network of medical experts including alternative/complementary medicine.

Provision of HM specialist teams in Europe is scant and needs to be expanded, as the number of postmenopausal women is increasing. HM medical specialist teams should follow standard quality criteria and receive internationally acknowledged quality management certification.

Accreditation of the subspecialty Women's Health should be actively promoted.

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SESSION 2

PREVENTION/IMPACT OF LIFESTYLE

Impact of lifestyle versus HRT on different cancers after menopause

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Firstly we have to focus on the importance of lifestyle in cancer after menopause. Lifestyle can be summarized in obesity/overweight, physical activity, smoking, diet, alcohol.

It has been demonstrated that lifestyle has a strong impact on death [1] (• Table 1), this controlling diet/nutrition, PA, BMI may lead to a decrease of cancer by 26% in the UK, 24% in the USA, 19% in Brazil and 20% in China. In particular colorectal, endometrial, breast and ovarian cancers are impacted by lifestyle and hormone replacement therapy (HRT).

Obesity and overweight can dramatically influence the onset of cancer [2] as the ovarian and breast ones, among others.

In addition hormone therapy can impact cancer, for example breast, endometrial, colorectal [3]. Yet Simin *et al.* [4] showed that in a Swedish population-based cohort

• **Table 1.** Deaths attributable to lifestyle in 2010 worldwide

Risk factor	Number of deaths	95% intervals of uncertainty
Smoking	1,443,924	920,763-1,743,849
Second-hand smoke	346,304	252,702-439,439
Alcohol	1,720,059	1,541,469-1,886,125
High body mass index	1,738,466	1,454,008-2,036,059
Dietary factors and physical inactivity	5,815,748	5,380,274-6,261,225

Source: Gompel *et al.*, 2013 [1].

study, women with HRT suffers from an increase in breast (1.40), endometrial (1.78) and ovarian cancer (1.15), however gastrointestinal cancers decreased (0.88).

Physical activity is another way of modifying obesity, and consequently cancer upcoming. Moore *et al.* [5] showed in a cohort study that physical activity decreased most of cancer, except of melanoma.

What is the interaction between physical activity and hormone therapy? HRT does not oppose physical activity effects.

Menopause hormone therapy (MHT) does not affect the risk of death from all causes [6] or somehow it decreases the mortality. In addition, MHT reduces the incidence of diabetes 2 and consequently of specific types of cancer [7], this probably related to the improvement in insulin resistance induced by MHT.

In conclusion, MHT could actually represent an inducer of cancer incidence in case of breast cancer, endometrium cancer and ovarian cancer, nonetheless alcohol, obesity and the absence of physical activity showed a powerful power to increase cancer incidence in the same tissues [8].

In fact, in obese women, the hormone treatment does not increase the risk of breast cancer as due to obesity [9], as well as of endometrial cancer [10] which was even reduced by MHT. In case of ovarian cancer, the increase due to obesity was found only in women that did not ever use HRT.

All these evidences led us to the conclusion that:

- lifestyle modification can reduce risk [11];
- obesity is a major factor for cancer;
- combined hormone therapy is a risk factor for breast cancer, but can be attenuated in selecting patients and modulating other factors.

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Can we protect the aging female brain?

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Alzheimer disease (AD) is the most common form of dementia, and the burden of this disease is greater for women than men. Two-thirds of AD patients are women. At 65 women have more than a 1 in 6 chance of developing AD during the remainder of their lives, compared with a 1 in 11 chance for men [1]. Women in their 60s are about twice as likely to develop AD over the rest of their lives as they are to develop breast cancer. The major contributing factor to higher burden of AD in women is that women live longer than men, and age is the major risk factor for AD [2]. There are about 34 million people living with AD, and although current pharmacotherapies for AD can improve memory symptoms they do not alter the underlying disease. So what can we do? We can prevent the onset of the disease.

It is estimated that up to half of the total number of AD cases worldwide could be prevented by reducing the burden of well-established risk factors for AD such as diabetes, hypertension, obesity, depression, smoking, physical and cognitive inactivity [3]. Yet women show higher prevalence of certain risk factors for AD. In fact, when compared to men, they show higher body mass index (BMI), higher rates of depression, lower rates of exercise, higher cholesterol levels, and greater risk due to the predominant genetic risk factor (apolipoprotein epsilon 4 allele; APOE4) [4]. The analysis of individual effects of these risk factors show that their action is synergistic, not additive. BMI is a relevant risk factor for AD, where either high BMI or low BMI increase the risk of AD 21 years later. It has been demonstrated that TV watching increases the risk for AD [5]. Randomized trials tell us that by modifying lifestyle we actually can counteract the onset of dementia. In particular Mediterranean diet, supplemented with olive oil, soy isoflavone supplements and Tai chi exercise can prevent the onset of AD [6].

The APOE4 gene has widely been recognized as crucial in the development of AD, and APOE genotype matters more in healthy older women than in men. A single

APOE4 allele increases the risk of clinical decline in healthy older women, but not in men [7]. Nevertheless cardiovascular exercise, such as brisk walking, reduces risk of AD later in life, even among those with an APOE4 allele.

For women it is important to consider the role of menopause in cognition and brain aging. The main symptoms of menopause are hot flashes and vaginal dryness, however memory performance is another dominant symptom related to the menopause transition. Memory performance is strongly affected during the transition through menopause, decreasing right before the onset of perimenopause, worsening during early menopause and then likely reverting in postmenopausal period [8].

Different hypotheses have been formulated for this change in memory performance. One focuses on changes in circulating levels of estradiol, since memory decreases in oophorectomized women unless they are treated with estradiol. If oophorectomy occurs before the menopause, the risk of cognitive impairment or dementia increases up to 70%. Memory appears to be the most affected cognitive capacity during menopause, and neuroimaging studies show that estrogen therapy can act on the hippocampus and prefrontal cortex to improve memory.

Hot flashes are the main menopausal symptom and their role in memory problems during the menopause is just beginning to be understood. Most studies so far used measures of hot flash symptoms that were based on diaries or questionnaires, and this method is limited by the need for women to recall the hot flashes they had, including those at night. My group and I have recently been utilizing a Biolog Skin Conductance Monitor to measure physiologic hot flashes. This instrument allow us to measure the onset of a hot flash, and also to register the subjective experience of hot flash, since the patient can press the button by herself to register a hot flash when it occurs. This technique appears to be valid because unlike subjective hot flashes, physiologic hot flashes show no placebo effect [9]. Additionally, physiologic hot flashes but not subjective hot flashes are linked to memory decline. The more physiologic hot flashes the women are having, the worst their memory performance.

To demonstrate that hot flashes are specifically related to memory decline, we used stellate ganglion blockade, which can reduce hot flashes but which does not appear to directly influence the brain circuitry underlying memory performance [10]. We found that memory performance improved in direct relation to the improvement in hot flashes, suggesting a potential direct relationship between hot flashes and memory problems. Then why do hot flashes impair memory? Following a hot flash, there is a surge in cortisol that might contribute to memory problems. Cortisol does affect memory, and this working hypothesis could explain the relation between hot flashes and memory impairment in menopausal women. We also conducted neuroimaging studies, and found that both brain structure and functions are associated with the frequency of hot flashes [11]. In particular white matter hyperintensities increase with hot fla-

shes and the resting state of the brain is also altered in relation to hot flash burden.

This evidence raises questions about the role of hormone therapy (HT) not only in treating hot flashes but also in possibly improving memory performance. A prominent theory says that the neuroprotective effects of HT depend on timing of initiation in relation to the menopause and/or age [12]. In fact there is some evidence that initiation of HT early in the menopausal transition is associated with cognitive benefit but later initiation confers no cognitive benefit. In contrast to Women's Health Initiative Memory Study (WHIMS), which was conducted in elderly postmenopausal women, three other studies (WHIMSY, KEEPS, and ELITE) demonstrated that early use of HT has neutral effect on cognitive function in early menopause. Yet these studies were conducted on healthy women without hot flashes so it is unknown how HT affects memory function in women with moderate to severe hot flashes. Notably, neuroimaging findings in KEEPS suggests that transdermal estradiol decreases AD neuropathology as measured by the amount of beta amyloid in the brains of women randomized to estradiol versus placebo. Interestingly these improvements were observed in women with a genetic predisposition for AD. There are still many gaps in understanding about HT and cognition (• Table 1).

• **Table 1.** Much is not yet known about hormone therapy (HT) and cognition

Does HT affect cognition in women for whom HT is indicated – i.e., women with moderate to severe VMS?
Does use of HT or oral contraceptives in the perimenopause – as distinct from the early postmenopause-enhance cognition?
Does early use of HT have effects on Alzheimer's disease risk and the neuropathology underlying risk?
Is HT effective in preventing cognitive decline in women who undergo early surgical menopause?

We still do not know if:

- HT affects cognition in women with hot flashes – the very women for whom HT is indicated;
- HT or oral contraceptives enhance cognition in the perimenopause, the menopausal stage when memory starts to decline;
- early use of HT has any effect on AD risk and neuropathology underlying risk;
- HT is effective in preventing cognitive decline in women who undergo early menopause.

Studies must be carried on to elucidate these key questions.

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Role of estrogens for cardiovascular health in women: preclinical data

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Cardiovascular disease (CVD) is the leading cause of mortality in women. Importantly the incidence for CVD increases with age, especially in the postmenopausal women, compared to age matched men. Multiple clinical and observational studies provide evidence that estrogen therapy can induce deleterious as well as beneficial actions on the cardiovascular system.

Several experimental studies conducted in animals over the last 30 years, demonstrated that the protective actions of estrogens against CVD depends on the timing of treatment initiation and the stage of disease progression. Results from animal and clinical studies provide disparate outcomes of both beneficial and deleterious effects of estrogen therapy. The current focus of our research is to clarify and test the test the hypothesis that estrogen protect PMW against CVD and to delineate the mechanisms involved.

With regard to coronary arteries, it is well established that multiple factors including stress, diet and endogenous/exogenous factors can damage the endothelium thereby triggering coronary artery disease. Importantly loss of endogenous protective factors may also trigger a dysbalance leading to CVD, which interestingly happens more frequently in postmenopausal women. In general, aging is associated with CVD, moreover in women this is associated with circulating estrogen levels, which negatively effects (inhibits/prevents) intimal thickening [1].

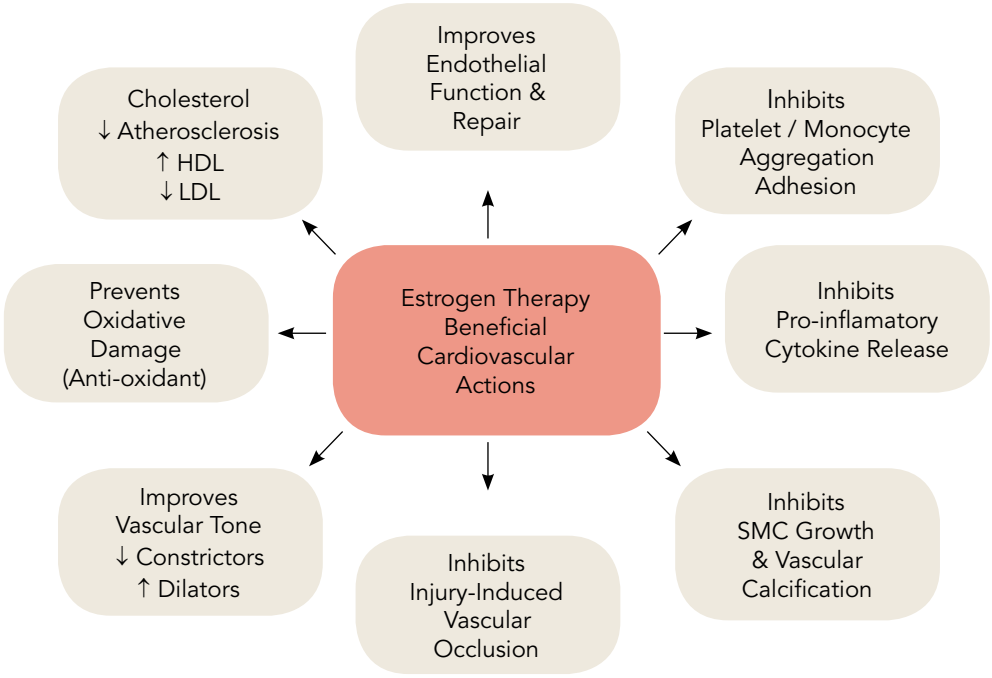
The intimal thickening of the blood vessels is largely caused by a cascade of cellular processes including endothelial damage/dysfunction, platelet adhesion, inflammation, macrophage/monocyte invasion, local release of growth factors, migration/proliferation of smooth muscle cells and vascular calcification. Drugs that can target these processes are protective against progression of vascular remodeling and CVD.

Interestingly, as summarized in • **Figure 1** estradiol mediates its cardiovascular protective actions by blunting/inhibiting inflammation, vascular calcification, smooth muscle growth, hypoxia and oxidative stress, decreasing vasoconstrictors (endothelin), immune cell macrophages, adhesion molecules, cholesterol and increasing vasodilators (nitric oxide and prostaglandins). Early studies conducted in our laboratory also demonstrated that estradiol induces its vasoprotective actions, in part, via increased nitric oxide and prostaglandin production [2, 3].

Subsequent studies done in monkeys demonstrated that estradiol inhibits vascular LDL accumulation [4], suggesting that lack of estradiol would promote LDL accumulation. Osako *et al.* [5] demonstrated that estradiol inhibits atherosclerosis and vascular calcification, which is a good indicator for coronary artery disease. Moreover, estradiol was demonstrated to promote endothelial recovery and growth [6]. Studies from group of Oparil *et al.* [7] demonstrated that estradiol inhibits injury-induced vascular occlusion, whereas studies from our laboratory showed that the inhibitory effects of estradiol is mediated via the estradiol receptor ERs, as SMCs expressed both ERα and ERβ [8].

On the other hand, Oparil *et al.* (7) found that male mice treated with estradiol, were not protected against injury-induced neo-intima formation in contrast to females. Since

• **Figure 1.** Estrogen therapy's cardiovascular protective actions



male rats express ERs, the above findings suggested that the effects of estradiol may be ER independent. The specific role of ERα and ER β was investigated in knock out mice. The inhibitory effects of estradiol were not lost and maintained, suggesting that the antimitogenic actions of estradiol are not solely dependent on ERs and may involve ER-independent mechanism. We then investigated the actions of endogenous estradiol metabolites and found that 2-methoxyestradiol inhibits SMC proligeration and prevents neointima formation [9]. Although cell based vitro studies and in vivo animal studies provide evidence that estrogen protects against CVD, yet the outcome of the WHI study showed no protective effects of HT on cardiovascular disease. Subsequent analysis of the trial findings was initiated to understand the possible factors responsible for the negative outcomes of HT in WHI study. Various factors that may have neutralized the cardioprotective effects of estrogens including lifestyle factors, the type of estrogen used, the type of synthetic estrogens, and the timing of treatment initiation and years after menopause were highlighted and investigated in animal models.

Interestingly it was shown that MPA, a synthetic progestin, blocks the anti vaso-occlusive actions of estradiol [10], suggesting that this molecule can interfere with the positive action of estradiol. It was also demonstrated that different estrogens produce different effects, thereby rendering the choice of hormone for therapy as an important factor for therapeutic success [8].

We know that in cardiovascular terms the age-dependent obstruction of the vessels happens, so we have to consider that the time of treatment may define the cardiovascular protective effects of hormone therapy [11].

In the WHI study a large population analyzed/studied were in their late menopause period, when the degenerative process of vessels was already established. Hence, it is conceivable that hormone therapy was not sufficient to overcome or reverse the established occluded condition of the vessels. This notion is supported by the observations made by Clarkson *et al.* in monkeys given healthy or atherosclerotic diet and the capability of estrogen to subvert the atherosclerotic effects when the treatment was initiated early, but not later when atherosclerosis was established [12].

Moreover, basic study by Huang *et al.* [13] revealed that timing decreases the expression of estrogen receptors, in accordance with the observation by Lindsey *et al.* [14] that estrogen mediated relaxation is lost in aged arteries. Many other studies demonstrated that in aged mice estradiol can even worsen atherosclerosis. The concept for the window of opportunity for initiation of estrogen therapy is also supported by outcome in younger women taking estrogen therapy within 10 years of menopause. Promising positive findings regarding the window of opportunity for estrogen replacement have recently been demonstrated in a clinical trial [15]. In addition, some preclinical data revealed that lowering the dose of estradiol could be effective in inhibiting the intimal thickening, thus atherosclerosis [16].

Finally the impact of route of estrogen administration should also be considered. Interesting data, in fact, suggest that transdermal estradiol therapy has less adverse effects on thromboembolism, even if its efficacy in preventing intimal thickening is comparable to oral administration [17].

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Estrogenic and non-estrogenic measures to maintain cardiovascular health in women: clinical data

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Cardiovascular disease (CVD) is the leading cause of death in women and its incidence increases with age, especially after menopause. The well-known risk factors for CVD include family history, diabetes, smoking, hyperlipidemia, blood pressure and obesity, and many of these risk factors are modifiable. However, also female sex-specific risk factors for CVD have been identified, such as autoimmune diseases, hypertensive pregnancy disorders, PCOS, and early menopause.

Smoking is one of the most preventable risk factor for atherosclerosis. It induces vascular dysfunction and is a more potent risk factor for myocardial infarction in women than in men. Smoking women also reach menopause 1-2 years earlier than non-smokers [1].

Hypertension is another significant risk factor, but in women it is often underdiagnosed and under-treated. It has a prevalence of 30% in developed countries, and it affects especially women after 60 years age [2]. Low HDL cholesterol and high triglycerides are better predictors of CV mortality in women than in men, and also diabetes appears to be a greater CV risk factor in women than in men. Obesity is a globally growing health problem. Furthermore, in menopause we observe a relative increase in total and abdominal fat, increasing the risk for metabolic syndrome, diabetes and CVD.

All the cited risk factors are modifiable with life style changes. Specifically, adopting a Mediterranean diet, maintaining a normal weight (BMI 19-25), practicing physical activity and quitting smoking will contribute to a lower CVD risk.

Although CVD is the leading cause of death in women, the majority of the women feel their main health concerns are breast cancer or other cancer types, evidencing that there is a big underestimation of CVD risk in female population [3]. We then have a big duty to sensitize women to the topic. Cardiovascular risk should be

assessed in all women consulting a gynecologist at menopause. We should also keep in mind that CVD often does not cause any symptoms, and that 2/3 sudden cardiac deaths in women occur without any prior symptoms.

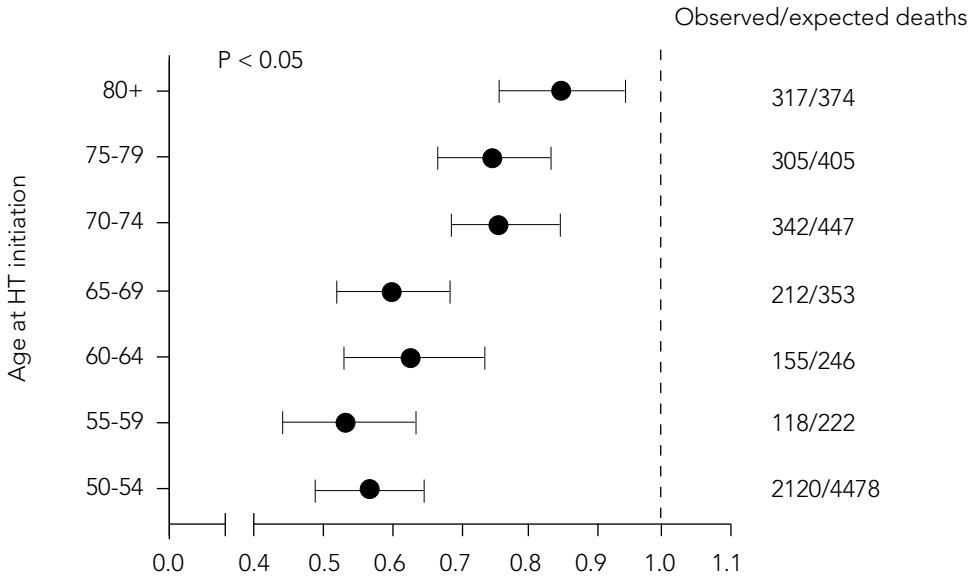
What about the role of estrogens? It is clear that women in premenopausal age have a lower risk for cardiovascular disease than men. Experimental studies indicate that this may be due to the vasculoprotective effects of estrogen. Also, several observation studies on the effects of hormone therapy (HT) on cardiovascular disease conclude that HT is protective against CVD. However, the original Women's Health Initiative (WHI) results indicated that HT increases coronary heart disease events and strokes [4]. This strongly influenced the use of HT in various countries [5-8].

The discrepancies between observational studies and the WHI study may be explained by different timing of the HT initiation or by the different hormone regimens used. Indeed, the timing of HT seems to be fundamental, since administration of HT within the first 10 years after menopause reduces the CVD risk, in contrast to what happens if HT is administrated later, as evidenced by Cochrane meta-analysis [9] and a recent randomized controlled trial [10].

In Finland we have collected national data on HT and cardiovascular mortality. We used our Medicine Reimbursement Register to identify all the women (n = 489,105) that had used HT between 1994 and 2009. All cardiovascular deaths in women were retrieved from the Causes of Death Register, and cardiac deaths in HT users were compared to the expected number of deaths in the age- and year-matched background population (standardized mortality ratio). First, we found that the longer women had used hormone therapy the lower was the risk of cardiac death [8, 11]. Then, analyzing our data by the timing hypothesis point of view, we were able to show that the earlier the women had started HT, the lower was the cardiac mortality risk (• Figure 1). Finally, we wanted to compare the impact of different progestins on cardiovascular death risk, as progestins similar to progesterone may show lower impact than the more androgenic progestins on the beneficial estrogen-mediated cardiovascular effects. In our data dydrogesterone appeared superior to MPA or NETA on all-cause mortality risk, but none of the progestins significantly modified the cardiovascular effects of estradiol [12] (• Table 1).

In conclusion, estradiol-based HT was associated with a reduced CVD mortality risk in our nationwide study, and furthermore, estradiol-based HTs were accompanied with larger CVD mortality risk reduction, the earlier the therapy was initiated. However, various progestins as complements to estradiol did not modify this timing effect. Our data indicate that HT is appropriate for symptomatic women near menopause who have no major contraindications. Yet, HT needs to be personalized, considering individual lifestyle and CVD risks.

● **Figure 1.** Risk of cardiac death in women initiating the use of hormone therapy at different ages."The Timing Hypothesis"



The data are expressed as standardized mortality ratio (SMR) and 95% confidence intervals (CI). Line at 1.0 indicates the cardiac mortality risk in the age-matched background population.

Source: Savolainen-Peltonen *et al.*, 2016 [12], mod.

● **Table 1.** Risk of all-cause death in women younger or older than 60 years when initiating different hormone therapies, classified by the type of progestin

	Age at hormone therapy initiation					
	< 60 years			≥ 60 years		
	Obs deaths	Exp deaths	SMR (95% CI)	Obs deaths	Exp deaths	SMR (95% CI)
Estradiol only	5 002	6 594	0.76 (0.74-0.78)	3 049	3 993	0.76 (0.74-0.79)
NETA	6 116	9 122	0.67 (0.65-0.69)	1 956	2 549	0.77 (0.73-0.80)
MPA	4 888	6 712	0.73 (0.71-0.75)	672	1 001	0.67 (0.62-0.72)
Dydrogesterone	1 565	2 743	0.57 (0.54-0.60)	116	182	0.64 (0.53-0.76)
Other progestins	2 245	6 466	0.65 (0.62-0.68)	159	276	0.58 (0.49-0.67)
Tibolone	839	1 178	0.71 (0.66-0.76)	143	125	1.14 (0.96-1.35)

The data are expressed as standardized mortality ratio (SMR) and 95% confidence intervals (CI).

Source: Savolainen-Peltonen *et al.*, 2016 [12], mod.

Finally, another important issue is the decision of the time to stop HT use. Menopausal vasomotor symptoms last for a median duration of 7,4 years. However, current guidelines recommend that HT should be used for the shortest possible time. Analyzing the register-based data in our hand, we found that during the first year after HT discontinuation cardiovascular mortality risk was significantly increased, especially in women younger than 60 years of age. Our findings then question the cardiovascular safety of annual/biannual HT pause practice to evaluate whether young /symptomatic postmenopausal woman could manage without HT. These results need to be further elaborated in a randomized controlled setting.

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Fracture prevention from menarche to menopause

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Osteoporosis is a disease characterized by a low bone mass, microarchitectural deterioration of bone tissue leading to increased bone fragility and a consequently higher risk of fracture. Microarchitectural deterioration is not clinically revealable today, although it is a key component in osteoporosis.

Osteoporosis is one of the main complications after menopause, with a prevalence increasing with age. However, fracture can easily be prevented in a specific life period of a woman: from menarche to menopause. From the first menstrual bleeding bone becomes an estrogen dependent tissue, and then its density becomes very stable with osteoblasts and osteoclasts in balance during regular menstrual cycle.

During pre-menopause, Bone Mass Density (BMD) does not change. In this period, oral contraception treatment (COC) does not negatively affect BMD [1]. In contrast, recent studies have reported that use of oral contraceptives may even reduce the risk of fracture, moreover the longer the treatment was, the lower the risk of fracture [2] (• Table 1).

Interestingly, the risk of fracture in perimenopausal women treated with oral contraception is absent. On the other hand, DMPA (depot medroxyprogesterone acetate) as contraception did not have benefic effects, and the loss of bone mineral density was consistent when compared to total population, in addition the fracture risk was augmented by the use of DMPA, even in young women [3].

Another important condition to be considered are the premature ovarian failure and bilateral oophorectomy. Both share a significant decrease in BMD [4].

The same happens in hypothalamic induced amenorrhea, as in anorexia nervosa, with the additional risk of trabecular perforation [5] which persists even after that Bone Mass Density has been recovered. In anorexia nervosa patients, BMD is severely affected, and in those cases the estrogen therapy can difficultly be considered.

The other group of patients consists of premenopausal women who received bi-

Table 1. Oral contraceptive use and fracture risk

Variables	Odds ratio (95% CI)*	P-value
Oral contraception use ≤ 1 year *vs* never use	0.92 (0.82-1.04)	0.184
Oral contraception use 2-3 years *vs* never used	0.81 (0.71-0.93)	0.003
Oral contraception use 4-5 years *vs* never used	0.79 (0.65-0.94)	0.008
Oral contraception use > 5 years *vs* never used	0.62 (0.53-0.74)	<0.001

* Logistic regression model adjusted for smoking status, BMI, diagnosis of alcohol abuse, diabetes (%), bone density disorder, dementia/Alzheimer's, thyroidal disorder, anorexia nervosa, premature menopause, epilepsy, endometriosis, and corticosteroid treatment (N = 6485/12.970).

Source: Dombrowski *et al.*, 2017 [2].

lateral oophorectomy. Even in this case the rate of fracture is dramatically increased [6] already in young women. However, estrogen treatment has beneficial effect independently on the time of the beginning.

In peri- and postmenopausal patients we observe a decrease in estradiol and inhibins, accompanied by an increase in FSH and BTM, however the chances to develop severe bone loss or not are based on a genetic predisposition.

What we can do is to approach postmenopausal osteoporosis with either a primary or a secondary prevention approach. The primary prevention prevents the first fracture, while the secondary one decreases fracture risk and restores bones.

However, to prevent osteoporosis we have to keep in mind that Mineral Bone Mass is just a façade of the problem, we have to remember about the micro-architectural structure of the bones, since a great part of fractures are not related either to osteoporosis or osteopenia [7]. The best way to obtain a projection of hip fracture rate combining the BMD with the number of risk fracture.

Germany, Austria, and Switzerland share guidelines (DVO) from 2006 on risk factors and patients to be treated or not, currently they are being updated. The number of risk factors is higher than in FRAX (Who Fracture Risk Assessment Tool), to more individualize patient treatment.

Hormone Replacing Therapy remains the only effective primary prevention. Estrogens is the most effective, independently on the dose, and the percentage of responding bones are significantly high (90% as reported by Lindsay *et al.*) [8].

Interestingly, in elderly women, the dose of treatment does not necessarily have to be high to be effective. The ULTRA study demonstrated that even 0.014 mg patch estradiol could be effective in postmenopausal women [9], the older the women get, the lower the needed doses are.

Finally, the Cochrane analysis [10] stated that the risk of fracture was the only outcome for which strong evidence showed clinical benefit derived from hormone therapy, thus

defining HT as fundamental in primary prevention against loss of Mineral Bone Mass.

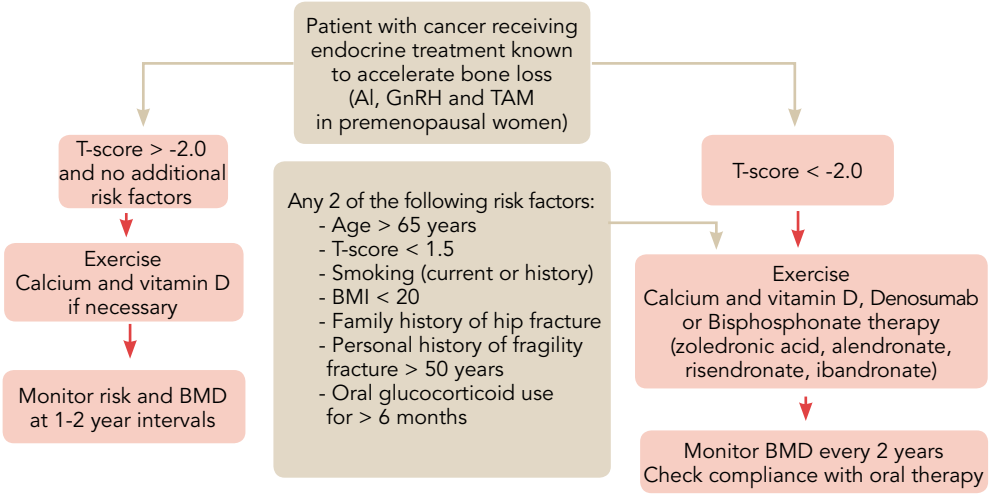
For secondary prevention there are a lot of compounds available in Europe which have been demonstrated as effective, although primary prevention remains the best.

In conclusion, we can assume that estrogen regulates bone balance in turnover and its deficiency is a strong risk factor for fracture in pre and post menopausal women.

Thus, these women need to be informed about their increased fracture risk and should be offered HRT/ERT for fracture prevention (• **Figure 1**). HRT is still the first line and effective option in the primary prevention. In addition, multiple secondary prevention options are available and should be applied.

Lastly it is important to know that breast cancer is a condition that represents a higher risk of fracture, since aromatase inhibitors treatments leads to endogenous estradiol serum levels reduction [11]. Treatment with bisphosphonate for bone health in these patients [12] leads to a reduction in the development of bone metastasis and in an improved survival.

• **Figure 1.** Recommended algorithm for managing bone health in women receiving aromatase inhibitor (AI) therapy for breast cancer



Source: Hadji *et al.* [11].

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Sexual health in aging women

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Among sexual disorders lack of female sexual desire, the absence of interest and passion is the most frequent in women. Lack of sexual desire occurs irrespective of age but is an important problem also at women of higher age [1]. This lack is often referred to partnership sexuality, and involves sexual phantasies and masturbation to a far lower degree. A main reason behind is the absence of sexual satisfaction, which is often due to a little consciousness of womens' own desires and to the inability of communicating them to the partner and integrating them into partnership sexuality.

The role of a sexual therapist is then mainly to guide a couple to discovery and discussion of their sexual desires and satisfaction because it is evident that sexual satisfaction does not depend on age but on the quality of the relation and on the energy the couple puts into their sexual life; moreover we must consider differences in sexual needs between women and men, and their usual reaction to different stimuli. The lack of sexual desire is felt as a relevant problem, especially in single women, together with lack of interest and tenderness. This has to be considered together with the fact that physiologically the arousal of orgasm decreases with the age.

The decrease in testosterone level is not sufficient to explain the lack of sexual desire, so different studies have been conducted on the issue. Shifren *et al.* [2] analyzed women after surgical menopause and found that testosterone increased sexual functioning as well as placebo did.

A study from Kleinplatz *et al.* [3] elaborated a list of factors associated with long term "great sex", which included being present, connection, deep sexual and erotic intimacy, extraordinary communication, interpersonal risk-taking and exploration, authenticity, vulnerability, and transcendence, e.g. factors which are independent from a testosterone level.

The use of testosterone is actually difficult because of lacking adequately low-dosed products for women as well as lacking long-term data on the safety in women. The use of flibanserin (available in the US), a medication originally developed as an antidepressant, which has to be taken on a daily basis and is associated with different side effects, only increases the number of sexual contacts very slightly.

In contrast, the physiological situation in post-menopausal women can certainly be improved by the use of estrogen, which is deeply involved in vaginal health.

General health is involved in sexual function as well, as it can suffer from many conditions connected to age. Sexual activity is associated with cognitive function in older age [4], so it might represent a resource for keeping mental health.

Age structures in couples and society, orientages of men towards younger partner, hamper the initiation of new relationships in elder women. There are new tools today, for example dating platforms, to support such women in finding an adequate partner, even if they suffer from some tricks, as misrepresentation of age and condition.

Adressing sexual health within the counselling of women, adjusting for physiological limitations and encouraging women to realize their partnership and sexual needs will likely improve quality of life in elder women.

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SESSION 3

FUTURE

Menopausal hormone therapy: available alternatives and substitutes in development

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"New Thinking" after WHI. The place of alternatives to MHT

Menopausal hormone therapy (MHT) is the most efficient therapeutic option for the treatment of climacteric symptoms. MHT has been shown to possess several additional benefits that non-hormonal methods cannot offer. Although it is evident that non-hormonal alternatives are indispensable for women not wanting to use hormones or for patients having personal risk factors not allowing the administration of MHT, it is less evident why these alternatives should be recommended to a woman presenting a clear indication for and no contraindications against MHT. To prefer non-hormonal alternatives to MHT in such a case is still the fruit of a serious misunderstanding of the evidence presented in the first publication of data emerging from the Women's Health Initiative trial (WHI) in 2002 [1]. The result is a fear of hormones persisting until today in many patients and doctors, a fear that is based on just one article and the media storm it did provoke in 2002. Today, much better evidence is available for the evaluation of the risk/benefit ratio of MHT in healthy women in their peri- and early post-menopause. Recently, the WHI authors recognized themselves that they have been wrong in 2002 [2, 3], and that to withhold estrogens to women presenting an indication for MHT has been a mistake.

Still today, five unproven claims are repeated again and again to support the postulated dangers and absent benefits of MHT.

1. **"The excess risk of cardiovascular death that can be attributed to menopause is uncertain".**

This statement does not consider the solid evidence from the Framingham Study [4]. This study demonstrates that menopause itself is the primary factor increasing the risk of cardiovascular mortality in women.

2. **"Currently, evidence is limited to determine whether different types of hormone therapy affect its benefit-to-harm profile or the prevention of chronic conditions".**

This statement does not consider the strong evidence from human and animal trials demonstrating different effects on coronary arteries between the different progestogens used in MHT. Similar evidence has been collected for the breast from population studies and animal experiments, demonstrating reduced proliferative stimulation in breast tissue with progesterone compared with MPA.

3. **"Currently, evidence is limited to determine whether different doses of hormone therapy affect its benefit-to-harm profile or the prevention of chronic conditions".**

The dogma of the minimal effective dose does not take into consideration that the WHI tested only one dose. There is no evidence supporting a lowest effective dose from this study. Although many other studies suggest that a lower dose can be used effectively for the treatment of vasomotor symptoms (VMS), the lowest effective dose may be different for vasomotor symptoms, for somatic changes or for fracture prevention. There is no identical minimal dose for all target organs of estrogens.

4. **"Currently, evidence is limited to determine whether different modes of delivery of hormone therapy affect its benefit-to-harm profile or the prevention of chronic conditions".**

This statement suffers from the mistaken idea that oral hormone therapy shares the same metabolic properties with transdermal hormone administration. In contrast, there is consistent evidence from big population studies, along with strong biological plausibility, for no increased risk of venous thromboembolic events and stroke with transdermal estradiol.

5. **"Evidence about whether the benefits and harms of MHT vary by age or time since menopause is limited".**

This statement leads to the wrong conclusion that data from older women with pre-existing risk factors can be applied to younger women, as did the Women's Health Initiative trial [1]. Instead, the Nurse's Health study [5], DOPS [6] and the recent ELITE trial [7] support all the conclusion that estrogens prevent the consequences of several chronic diseases such as fragility fractures or myocardial infarction when MHT is initiated early after menopause, within the "window of opportunity". This hypothesis has been confirmed first in the PEPI trial [8], a RCT. The PEPI trial recruited only women within the first 10 years after menopause. In addition, the HERS trial [9], also a RCT, demonstrated that there was no cardiovascular harm (but no benefit either) in elderly healthy women without pre-existing risk factors starting MHT later (mean age at inclusion 67 years). In contrast to these classical five misinterpretations of the evidence presented by the WHI trial, the actual knowledge on the effects of MHT allows the following conclusions [10].

- MHT may reduce climacteric symptoms and preserve bone density. In symptomatic women, a positive effect on quality of life can be expected.

- In Primary Ovarian Insufficiency, MHT is advised to be continued at least until the average age of menopause.
- MHT is the most appropriate therapy for fracture prevention in the early post-menopause.
- Healthy women younger than 60 years should not be unduly concerned about the safety profile of MHT. In this group of age, the benefits of MHT outweigh the risks.
- MHT has the potential for improving the cardiovascular risk profile through its beneficial effects on vascular function, lipid levels and glucose metabolism.
- MHT has been shown to reduce the incidence of new- onset diabetes mellitus.
- Cochrane analysis, other meta-analyses, and the WHI 18-year results all show a consistent reduction in all-cause mortality.
- There are no reasons to place mandatory limitations on the duration of MHT
- However, MHT should not be recommended without a clear indication for its use, such as significant climacteric symptoms or physical effects of oestrogen deficiency.

Therefore, alternative methods to MHT (• **Tables 1-2**) should be reserved for women having moderate symptoms only, not wanting a hormonal treatment, or having a contraindication against estrogens.

• **Table 1.** Alternative methods to MHT*

Life style changes, cognitive behavioural therapy	
includes alimentation, exercise, smoking cessation, alcohol use, partnership et.	
Non-hormonal treatments	
SSRI or SSRI/SNRI - low dose (also treats menopausal mood disorder)	Venlafaxine 75 mg, desvenlafaxine 50 mg, escitalopram 10 mg, paroxetine 7.5 mg daily
Clonidine	100 µg daily
Gabapentin	300-900 mg daily
Pregabalin	75-150 mg twice a day
Hypnosis	
Cognitive behavior therapy	
Weight loss for obese women	
Stellate ganglion blockade (specialist referral)	Severe resistant VMS
Phytotherapy (e.g. *C. racemosa*, phytoestrogens); complementary medicine	

* Availability of hormonal/nonhormonal treatment and indications for use from regulatory bodies vary between countries.

Source: Birkhäuser *et al.*, 2008 [11]; Jane, Davis, 2014 [12].

Table 2. Effect of recommended alternatives to MHT on vasomotor symptoms

*Lifestyle changes, cool environment	+
*Cognitive Behavioural Therapy (CBT)	+
Vitamin E, dong quai, and other herbal products: no significant difference compared with placebo	
*Acupunture	+/-
*Phytoestrogens, Isoflavones	+/-
*Black cohosh	+/-
*Antidepressants (SSRI/SNRI)	+
Clonidine (adrenergic agonist)	+/side effects (constipation, insomnia, dry mouth)
Gabapentin/Pregabalin	+/side effects (dizziness, headache, somnolence etc)
Dopamin agonists	+/side effects!
Ganglion stellatum blockade	

+ = good evidence; +/- = evidence contradictory.

* Recommended for current use.

Non-pharmaceutical alternatives

Non-pharmaceutical methods are largely underestimated. Importantly, we have to recommend **life style modifications and exercise**, having a highly beneficial impact on the climacteric syndrome, particularly on vasomotor symptoms [13-15].

It is well known that self-confidence is related to the suffering from menopause symptoms and to their intensity: the higher the self-confidence is, the lower are the menopausal symptoms [16]. Therefore, the **Cognitive Behavioral Therapy** might become relevant in reducing menopausal symptoms. Cognitive Behavioral Therapy (CBT) [17, 18] is a psychological intervention developing strategies to reduce unhelpful thought patterns, which improve responses to stressors. CBT protocols should not focus only on vasomotor symptoms, but also on depression, anxiety, sleep and sexuality. It has been recently reported that CBT reduced significantly VMS and depressive symptoms, as well as sleep difficulties [17] in postmenopausal women.

In several RCT's, **acupuncture and applied relaxation** have been shown to decrease hot flashes compared to placebo, being almost as effective as estrogens [19]. However, the data available on acupuncture are contradictory [20].

Herbal alternatives

In clinical trials and meta-analyses, **soy isoflavones** have been reported effective [21-23]. In addition, **phytoestrogens** have been considered effective in preserving bone health in menopausal women [24]. However, there are no fracture data. The effect of phytoestrogens on VMS has been analyzed in a Cochrane Review [21] which evaluated the efficacy, safety and acceptability of food products, extracts and dietary supplements containing high levels of phytoestrogens in comparison to no treatment, placebo or hormone therapy. 43 RCTs (4,364 participants) were included in this review. Only five trials yielded data suitable for inclusion in a meta-analysis and could be analysed. It was concluded that phytoestrogens might alleviate the frequency and severity of hot flushes and night sweats when compared to placebo. However, the Cochrane Review [21] states that there is no conclusive evidence on the ability of phytoestrogens to effectively reduce the frequency or severity of hot flushes and night sweats in peri- and post-menopausal women. Placebo effect in most trials was high with a reduction in frequency of hot flushes up to -59% in the placebo arm.

The Cochrane Review [10] recommends that concentrates of genistein having presented the most convincing benefits should be further investigated.

Also in a Cochrane review, **black cohosh** has been found to have no significant effect on hot flushes or other menopausal complaints [25]. However, in this analysis the different Cimicifuga species have been confounded and analyzed together. Most plant extracts were suboptimal, some preparations consisted of badly defined mixtures with other herbal substances, and the dosages used were in part incorrect.

However, trials done with the few available well-defined extracts of ***Cimicifuga racemosa*** show a significant effect on VMS that was superior to placebo. Several studies [26-28] report positive effects of *Cimicifuga racemosa* on major climacteric complaints, comparable to the well established effects of conjugated estrogens, transdermal estradiol or tibolone. Recent reviews looking selectively at *Cimicifuga racemosa* confirm a significant reduction of menopausal symptoms [29, 30]. It has to be stressed that such an effect has been observed with specific well-defined extracts of *Cimicifuga racemosa* only, and that these results cannot be generalized to other *Cimicifuga* species.

Cimicifuga racemosa has no phyto- or estrogenic properties and shows an excellent safety profile. It has no significant effect on the vaginal epithelium, and does not stimulate the endometrium or the breast. Preliminary data suggest that *Cimicifuga racemosa* has no negative impact on breast cancer survivors.

In conclusion, the standardized preparations of *Cimicifuga racemosa* are safe and present an efficient alternative to menopausal hormone therapy.

Non-hormonal pharmaceutical drugs

SSRIs and NSRIs: Considering the relevant role of norepinephrine in hot flushes, and its ability to act through central 2-adrenergic receptors, some SSIRs and SNIRs might exert beneficial effects on climacteric symptoms. As expected, several SSRIs and NSRIs have been demonstrated to relieve vasomotor symptoms and sleeping disorders. In a recent review, Stubbs *et al.* [31] conclude that SSRIs and SNRIs reduce the frequency and severity of hot flushes in peri- and post-menopausal women significantly. Paroxetine, citalopram and escitolapram are the most effective SSRIs, whereas Venlafaxine is the most effective SNRI (first-line), with desvenlafaxine as a second option. Treatment choice should be patient-specific and begin with the lowest dose available [31]. In contrast to the USA, SSRI and NSRI are not yet approved for the treatment of VMS in Europe. The most common side effects reported for both SSRIs and SNRIs are nausea and constipation, mostly resolving within the first week of treatment. SNRIs have been associated with increased blood pressure in some patients and should be used with caution in women with hypertension. SSRIs, including fluoxetine, duloxetine, bupropion, and especially paroxetine, have been shown to interfere with tamoxifen metabolism (inhibition of CYP2D6 > reduction of the formation of endoxifene, the active metabolite of tamixifene). Sertraline, citalopram, escitalopram, and venlafaxine induce this metabolic inhibition to a lesser degrees. However, women with a history of breast cancer and taking tamoxifen should better avoid all SSRIs. For this special population, SNRIs are the safest drugs. The first choice is venlafaxine/desvenlafaxine.

Clonidine, gabapentin and **dopamine agonists** have all been shown to have beneficial effects on VMS, although with in part serious side effects affecting quality of life. The effects of **vitamin E, dong quai** and **other herbal products** on VMS are not significantly different from placebo.

Finally, as a mean of last resort, **Ganglion stellatum blockade** may be beneficial [32].

Alternatives in development

Nowadays, not many new projects in the field of menopause are launched. Two new promising candidates being in evaluation for the treatment of VMS are estetrol and a neurokinin 3 receptor antagonist.

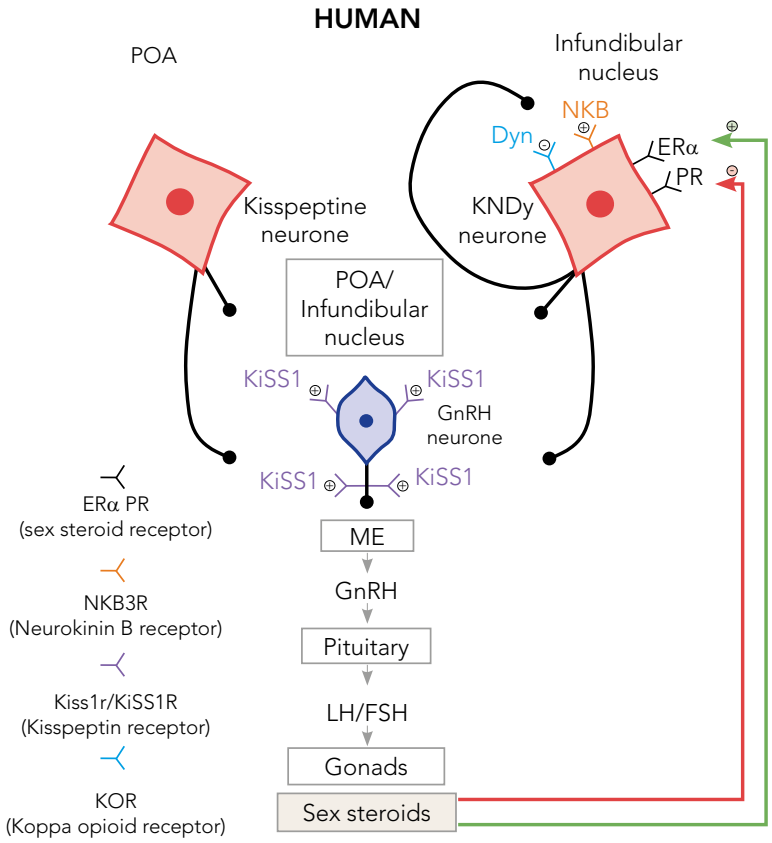
Estetrol (E4) is a natural estrogen produced exclusively by the human fetal liver during pregnancy; it has been shown to be remarkably safe in in vivo models and had limited interaction with liver and its function. E4 does not

- bind to the carrier protein SHBG, and
- induce its synthesis in hepatocytes cultured in vitro,
- change the activity of relevant cytochrome P-450 related liver enzymes involved in drug metabolism.

A recent trial on E4 [33] showed dose dependent estrogenic effects on endocrine parameters, bone turnover markers and on lipids and lipoproteins, supporting further investigation as a candidate for MHT. The first clinical results show an excellent benefit-risk ratio. Quantitatively, the effects of 10 mg estetrol were similar to the study comparator 2mg E2-valerate. Estetrol is a promising new estrogenic agent having the advantages of estradiol on VMS and on bone but less metabolic side-effects.

A new **neurokinin 3 receptor antagonist** has to be mentioned as a potential novel treatment for menopausal hot flushes [34]. In the human, projections of KNDy neurons to both GnRH neurons and preoptic structures involved in thermoregulation could explain the temporal link between hot flushes and LH pulses in postmenopausal women [35]. The kisspeptin-neurokinin B (NKB)-dynorphin (KNDy) signalling system in the hypothalamus is the proximate and obligate stimulus of GnRH secretion, and is hypertrophied after the menopause (• Figure 1).

• **Figure 1.** The neuroanatomy of the kisspeptin-GnRH pathway and the relationship between KNDy neurones and GnRH neurones in humans



The therapeutic action of neurokinin 3 receptor antagonists on VMS is based on the evidence that neurokinin B signalling is increased in menopausal women, and has been implicated as an important mediator of hot flushes. In a recent pilot study, the neurokinin 3 receptor antagonist MLE4901 significantly reduced the total weekly number of hot flushes by 45 percentage points (95% CI 22-67) compared with placebo (intention-to treat adjusted means: placebo 49.01 [95% CI 40.81-58.56] vs MLE901 19.35 [15.99-23.42]; adjusted estimate of difference 29.66 [17.39-42.87], p<0.0001) [32]. It may open unexpected new opportunities for targeted pharmacological interventions to normalize central thermo- and vaso-regulation.

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Conclusions

The Forum "Female Healthy Aging" was opened by Bruno Imthurn, Full Professor at the Department of Reproductive Endocrinology, University Hospital of Zurich, and Chairman.

In the first session, "Demography/Global health", Giuseppe Benagiano, Full Professor of Gynecology and Obstetrics at the University La Sapienza in Rome, presented remarkable data on the demographic revolution. It is interesting to notice that the demographic pyramid tends to revert, because of the growing healthy ageing and the decreasing birth rate in the Western countries. Moreover, as Bruno Imthurn brilliantly told, new aspects of infertility related to ageing have to be considered.

These facts prompted us to the need of conceiving new care models, presented by Petra Stute, Deputy Director of Gynaecological Endocrinology and Reproductive Medicine at the Women's Hospital, University Hospital of Berne, able to assist menopause women with a network of specialists.

In the second session, "Prevention/Impact of lifestyle", the impact of lifestyle on ageing has been deeply discussed.

First, Anne Gompel, Professor of Gynecology-Endocrinology at the University Paris Descartes, analyzed the differences between lifestyle intervention and hormone replacement therapy (HRT) on cancers after menopause, to conclude that while lifestyle modification can greatly reduce cancer risk, HRT should be carefully considered in each patient, since it could be a risk factor for breast cancer.

Yet one another essential aspect of ageing which needs to be considered is brain and its aging. Pauline Maki, Professor of Psychiatry and Psychology and Director of Women's Mental Health Research, Chicago, brilliantly showed how cognitive complaints are widely suffered from patients, and how they have been shown to be deeply related to hot flushes. Then, the early use of hormone therapy should also be considered as a possible approach to prevent cognitive decline in eligible patients.

Raghvendra Dubey, Professor and Head of Basic Research at the Department of Reproductive Endocrinology, University Hospital Zurich, instead, explained the other face of estrogen therapy, for which both positive and negative effects on cardiovascular disease have been demonstrated. In particular, considering the basic research carried on animal models, we have to consider that different estrogens can elicit different effects, rendering the choice of hormone therapy essential in the chances of success.

On the other hand, Hanna Savolainen-Peltonen, Professor at the Helsinki University Hospital, discussed the use of estrogen in preventing cardiovascular disease, and concluded that estradiol based HT is associated with reduced CVD mortality risk in a nationwide study.

Peyman Hadji, Head of the Department of Bone Oncology, Endocrinology and Reproductive at the Krankenhaus Nordwest in Frankfurt/Main and Professor of Obstetrics, Gynaecology and Endocrinology at Philipps-Universität, Marburg, moved to another relevant topic in woman ageing, the fracture prevention. This topic needs to be considered early for both primary and secondary prevention. Another time, the conclusion leads to estrogen, which regulates bone balance in turnover and which deficiency is a strong risk factor for fracture in pre-and post-menopausal women.

Even sexual life should be taken in consideration, as related to cognitive ability, as interestingly discussed by Brigitte Leeners, Professor and Deputy Director at the Department of Reproductive Endocrinology, University Hospital Zurich, in her talk.

Finally, Martin Birkhaeuser, Professor emeritus for Gynaecological Endocrinology and Reproductive Medicine at the University of Berne, explained in the third session, "Future", the available alternatives to hormone therapy, In the intervention for healthy ageing, in fact, interventions on lifestyle and exercise, as with cognitive behavioral therapy and acupuncture should be considered as valid approaches. In addition, some compounds as phytoestrogens, isoflavones, black cohosh and cimifuga racemose shown significant effect on menopausal symptoms.

Hormonal changes in the perimenopause/menopause have important consequences for women's health: they generate a series of disorders – heat waves, profuse sweats, tachycardia, insomnia, unstable mood – and in the long-term increase the risk of bone and cardiovascular diseases.

The Forum "Female Healthy Aging", organized by IBSA Foundation for scientific research in collaboration with the Department of Reproductive Endocrinology at the University Hospital Zurich, brought together internationally renowned experts to discuss actual and future therapies to overcome women's disorders and to live in good health by aging.