

A. Rübige

New Perspectives in Hormonal Therapy

DRoSPirenone - Profile of A Cardio-vascular Active Progestin - Offering New Perspectives in Hormone Therapy

Prof. Dr. Alexander Rübige

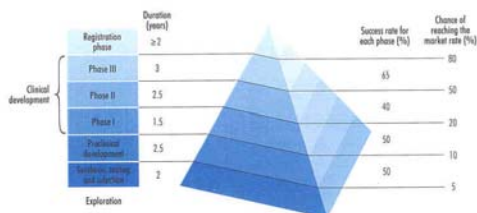


Research- and Development-Costs
(from first idea till final registered product)

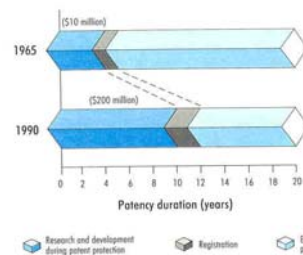
i. e. in the area of hormones:

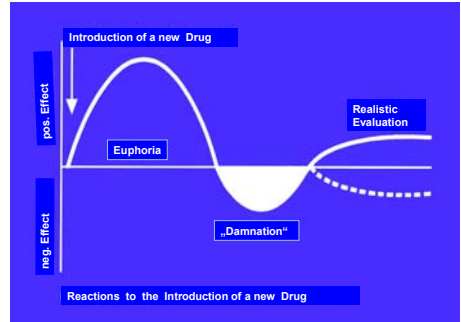
> \$ 500 Mio

The duration and success rate of preclinical and clinical development of selected compounds



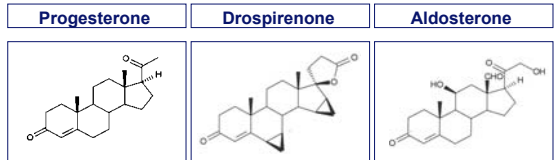
The impact of a longer research and development period on the effective patent life of a product. The effective patent life is when the research and development costs can be recouped through sales



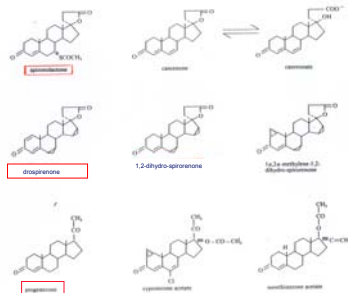


Origin of progestogens

19-Nortestosterone	17 α -Hydroxy-progesterone	17 α -Spirolactone
Norethisterone (1954)	Hydroxyprogesterone caproate (1953)	Drospirenone (1987)
↓	↓	
Levonorgestrel (1963)	Chlormadinone acetate (1960)	
↓	↓	
Gestodene/Desogestrel (1975)	Cyproterone acetate (1961)	
↓		
Norgestimate (1977)		

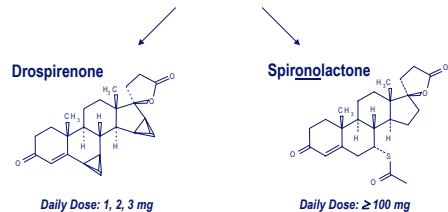


Drospirenone

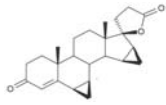


Spirolactone vs. Spiroglactone

The Spirolactones



Drospirenone (DRSP)



- is a novel 17 α -spirolactone derivate
- pharmacodynamic profile is more closely related to endogenous progesterone than that of other synthetic progestogens in use today
- displays progestational, antimineralocorticoid and antiandrogenic activity
- is devoid of any estrogenic, androgenic, glucocorticoid and antiglucocorticoid activity

Pharmacodynamic profile of Drospirenone

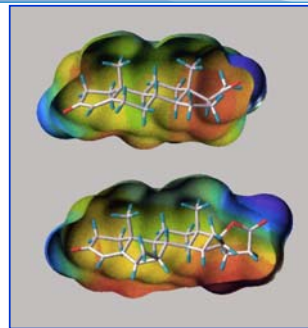
- **Therapeutic important activities:**
 - progestational activity
 - anti-mineralocorticoid activity
 - anti-androgenic activity
- **Other hormonal activities:**
 - no glucocorticoid activity
 - no anti-glucocorticoid activity
 - no estrogenicity
 - no androgenicity

Pharmacodynamic activities of various progestogens

	Androgenic activity	Antiandrogenic activity	Glucocorticoid activity	Antimineralo-corticoid activity
Progesterone	-	+	-	+
Levonorgestrel	+	-	-	-
Desogestrel	+	-	-	-
Gestodene	+	-	-	(+) ^{*)}
Norgestimate	+	-	-	-
MPA	+	-	+	-
NETA	+	-	-	-
CPA	-	+	+	-
Dienogest	-	+	-	-
Chlormadinone acetate	-	+	+	-
DRSP	-	+	-	+

^{*)} negligible activity at therapeutic doses

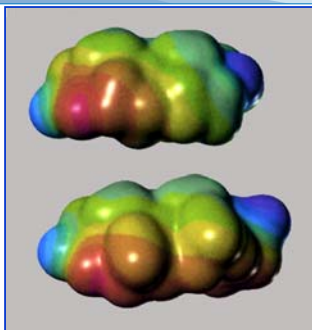
Tibolone: progestogenic metabolite; estrogenic + androgenic-anabolic drug



Progesterone

Drospirenone

Sybyl Version 6.6, Tripos Inc., E. Ecker 2000

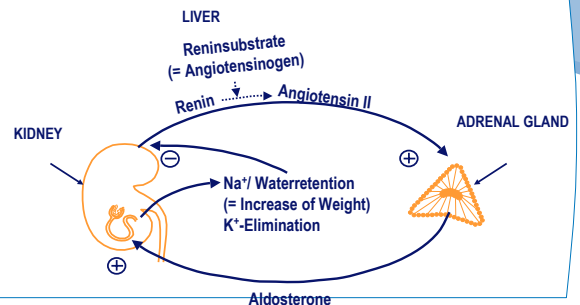


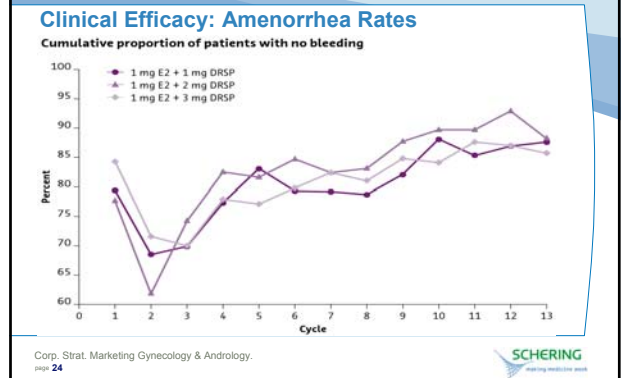
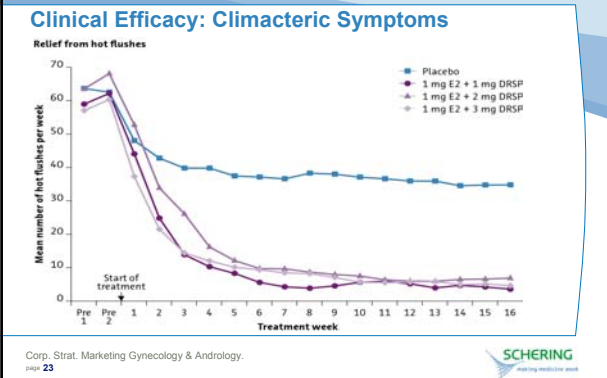
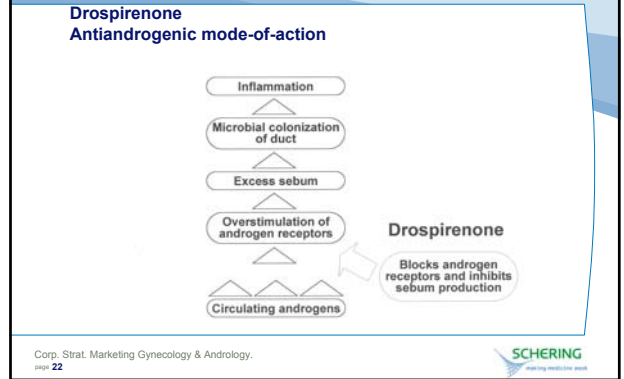
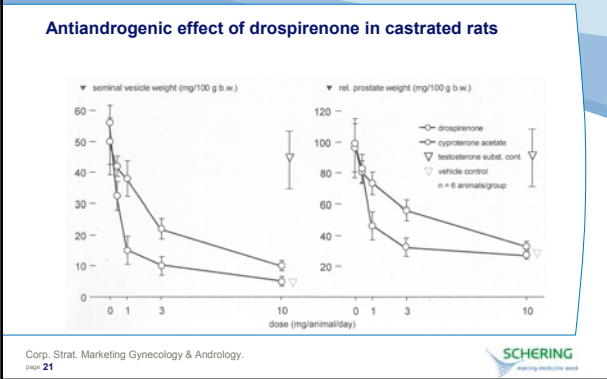
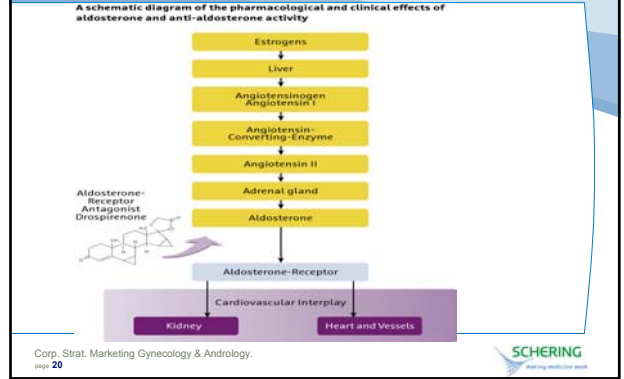
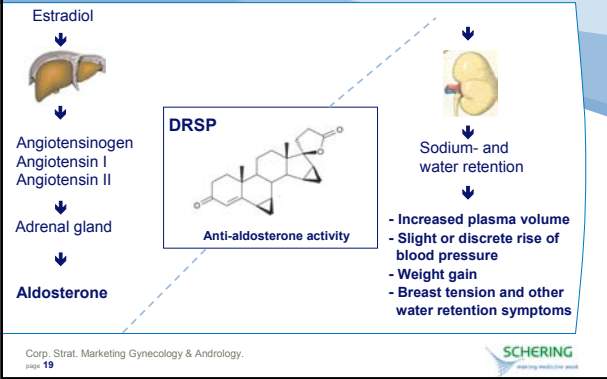
Progesterone

Drospirenone

Sybyl Version 6.6, Tripos Inc., E. Ecker 2000

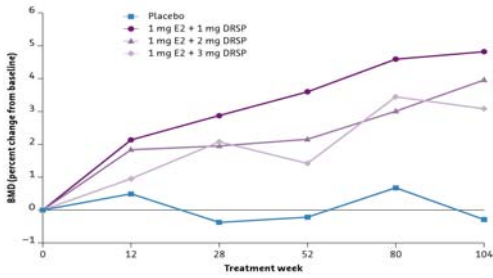
The Renin-Angiotensin-Aldosterone-System (RAAS)





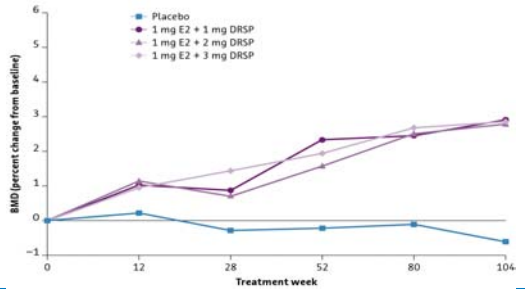
Clinical Efficacy: Prevention of pmp Osteoporosis

BMD changes in osteopenic patients (left hip)



Clinical Efficacy: Prevention of pmp Osteoporosis

BMD changes in non-osteopenic patients (left hip)



Safety: Endometrial Protection

1-year data

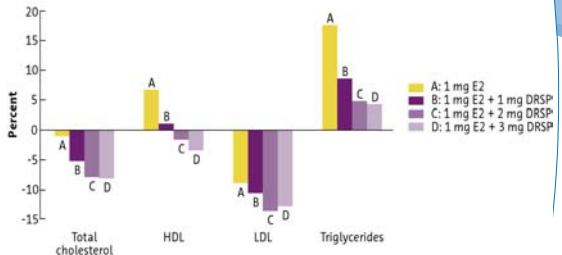
- R Proliferation rate as low as 4.1-6.3%
- R Endometrial atrophy in 72-82% of cases
- R No hyperplasia or cancer

2-year data

- R Proliferation rate 0-0.4%
- R Endometrial atrophy in 85-92% of cases
- R No hyperplasia or cancer

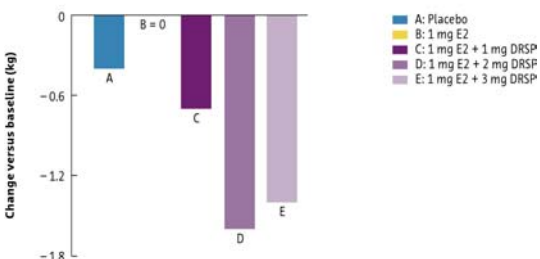
Safety: Lipids

Mean changes from baseline in total cholesterol, HDL- and LDL-cholesterol and triglycerides



Safety and Tolerability: Body Weight

Changes in body weight from baseline after one year

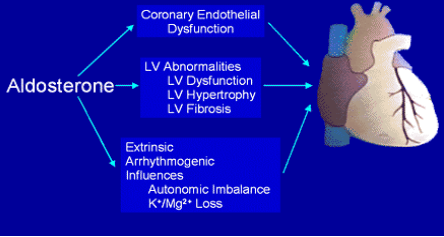


Safety and Tolerability: AE/SAE Profile

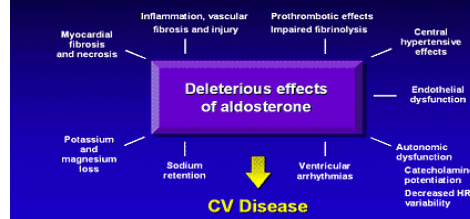
- AE/SAE profile does not differ from usual HRT pattern
- ADR for

Placebo	25%
E2 mono	64%
Angeliq	49%
- Side-effects due to water retention showed dose-dependency for DRSP, e.g. breast tension 23%, 19%, 17% (1-3 mg)
- Most common reasons for discontinuation with Angeliq were vaginal bleeding (3.9%), breast pain (2.1%), headache (0.7%)
- Related SAEs in 18 women (1.2%) on Angeliq
- No SAEs could be specifically attributed to DRSP and no safety concerns were raised

Effects of Aldosterone on the Cardiovascular System



Pathophysiologic Effects of Aldosterone in CV Disease



New Insights Into the Role of Aldosterone in Cardiovascular Disease and the Clinical Implications

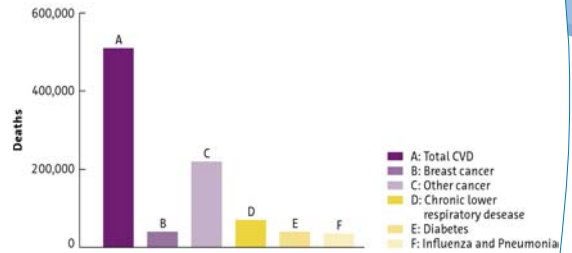
Bertram Pitt, MD

Hypertension: Incidence and Prevalence

- Main factor contributing to CVD
- CVD most frequent cause of death in Western nations
- Hypertension preceded CHF in 91% of cases
- US 1999: due to hypertension 17.000 females died and 267.000 were discharged from hospital
- Estrogen deficiency contributes to hypertension
- Postmenopausal women are twice as likely to have hypertension than premenopausal women (adjusted data for age and BMI)

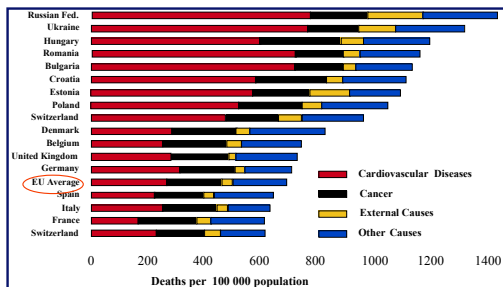
Relevance of Cardiovascular Disease

Leading causes of death for females in US 1999



Relevance of Cardiovascular Disease

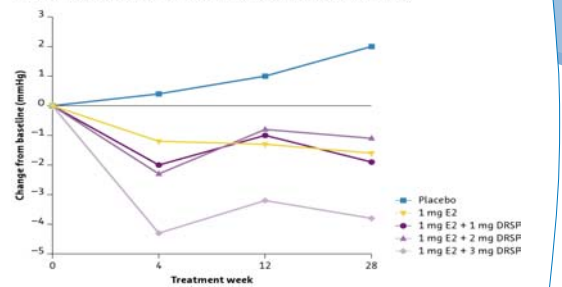
Leading causes of death for females - Europe 2000



Source: World Health Report 2000

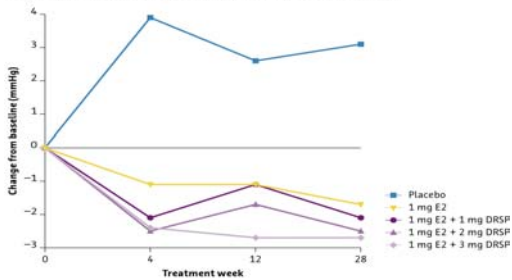
Systolic Blood Pressure: Total Study Population

Mean change in systolic blood pressure (total study population)



Diastolic Blood Pressure: Total Study Population

Mean change in diastolic blood pressure (total study population)



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page 37



Blood Pressure: Conclusion

In conclusion, the blood pressure lowering effect of Angeliq® - partly due to the anti-aldosterone activity of drospirenone - is more pronounced in combinations with high drospirenone dosages and has a beneficial treatment effect.

Due to the combination of estradiol with the unique progestogen drospirenone, the well known favorable effects of estradiol are not attenuated by the progestogen. Moreover, at higher drospirenone doses (i.e. 3 mg), the beneficial blood pressure lowering effect is even more pronounced with Angeliq compared to estradiol alone, offering added cardiovascular benefit.

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page 38



Cardiovascular Benefits - Summary

Estradiol and DRSP are perfect partners working synergistic via separate ways.

DRSP does not counteract estrogen action like common used progestins, but in addition contributes to the beneficial effects via a separate regulatory circuit due to its antialdosterone activity and lack of androgenicity.

The combination of estradiol and drospirenone offers a dimension on cardiovascular benefit which no other HRT product

up to now is able to fulfil
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page 39



Angeliq: Key benefits

- A natural estrogen (E₂) combined with a novel progestogen (DRSP) offering a unique combination of progestational, anti-aldosterone and anti-androgenic properties
- Cardiovascular benefits due to the combination of an estrogen with a progestogen that has anti-aldosterone properties and lack of androgenicity
- Quick and effective relief of climacteric symptoms with only 1 mg E₂
- Good bleeding control
- Prevention of the development of postmenopausal osteoporosis
- Reliable endometrial protection

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Angeliq: Future Research Projects

Further evaluation and proof of unique benefits in cardiovascular protection by studies on

- R coronary flow reserve
- R large scale blood-pressure studies
- R DRSP effect on myocardial fibrosis and vessel wall

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page 41

