Hypertension artérielle : *polypill* aujourd'hui ou demain ?

Jacques Blacher
Unité HTA et prévention cardiovasculaire
Centre de diagnostic et de thérapeutique, Hôtel-Dieu, Paris

Sept 2011

Déclaration de conflits d'intérêt de Jacques Blacher:

- Absence de participation financière dans le capital d'une entreprise liée aux médicaments.

- Absence de lien durable avec une entreprise liée aux médicaments (contrat de travail, rémunération régulière...).

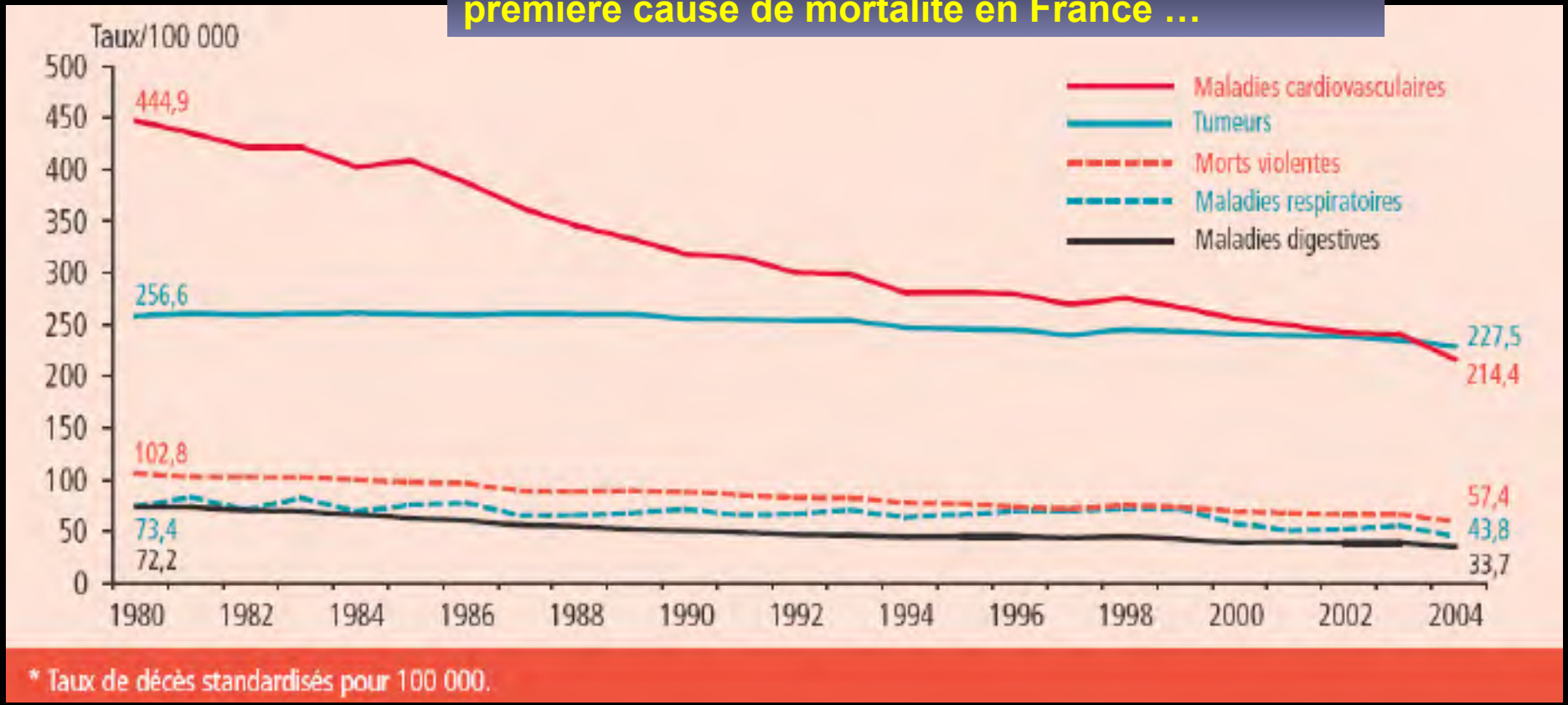
- Interventions ponctuelles en rapport avec des entreprises liées aux médicaments (essais cliniques, travaux scientifiques, comités scientifiques, rapports d'expertise, conférences, colloques, actions de formation, participation à divers symposia, rédaction de brochures...) avec, le cas échéant, facturation d'honoraires ; et ceci avec la majorité des entreprises du médicaments commercialisant des produits cardiovasculaires et autres produits en rapport avec mes domaines de spécialité (SERVIER, NOVARTIS, PFIZER, MSD, SANOFI, BRISTOL-MYERS SQUIBB, GLAXO SMITHKLINE, PIERRE FABRE, DANONE, MEDICASOFT, PHILIPS, ASTRA-ZENECA, ABBOTT, AMGEN, IPSEN, MERCK SERONO, EUTHERAPIE, BOEHRINGER INGELHEIM, MENARINI, DAIICHI-SANKYO, TAKEDA, ROCHE...).

BEH Bulletin épidémiologique hebdomadaire

Septembre 2007

Evolution des taux* de décès par grande catégorie de causes de décès, 1980-2004, France métropolitaine, deux sexes

Les maladies cardiovasculaires ne sont plus la première cause de mortalité en France …



* Taux de décès standardisés pour 100 000.

Table 2. Changes in Rankings for 15 Leading Causes of Death, 2002 and 2030 (Baseline Scenario)

Category	Disease or Injury	2002 Rank	2030 Ranks
Within top 15	Ischaemic heart disease	1	1
	Cerebrovascular disease	2	2
	Lower respiratory infections	3	5
	HIV/AIDS	4	3
	COPD	5	4
	Perinatal conditions	6	9
	Diarrhoeal diseases	7	16
	Tuberculosis	8	23
	Trachea, bronchus, lung cancers	9	6
	Road traffic accidents	10	8
	Diabetes mellitus	11	7
	Malaria	12	22
	Hypertensive heart disease	13	11
	Self-inflicted injuries	14	12
	Stomach cancer	15	10
Outside top 15	Nephritis and nephrosis	17	13
	Colon and rectum cancers	18	15
	Liver cancers	19	14

Epidémiologie cardiovasculaire

+

- Maladie cardiovasculaire : première cause de décès et d'incapacité dans le monde.
- La moitié des individus développeront une maladie CV à un quelconque moment de leur vie.
- Stratégies efficaces de prévention et de traitement : réduction du poids des maladies CV dans les pays industrialisés.

-

- Acquis menacés par l'augmentation de l'obésité, de la sédentarité et du diabète.
- Augmentation de la prévalence des maladies CV dans les pays pauvres.
- En 2020, 80 % de la mortalité imputable aux maladies CV : pays pauvres.

Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): a prospective epidemiological survey

Salim Yusuf, Shofiqul Islam, Clara K Chow, Sumathy Rangarajan, Gilles Dagenais, Rafael Diaz, Rajeev Gupta, Roya Kelishadi, Romaina Iqbal, Alvaro Avezum, Annamarie Kruger, Raman Kutty, Fernando Lanas, Liu Lisheng, Li Wei, Patricio Lopez-Jaramillo, Aytekin Oguz, Omar Rahman, Hany Swidan, Khalid Yusoff, Witold Zatonski, Annika Rosengren, Koon K Teo, on behalf of the Prospective Urban Rural Epidemiology (PURE) Study Investigators

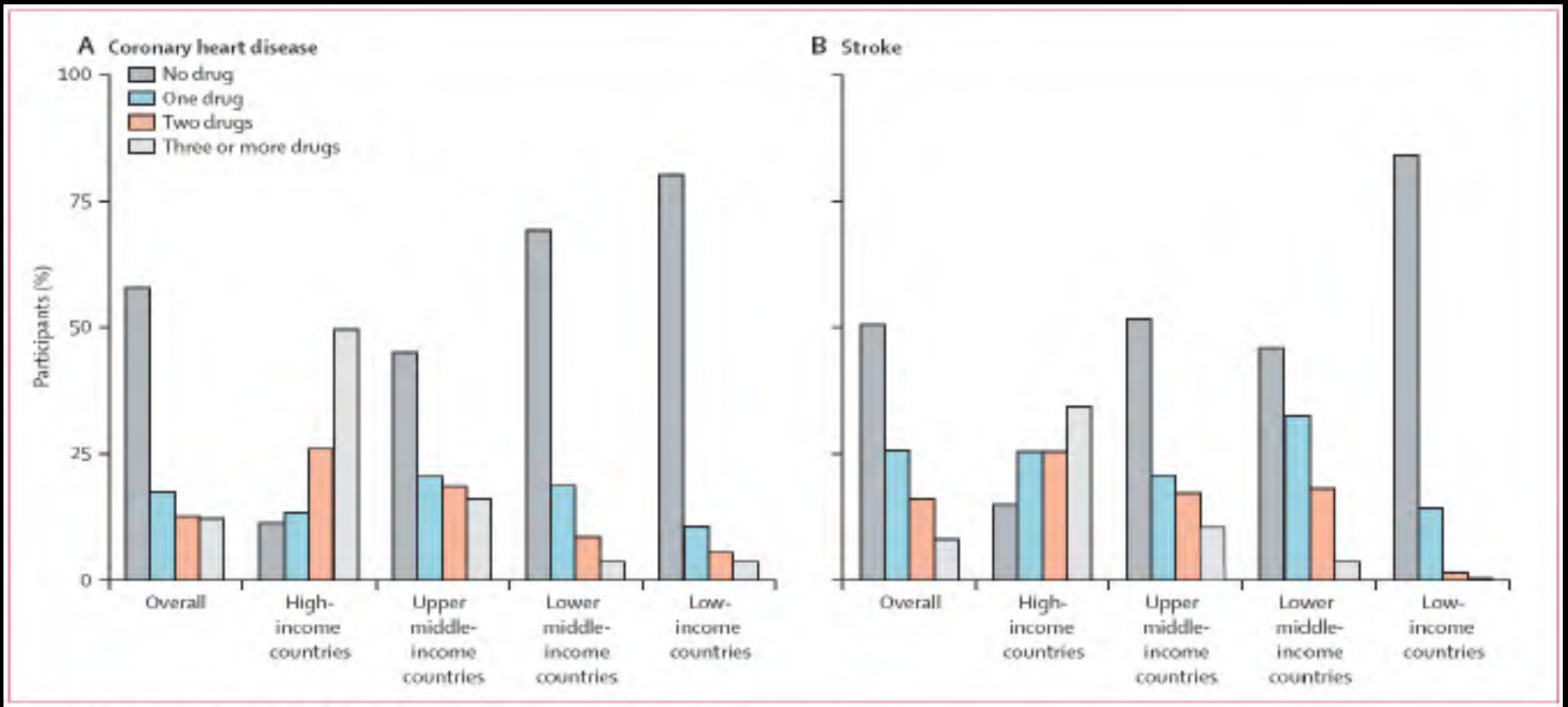


Figure 2: **Number of drugs taken by individuals by country economic status**

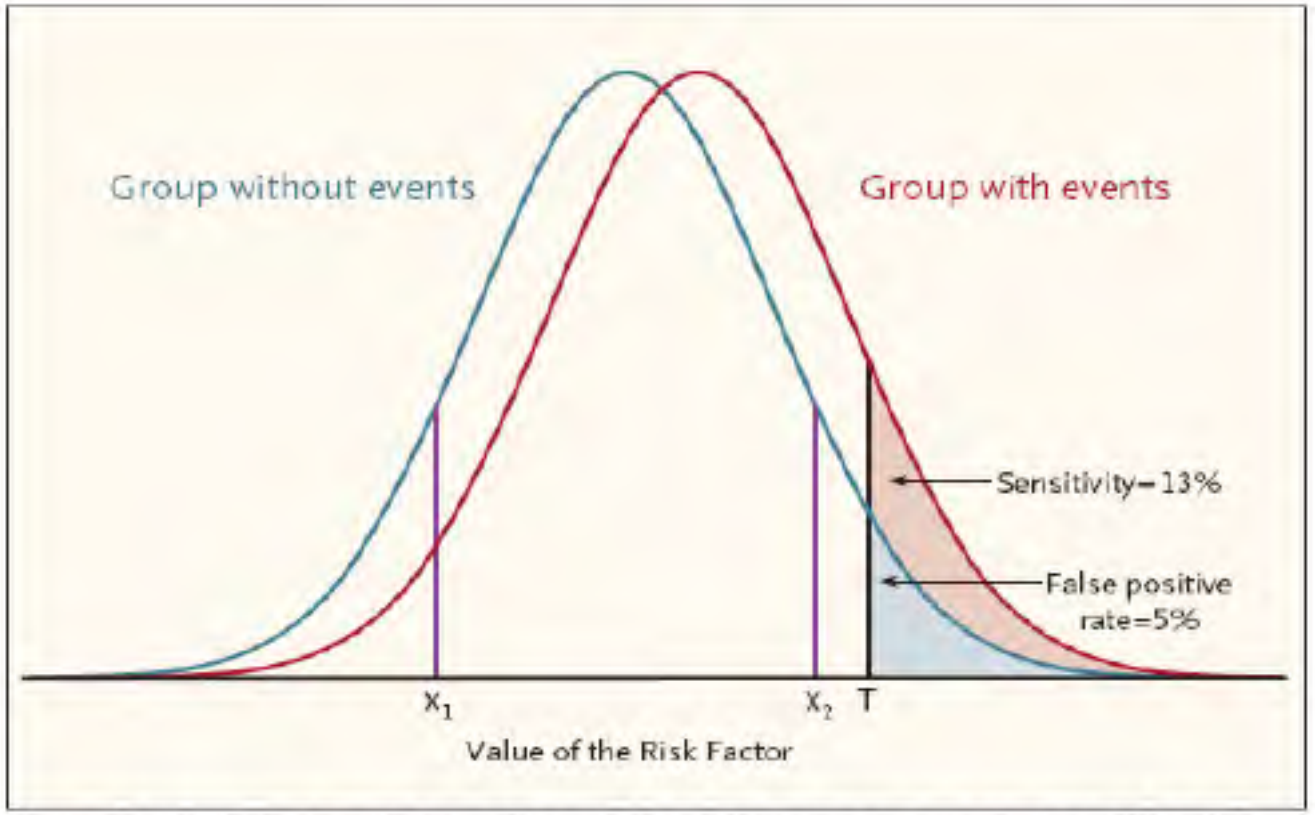
For coronary heart disease (A), drugs counted were aspirin, β blockers, ACE inhibitors or ARBs, or statins. For stroke (B), drugs counted were aspirin, statins, ACE inhibitors or ARBs, or other blood-pressure-lowering drugs (eg, β blockers, diuretics, and calcium-channel blockers). ACE=angiotensin-converting enzyme. ARB=angiotensin-receptor blocker.

Limites de l'impact des actuelles stratégies de prévention.

- Complexité et imperfection des algorithmes de stratification des risques en prévention primaire
- Usage incomplet des thérapeutiques efficaces
- Coût élevé des thérapeutiques limitant leur accessibilité
- Problématique de tolérance
- Problématique d'observance

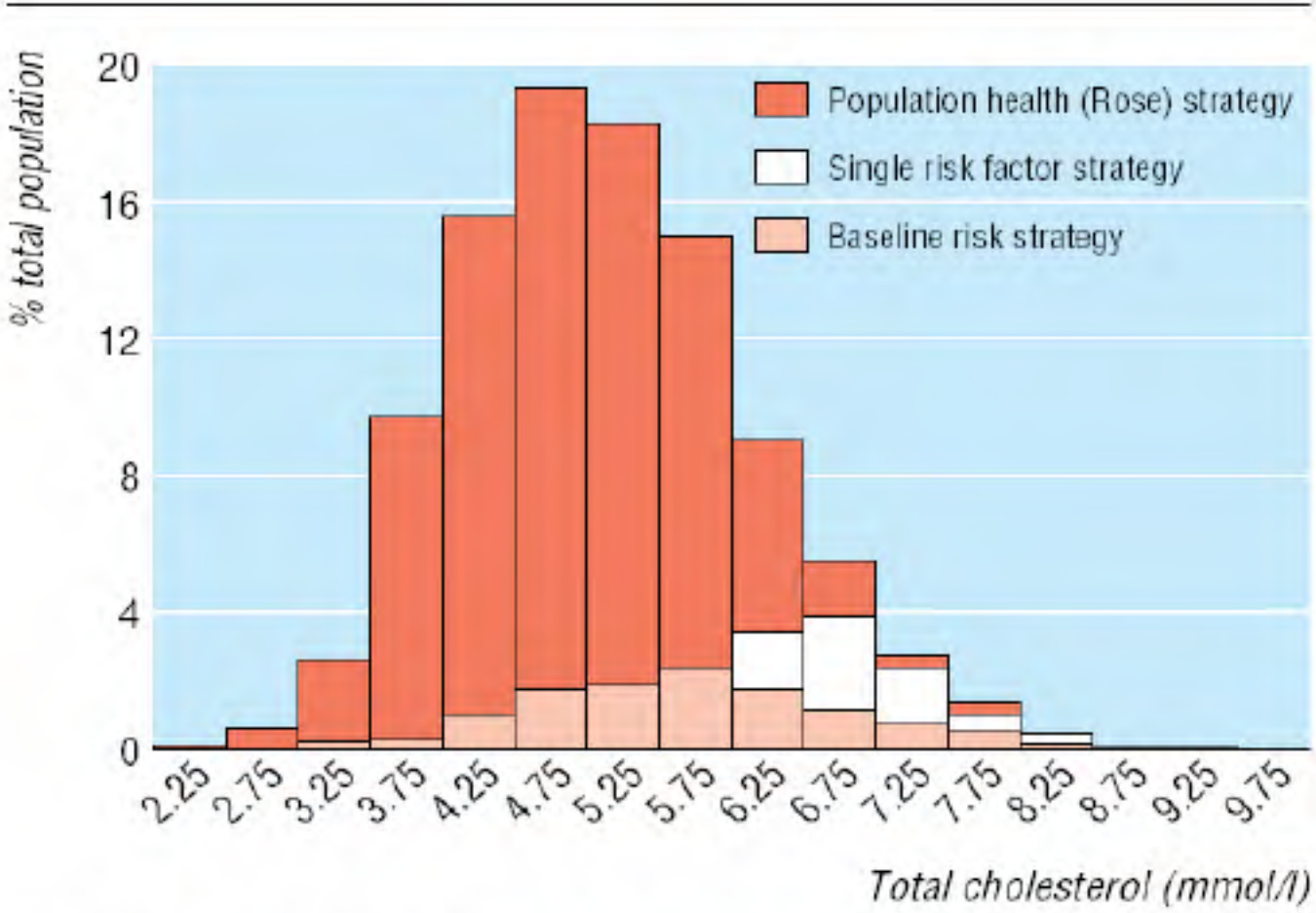
Stratégies de prévention primaire

- **Stratégies individuelles**
  - Personnalisation de la prise en charge
  - Optimisation du rapport bénéfice/risque
  - Nécessité de campagnes de dépistage très couteuse
  - Imprécision de l'évaluation du risque
  - Seuil de risque arbitraire
  - « Paradoxe de la prévention » (la majorité des évènements surviendront chez des individus ayant un niveau de risque modéré)
- **Stratégies à l'échelle de la population.**
  - Action sur les facteurs environnementaux
  - Modifications des comportements individuels (coût élevé, efficacité non prouvé)
  - Modifications des politiques sanitaires (modifications des habitudes alimentaires, arrêt du tabac).



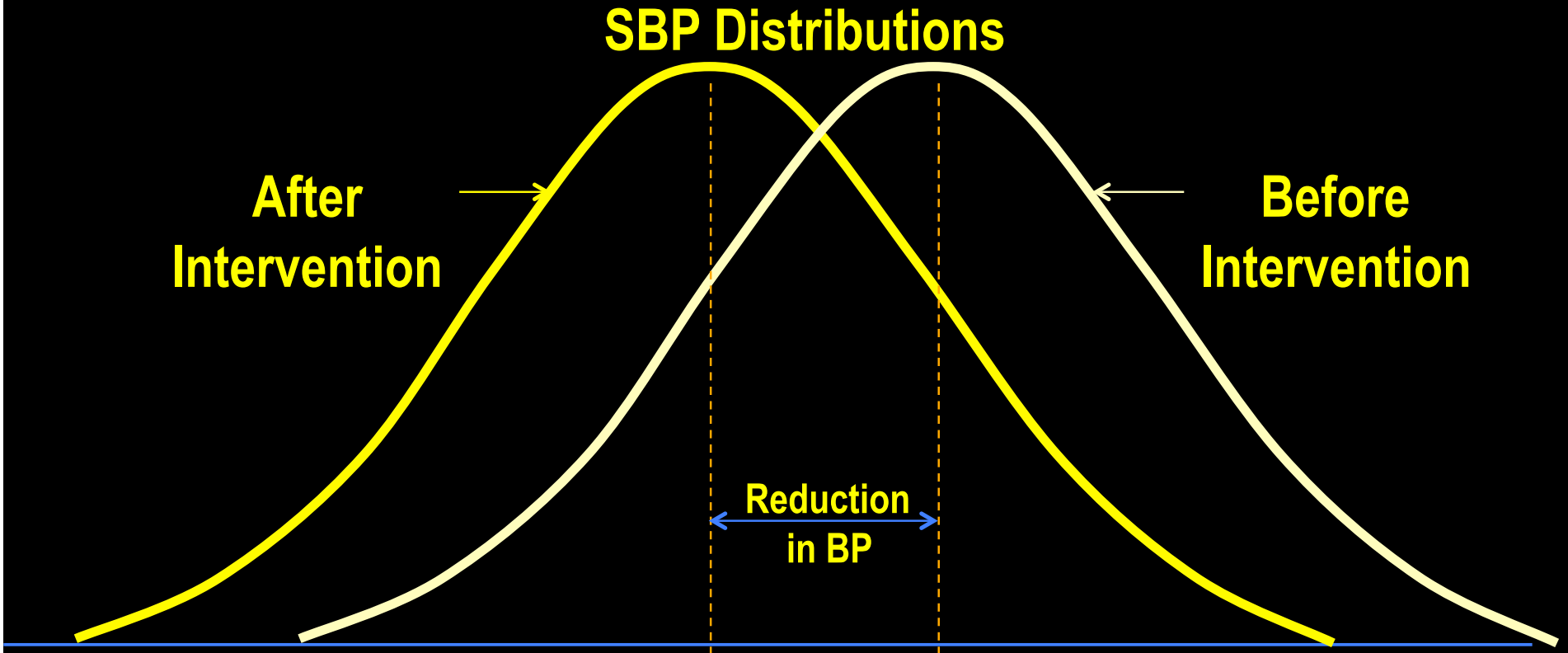
Normal Probability Density Functions of the Risk Factor among Persons Who Will Not Have the Event (Blue) and among Those Who Will (Red).

The 10th and 90th percentiles of the distribution in the event-free group are labeled as x_1 and x_2, respectively. The cutoff value for a diagnostic test with 95% specificity (false positive probability=0.05) is labeled as T. To calculate the conditional probability of membership in the group with an event, given a value of the risk factor, one assigns weights to the probability densities in the two groups according to their population prevalence of either 5% or 95%.



Total cholesterol concentration in populations targeted by three preventive strategies. Based on data from Canadians aged 20-74 in 1990

Population-Based Strategy



Reduction in SBP mmHg	% Reduction in Mortality Stroke	CHD	Total
2	–6	–4	–3
3	–8	–5	–4
5	–14	–9	–7

Objectif no 71

A strategy to reduce cardiovascular disease by more than 80%

N J Wald, M R Law,

BMJ 2003;326:1419

Polypill: info ou intox ?

Results The formulation which met our objectives was: a statin (for example, atorvastatin (daily dose 10 mg) or simvastatin (40 mg)); three blood pressure lowering drugs (for example, a thiazide, a Bblocker, and an angiotensin converting enzyme inhibitor), each at half standard dose; folic acid (0.8 mg); and aspirin (75 mg).
We estimate that the combination (which we call the Polypill) reduces IHD events by 88% (95% confidence interval 84% to 91%) and stroke by 80% (71% to 87%).
Summing the adverse effects of the components observed in randomised trials shows that the Polypill would cause symptoms in 8-15% of people (depending on the precise formulation).

Conclusion The Polypill strategy could largely prevent heart attacks and stroke if taken by everyone aged 55 and older and everyone with existing cardiovascular disease.

Polypill

- **Absence d'interaction : 1 + 1 = 1**
  - Statine réduit le RCV de 30%
  - Thiazide réduit le RCV de 30%
  - Béta-bloqueur réduit le RCV de 20%
  - IEC réduit le RCV de 30%
  - Aspirine réduit le RCV de 20%
  - Acide folique réduit le RCV de 15%
- **Risque initial = 100 → 18,6592 : RRR = 81,3408 %**
  - Statine : 100 → 70
  - Thiazide : 70 → 49
  - Béta-bloqueur : 49 → 39,2
  - IEC : 39,2 → 27,44
  - Aspirine : 27,44 → 21,952
  - Acide folique : 21,952 → 18,6592

« Polypill », one size fits all

A strategy to reduce cardiovascular disease by more than 80%

N J Wald, M R Law,
BMJ 2003;326:1419

La négation de l'individualisation des traitements
(donc de l'inutilité des médecins en matière de prévention)

Paternité de la *polypill*

- Salim Yussuf (Lancet. 2002; 360: 2-3).
- Nicholas Wald et Malcolm Law (BMJ. 2003; 326: 1419-1424).

Populations cibles de la *polypill*

- **Individus en prévention cardiovasculaire secondaire.**
  - **Situation actuelle non optimale (EUROASPIRE, PURE…).**
- **Individus en situation de prévention cardiovasculaire primaire.**
  - **90 % des décès de cause CV surviennent chez les 55 ans et plus.**
- **Les stratégies classiques se heurtent au difficile problème d'observance (facteurs sociaux, culturels, psychologiques, économiques, cliniques, médicaux, systèmes de soins).**
- **Accessibilité et coût des traitements, des consultations, des bilans réalisés.**

Avantages potentiels de la *polypill*

- **Meilleure délivrance des soins.**
  - Suppression des algorithmes complexes.
  - Suppression des étapes successives d'ajustement et de contrôle.
  - Concept acquis pour l'HTA, le SIDA, la tuberculose.
- **Meilleure observance thérapeutique.**
  - Démonstration incomplète, observance : processus complexe.
- **Réduction des dépenses.**
  - 0.20 - 1 $,
  - Réduction des frais de conditionnement, de distribution, de commercialisation, de consultation et de bilan biologique.
  - A.M.M. en Inde pour une *polypill*.
- **Base à de nouvelles stratégies de prévention.**
  - Stratégies actuelles non adaptées à une épidémie mondiale.
  - Stratégie faisant appel à des professionnels de santé non médecins.
  - Médicalisation : effets adverses, symptômes nouveaux, échec d'obtention des cibles thérapeutiques.

Diabète 2 : Intérêt d'une intervention multifactorielle : étude STENO 2 Patients ayant atteint les objectifs

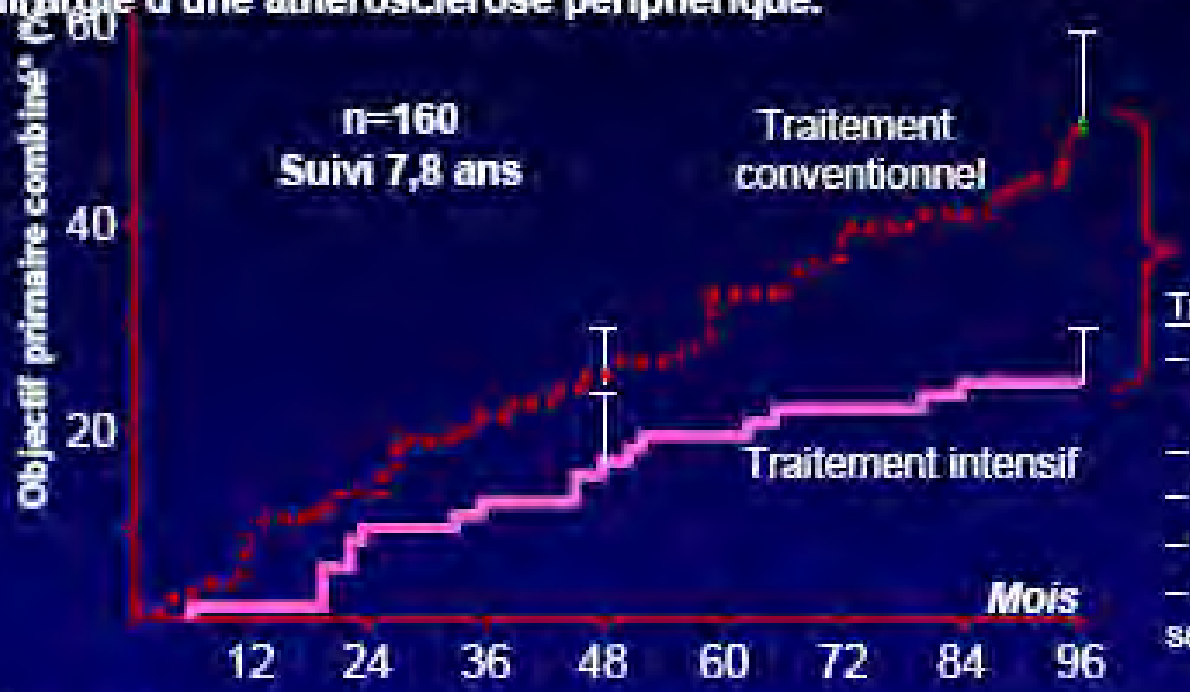
	Conventionnel	Intensif
HbA1c < 6,5%	< 5%	15%
Chol. T < 1,75 g/l	25%	75%
Tg < 1,5 g/l	45%	60%
PAs < 130 mm Hg	20%	47%
PAd < 80 mm Hg	60%	75%

Objectif primaire combiné: traitement conventionnel (44%) traitement intensif (24%).
*Décès CV, IDM non fatal, angioplastie ou pontage, AVC non fatal, amputation ou chirurgie d'une athérosclérose périphérique.

N. Engl. J. Med. 2003; 348 (5): 383-393

Diabète 2 : Intérêt d'une intervention multifactorielle : étude STENO 2

Objectif primaire combiné: traitement conventionnel (44%) traitement intensif (24%).
***Décès CV, IDM non fatal, angioplastie ou pontage, AVC non fatal, amputation ou chirurgie d'une athérosclérose périphérique.**



RRA : 20%

Traitement "aggressif"†:
- Microalbuminurie avec IEC ARAII ou association
- HTA
- Hyperglycémie
- Dyslipidémie
- Prévention CV secondaire

†Mesures hygiéno-diététiques et traitement pharmacologique.

Prise en charge intensive de 5 patients pour éviter 1 événement cardiovasculaire (pdt 7,8 ans)

Gæde P et al. N Eng J Med. 2003;348:383-393

Effects of a polypill (Polycap) on risk factors in middle-aged individuals without cardiovascular disease (TIPS): a phase II, double-blind, randomised trial

The Indian Polycap Study (TIPS)*

Summary

Background The combination of three blood-pressure-lowering drugs at low doses, with a statin, aspirin, and folic acid (the polypill), could reduce cardiovascular events by more than 80% in healthy individuals. We examined the effect of the Polycap on blood pressure, lipids, heart rate, and urinary thromboxane B2, and assessed its tolerability.

Methods In a double-blind trial in 50 centres in India, 2053 individuals without cardiovascular disease, aged 45–80 years, and with one risk factor were randomly assigned, by a central secure website, to the Polycap (n=412) consisting of low doses of thiazide (12·5 mg), atenolol (50 mg), ramipril (5 mg), simvastatin (20 mg), and aspirin (100 mg) per day, or to eight other groups, each with about 200 individuals, of aspirin alone, simvastatin alone, hydrochlorothiazide alone, three combinations of the two blood-pressure-lowering drugs, three blood-pressure-lowering drugs alone, or three blood-pressure-lowering drugs plus aspirin. The primary outcomes were LDL for the effect of lipids, blood pressure for antihypertensive drugs, heart rate for the effects of atenolol, urinary 11-dehydrothromboxane B2 for the antiplatelet effects of aspirin, and rates of discontinuation of drugs for safety. Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00443794.

Findings Compared with groups not receiving blood-pressure-lowering drugs, the Polycap reduced systolic blood pressure by 7·4 mm Hg (95% CI 6·1–8·1) and diastolic blood pressure by 5·6 mm Hg (4·7–6·4), which was similar when three blood-pressure-lowering drugs were used, with or without aspirin. Reductions in blood pressure increased with the number of drugs used (2·2/1·3 mm Hg with one drug, 4·7/3·6 mm Hg with two drugs, and 6·3/4·5 mm Hg with three drugs). Polycap reduced LDL cholesterol by 0·70 mmol/L (95% CI 0·62–0·78), which was less than that with simvastatin alone (0·83 mmol/L, 0·72–0·93; p=0·04); both reductions were greater than for groups without simvastatin (p<0·0001). The reductions in heart rate with Polycap and other groups using atenolol were similar (7·0 beats per min), and both were significantly greater than that in groups without atenolol (p<0·0001). The reductions in 11-dehydrothromboxane B2 were similar with the Polycap (283·1 ng/mmol creatinine, 95% CI 229·1–337·0) compared with the three blood-pressure-lowering drugs plus aspirin (350·0 ng/mmol creatinine, 294·6–404·0), and aspirin alone (348·8 ng/mmol creatinine, 277·6–419·9) compared with groups without aspirin. Tolerability of the Polycap was similar to that of other treatments, with no evidence of increasing intolerability with increasing number of active components in one pill.

Interpretation This Polycap formulation could be conveniently used to reduce multiple risk factors and cardiovascular risk.

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*Members listed at end of paper

Correspondence to:
Salim Yusuf, Population Health Research Institute, Hamilton Health Sciences and McMaster University, 237 Barton Street East, Hamilton, ON L8L 2X2, Canada
yusufs@mcmaster.ca

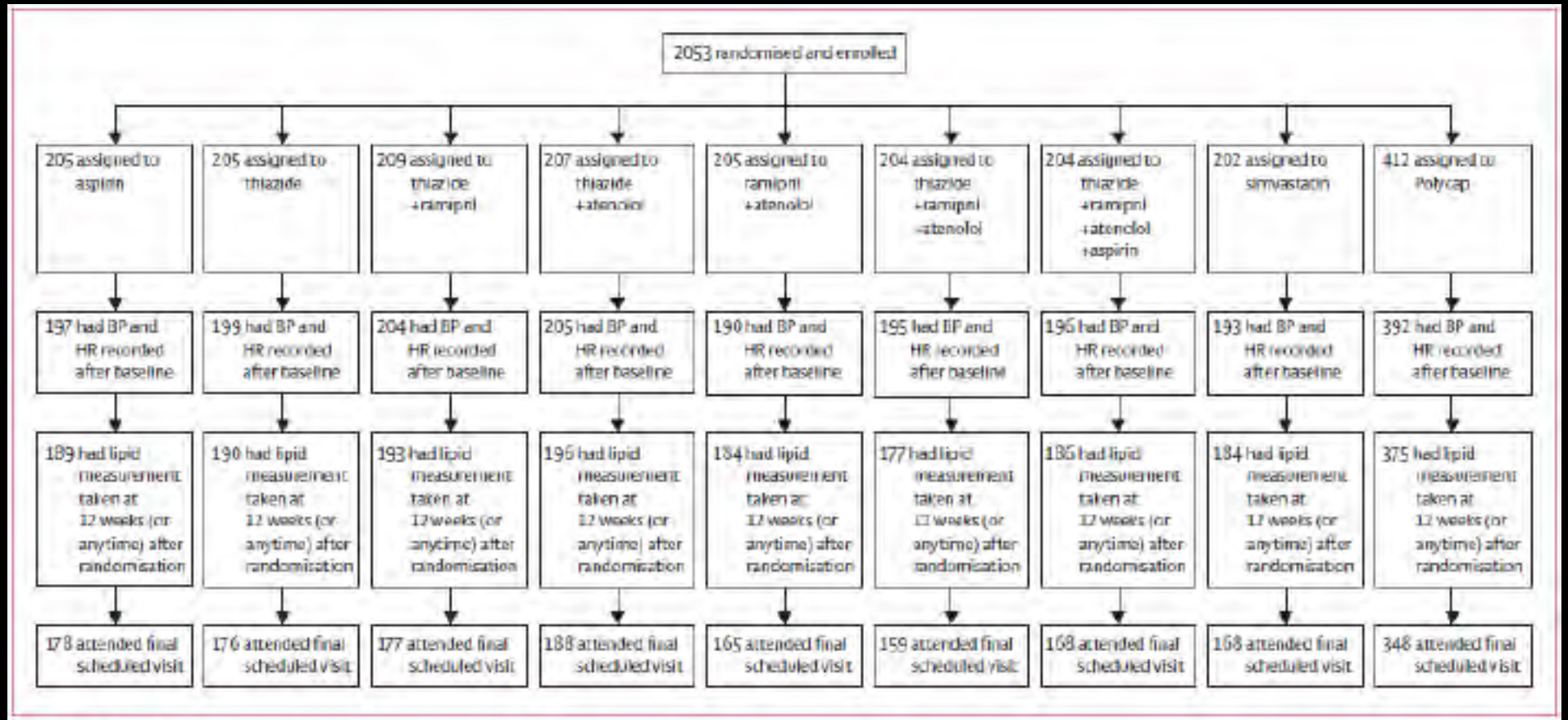


Figure 1: Trial profile

The number of people screened for eligibility was not recorded. BP=blood pressure. HR=heart rate.

Effects of a polypill (Polycap) on risk factors in middle-aged individuals without cardiovascular disease (TIPS): a phase II, double-blind, randomised trial

Summary

Background The combination of three blood-pressure-lowering drugs at low doses, with a statin, aspirin, and folic acid (the polypill), could reduce cardiovascular events by more than 80% in healthy individuals. We examined the effect of the Polycap on blood pressure, lipids, heart rate, and urinary thromboxane B2, and assessed its tolerability.

Between March 5, 2007, and August 5, 2008, we recruited individuals without previous cardiovascular disease, aged between 45 years and 80 years, and with one risk factor (type 2 diabetes; blood pressure >140 mm Hg systolic or 90 mm Hg diastolic, but <160/100 mm Hg; smoker within past 5 years; increased waist to hip ratio [>0·85 for women and >0·90 for men]; or abnormal lipids [LDL cholesterol >3·1 mmol/L or HDL cholesterol <1·04 mmol/L]). Patients were recruited from 50 centres in India, with coordinating centres at St John's Medical College, Bangalore, India, and at the Population Health Research Institute, Hamilton Health Sciences and McMaster University, Canada. Individuals were excluded if they were receiving one of the study drugs, taking two or more antihypertensive drugs, had a serum LDL cholesterol greater than 4·5 mmol/L, had creatinine greater than 177 μmol/L (2·0 mg/dL) or potassium greater than 5·5 mmol/L, had abnormal liver function, had asthma, or were pregnant or lactating.

Effects of a polypill (Polycap) on risk factors in middle-aged individuals without cardiovascular disease (TIPS): a phase II, double-blind, randomised trial

Summary

	Overall (N=2053)	As (n=205)	T (n=205)	T+R (n=209)	T+At (n=207)	R+At (n=205)	T+R+At (n=204)	T+R+At+As (n=204)	S (n=202)	P (n=412)
Age (years)	54·0 (7·9)	53·4 (7·7)	55·0 (8·5)	54·9 (7·9)	54·1 (8·4)	53·9 (7·5)	54·0 (7·8)	53·6 (7·7)	53·6 (7·9)	53·7 (7·7)
BMI (kg/m²)	26·3 (4·5)	26·5 (4·5)	25·9 (4·4)	26·2 (4·3)	27·1 (4·6)	26·5 (4·0)	26·0 (4·8)	26·7 (4·4)	26·0 (4·4)	26·2 (4·5)
Systolic BP (mm Hg)	134·4 (12·3)	132·0 (12·4)	134·0 (12·2)	134·6 (12·7)	134·5 (12·5)	135·3 (11·4)	133·4 (11·7)	134·9 (12·4)	134·5 (12·4)	134·8 (12·2)
Diastolic BP (mm Hg)	85·0 (8·1)	83·6 (8·2)	84·5 (7·8)	84·6 (7·8)	85·6 (7·9)	86·0 (8·3)	84·8 (8·2)	85·5 (8·6)	84·6 (8·4)	85·6 (7·9)
Heart rate (beats/min)	80·1 (10·7)	79·1 (9·7)	80·2 (10·8)	80·3 (11·3)	80·7 (11·8)	79·6 (10·9)	80·0 (10·4)	80·8 (10·3)	79·4 (10·2)	80·2 (10·5)
Total cholesterol (mmol/L)	4·7 (0·9)	4·7 (0·9)	4·6 (1·0)	4·7 (0·9)	4·7 (0·9)	4·8 (0·9)	4·6 (0·9)	4·7 (0·9)	4·6 (1·0)	4·7 (0·9)
LDL cholesterol (mmol/L)	3·0 (0·8)	3·0 (0·8)	3·0 (0·7)	3·0 (0·8)	3·1 (0·7)	3·1 (0·8)	3·0 (0·7)	3·0 (0·8)	3·0 (0·8)	3·0 (0·7)
HDL cholesterol (mmol/L)	1·1 (0·3)	1·1 (0·3)	1·1 (0·3)	1·1 (0·3)	1·2 (0·3)	1·2 (0·3)	1·1 (0·3)	1·1 (0·3)	1·2 (0·3)	1·1 (0·3)
Triglycerides (mmol/L)	1·9 (1·2)	1·9 (1·1)	2·0 (1·3)	2·0 (1·4)	1·9 (0·9)	1·9 (1·4)	1·9 (1·4)	1·9 (1·0)	1·8 (1·0)	2·0 (1·3)
ApoB	0·9 (0·2)	0·9 (0·2)	0·9 (0·2)	0·9 (0·2)	0·9 (0·2)	0·9 (0·2)	0·9 (0·2)	0·9 (0·2)	0·9 (0·2)	0·9 (0·2)
ApoA	1·2 (0·2)	1·2 (0·2)	1·2 (0·2)	1·2 (0·2)	1·2 (0·2)	1·2 (0·2)	1·2 (0·2)	1·2 (0·2)	1·2 (0·2)	1·2 (0·2)
Diabetes	696 (33·9%)	70 (34·1%)	67 (32·7%)	78 (37·3%)	70 (33·8%)	67 (32·7%)	67 (32·8%)	64 (31·4%)	71 (35·1%)	142 (34·5%)
Current smoker	276 (13·4%)	18 (8·8%)	33 (16·1%)	24 (11·5%)	20 (9·7%)	30 (14·6%)	39 (19·1%)	32 (15·7%)	27 (13·4%)	53 (12·9%)
Women	901 (43·9%)	97 (47·3%)	90 (43·9%)	85 (40·7%)	96 (46·4%)	94 (45·9%)	83 (40·7%)	89 (43·6%)	96 (47·5%)	171 (41·5%)
Calcium-channel blockers	445 (21·7%)	43 (21·0%)	52 (25·4%)	43 (20·6%)	41 (19·8%)	50 (24·4%)	47 (23·0%)	37 (18·1%)	38 (18·8%)	94 (22·8%)

Data are mean (SD) or number (%). As=aspirin. T=thiazide. R=ramipril. At=atenolol. S=simvastatin. P=Polycap. BMI=body-mass index. BP=blood pressure. ApoB=apolipoprotein B. ApoA=apolipoprotein A_1.

Table 1: Baseline characteristics

Effects of a polypill (Polycap) on risk factors in middle-aged individuals without cardiovascular disease (TIPS): a phase II, double-blind, randomised trial

Thrombosis Prevention Trial (TIPS)

Summary

Background The combination of three blood-pressure-lowering drugs at low doses, with a statin, aspirin, and folic acid (the polypill), could reduce cardiovascular events by more than 80% in healthy individuals. We examined the effect of the Polycap on blood pressure, lipids, heart rate, and urinary thromboxane B2, and assessed its tolerability.

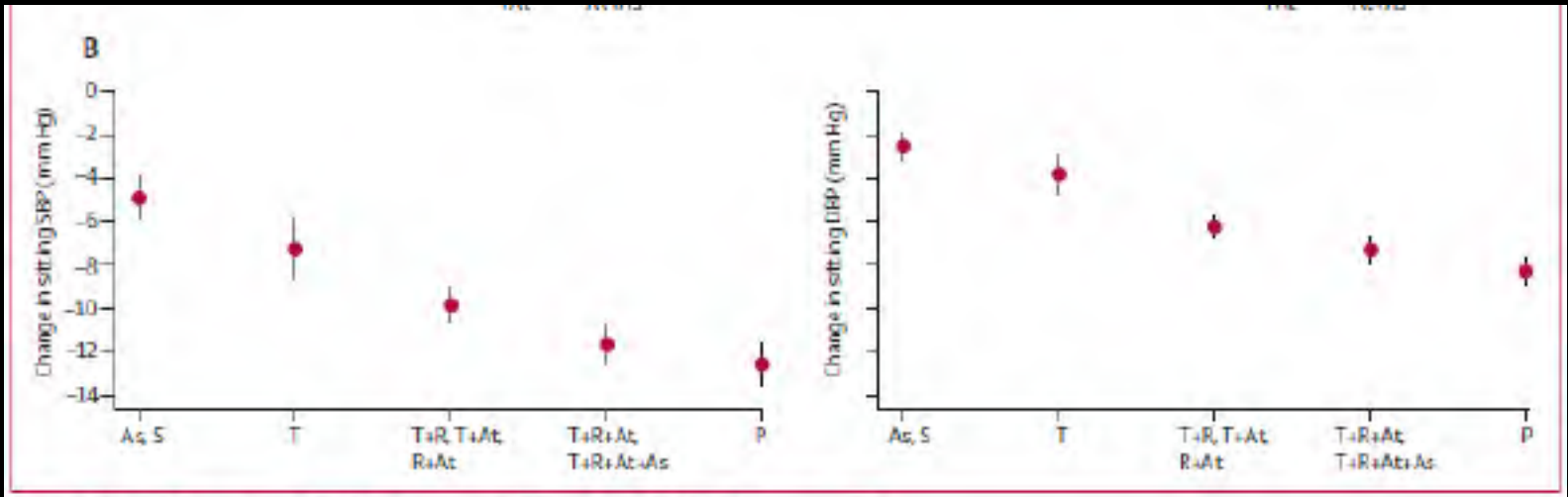
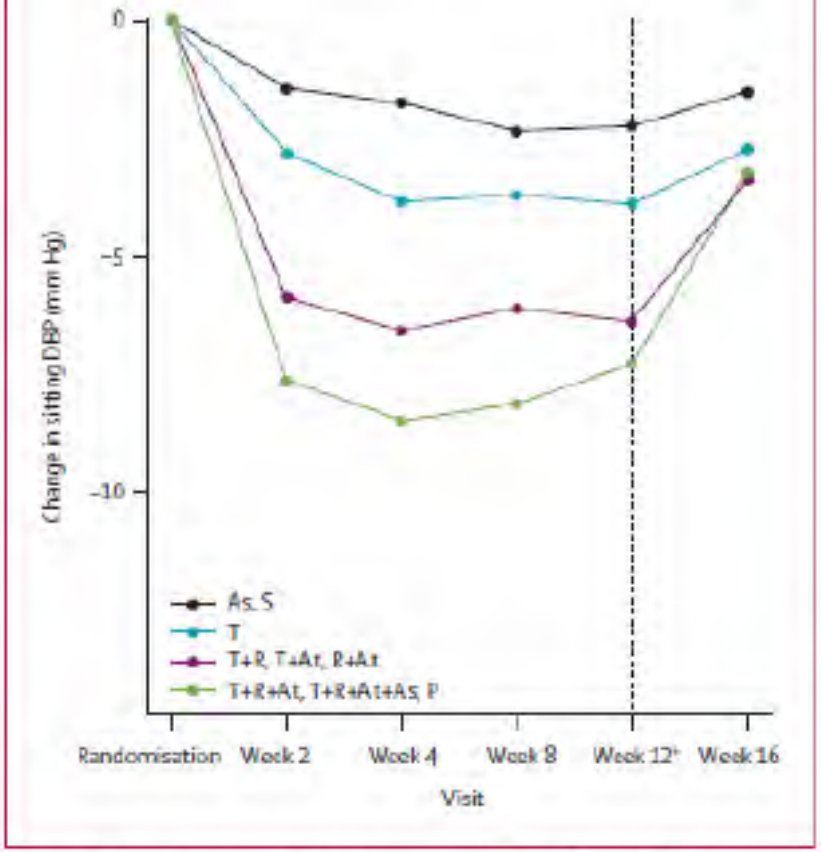


Figure 3: Mean changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP)

Error bars indicate 95% CI. Mean changes from baseline in the nine groups (A), and the effects of no blood-pressure-lowering drugs (As, S), one blood-pressure-lowering drug (T), two blood-pressure-lowering drugs (T+R, T+At, or R+At), or three blood-pressure-lowering drugs (T+R+At, T+R+At+S), or the Polycap (B). As=aspirin. T=thiazide. R=ramipril. At=atenolol. S=simvastatin. P=Polycap.

Effects of a polypill (Polycap) on risk factors in middle-aged individuals without cardiovascular disease (TIPS): a phase II, double-blind, randomised trial

Summary



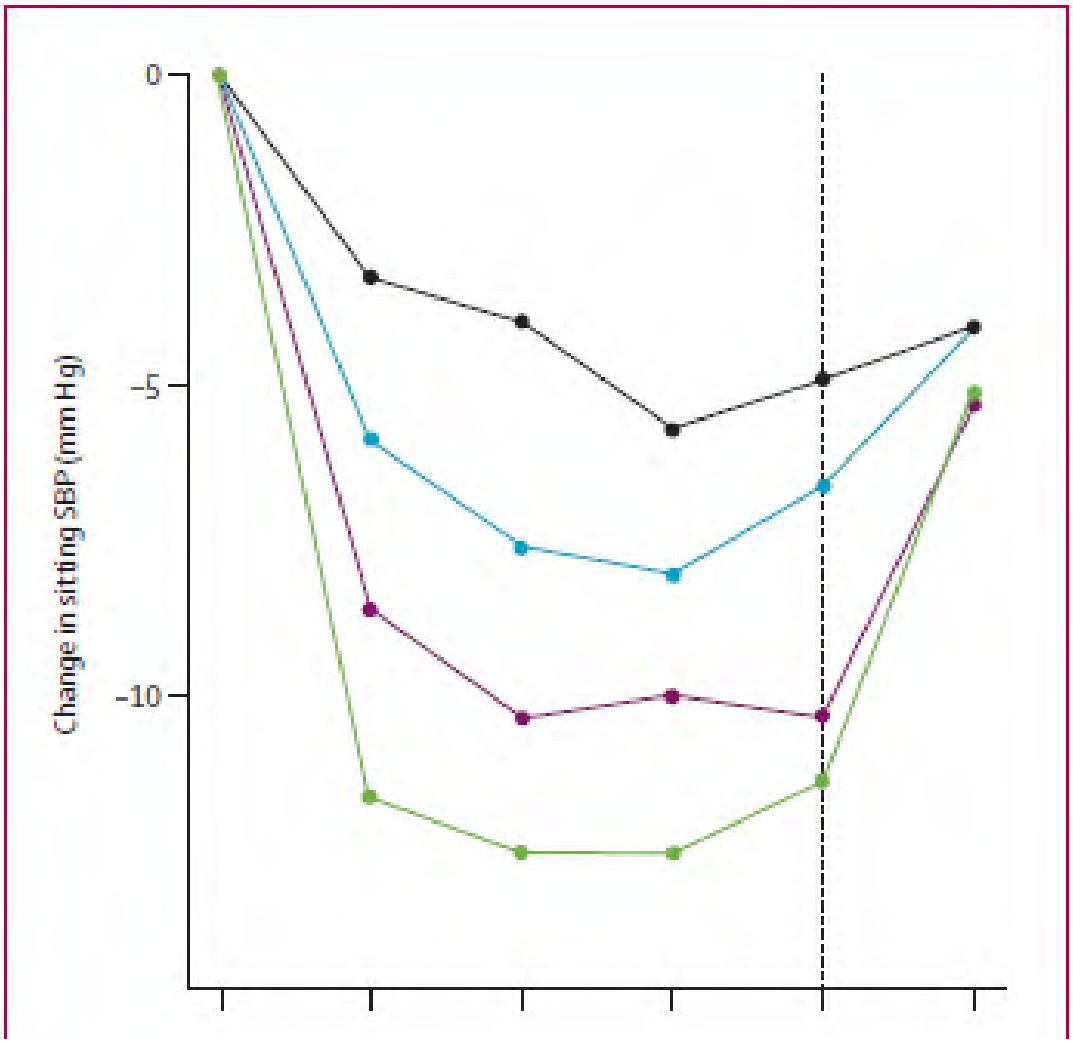


Figure 4: Changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) after randomisation over time
Most of the reduction in blood pressure was detected early and was sustained until the end of active treatment. As=aspirin. T=thiazide. R=ramipril. At=atenolol. S=simvastatin. P=Polycap. *End of treatment.

OPEN ACCESS Freely available online

PLoS one

An International Randomised Placebo-Controlled Trial of a Four-Component Combination Pill ("Polypill") in People with Raised Cardiovascular Risk

PILL Collaborative Group[*]

Abstract

Background: There has been widespread interest in the potential of combination cardiovascular medications containing aspirin and agents to lower blood pressure and cholesterol ('polypills') to reduce cardiovascular disease. However, no reliable placebo-controlled data are available on both efficacy and tolerability.

Methods: We conducted a randomised, double-blind placebo-controlled trial of a polypill (containing aspirin 75 mg, lisinopril 10 mg, hydrochlorothiazide 12.5 mg and simvastatin 20 mg) in 378 individuals without an indication for any component of the polypill, but who had an estimated 5-year cardiovascular disease risk over 7.5%. The primary outcomes were systolic blood pressure (SBP), LDL-cholesterol and tolerability (proportion discontinued randomised therapy) at 12 weeks follow-up.

Findings: At baseline, mean BP was 134/81 mmHg and mean LDL-cholesterol was 3.7 mmol/L. Over 12 weeks, polypill treatment reduced SBP by 9.9 (95% CI: 7.7 to 12.1) mmHg and LDL-cholesterol by 0.8 (95% CI 0.6 to 0.9) mmol/L. The discontinuation rates in the polypill group compared to placebo were 23% vs 18% (RR 1.33, 95% CI 0.89 to 2.00, p=0.2). There was an excess of side effects known to the component medicines (58% vs 42%, p=0.001), which was mostly apparent within a few weeks, and usually did not warrant cessation of trial treatment.

Conclusions: This polypill achieved sizeable reductions in SBP and LDL-cholesterol but caused side effects in about 1 in 6 people. The halving in predicted cardiovascular risk is moderately lower than previous estimates and the side effect rate is moderately higher. Nonetheless, substantial net benefits would be expected among patients at high risk.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12607000099426

Citation: PILL Collaborative Group (2011) An International Randomised Placebo-Controlled Trial of a Four-Component Combination Pill ("Polypill") in People with Raised Cardiovascular Risk. PLoS ONE 6(5): e19857. doi:10.1371/journal.pone.0019857

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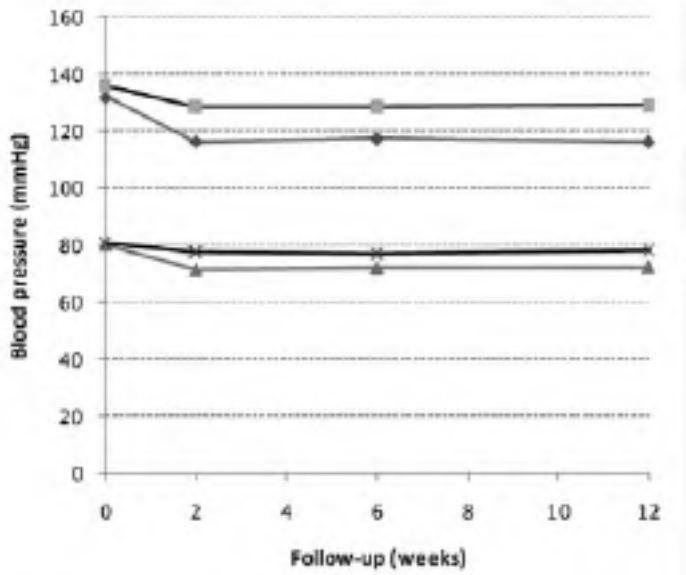
Table 1. Baseline characteristics.

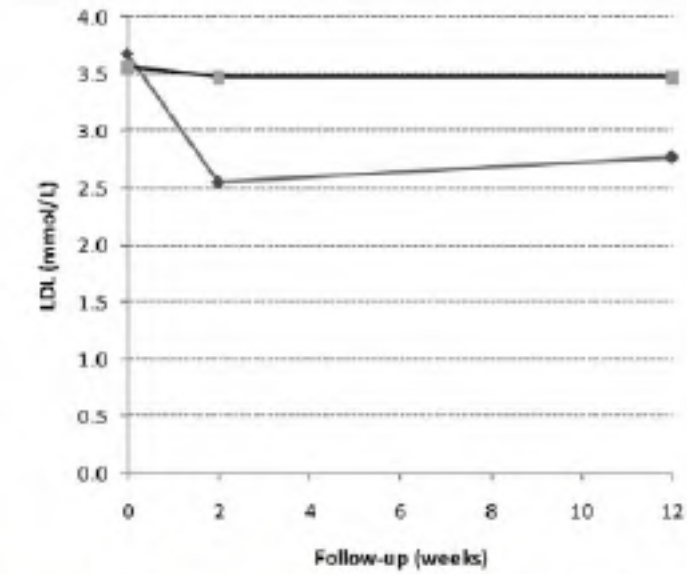
	Red Heart Pill n = 189		Placebo n = 189	
Cardiovascular risk factors in Framingham score				
Age (yrs)	61.2	(7.2)	61.6	(7.2)
Male	153	(81%)	152	(80%)
Blood pressure (mmHg)	132/80	(13/9)	136/81	(14/9)
LDL-cholesterol (mmol/L)	3.7	(0.9)	3.6	(0.9)
Total cholesterol (mmol/L)	5.6	(1.1)	5.4	(1.0)
HDL (mmol/L)	1.2	(0.3)	1.3	(0.4)
Smoker (or quit within the last year)	79	(42%)	74	(39%)
*Other cardiovascular risk factors**				
Body mass index >30 kg/m^2, waist circumference >102 cm in men or >88 cm in women	88	(47%)	90	(48%)
Heart rate >80 beats/min	48	(25%)	46	(24%)
Fasting glucose 5.6– <7 mmol/L	55	(29%)	60	(32%)
Family history of premature coronary heart disease or ischaemic stroke	87	(46%)	77	(41%)
Triglycerides >1.7 mmol/L	69	(37%)	53	(28%)
Glomerular filtration rate (GFR) <60 mL/min	18	(10%)	23	(12%)
At least 2 of the above*	120	(63%)	117	(62%)
Cardiovascular risk				
5-year cardiovascular risk – Framingham function	10%	(4.1%)	11%	(4.5%)
10-yr fatal cardiovascular risk – SCORE function	4.3%	(3.0%)	4.9%	(3.4%)
Medication:				
Prescribed or over-the-counter medicines	59	(31%)	43	(23%)
Vitamin and/or mineral capsules/tablets	43	(23%)	37	(20%)
Other dietary supplements	34	(18%)	31	(16%)
Any other complementary or alternative medicine	5	(3%)	7	(4%)
Current lifestyle factors				
Moderate physical exercise in last 7 days (mins)	211	(240)	256	(270)
Vigorous physical exercise in last 7 days (mins)	23	(104)	16	(49)
Formal exercise programme	4	(2%)	5	(3%)
Seeing a dietician or other nutritional counsellor or on a weight control programme	1	(1%)	1	(1%)
Smoking cessation programme	4	(2%)	2	(1%)
Other				
Currently drink alcohol once a week or more (on most weeks for at least the last year)	132	(69%)	142	(75%)

Data are mean (sd) or n (%).
*Participants with Framingham 5-yr CVD risk 5–7.5% were eligible for the trial if they had at least two such factors.
doi:10.1371/journal.pone.0019857.t001



ΔSBP 9.9 mmHg (7.1-12.1)

ΔDBP 5.3 mmHg (3.3-6.7)



ΔLDL-cholesterol 0.8 mmol/L (0.6-0.9)

Figure 3. Blood pressure and LDL-cholesterol changes. This figure shows the changes in blood pressure and LDL-cholesterol over the 12 week trial period, according to active (dark line) or placebo (grey line).
doi:10.1371/journal.pone.0019857.g003

Table 2. Main reasons for stopping study treatment and side effects.

	Reported side effects of sufficient severity to discontinue study treatment*					Reported side effects not necessitating discontinuation of study treatment				
	Red Heart Pill		Placebo		P-value	Red Heart Pill		Placebo		P-value
	n	%	n	%		n	%	n	%	
Gastric irritation	6	3%	1	1%	0.06	23	12%	6	3%	0.0005
Increased bleeding tendency	0	0%	0	0%		4	2%	1	1%	0.3
Cough	3	2%	2	1%	0.7	19	10%	3	2%	0.0002
Light headed/dizziness/hypotension	7	4%	2	1%	0.09	28	15%	8	4%	0.0002
Muscle pain or weakness	1	1%	2	1%	0.6	13	7%	14	7%	0.9
Headache	1	0%	0	0%		4	2%	3	2%	0.6
Diarrhoea	0	0%	0	0%		4	2%	5	3%	0.8
Fatigue	3	2%	2	1%	0.7	13	7%	10	5%	0.4
Abdominal pain	0	0%	0	0%		4	2%	1	1%	0.2
Constipation	0	0%	0	0%		10	5%	4	2%	0.08
Flatulence	0	0%	0	0%		6	3%	5	3%	0.7
Other side effect	13	6%	12	6%	0.8	39	21%	28	15%	0.07
Patient choice	0	0%	3	2%	0.08					
Total**	34	18%	24	13%	0.2	81	43%	59	31%	0.003

*participants without relevant follow-up data at 12 weeks (10 *vs* 9) were assumed to have stopped treatment in the definition of tolerability as the primary trial outcome, which was therefore 44 (23%) *vs* 33 (18%).

**for patients discontinuing treatment, the total is a direct sum as data reflect the main reason for stopping for each patient. For patients not discontinuing treatment, the total refers to the number of people reporting one or more side effects.

doi:10.1371/journal.pone.0019857.t002

Table 3. Estimated reductions in cardiovascular risk for those remaining on treatment.

Treatment	Risk factor reduction	Proportional risk reduction*						No. needed to treat for 5 yrs to prevent 1 major event	
		CHD	Ischaemic stroke	Haem-orrhagic stroke†	Major extra-cranial bleed	Any major event - moderate risk pop‡	Any major event - high risk pop‡	Moderate risk pop‡	High risk pop‡
Blood pressure lowering[14]	10 mmHg lower SBP	22%	41%	41%	0%	26%	29%	40	9
Cholesterol lowering[4]	0.8 mmol/L lower LDL	35%	25%	0%	0%	26%	27%	40	9
Aspirin[14]	Not applicable	20%	17%	−39%	−54%	8%	13%	125	20
All three treatments		60%	62%	18%	−54%	46%	53%	18	4

Table 4. Comparison with previous polypill studies.

	Formulation	Blood pressure (mmHg)		LDL-cholesterol (mmol/l)		Placebo-corrected absolute excess of side effects**		Estimated proportional risk reduction	
		Baseline level	Reduction	Baseline level	Reduction	Sufficient to stop treatment in short term	Causing any symptoms	CHD	Stroke
Wald and Law*[4,5,6]	Statin (e.g. simvastatin 40 mg), three ½ strength blood pressure drugs, aspirin 75 mg	150/90	20/11	4.8	1.8	2%	8–15%	88%	74%
TIPS[23]	Simvastatin 20 mg, hydrochlorothiazide 12·5 mg, atenolol 50 mg, ramipril 5 mg, aspirin 100 mg	134/85	7/6	5.0	0.7	n/a	n/a	62%	48%
Malekzadeh et al [33]	Atorvastatin 20 mg, enalapril 7.5 mg, hydrochlorothiazide 12.5 mg, aspirin 81 mg	128/79	5/2	3.0	0.5	n/a	n/a	34%	21%
Current trial	Simvastatin 20 mg, hydrochlorothiazide 12·5 mg, lisinopril 10 mg, aspirin 75 mg	134/81	10/5	3.7	0.8	5%	16%	60%	56%

*Estimated rather than observed risk factor reductions and side effects. Predictions for formulation without folic acid.

**Not estimable for TIPS due to lack of placebo control and side effects not reported reliably in Malekzadeh et al trial (see Discussion). Side effects 'causing any symptoms' refers to those observed in 12 weeks treatment for current trial and predictions for both short and long term treatment by Wald and Law. This excess was estimated at 8% for a formulation containing a thiazide, angiotensin II receptor blocker and calcium channel blocker and 15% for a formulation containing a thiazide, beta-blocker, and ACE inhibitor.

doi:10.1371/journal.pone.0019857.t004

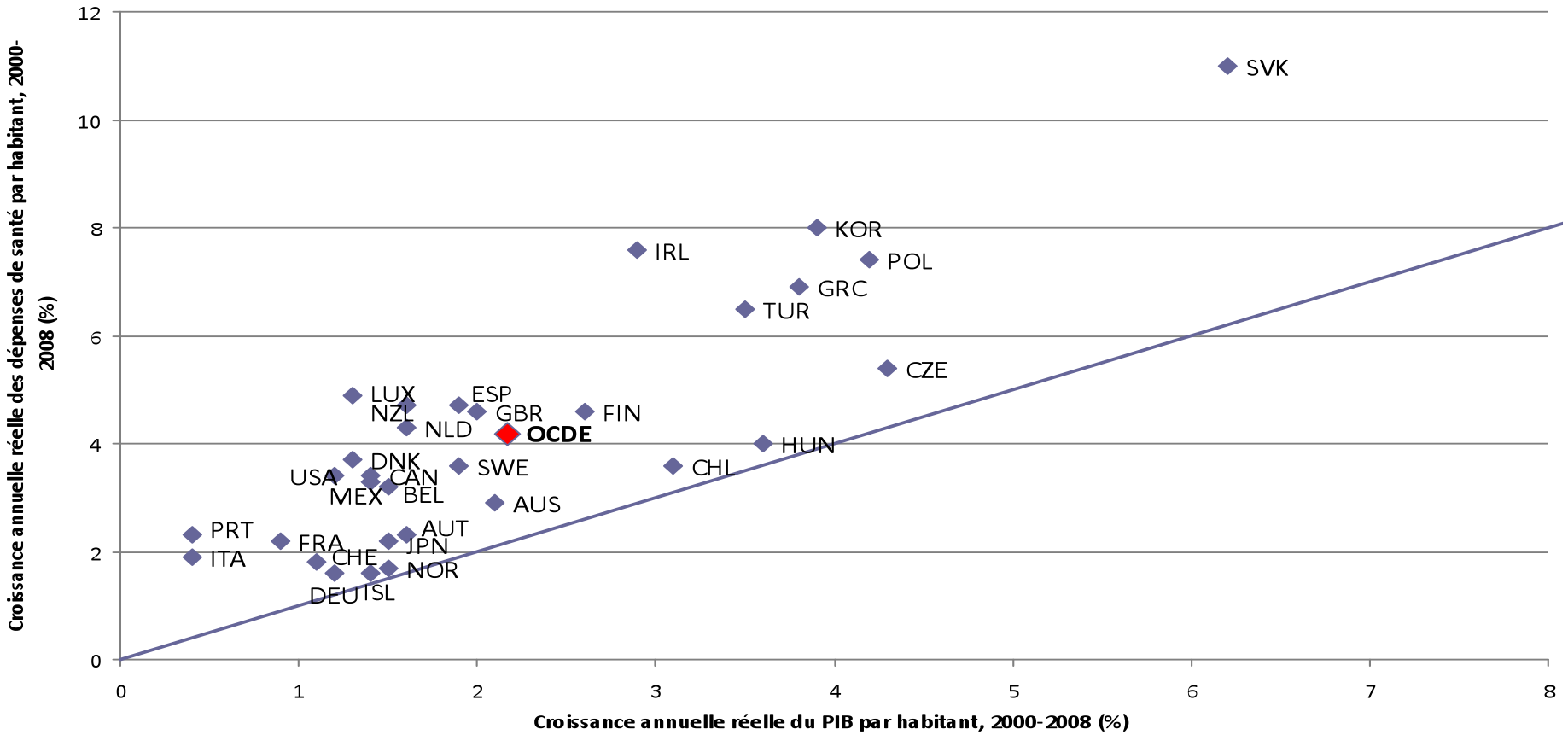
Limites à l'utilisation d'une *polypill*

- **Absence de preuve quant à la réduction des évènements CV et à son innocuité.**
- **Problèmes de galénique.**
- **Quelle est la *polypill* « idéale » ? (posologies, aspirine, IEC *vs* ARA2)**
  - ***Polypill* sans bétabloquant pour les asthmatiques ?**
  - ***Polypill* à forte dose pour la prévention secondaire ?**
- **Critères d'A.M.M. ? (critères intermédiaires ou évènements ?)**
- **Observance.**
- **Rapport coût / efficacité (matières premières, emballage, formulation, recherche, développement, A.M.M., marketing, distribution…).**
- **Impact sur le mode de vie (*magic pill* et comportements à risque CV).**
- **Acceptabilité (des médecins et des patients).**

HOPE-3 (Salim Yussuf. ClinicalTrials.gov.)

- 12 500 participants à risque modéré.
  - Hommes de plus de 55 ans,
  - Femmes de plus de 65 ans présentant un FDR,
  - Femmes de plus de 60 ans présentant deux FDR.
- Taux d'évènements attendus sous placebo de 1 % par an.
- Randomisation + double plan factoriel.
  - 10 mg de Rosuvastatine.
  - 16 mg de Candesartan et 12.5 mg d'hydrochlorothiazide.
  - Traitement complet.
  - Aucun médicament actif.
- Critères de jugement I: évènements cardiovasculaires majeurs.
- Critères de jugement II : modification des fonctions cognitives et rénales.
- Hypothèses : réduction de 25-30 % dans chacun des bras actifs et de 35-40 % dans le bras traitement complet.

Graphique 1. Croissance annuelle des dépenses de santé et du PIB, 2000-2008



Notes: 2000-2006: Luxembourg et Portugal. 2000-2007: Australie, Danemark, Grèce, Japon et Turquie. 2000-2009: Islande.

Source: *Eco-Santé OCDE 2010*.

Conclusion -

- Oui pour associer les médicaments de prévention cardiovasculaire, notamment les antihypertenseurs, dans un seul comprimé

- Oui à la haute couture, non au prêt-à-porter. Il faut viser le meilleur pour tous

- On soigne des individus, pas des populations

Conclusion +

- **Nécessité d'évaluation de la morbi-mortalité CV.**
- ***Polypill* complémentaire à d'autres stratégies de prévention des évènements CV (alimentation, tabac, activité physique).**
- **Modélisation : *polypill* + alimentation + activité physique + tabac = réduction de 80-90 % du risque d'évènement cardiovasculaire à l'échelle mondiale.**
- **Couverture de 50 % : réduction de moitié de l'incidence mondiale des maladies CV au cours des 20 prochaines années.**