Heart Outcomes Prevention Evaluation (HOPE) - 3

Combined Lipid Lowering and Blood Pressure Lowering in Moderate Risk People

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HOPE-3 Rationale

- CVD is a pandemic and it is largely preventable
- Most urban societies have elevated levels of risk factors
- The relationship of most risk factors to outcomes is continuous with risk extending to ‘normal’ levels of CV risk factors
- Most CV events will occur in average risk people (“the prevention paradox”)
- Lifetime risk
- Affecting multiple risk factors to a large extent will likely lower risk of CVD to a large extent

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Choice of Interventions

- In INTERHEART abnormal lipids (Apo B/Apo A-1 ratio) accounted for about 55% of the PAR for MI
- In INTERHEART elevated blood pressure accounted for about 25% of the PAR for MI
- Modifying lipids and lowering BP simultaneously may prevent 50 to 60% of CVD, when these interventions are applied over a long period of time

HOPE 3: Study Design Features

- Polypill concept
- Simple eligibility criteria:
  - moderate risk (age +one or more risk factors)
  - Uncertainty principle
  - Participants are NOT selected based on BP and lipid levels
- Multiple regions → globally applicable
- Range of vascular outcomes

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HOPE-3: Primary Study Objectives

To evaluate in people at moderate risk the effects on major CV events of:

1. Lipid modification (LDL lowering & HDL raising) with rosuvastatin 10 mg/day.
2. BP lowering with combined candesartan 16 mg/HCT 12.5 mg daily.
3. Combined lipid modification (rosuvastatin 10 mg/day) & BP lowering (candesartan 16 mg/HCT 12.5 mg/day).

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Inclusion Criteria

Women ≥ 60 yrs + at least two CV risk factors

Women ≥65 yrs & Men ≥ 55 yrs + at least one CV risk factor:

- **↑Waist/hip ratio: women ≥ 0.85, men ≥ 0.90**
- **Current or recent smoking (regular tobacco use within 5 years)**
- **Low HDL (women <1.3 mmol/L, men < 1.0 mmol/L)**
- **Dysglycemia (impaired fasting glucose, impaired glucose tolerance or uncomplicated DM treated by diet only)**
- **Renal dysfunction**
  - **Microalbuminuria**
  - **Estimated GFR <60 ml/min/1.73 m^2 or creatinine >124 µmol/L (1.4 mg/dL) (unless proteinuria or blood pressure > 130/80 mmHg)**
- **Family history of premature CHD in first degree relatives (women < 65 years, men <55 years)**

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Key Exclusion Criteria

- Documented clinically manifest atherothrombotic CVD
- Clear indication or contraindication for statin, ARB, ACE inhibitor, or thiazide diuretic
- Symptomatic hypotension
- Chronic liver
- Inflammatory muscle disease
- Moderate renal dysfunction (eGFR <45 ml/min/1.73 m^2 or serum creatinine > 180 µmol/L)
- Mild renal dysfunction (eGFR <60 ml/min/1.73 m^2 or serum creatinine > 124 µmol/L) and proteinuria or BP>13080 mmHg

HOPE-3: 2 x 2 Factorial Design

N = 12,700 people at intermediate risk without CVD

Rosuvastatin 10 mg/day; Candesartan/HCT 16/12.5 mg/day

Polypill Concept

	Candesartan/HCT	Placebo
Rosuvastatin	Rosuvastatin + Candesartan/HCT	Rosuvastatin + Placebo
Placebo	Candesartan/HCT+ Placebo	Placebo + Placebo

Lifestyle advice provided to all study participants
Active run-in of 4 weeks
Follow-up: 6 weeks, 6 months, q 6 monthly for an average of 5 years
Long-term passive follow-up for 10 years

HOPE-3: Study Organization and Funding

- Investigator initiated trial coordinated by the Population Health Research Institute (PHRI), Hamilton, Canada
- Funding: Astra-Zeneca and the CIHR
- PHRI and National Leaders responsible for
  - Protocol development
  - Site selection
  - Regulatory approvals
  - Drug packaging and distribution
  - Monitoring
  - PHRI - Data management/ Statistical Centre

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Outcomes

Co- Primary Outcomes:

1. The composite of CV death, non-fatal MI, and non-fatal stroke
2. The composite of CV death, resuscitated cardiac arrest, non-fatal MI, non-fatal stroke, heart failure and arterial revascularizations

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Outcomes

Secondary Efficacy Outcomes:

1. Total mortality.

2. The components of the co-primary endpoints.

Tertiary Efficacy Outcomes:

- Renal dysfunction (ESRD, doubling of serum creatinine, development or progression of microalbuminuria /proteinuria)
- Arterial revascularizations
- New diagnosis of diabetes
- All components of the co-primary and secondary outcomes
- Cognitive function
- Erectile dysfunction in men
- Visual acuity

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Timelines

- Study start:
  - January 2007
- Randomization:
  - May 2007 to March 2009.
- Follow-up:
  - 4-7 years(close out visits in July to October 2014)
- Trial results by March 2015
- Passive follow-up October 2014-October 2024

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Power Calculations: Each Active Therapy vs its Placebo

Sample Size	RRR (%)	1st Co-Primary (2α=0.04) Control Event Rate/yr 0.67*	1st Co-Primary (2α=0.04) Control Event Rate/yr 0.85*	2nd Co-Primary (2α=0.0228) Control Event Rate/yr 0.91*	2nd Co-Primary (2α=0.0228) Control Event Rate/yr 1.15*
	25	67.8	78.1	74.2	84.3
12,700	***30***	***84.3***	***91.8***	***90.0***	***95.7***
	35	94.2	97.8	97.4	99.3

non-adherence rates of: 6% year 1; 5% year 2, 4% in years 3 – 7 for each active therapy (31% at 7yrs); drop-in rates of 2% in year 1 and 2%/year in subsequent years (14% over 7 years).

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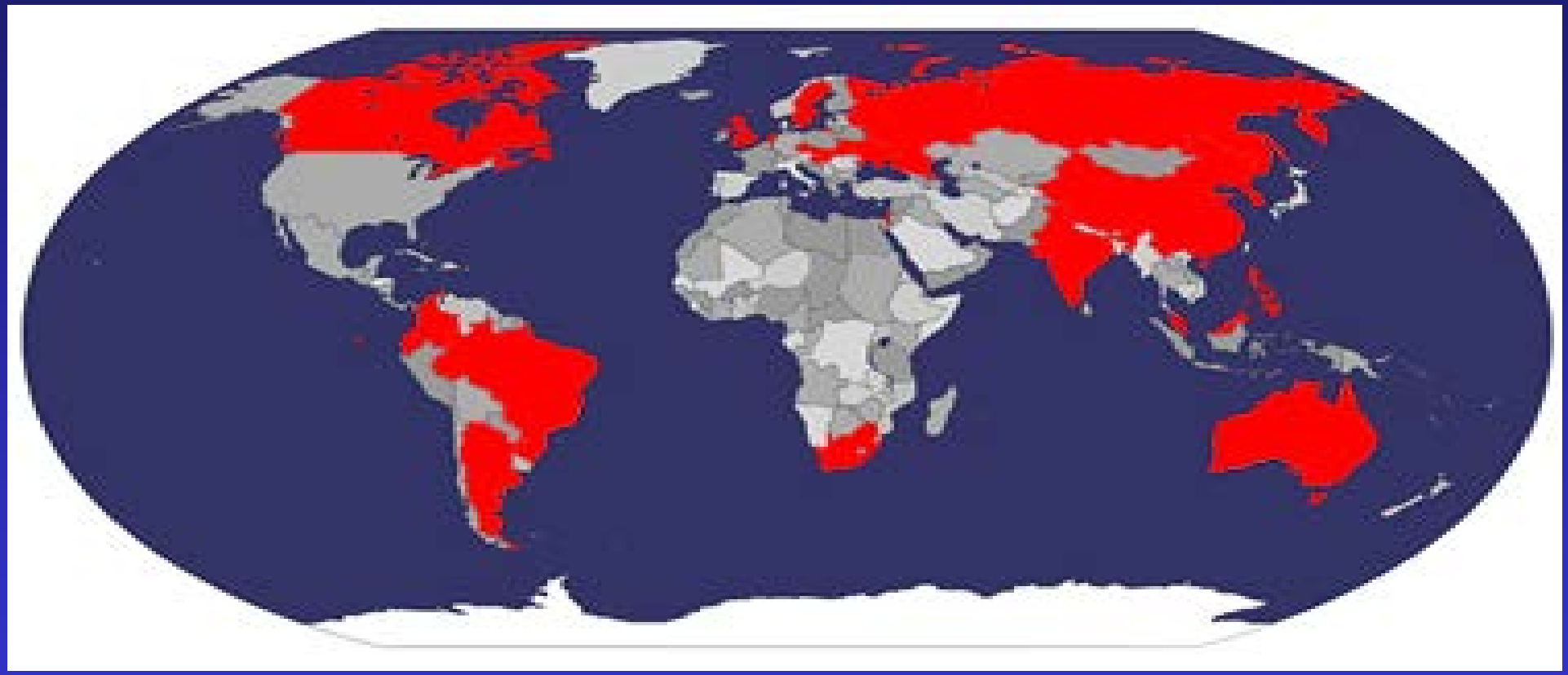
Power Calculations: Double Active vs Double Placebo

Sample Size	RRR (%)	1st Co-Primary (2α=0.04)		2nd Co-Primary (2α=0.0228)	
		Control Event Rate/yr		Control Event Rate/yr	
		0.79*	1.00*	1.07*	1.35*
½ of 12,705	40	87.9	94.1	92.9	97.2
	45	***94.8***	***98.1***	***97.9***	***99.4***
	50	98.2	99.6	99.5	99.9

Where in the World is HOPE-3



Argentina, Australia, Brazil, Canada, China, Colombia, Czech Republic, Ecuador, Hungary, India, Israel, Korea, Malaysia, Netherlands, Philippines, Russia, Slovakia, S.Africa, Sweden, United Kingdom, Ukraine

21 countries; 228 centres

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Baseline Characteristics

	Rand N=12705	S.America N=3870	Can/Eur/Aus/S. Africa N=2662	Asia N=6173
Mean Age (yrs)	65.1 (6.4)	66.8 (6.7)	64.9 (6.3)	64.5 (6.0)
Women (%)	46.2	50	39	47
Risk Factors	%	%	%	%
Elevated WHR	78	84	74	76
Low HDL	28	36	21	27
Smoking	28	22	29	32
Dysglycemia	17	19	19	17
Family Hx CHD	26	14	26	33
Renal dysfunction	3	5	3	1
2 risk factors (%)	47	42	40	54
≥ 3 risk factors (%)	13	15	12	13

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Baseline Characteristics

	Rand N=12705	S.America N=3870	Can/Eur/Aus/ S.Africa N=2662	Asia N=6173
Total Cholesterol (mmol/L)	5.3 (1.0)	4.5 (1.2)	4.3 (1.3)	4.1 (1.2)
LDL-Cholesterol (mmol/L)	3.2 (0.9)	3.3 (0.9)	3.4 (0.9)	3.1 (0.9)
HDL-Cholesterol (mmol/L)	1.3 (0.4)	1.2 (0.3)	1.4 (0.5)	1.3 (0.4)
Triglycerides (mmol/L)	1.6 (0.9)	1.6 (0.8)	1.6 (0.9)	1.6 (0.9)
Systolic Blood Pressure Run-in	137.7 (15.2)	135.4(14.8)	138.0 (15.1)	140.0 (14.3)
Diastolic Blood Pressure Run-in	81.7 (9.4)	79.8 (9.5)	83.5 (9.0)	82.4 (9.1)
Fasting glucose (mmol/L)	5.5 (1.2)	5.3 (1.1)	5.5 (1.0))	5.6 (1.3)

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HOPE-3: Potential Impact

- Pandemic of CVD associated with major shifts in lifestyle patterns
- CVD are largely preventable
  - Societal and lifestyle changes should be pursued
  - In the near future pharmacological approaches are essential
- Pharmacological interventions aimed at cholesterol and BP lowering could dramatically reduce CVD burden with minimal side effects
- HOPE-3 tests a novel approach to CV prevention, which could result in substantial benefits that may have a large public health impact