

## **BLACE**

**A new approach to enhance pre- and post-menopausal life quality  
with reduced OC- and HRT therapy related side effects.**

### **HRT challenge**

Peri- or post menopausal women with climacteric symptoms are frequently treated by hormone replacement therapy (HRT), i.e. an estrogen with or without a progestogen. In women with an intact uterus, progestogen treatment is required to protect the endometrium from developing hyperplasia and carcinoma, which may result from continuous stimulation by estrogen administration. The most widely used HRT regimens are sequentially combined HRT (continuous estrogen and intermittent progestogen administration for 10 to 14 days, e.g. every 28 days) or continuously combined HRT (daily use of estrogen combined with a progestogen). A major clinical difference is the occurrence of a scheduled bleeding starting at the end of the combined estrogen/progestogen phase in sequentially combined HRT (withdrawal bleeding), whereas no bleeding episodes are scheduled in continuously combined HRT. Continuously combined administration of estrogen and progestogen is supposed to induce endometrial atrophy and, as a result, the absence of bleeding (amenorrhea). Unfortunately, continuous combined HRT is associated with high rates of breakthrough bleeding particularly in the first months of treatment.<sup>i</sup> Many efforts have been made to resolve bleeding problems by adjusting dosages of the components or changing the type of progestogen. There are indications that primarily the estrogen dose is associated with the occurrence of breakthrough bleeding during intake of combined HRT preparations.<sup>ii</sup>

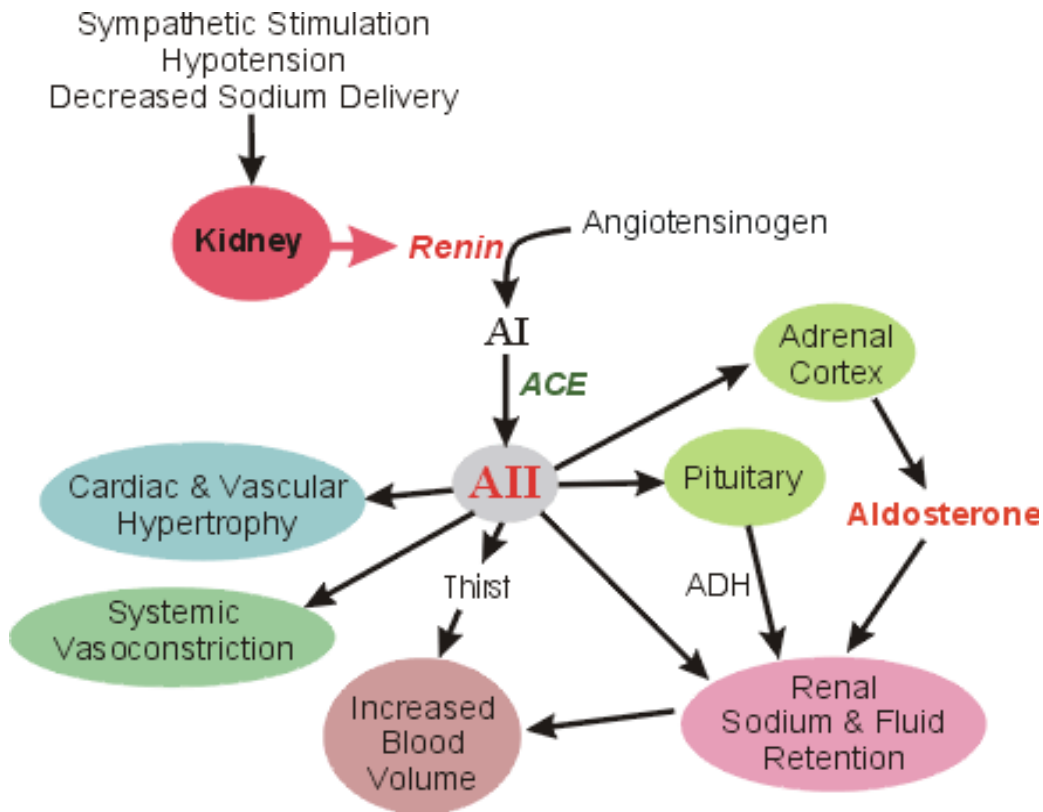
Breakthrough bleeding is occurring unexpectedly and irregularly, and is considered inconvenient to women regardless of whether this occurs during intake of sequential or continuous HRT preparations.

### **Concept**

Pantarhei believes that it will be possible to wipe out the issue of the unscheduled bleeding and spotting, by adding to HRT a suppressor of the Renin Angiotensin System (RAS). Well known examples of compounds suppressing the RAS, are angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists (ARA), or renin inhibitors; and combinations thereof. These compounds do inhibit the angiogenesis and neovascularisation within the endometrium, resulting in substantially less unscheduled bleeding.

RAS suppressing agents act on the RAS system in different ways. Angiotensinogen is an  $\alpha_2$ -globulin circulating in plasma and is produced by the liver. The synthesis of angiotensinogen is affected by many factors such as estrogens, glucocorticoids, thyroid hormones, and angiotensin II. Angiotensinogen is converted into biologically inactive angiotensin I through renin, which is secreted by the juxtaglomerular cells of the kidney depending on e.g. blood pressure, renal perfusion. Angiotensin I, a decapeptide, is converted into angiotensin II, an octopeptide, by ACE. Angiotensin II elicits pharmacological action through binding to the angiotensin II receptors of which two types are known: type1 (AT<sub>1</sub>) and type 2 (AT<sub>2</sub>). All known clinical effects of angiotensin II are mediated by the AT<sub>1</sub> receptor, which has been localized in kidney, heart, smooth-muscle cells, brain, adrenal gland and some other tissues. AT<sub>2</sub> receptors are important in fetal life but the numbers decrease after birth. AT<sub>2</sub> receptors

are found in the uterus, central nervous system and heart at low levels. The function of AT<sub>2</sub> receptors is controversial.<sup>iii</sup>



### Renin Angiotensin (aldosterone) System

Angiotensin II can be considered a multifunctional hormone that plays a key role in regulating the RAS, which is essential for maintaining cardiovascular homeostasis. The way, RAS and thus angiotensin II regulates the system by controlling sodium homeostasis and vascular resistance is well established. In the last decade, much attention has also been paid to the role of angiotensin II as a regulator of microvessel density. It has been observed that angiotensin II is involved in angiogenesis.<sup>iv</sup> Therefore, ACE inhibitors or ARA may inhibit angiogenesis and neovascularization. Atrophic endometrium is known to have a high microvessel count and fragile capillaries that may be major factors involved in bleeding from atrophic endometrium.<sup>v</sup> Those observations have led to the hypothesis that co-treatment of (continuous) HRT and ACE-inhibitor/ARA may be able to reduce bleeding from atrophic endometrium.

Additional benefits from co-treatment with an ACE inhibitor/ARA may result from the cardiovascular protective properties. Estrogen treatment tends to water retention, an effect that may be counteracted by low dose ACE-inhibitor/ARA. These compounds may act synergistically with estrogens on cardiovascular function e.g. reduction of vasoconstriction, endothelin production, smooth muscle cell hypertrophy. Furthermore, these classes of

compounds have been associated with protection vis-à-vis the risk of breast cancer, colorectal and other, specific female, cancers.<sup>vi</sup>

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- i Udoff L, Langenberg P, Adashi EY. Combined continuous hormone replacement therapy; a critical review. *Obstet Gynecol* 1995; 86: 306-16.
  - ii Weijer PHM van de, Barentsen R, Vries MH de, Kenemans P. Relationship of estradiol levels to breakthrough bleeding during continuous combined Hormone Replacement Therapy. *Obstet Gynecol* 1999; 93: 551-7.
  - iii Burnier M, Brunner HR. Angiotensin II receptor antagonists. *Lancet* 2000; 355: 637-45.
  - iv Greene AS, Amaral SL. Microvascular angiogenesis and the renin-angiotensin system. *Curr Hypertens Rep* 2002; 4: 56-62.
  - v Ferenczy A. Pathophysiology of endometrial bleeding. *Maturitas* 2003; 45: 1-14.
  - vi Lever AF, Hole DJ, Gillis CR, McCallum IR, McInnes GT, McKinnon PL et al. Do inhibitors of angiotensin-I-converting enzyme protect against risk of cancer? *Lancet* 1998; 352: 179-84.

### **OC challenge**

Also during oral contraceptive (OC) use, breakthrough bleeding is a major side effect, which is one of the important reasons for women to stop taking OC's or to change brand. In principle, the concept will be applicable on OC's as well.

### **Clinical status**

Due to budget constraints, Pantarhei has not had the opportunity to conduct a feasibility study yet. This concept typically uses registered compounds, which allows for conducting a study in phase IIA immediately. Based on these principle, a protocol has been drafted including a budget- and time estimate.

### **IP**

Pantarhei has filed a patent application, covering the concept in the most broadest way. The application is currently pending in several regions. The IPER indicates that all claims of the PCT application are grantable.

### **Opportunity**

PRB is looking for a partner that is interested to further develop and subsequently commercialize the concept.

### **Pantarhei Bioscience B.V**

PRB is a clinical concept research institute, focusing its interest on designing better treatment using existing compounds in the field of gender related diseases. For further information on the company, please visit our website at: [www.pantarheibio.com](http://www.pantarheibio.com)