Département de gynécologie et d'obstétrique

Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women

Hulley et al. JAMA 1998, Vol 280, N°7, 605

D Chardonnens

Clinique et policlinique de stérilté et d'endocrinologie gynécologique

HERS

- 1ère étude prospective randomisée multicentrique
- Double aveugle
- Placebo vs contrôles
- Substitution hormonale combinée continue
  - 0.625 mg oestrogènes conjugués équins
  - 2.5 mg d'acétate de médroxyprogestérone
- Prévention secondaire

Design: prévisions statistiques

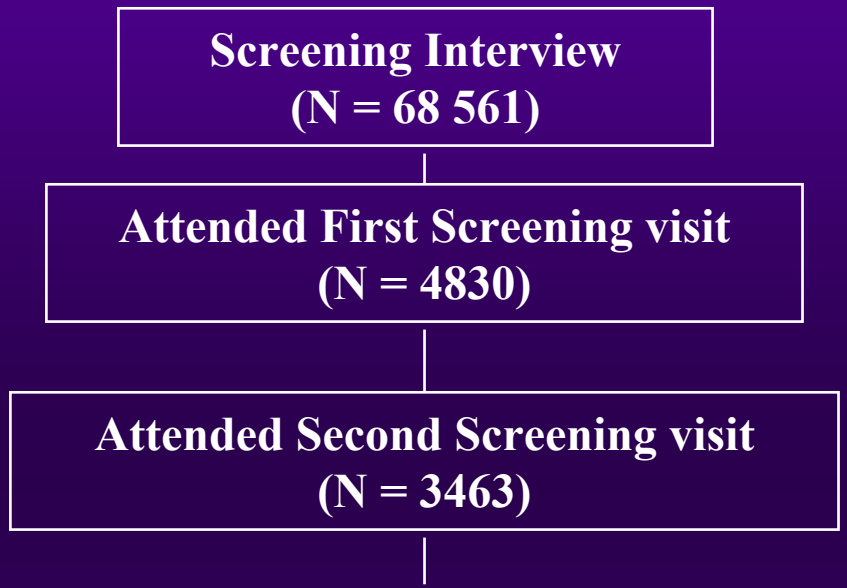
- Incidence d ’un événement coronarien dans le groupe placebo
  - 5 %
- Perte de follow-up et / ou mort non coronarienne
  - 2 % / an
- Follow - up
  - 4 . 75 ans

Design: prévisions statistiques

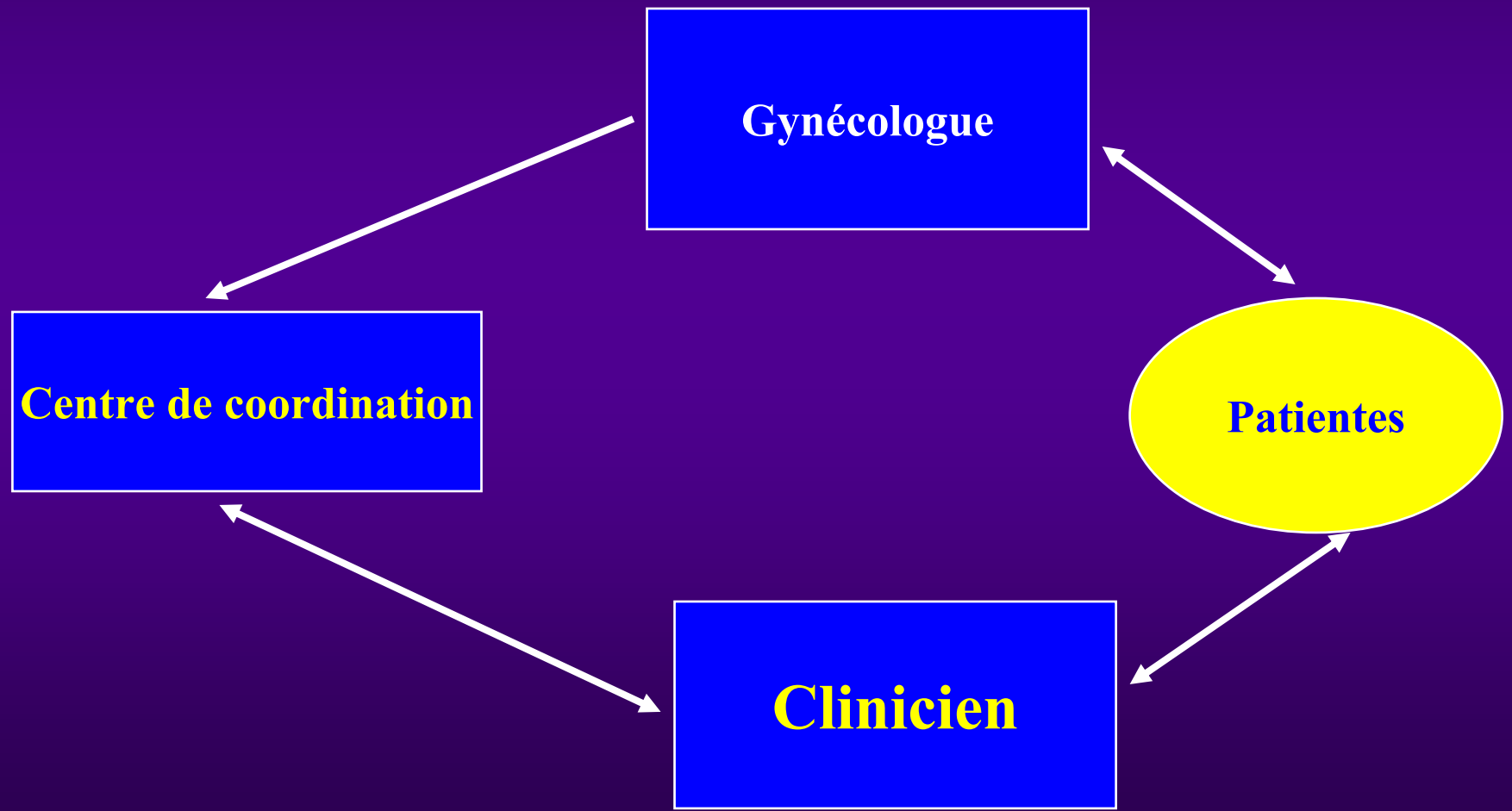
- Crossover hormones - placebo
  - 5 %, 4 %, 3 %, 2 %
- Crossover placebo - hormones
  - 1% / an
- Intent to treat effect
  - 24 %

2340 patientes

The Heart and Estrogen/progestin Replacement Study trial profile, showing numbers of participants from screening to closeout



Design



Visites de base

- Données démographiques
- Anamnèse gynécologique approfondie
- Anamnèse cardiovasculaire approfondie
- Anamnèse médicamenteuse
- Anamnèse sur la qualité de vie

Visites de base

- Examen clinique standard
- Status gynécologique
- Evaluation de l ’endomètre (Pipelle ou US)
- Examen sénologique et mammographique
- ECG 12 dérivations avec analyse computérisée
- Dosage à jeun
  - Cholestérol total
  - LDL cholestérol
  - triglycérides

Critères d ’inclusion

- < 80 ans
- Ménopause
- Utérus présent
- Maladie coronarienne

Définition de la ménopause

- > 55 ans avec une aménorrhée de 5 ans
- Aménorrhée > 1 an
  - FSH > 40 IU / L
- Certitude d ’ovariectomie bilatérale
- Anamnèse d ’ovariectomie bilatérale
  - FSH > 40 IU / L
  - E2 < 25 pg / ml

Définition de l ’atteinte coronarienne

- Antécédents d ’infarctus du myocarde
- Antécédents de pontage coronarien
- Antécédents d ’angioplastie coronarienne per-cutanée
- occlusion > 50% sur un des troncs coronariens à la coronarographie

Critères d ’exclusion cardiovasculaires

- Antécédents coronariens < 6 mois
- Insuffisance cardiaque sévère (III -IV NYHA)
- Hypertension non contrôlée (syst. > 200 mmHg ou diast > 105 mmHg)
- Anamnèse de maladie thromboembolique

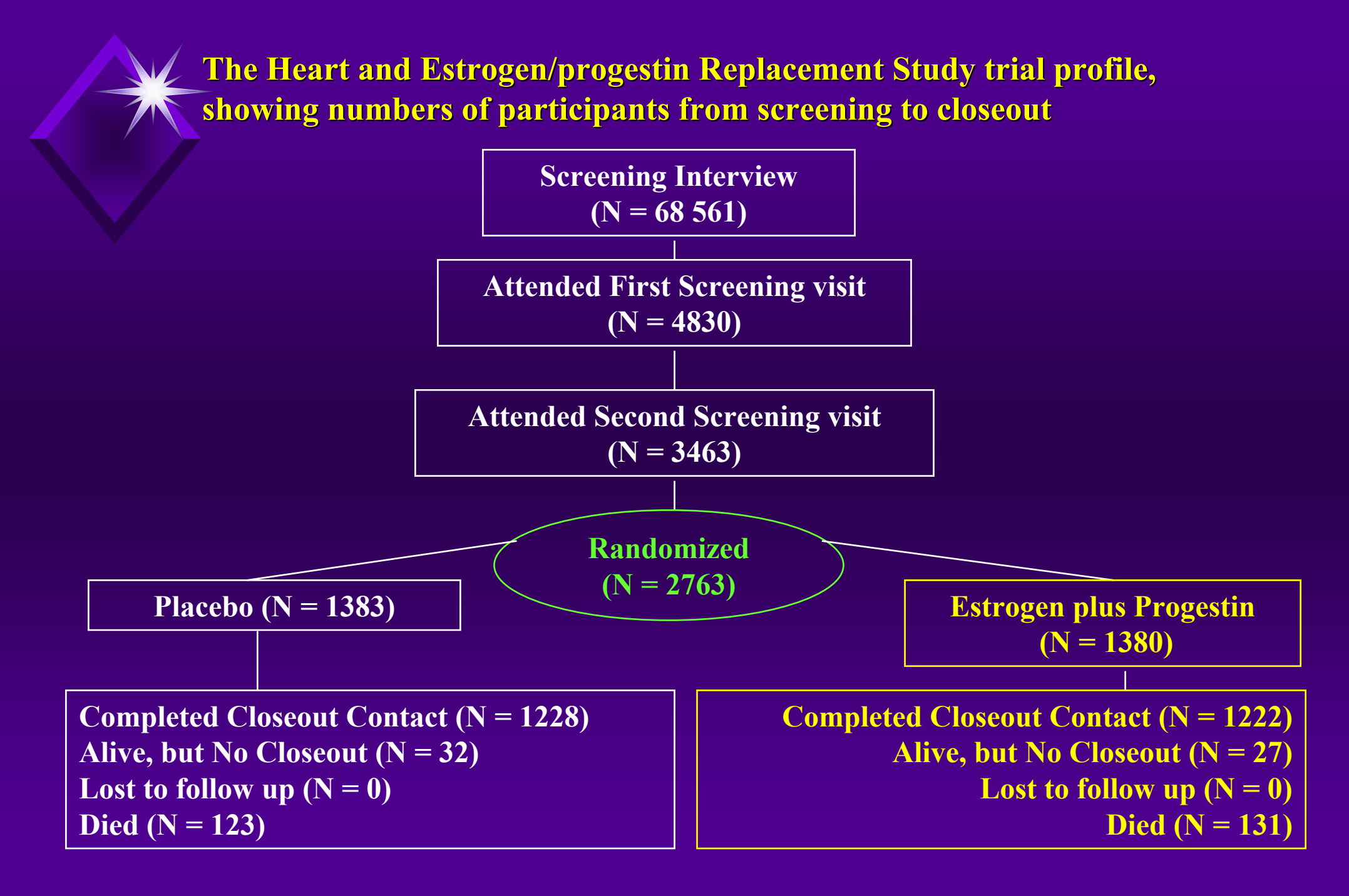
Critères d ’exclusion gluco-lipidiques

- Triglycérides > 3.39 mmol / L (300 mg/dL)
- Diabète non contrôlé
  - glycémie à jeun > 16.7 mmol / L

Critères d ’exclusion gynécologiques

- Anamnèse de cancers gynécologiques
- Anamnèse de substitution hormonale dans les 3 mois
- Examen sénologique ou mammographique suspect
- Hyperplasie de l ’endomètre ou épaisseur de l ’endomètre > 5 mm sur l ’évaluation de base

The Heart and Estrogen/progestin Replacement Study trial profile, showing numbers of participants from screening to closeout



Baseline characteristics of Heart and Estrogen/progestin Replacement Study (HERS) participants (n = 2763) by treatment group

Characteristics	Estrogen-Progestin (n=1380)	Placebo (n=1383)	*P* value
Demographics			
Age, mean±SD, y	67 ± 7	67 ± 7	.32
White, %	88	90	.14
Education, mean±SD, y	13 ± 3	13 ± 3	.84
Coronary heart disease (CHD) risk factors			
Current smoker, %	13	13	.84
Diabetes on rola medication or insulin, %	19	18	.44
Systolic blood pressure, mean±SD, mm Hg	135 ± 19	135 ± 19	.88
Diastolic blood pressure, mean±SD, mm Hg	73 ± 10	73 ± 10	89
LDL cholesterol, mean±SD, mmol/L (mg/dL)	3.75 ± 0.96 (145 ± 37)	3.75 ± 0.98 (145 ± 38)	.83
HDL cholestrol, mean±SD, mmol/L (mg/dL)	1.29 ± 0.34 (50 ± 13)	1.29 ± 0.34 (50 ± 13)	.41
Triglyceride, mean±SD, mmol/L (mg/dL)	1.90 ± 0.72 (168 ± 64)	1.86 ± 0.72 (165 ± 64)	.25
Time since last menstrual period, mean±SD, y	18 ± 8	18 ± 8	.31
Body mass index > 27 kg/m^2, %	57	55	.44
Exercises > 3 times weekly, %	39	38	.72
No. Of drinks per week, mean±SD	1.4 ± 4	1.3 ± 4	.83
General health poor or fair, %	24	24	.94
Postmenopausal estrogen use, %*	24	23	.43

*Estrogen use refers to use after menopause but not within 3 months of HERS screening

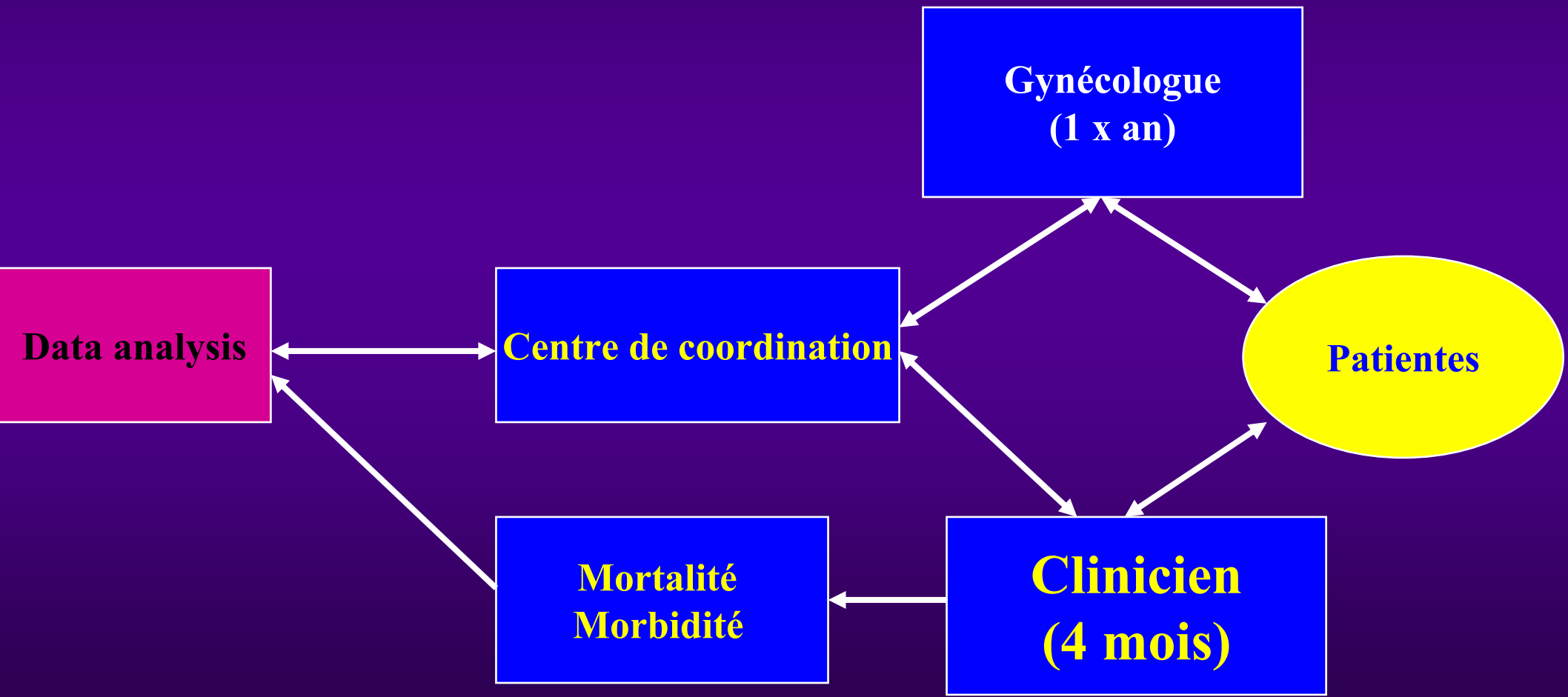
Baseline characteristics of Heart and Estrogen/progestin Replacement Study (HERS) participants (n = 2763) by treatment group

Characteristics	Estrogen-Progestin (n=1380)	Placebo (n=1383)	*P* value
Coronary heart disease (CHD) manifestations			
Signs of congestive heart failure, %*	10	9	.38
Q-wave myocardial infarction, %	17	17	.94
Percutaneous coronary revascularization, %	45	45	.96
Coronary artery bypass graft surgery, %	42	41	.64
Medication use			
Aspirin, %	78	78	.73
β-blockers, %	33	32	.72
Lipid-lowering medications, %	45	47	.26
Calcium channel blockers, %	55	55	.83
Angiotensin-converting enzyme inhibitors, [5]	17	18	.57
Diuretics, %	28	28	.79
Multivitamins, %	29	30	.45

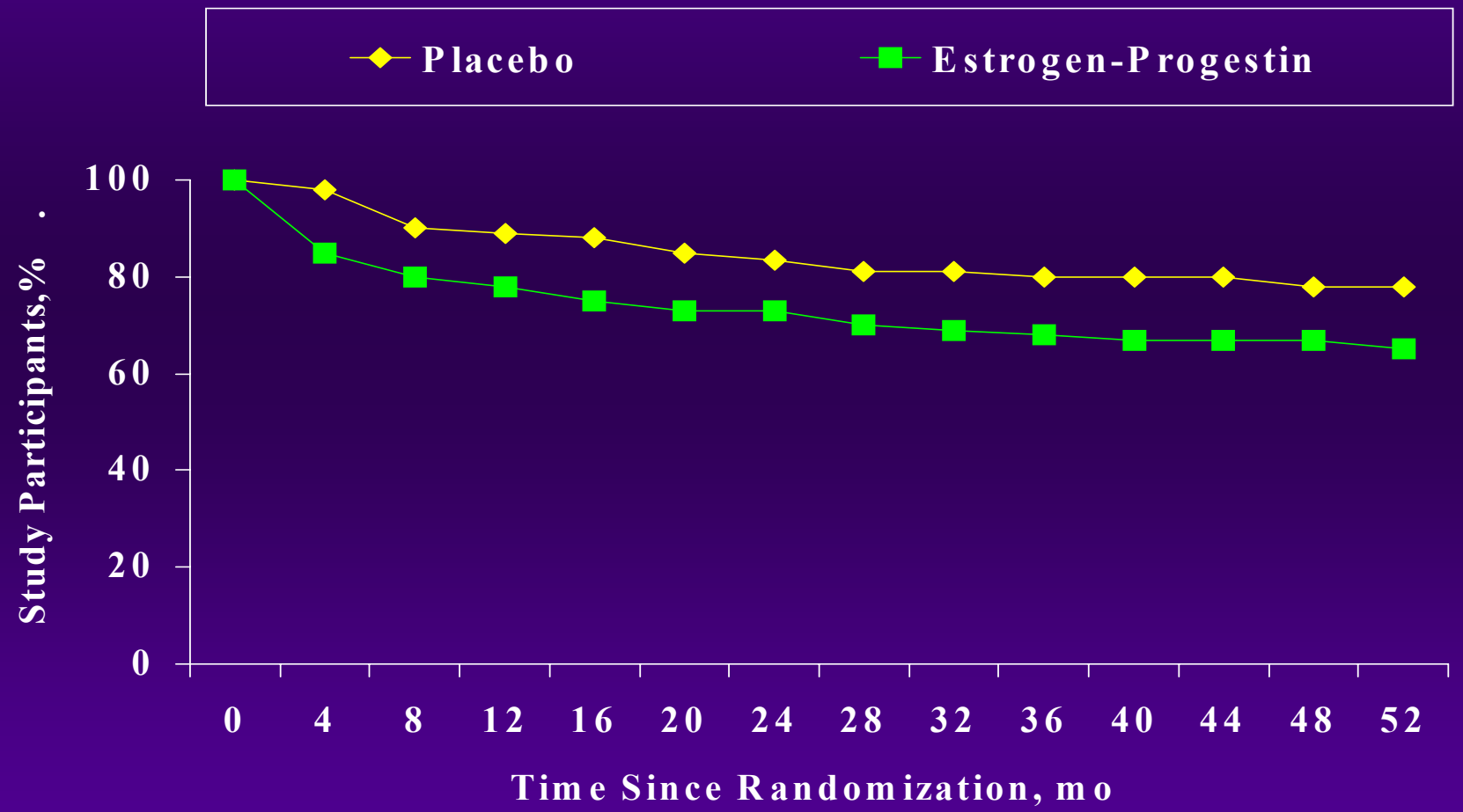
*Presence of jugular venous distention more than 8 cm H_20, S_3 heart sound, rales or pitting peripheral edema
P values are for difference between treatment groups by *t* test or x^2

Hulley S and al, JAMA 1998, 280 : 605-613

Follow-up


Gynécologue
(1 x an)
Data analysis
Centre de coordination
Patientes
Mortalité
Morbidité
Clinicien
(4 mois)

Participants taking protocol medications and with pill count of 80 % or more, as a percentage of all women at risk for a primary coronary heart disease event



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Objectifs primaires

- Evènements coronariens
  - Infarctus du myocarde non mortel
  - Mort d ’origine coronarienne
    - Infarctus du myocarde documenté
    - Mort subite
    - Mort survenant hors d ’un hôpital sans autre cause connue

Objectifs secondaires

- Cardiaques et artériels
  - Pontage coronarien
  - Angioplastie coronarienne percutanée
  - Hospitalisation pour angor instable
  - Arrêt cardiaque avec réanimation
  - Insuffisance cardiaque congestive
  - AVC ou AVC transitoire
  - Maladie artérielle périphérique

Objectifs secondaires

- Autres
  - mortalité totale
  - mortalité liée aux cancers
  - autres mortalités
  - cancers gynécologiques (sein, endomètre)
  - maladie thromboembolique
  - fractures
  - atteintes de la vésicule biliaire

Coût de l ’étude

40 millions de dollars

Cardiovascular Outcomes by Treatment Group[1]

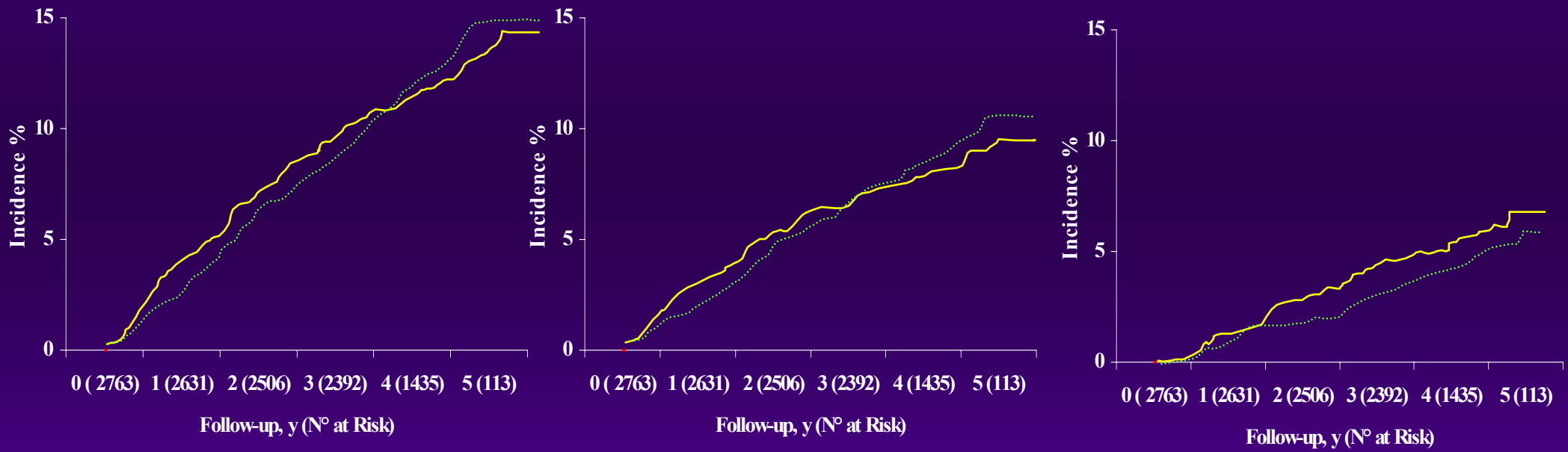
Outcomes	Estrogen-Progestin (n=1380)	Placebo (n=1383)	*RH (95 % CI)*	*P* value
Primary CHD events*	172	176	0.99 (0.80-1.22)	.91
CHD death	71	58	1.24 (0.87-1.75)	.23
Nonfatal MI	116	129	0.91 (0.71-1.17)	.46
Other cardiovascular outcomes				
Coronary artery bypass graft surgery	88	101	0.87 (0.66-1.16)	.36
Percutaneous coronary revascularization	164	175	0.95 (0.77-1.17)	.62
Hospitalization for unstable angina	103	117	0.89 (0.68-1.16)	.38
Hospitalization for congestive heart failure	128	112	1.07 (0.84-1.38)	.58
Resuscitated cardiac arrest	19	13	1.48 (0.73-3.00)	.28
Other CHD event	3	1	3.03 (0.32-29.1)	.34
Peripheral arterial disease	94	108	0.87 (0.66-1.15)	.34
Stroke/transient ischemic attack	108	96	1.13 (0.85-1.48)	.40

*Primary CHD events include coronary death and nonfatal MI. Among the 245 nonfatal Mis, there were 7 silent Mis, found on annual electrocardiogram. There were 26 women with nonfatal MI who subsequently suffered CHD death.

(1) RH indicates relative hazard; CI, confidence interval; CHD coronary heart disease; and MI, myocardial infarction. Each row represents the number of women with the designated event; women with more than1 type of event may appear in more than 1 row.

Hulley S and al, JAMA 1998, 280 : 605-613

Kaplan-Meier estimates of the cumulative incidence of primary coronary heart disease (CHD) events (left) and to its constituents : nonfatal myocardial infarction (MI) (center) and CHD death (right).



Estrogen-Progestin

Placebo

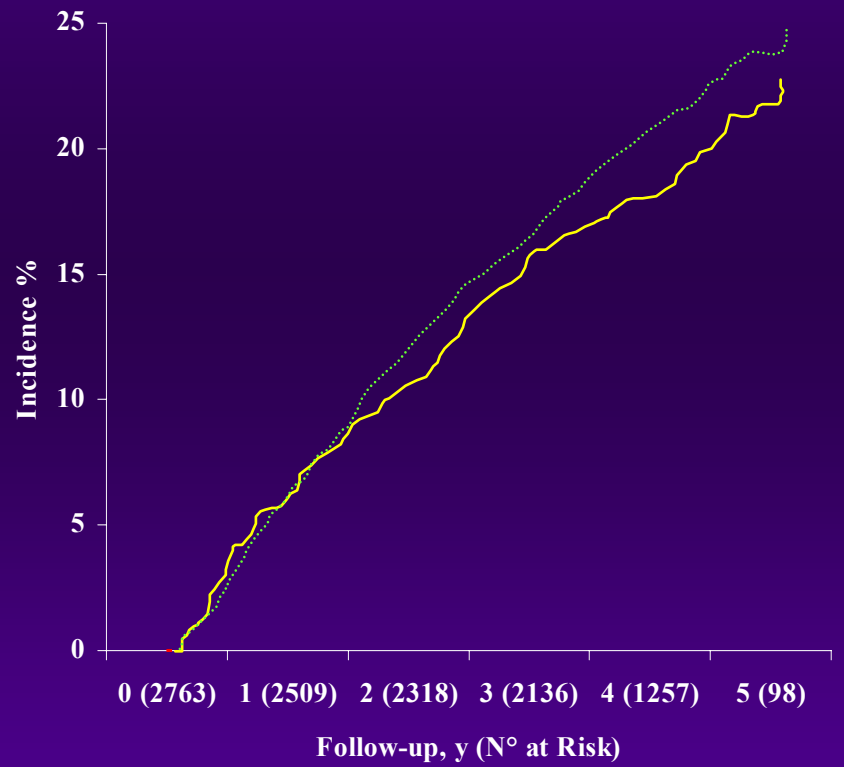
Hulley S and al, JAMA 1998, 280 : 605-613

Outcomes by treatment group and year since randomization *(RH indicates relative hazard; CI, confidence interval and CHD, coronary heart disease)*

Outcome and Period	Estrogen-Progestin N°	Estrogen-Progestin Rate[1]	Placebo N°	Placebo Rate[1]	RH (95 % CI)	*P*[2]
Primary CHD event[3]						
Year 1	**57**	**42.5**	**38**	**28.0**	**1.52 (1.01-2.29)**	
Year 2	**47**	**37.0**	**48**	**37.1**	**1.00 (0.67-1.49)**	**.009**
Year 3	**35**	**28.8**	**41**	**33.1**	**0.87 (0.55-1.37)**	
Year 4 and 5	**33**	**23.0**	**49**	**34.4**	**0.67 (0.43-1.05)**	
Nonfatal myocardial infarction						
Year 1	42	31.3	29	21.4	1.47 (0.91-2.36)	
Year 2	34	26.8	37	28.6	0.94 (0.59-1.49)	.01
Year 3	20	16.5	29	23.4	0.70 (0.40-1.24)	
Year 4 and 5	20	13.9	34	23.9	0.58 (0.34-1.02)	
CHD death						
Year 1	17	12.5	11	8.0	1.56 (0.73-3.32)	
Year 2	19	14.4	13	9.7	1.48 (0.73-2.99)	.34
Year 3	18	14.0	16	12.3	1.14 (0.58-2.24)	
Year 4 and 5	17	11.0	18	11.6	0.95 (0.49-1.84)	

(1) Event rates per 1000 women-years in the estrogen plus progestin or placebo group
(2) *P* values for tests of continuous trend in log-relative hazard
(3) Primary CHD events include non fatal myocardial infarction and CHD death

Kaplan-Meier estimate of the cumulative incidence of definite unstable angina or coronary artery bypass graft or percutaneous coronary revascularization.



Hulley S and al, JAMA 1998, 280 : 605-613

Outcomes by treatment group and year since randomization *(RH indicates relative hazard; CI, confidence interval and CHD, coronary heart disease)*

Outcome and Period	Estrogen-Progestin N°	Estrogen-Progestin Rate[1]	Placebo N°	Placebo Rate[1]	RH (95 % CI)	*P*[2]
Unstable angina or coronary revascularization[3]						
Year 1	101	77.1	94	71.1	1.08 (0.82-1.44)	
Year 2	52	43.3	85	70.6	0.61 (0.43-0.87)	.42
Year 3	69	61.9	56	50.5	1.22 (0.86-1.74)	
Year 4 and 5	47	36.6	67	54.2	0.67 (0.46-0.98)	

(1) Event rates per 1000 women-years in the estrogen plus progestin or placebo group
(2) *P* values for tests of continuous trend in log-relative hazard
(3) Coronary revascularization includes coronary artery bypass graft surgery and percuatneous coronary revascularization

Hulley S and al, JAMA 1998, 280 : 605-613

Death and secondary noncardiovascular outcomes by treatment group *(RH indicates relative hazard; CI, confidence interval and CHD, coronary heart disease)*

Outcomes	Estrogen-Progestin (n = 1380)	Placebo (n = 1383)	RH (95 % CI)	*P*
Death				
CHD death	71	58	1.24 (0.87-1.75)	.23
Cancer death	19	24	0.80 (0.44-1.46)	.47
Non-CHD, noncancer death	37	36	1.04 (0.66-1.64)	.87
Unadjudicated death	4	5	...	...
Total death	131	123	1.08 (0.84-1.38)	.56
Venous thromboembolic event				
Deep vein thrombosis	25	8	3.18 (1.43-7.04)	.004
Pulmonary embolism	11	4	2.79 (0.89-8.75)	.08
Any thromboembolic event	34	12	2.89 (1.50-5.58)	.002

Each row represents the number of women with the designated event; women with more than 1 type of event may appear in more than 1 row.

Hulley S and al, JAMA 1998, 280 : 605-613

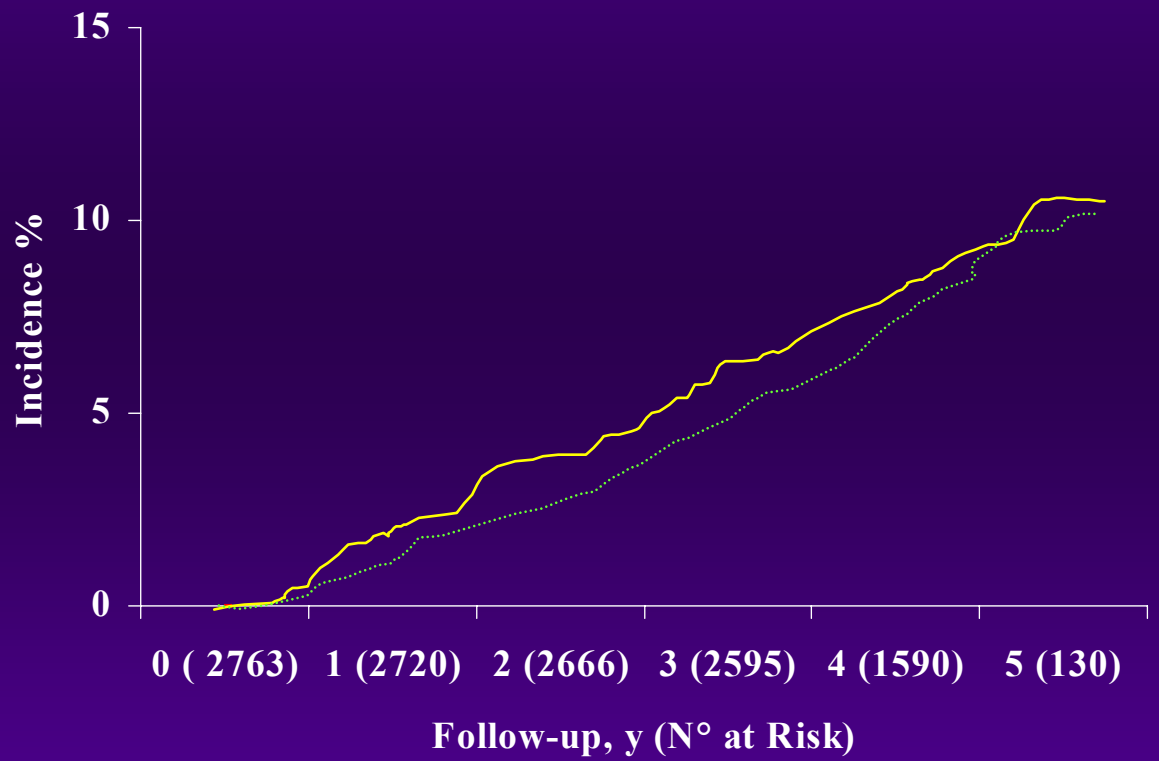
Death and secondary noncardiovascular outcomes by treatment group *(RH indicates relative hazard; CI, confidence interval and CHD, coronary heart disease)*

Outcomes	Estrogen-Progestin (n = 1380)	Placebo (n = 1383)	RH (95 % CI)	*P*
Cancer				
Breast	32	25	1.30 (0.77-2.19)	.33
Endometrial	2	4	0.49 (0.09-2.68)	.41
Other	63	58	1.10 (0.77-1.57)	.60
Any cancer	96	87	1.12 (0.84-1.50)	.44
Fracture				
Hip	12	11	1.10 (0.49-2.50)	.82
Other	119	129	0.93 (0.75-1.21)	.59
Any fracture	130	138	0.95 (0.75-1.21)	.70
Gallbladder disease	84	62	1.28 (1.00-1.92)	.05

Each row represents the number of women with the designated event; women with more than 1 type of event may appear in more than 1 row

Hulley S and al, JAMA 1998, 280 : 605-613

Kaplan-Meier estimate of cumulative incidence of death from any cause.



Hulley S and al, JAMA 1998, 280 : 605-613

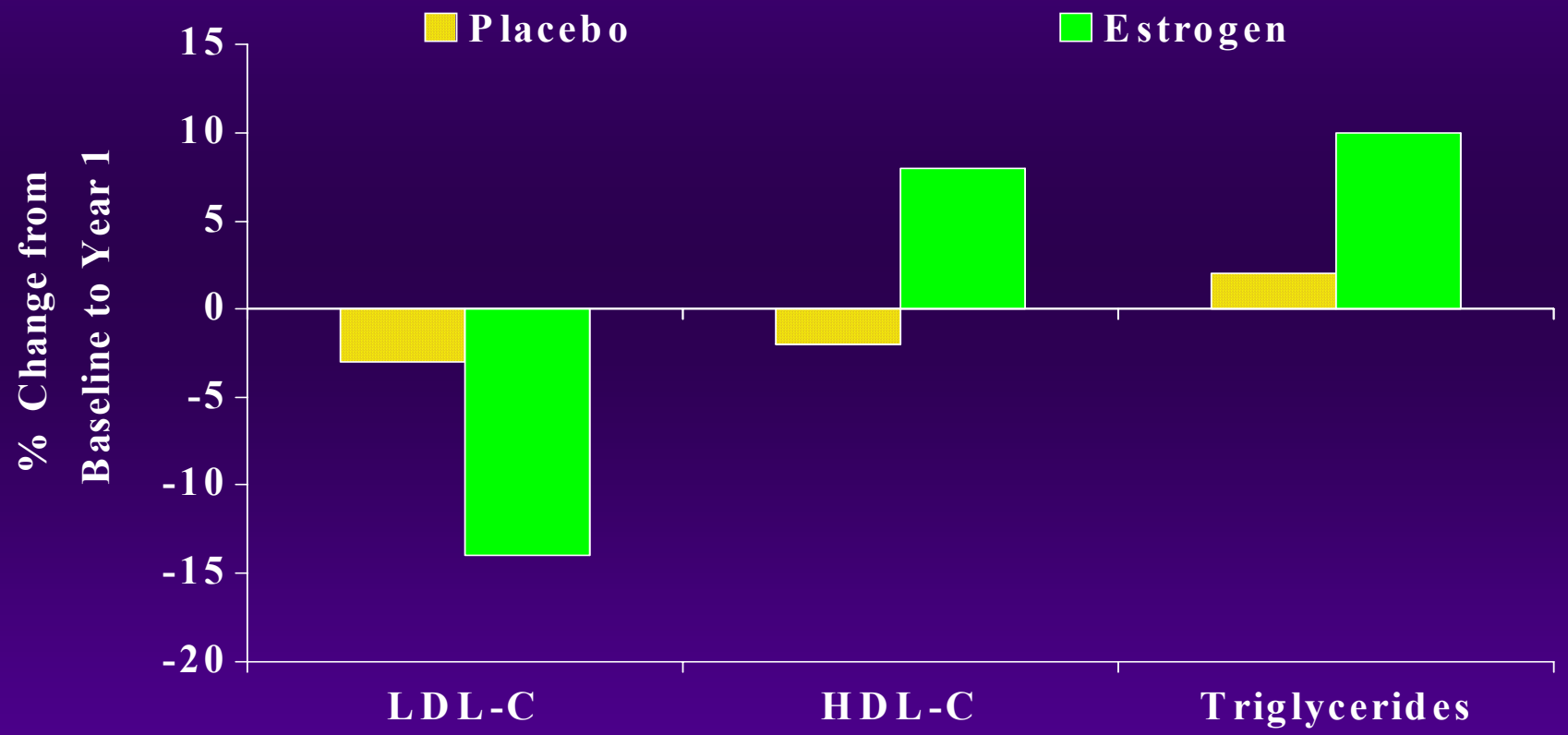
Outcomes by treatment group and year since randomization *(RH indicates relative hazard; CI, confidence interval and CHD, coronary heart disease)*

Outcome and Period	Estrogen-Progestin N°	Estrogen-Progestin Rate[1]	Placebo N°	Placebo Rate[1]	RH (95 % CI)	*P*[2]
Venous thromboembolic event						
Year 1	13	9.6	4	2.9	3.29 (1.07-10.08)	
Year 2	8	6.1	2	1.5	4.09 (0.87-19.27)	.28
Year 3	7	5.5	3	2.3	2.40 (0.62-9.28)	
Year 4 and 5	6	4.0	3	2.0	2.05 (0.15-8.18)	

(1) Event rates per 1000 women-years in the estrogen plus progestin or placebo group
(2) *P* values for tests of continuous trend in log-relative hazard
(3) Coronary revascularization includes coronary artery bypass graft surgery and percuatneous coronary revascularization

Hulley S and al, JAMA 1998, 280 : 605-613

Mean change in low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride levels during the first year of the study, expressed as percent change ± SEM



Hulley S and al, JAMA 1998, 280 : 605-613

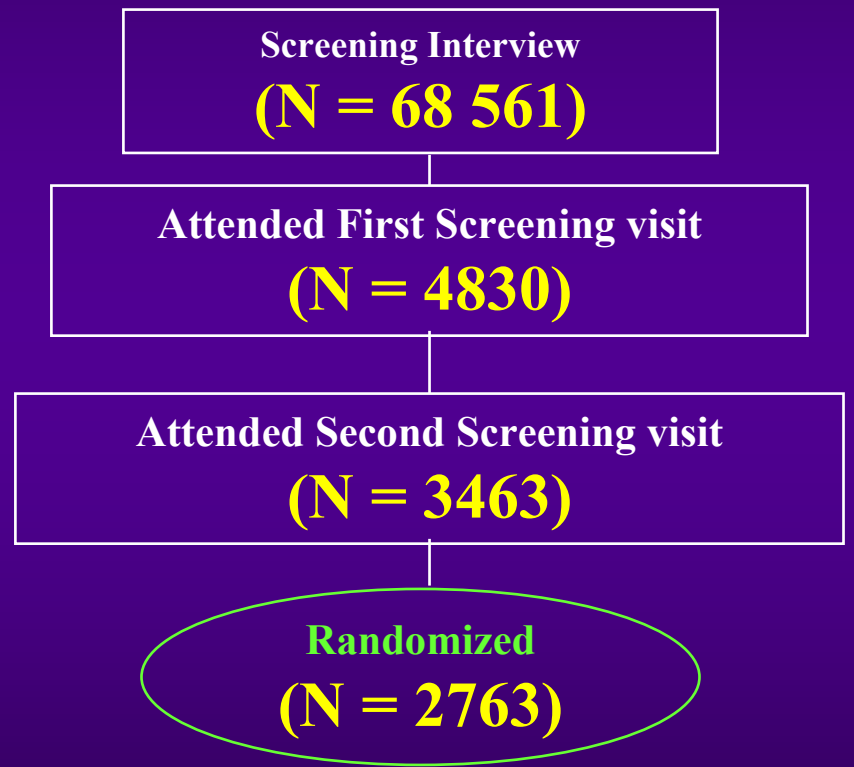
Conclusions pour la prévention secondaire

- Pas de réduction du risque cardiovasculaire
- Légère augmentation du risque cardiovasculaire en phase initiale du traitement
- Augmentation du risque thrombotique
- Effet protecteur possible à long terme

Conclusions

- Absence de justification pour débuter ce traitement pour une prévention secondaire
- Pas de nécessité de stopper ce traitement

Critiques


Screening Interview
(N = 68 561)
Attended First Screening visit
(N = 4830)
Attended Second Screening visit
(N = 3463)
Randomized
(N = 2763)

?

Critiques

	Assumption	Actual
Clinical event rate in the placebo group	5 % / year	3.3 % / year
Drop-out rate	5 % / year	18 % / year
Conversion of placebo to treatment rate	1 % / year	1.7 % / year
Average follow-up	4.75 years	4.1 years
Recruitment	Placed	Late

Speroff L, Maturitas 1998, 31 : 9-14

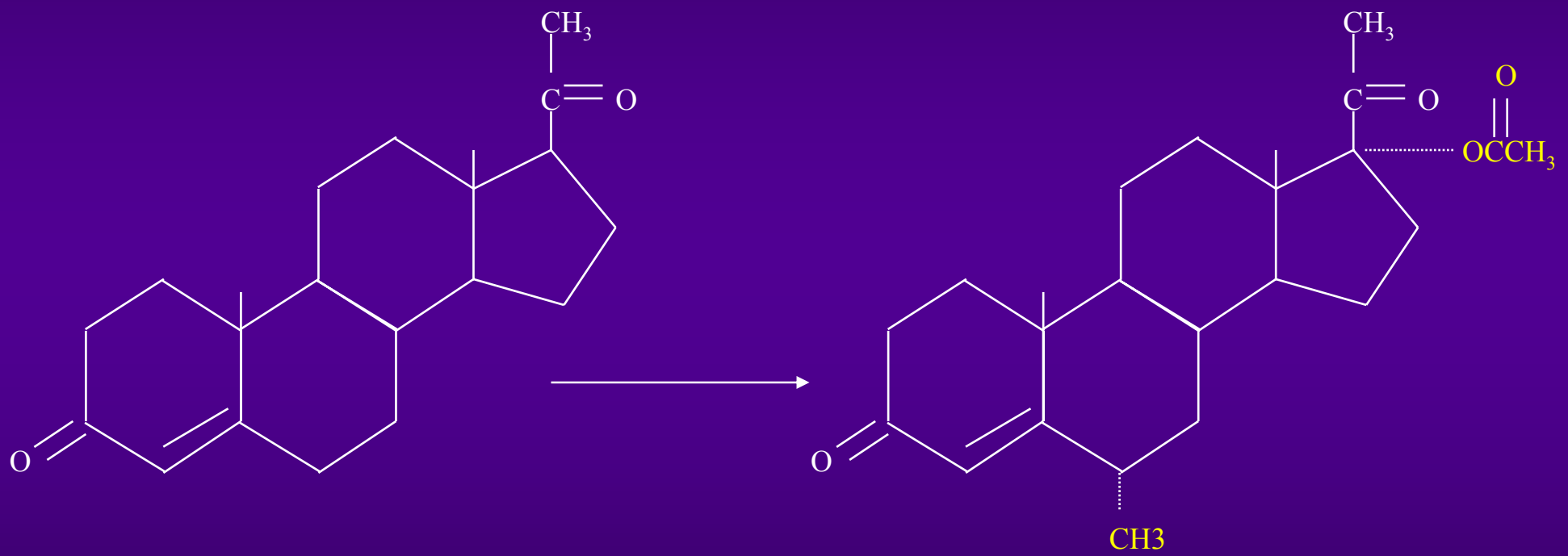
Critiques

- Certains facteurs importants ne sont pas abordés
  - facteur de risques familiaux
  - tabagisme
  - activité physique
  - nutrition
  - changements de traitements en cours d ’étude
- Les changements de profil lipidiques décrits sont-ils suffisants pour une prévention cardiovasculaires?

Oestrogènes conjugués équins

- Estrone
- Equiline
- 17 α et β-dihydroéquiline
- 17 α et β-estradiol
- Equilénine
- 17 α et β-dihydroéquilénine
- Delta 8,9-déhydroestrone

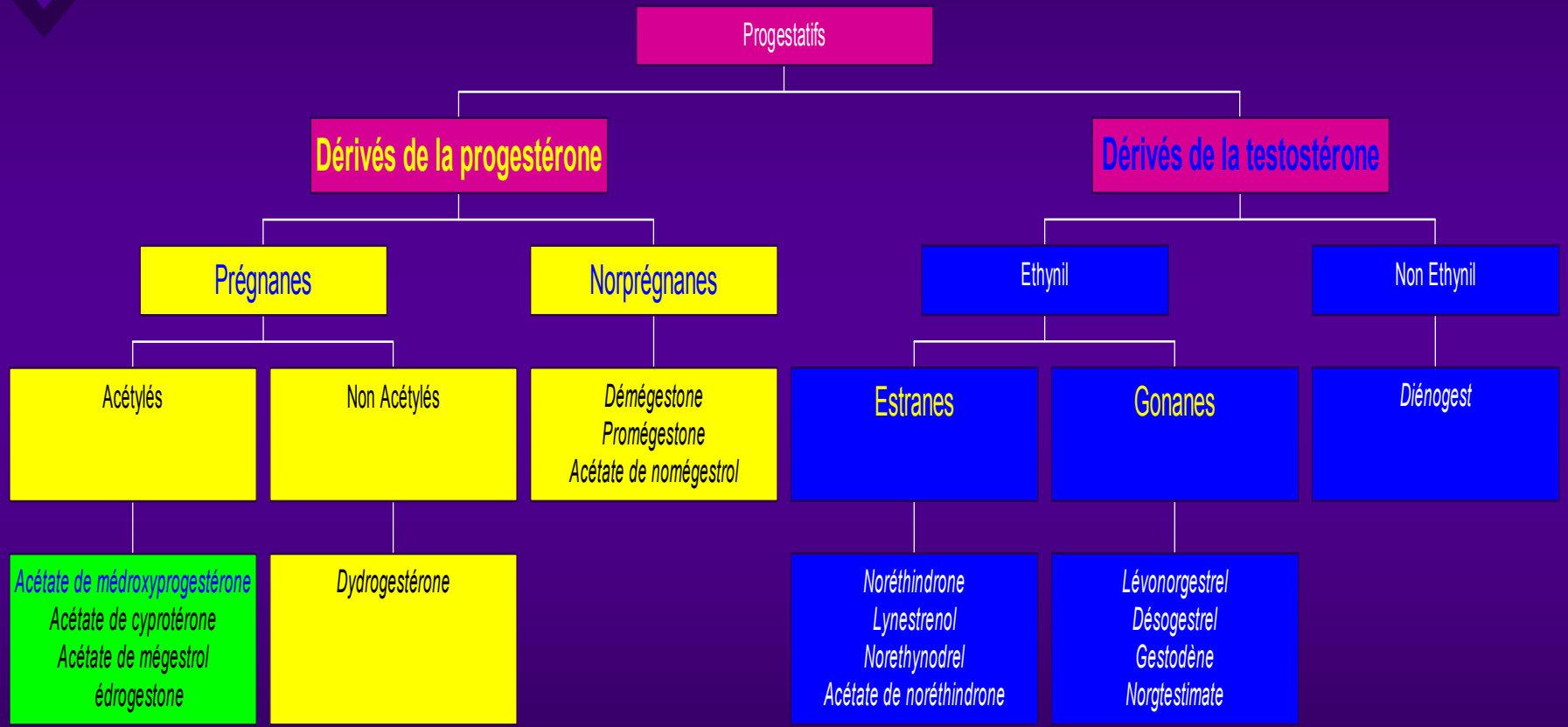
Acétate de médroxpyprogestérone



Progestérone

Acétate de médroxyprogestérone

Les progestatifs de synthèse



MPA ?

- Diminution de l ’effet E_2 sur les lipides
  PEPI trial JAMA 1995
- Diminution de l ’effet E_2 sur l ’athérosclérose chez le primate. *Arteriosclero Throm Vasc Biol 1994*
- Diminution de l ’effet vasodilatatateur de E_2 sur les coronaires chez le primate. *J Am Coll Cardiol 1994*

Conclusions ?

- Aborder les patientes âgées avec prudence dans la prévention secondaire
- La voie orale pour la prise de HRT n ’est peut-être pas la meilleure voie d ’administration dans cette situation
- Le progestatif de type MPA n ’est probablement pas le meilleur

Ongoing clinical trials

Primary prevention	**WHI** (Women's Health Initiative)	N = 16500
	WISDOM (Women's International Study of Long Duratipon Oestrogen for menopause	N = 34000
Secondary prevention	**WEST** (Western Connecticut Estrogen for Prevention of Stroke Trial)	N = 650
	ESPRIT (Estrogen in Prevention of Reinfarction Trial)	N = 2000
Angiographic end-point	**ERA** (Estrogen in the Prevention of Reinfarction Trial)	N = 300
	WAVE (Women's Atherosclerosis Vitamin/Estrogen Trial)	N = 400
	WELLHART (Women's Lipid Lowering Heart Atherosclerosis Trial)	N = 214

Speroff L, Maturitas 1998, 31 : 9-14