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Heart Outcomes Prevention Evaluation (HOPE) Study

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Disclosure

- I was not involved with HOPE Study
  - I am not Salim Yusuf
- Spend most of my time doing large (simple) trials
  - passionately believe in value of large trials

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Summary of Design

Aim

Effect of Ramipril (up to 10mg/d) or Vit E (400 IU/d) vs its placebo on CV death, MI or stroke (primary)

Design

Randomized blinded, 2x2 factorial

Size

9541 patients followed for 4 to 6 years

powered to detect RRR of 12%

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Key Inclusion/Exclusion Criteria

Inclusion Criteria

Patients (age ≥55) at *high risk* for cardiovascular events because of:

- any evidence of vascular disease (CHD, stroke, PVD)
- diabetes + one other coronary risk factor

Exclusion Criteria

Heart failure or low EF

On ACE-I or Vitamin E

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Study Organization

267 Centres from 19 Countries in North & South America & Europe

↓

National Coordinators/ Regional Coordinators

↓

Project Office (Hamilton)

European (London, UK), Brazilian (São Paulo), Argentinian (Rosario)

↓

International Steering Committee

↓

Events Adjudication Committee	Substudy/ Publication Policy Committee	Data, Safety & Monitoring Board

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Sponsors

- Medical Research Council of Canada
- Heart & Stroke Foundation of Ontario
- Hoechst Marion Roussel
- Astra-Zeneca
- King Pharmaceuticals
- Natural Source Vitamin E Assoc.
- NEGMA Pharma

Study independently designed, organized, conducted, analyzed and reported by the Canadian Cardiovascular Collaboration and HOPE Steering Committee

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Primary Adjudicated Events - Ramipril vs Placebo

	Ramipril (%)	Plac (%)	RR	95% CI	p
No. Rand.	**4645**	**4652**			
1°Outcome					
MI,Stroke,CVDth	**14.1**	**17.7**	**0.78**	**0.70-0.86**	**0.000002**
CV Death*	**6.1**	**8.1**	**0.75**	**0.64-0.87**	**0.0002**
MI*	**9.9**	**12.2**	**0.80**	**0.71-0.91**	**0.0005**
Stroke*	**3.4**	**4.9**	**0.69**	**0.56-0.84**	**0.0003**
Non-CV Death	**4.3**	**4.1**	**1.03**	**0.84-1.25**	**0.78**
Mortality	**10.4**	**12.2**	**0.84**	**0.75-0.95**	**0.0058**

*not mutually exclusive

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Why is HOPE a large simple trial

- Large sample size well powered
- Broad simple eligibility criteria
- Simple intervention
- Data collection CRFs kept simple
  - 4 pages at entry (20 min)
  - 2 pages for follow-up visit (10 min)
  - 4 pages for at study end (20 min)
- Follow-up kept simple
  - ever 6 months

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Applicability, simplification, cost

- Applicability
  - broad eligibility criteria
  - 267 international centres (challenge of KT)
  - large enough for reasonable subgroup representation
  - simple intervention
- Simplification
  - data collection and follow-up
  - AE reporting
- Cost
  - $21 million plus drug and monitoring

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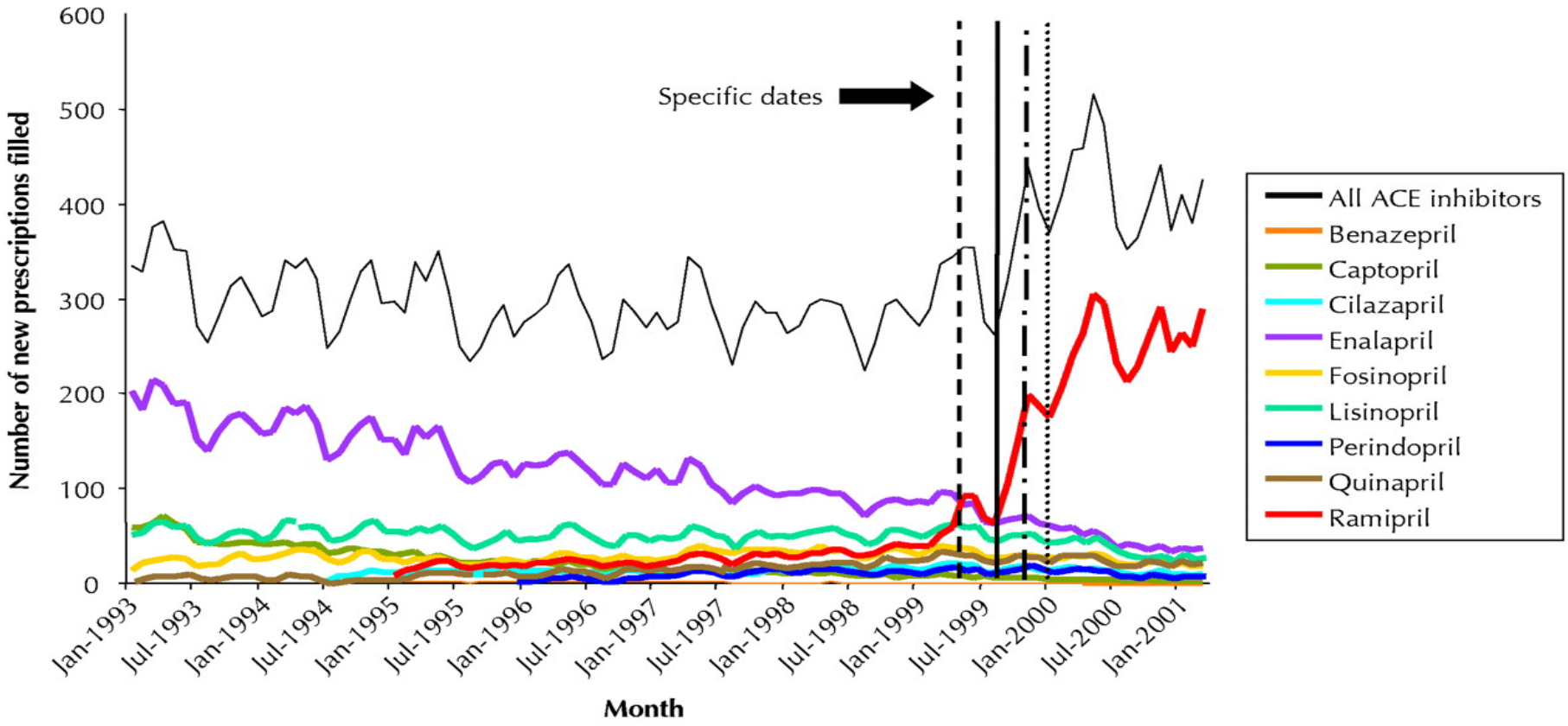
Completeness, Quality of Data and Close Out

DSMB recommends early termination on March 22, 1999
Results presented to investigators on April 17 and 24, 1999
Close out completed by August, 1999
Database closed on November 1, 1999
Vital status ascertained on 99.9%
Non-fatal outcomes ascertained on 99.3%
Adjudication completed in 99.9%
Percentage of forms clean 99.4%
Electronic publication in NEJM November 10, 1999
Print publication Jan 20, 2012

Number of new prescriptions for ACE inhibitors filled by elderly (aged 65 and over) Ontario residents per 100,000



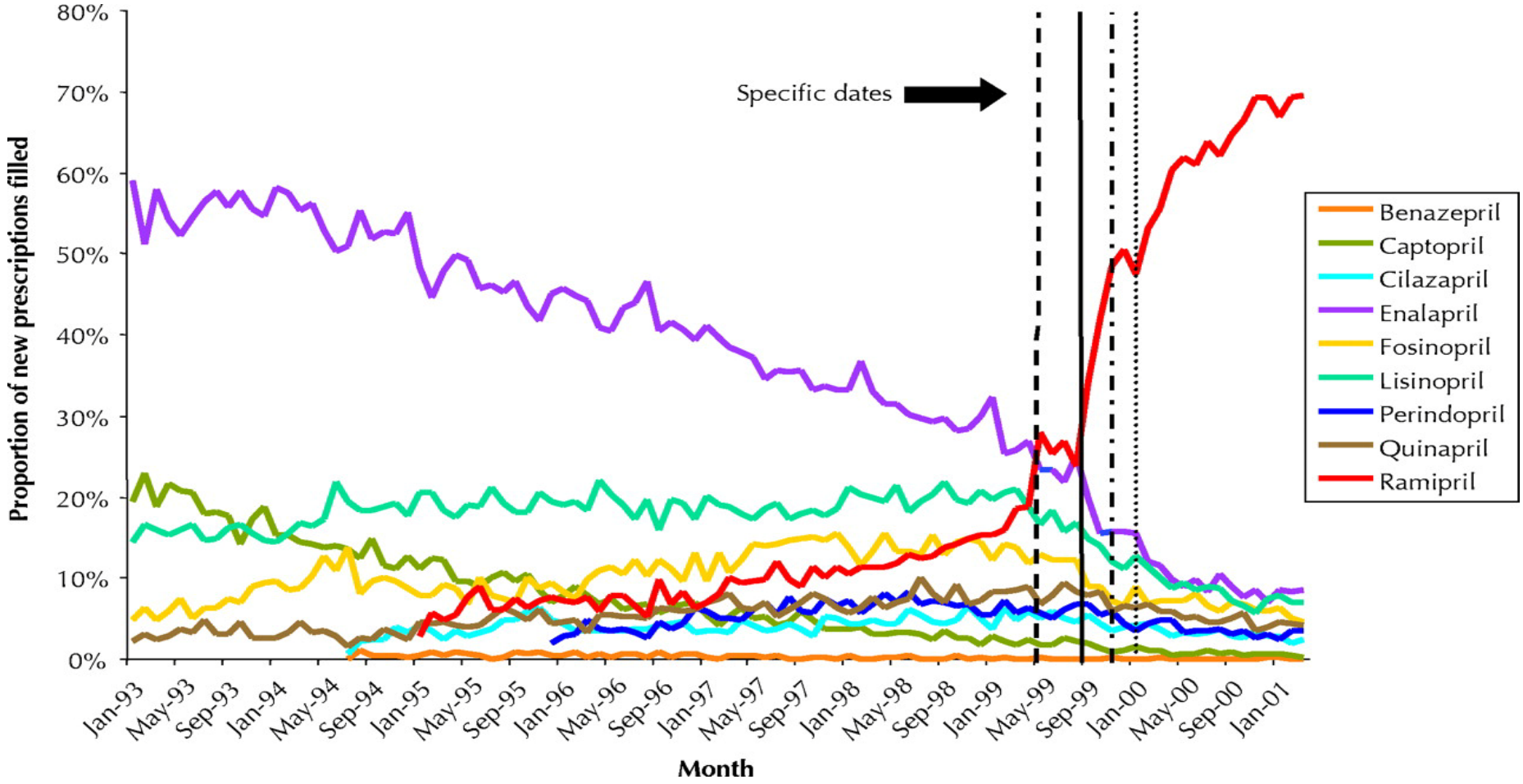
Specific dates:

- May 8, 1999: First newspaper coverage of early termination of Heart Outcomes Prevention Evaluation (HOPE)
- Aug. 31, 1999: First formal presentation of HOPE results, at European Society of Cardiology Congress, in Barcelona, Spain
- Nov. 10, 1999: American Heart Association meeting presentation and posting on the *New England Journal of Medicine* (*NEJM*) Web site
- Jan. 20, 2000: First print publication of HOPE results, in *NEJM*

Tu K et al. CMAJ 2003;168:553-557

CMAJ·JAMC

Proportions of new prescriptions for specific ACE inhibitors among the elderly residents with diabetes mellitus



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Risks and trade-offs

- Factorial design
- Only reported SUSARS
- Data collection

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Experience

- Stakeholder engagement
  - asked clinically important question
  - international
  - friends
- Infrastructure
  - 5 people worked on study in project office
  - bureaucracy has increased dramatically
- Regulatory
  - FDA approved
  - EU has changed

Future directions

- Consent and follow-up
  - INFORM Trial - old versus new blood
  - consent waived
  - 4000 patients recruited in first 6 months at 3 sites
  - f/u thru administrative data
  - 24,000 patient trial cost $2 Million
- Applicability, consent, cost
  - PADIT cluster cross-over trial
  - Abx regimens with pacemaker insertion - applicability
  - some centres have waived consent
  - at least half cost of individual patient trial

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Reliable research

- Dominant factor
  - large sample size
  - not 100% accuracy of all collected data

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2 hypothetical RCTs

- Evaluating new treatments to prevent MI
- Placebo controlled
- Outcome MI
- Identical methodology
  - concealed, blinded, complete f/u, ITT
    - high quality

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Final Trial 1	Tx A	Placebo	P value
	(n=100)	(n=100)	
MI	1	9	0.02

Trial 2	Tx B (n=4000)	Placebo (n=4000)	P value
MI	200	250	0.02

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Trial 1	Tx A (n=100)	Placebo (n=100)	RRR (95% CI)
MI	1	9	90% (23-100)

Trial 2	Tx B (n=4000)	Placebo (n=4000)	RRR 95% CI
MI	200	250	20% (5-37)

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Small variation in hypothetical trials

- Fragility Index (FI)
  - minimum number of patients required to switch from non-event to event in group with fewer events to reverse statistical significance
    - 1st trial AFI – 1
    - 2nd trial AFI - 9

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~~Trial 1~~ Final	Tx A (n=100)	Placebo (n=100)	P value	RRR (95% CI)	FI
MI	1	9	0.02	90% (23-100)	1

Trial 1	Tx B (n=4000)	Placebo (n=4000)	P value	RRR (95% CI)	FI
MI	200	250	0.02	20% (5-37)	9