Heart Outcomes Prevention Evaluation Study

A large, simple, randomized trial of Ramipril and vitamin E in patients at high risk for cardiovascular events

Hope

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 double blind, 2x2 factorial,

Wide entry criteria, large, simple trial

Size: 9541 patients followed for 4 to 6 years:

- High power to detect RRR of 12% overall;
- 15% to 25% in key subgroups and individual components of primary and secondary outcome (Revasc, CHF, UA, diabetes complications)

Organization: 267 hospitals from 19 countries in North & South America and Europe, Coordinated by the CCC at McMaster University, Hamilton, Canada

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

Outcomes

Primary Outcome

Composite of myocardial infarction, stroke or cardiovascular death

Secondary Outcomes

- Myocardial Infarction
- Stroke
- Cardiovascular death
- Hospitalization for Unstable Angina
- Hospitalization for Congestive Heart Failure
- Total Mortality
- Revascularization
- Overt Nephropathy
- Cancer

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Other Outcomes

- Diabetic complications (includes diabetic nephropathy, renal dialysis and laser therapy for diabetic retinopathy)
- Heart failure
- Cardiac arrest*
- Worsening angina*
- Development of diabetes*

* not pre-specified

Sample Size and Power Calculations

No. of Pts	Mean Follow-Up	Placebo Grp Event Rate 80% Power	90% Power
Anticipated No.			
6000	3.5 yrs (3 to 4 yrs)	17.4	20.0
8000*	3.5 yrs (3 to 4 yrs)	15.2	17.4
Actual No.			
9541	5.0 yrs+(3.5 to 5 yrs)	11.6	13.3

*additional 1000 planned to overcome possible lower event rates or poorer compliance

Extension of Follow Up

Original follow-up: Last randomized pt followed for 3 years (expected mean follow-up of about 3-4 yrs)

Revised follow-up:

- Concern about a lag of 1-2 yrs before treatment benefit would emerge
- Somewhat lower event rate (4.2% overall vs 5.0% placebo)

Process: Decision made by Steering Committee who had no knowledge of any of the blinded data

Approach: Extend follow-up by 2 years in two steps (study end in Nov 1999); mean follow-up 5.0 yrs

Study Organization

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

↓

National Coordinators/ Regional Coordinators

↓

Canadian Cardiovascular Collaboration Project Office (Hamilton)

European (London, UK), Brazilian (São Paulo), Argentinean (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

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

Number Entering Run-In

Total Screened	**10710**	**(100.0%)**
Ineligible	134	(1.3%)
≥ 1+ Proteinuria	96	(0.9%)
ACE-I	25	(0.2%)
Proteinuria & ACE-I	6	(0.1%)
Vitamin E	7	(0.1%)
Eligible	10576	(98.7%)

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Run-In

Pts received 7-10 days of 2.5 mg ramipril (single blind); check of Cr and K+, followed by 10-14 days of placebo (single blind)

No. entering Run-In	10,576
Common reasons for exclusion	
Non-adherence	395 (3.7%)
Creatinine/Potassium	61 (0.6%)
Cough	39 (0.4%)
Hypotension/Dizziness	56 (0.5%)
Refused	398 (3.7%)
Total Excluded	1035 (9.8%)
No. Randomized	9541

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Randomized

	Active	Placebo	SECURE low dose
Ramipril	4645	4652	244
Vitamin E	4761	4780	
Total No for Ramipril	N=9297		
Total No for Vitamin E	N=9541		

Baseline Age and Physical Exam

Characteristic	Ramipril Group (N=4645)	Placebo Group (N=4652)
Age – years	66	66
BP – mmHg	139/79	139/79
Ankle:Arm Ratio	0.98	0.98
Heart rate – beats/min	69	69
Body mass index	28	28
Waist:Hip Ratio	0.93	0.93
Serum Creatinine (umol/L)	97.0	96.8
Potassium (mmol/L)	4.4	4.4

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Baseline Drug Use

	Ramipril Group (N=4645)		Placebo Group (N=4652)	
	N	%	N	%
Aspirin and Other Antiplatelets	3497	75.3	3577	76.9
Oral Anticoagulants	185	4.0	172	3.7
Diuretics	713	15.3	706	15.2
Nitrates	1382	29.8	1499	32.2
Beta-blockers	1820	39.2	1853	39.8
Calcium Channel Blockers	2152	46.3	2228	47.9
Cholesterol Lowering Agent	1318	28.4	1340	28.8

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History

	Ramipril (N=4645)		Placebo (N=4652)	
	N	%	N	%
Females	1279	27.5	1201	25.8
Coronary artery disease	3691	79.5	3786	81.4
Myocardial infarction	2410	51.9	2482	53.4
Stroke or TIA	500	10.8	513	11.0
PAD/Low AABP	1859	40.0	1969	42.3
Hypertension	2212	47.6	2143	46.1
Diabetes	1808	38.9	1769	38.0
Elevated cholesterol	3036	65.4	3089	66.4

Concomitant Drugs

	Baseline overall (%)	2yrs (%)		End (%)	
		Ram	Plac	Ram	Plac
ASA/antiplatelet	76.1	73.5	74.8	71.7**	74.4
Lipid lowering	28.6	38.1	38.4	49.1	49.3
Beta-blockers	39.5	37.7**	40.5	37.5***	43.0
Diuretics	15.3	16.6**	19.2	19.5***	22.9
CCB	47.1	44.7	45.1	40.0	41.5
Any anti-ischemic agents	74.3	70.6**	73.4	68.2***	72.1

**p<0.01, ***p<0.001

Adherence to Allocated Medications

	Ramipril		Placebo	
	N	%	N	%
Study Medication Use				
1 Year	3904	85.5	4072	89.2
4 Year	2652	67.6	2730	70.8
Open Label ACE-I Use				
1 Year	101	2.2	153	3.4
4 Year	307	7.8	417	10.8

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% On Various Doses of Ramipril or Placebo

	Dose mg/day			
	0	2.5	5	10
At 1 Year				
Ramipril	14.4	1.6	1.0	83.0
Placebo	10.7	0.6	0.7	88.0
At 4 Year				
Ramipril	32.4	3.0	2.2	62.5
Placebo	29.2	1.4	1.4	68.1

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Reasons for Stopping Ramipril/Placebo

	Ramipril %		Placebo %		
	N	%	N	%	% Diff
Cough	340	7.3	85	1.8	+5.5
Hypotension/Dizz	88	1.9	70	1.5	+0.4
Hypertension	109	2.3	183	3.9	-1.6
Clinical Event	306	6.6	416	8.9	-2.3
Hospitalization	110	2.4	118	2.5	-0.1
On Non-study ACE-I	438	9.4	567	12.2	-2.8
Phys/Pt refusal	161	3.5	156	3.4	-0.1
Other	139	3.0	138	3.0	-

Angioneurotic Edema

Run-In: 5/10,546 (0.05%)

	Ramipril (N=4645)		Placebo (N=4652)	
	N	%	N	%
Any angioedema	16	0.34	7	0.15
Fatal	1	0.02	0	0
Hospitalization	1	0.02	0	0
Other	14	0.30	7	0.15

No pt required ventilation; 141 Blacks participated with no events

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Primary Adjudicated Events - Ramipril vs Placebo

	Ramipril N=4645 N(%)	Placebo N=4652 N(%)	RR (95% CI)	p-value
Primary Outcome (MI/Stroke/CV Death)	651 (14.0)	826 (17.8)	0.78(0.70-0.86)	<0.001
CV Death	282 (6.1)	377 (8.1)	0.74(0.64-0.87)	<0.001
MI	459 (9.9)	570(12.3)	0.80(0.70-0.90)	<0.001
Stroke	156(3.4)	226(4.9)	0.68(0.56-0.84)	<0.001
Non CV Death	200(4.3)	192(4.1)	1.03(0.85-1.26)	0.74
Mortality	482(10.4)	569(12.2)	0.84(0.75-0.95)	0.0053

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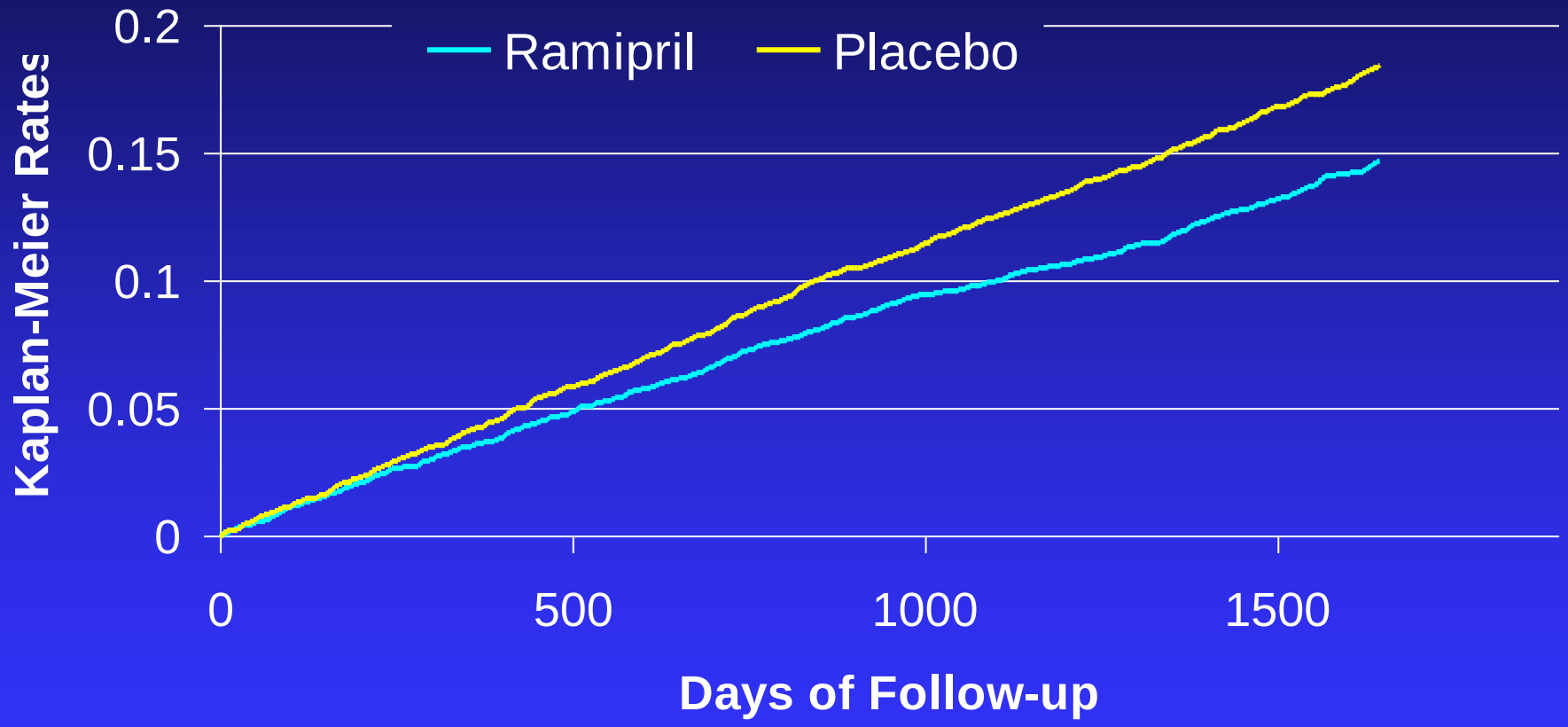
CV Death/MI/Stroke - Ramipril vs Placebo



RR=0.78 (0.70-0.86)

p<0.001

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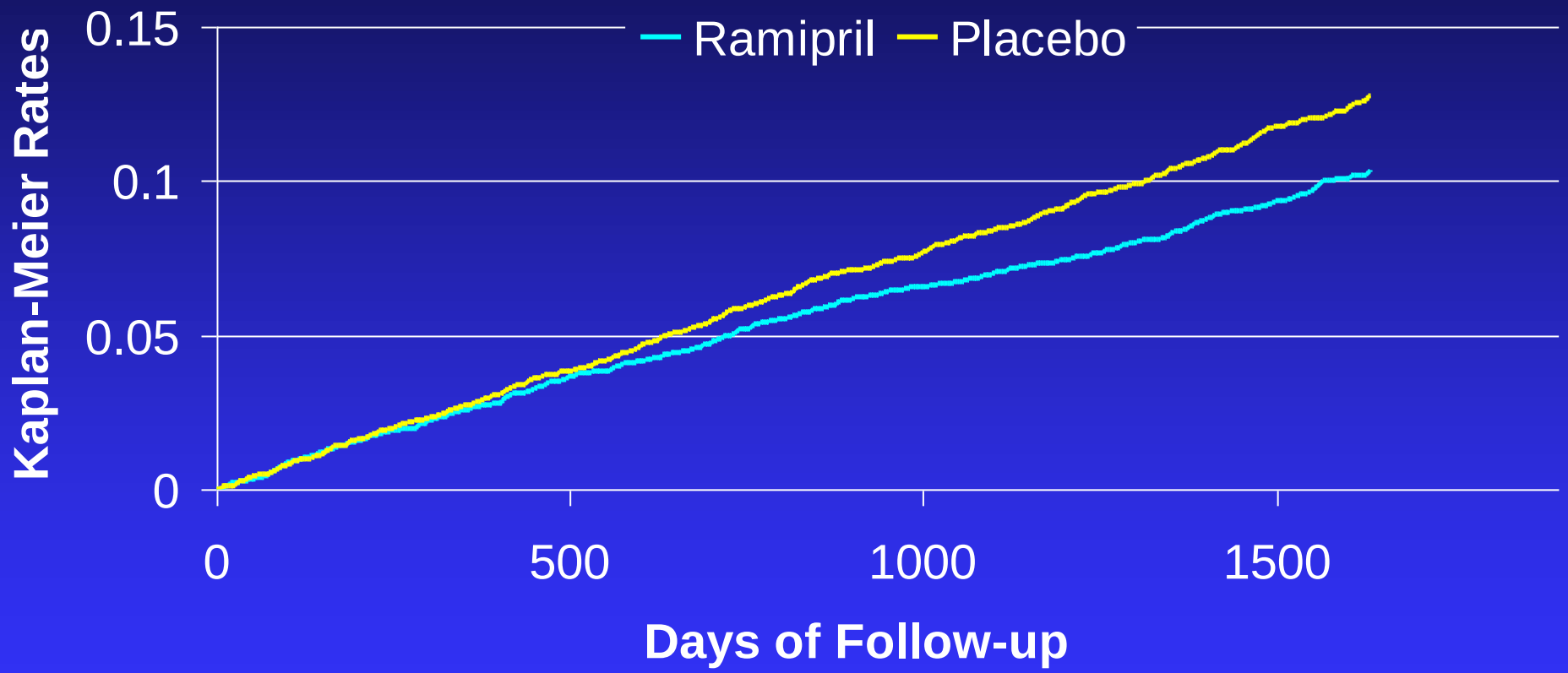
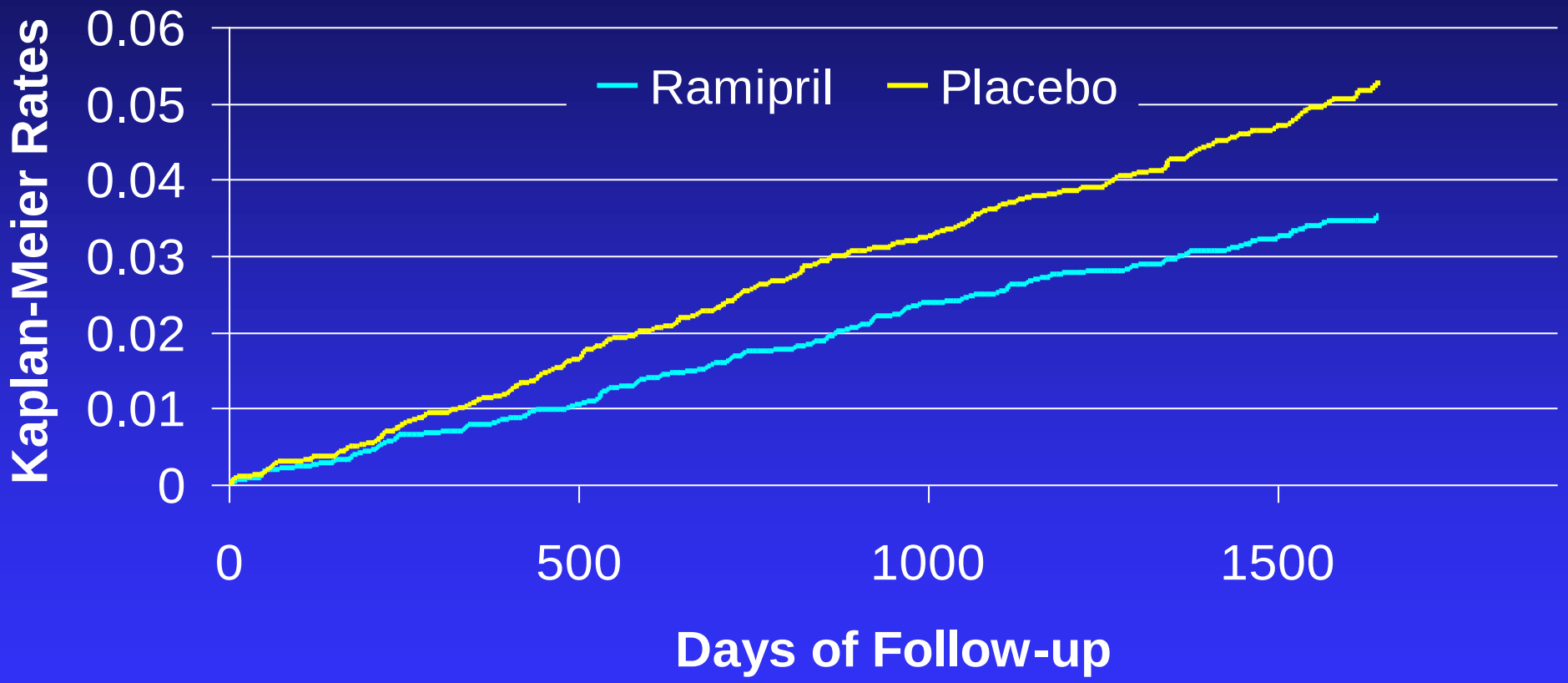
MI - Ramipril vs Placebo



RR=0.80 (0.70-0.90) p<0.001

Stroke - Ramipril vs Placebo



RR=0.68 (0.56-0.84) p<0.001

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Cerebrovascular Events - Ramipril vs Placebo

	Ramipril N(%)	Placebo N(%)	RR (95% CI)
Stroke	**156 (3.4)**	**226(4.9)**	**0.68(0.56-0.84)**
TIA	190(4.1)	227(4.9)	0.83(0.68-1.00)
Stroke/TIA	315(6.8)	405(8.7)	0.77(0.66-0.89)
Fatal	17(0.4)	44(1.0)	0.39(0.22-0.67)
Non-Fatal	139(3.0)	182(3.9)	0.76(0.61-0.94)

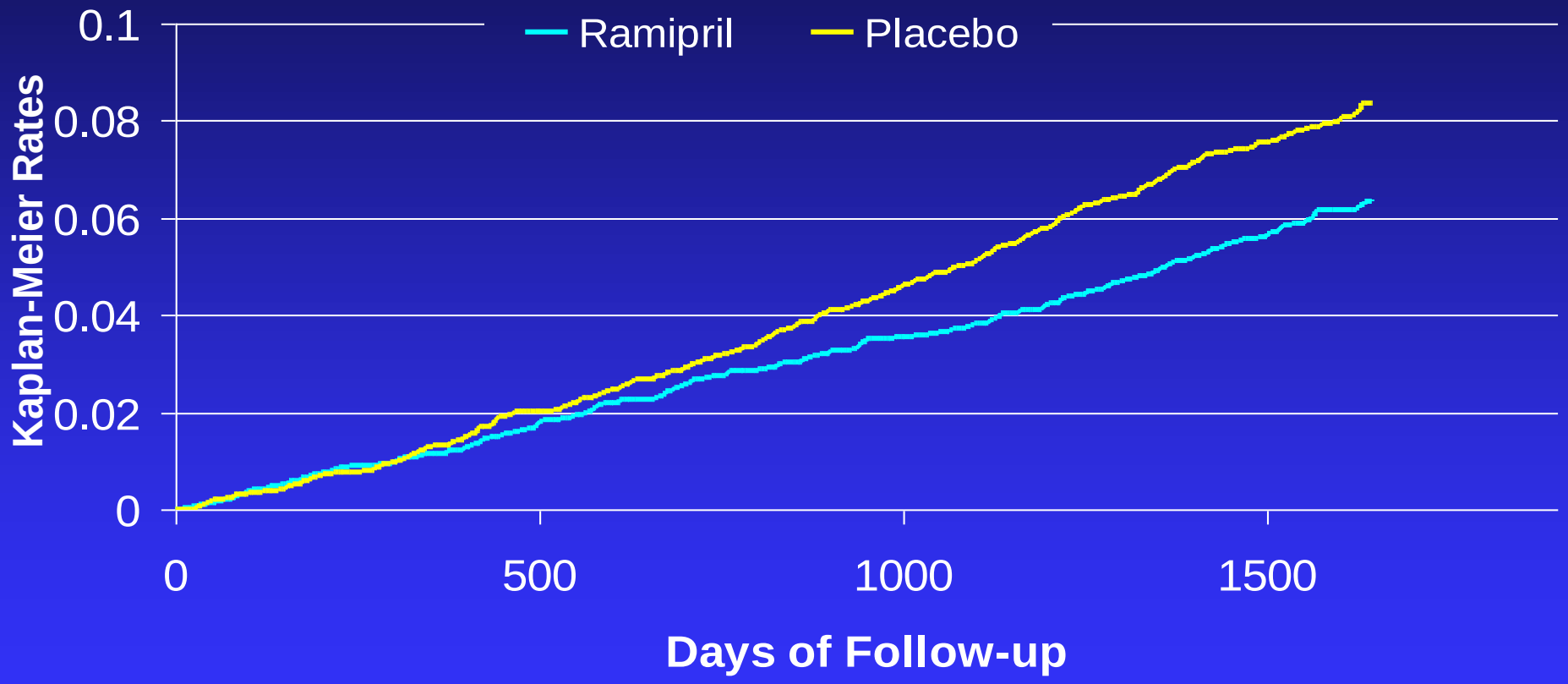
Stroke by Type - Ramipril vs Placebo

	Ramipril N(%)	Placebo N(%)	RR (95% CI)
Overall	156 (3.4)	226 (4.9)	0.68(0.56-0.84)
Ischemic	101 (2.2)	157 (3.4)	0.64(0.50-0.82)
Haemorrhagic	12 (0.26)	16 (0.34)	0.74(0.35-1.57)
Uncertain	52 (1.1)	65 (1.4)	0.79(0.55-1.14)

Stroke by Severity - Ramipril vs Placebo

	Ramipril N(%)	Placebo N(%)	RR (95% CI)
Overall	156 (3.4)	226 (4.9)	0.68(0.56-0.84)
Full Recovery/Non-Limiting	49 (1.1)	80 (1.7)	0.61(0.42-0.86)
Some Impairment	43 (0.9)	56 (1.2)	0.76(0.51-1.13)
Constant Help/Incapacitated	50 (1.1)	66 (1.4)	0.75(0.52-1.08)
Fatal	17 (0.4)	44 (1.0)	0.39(0.22-0.67)

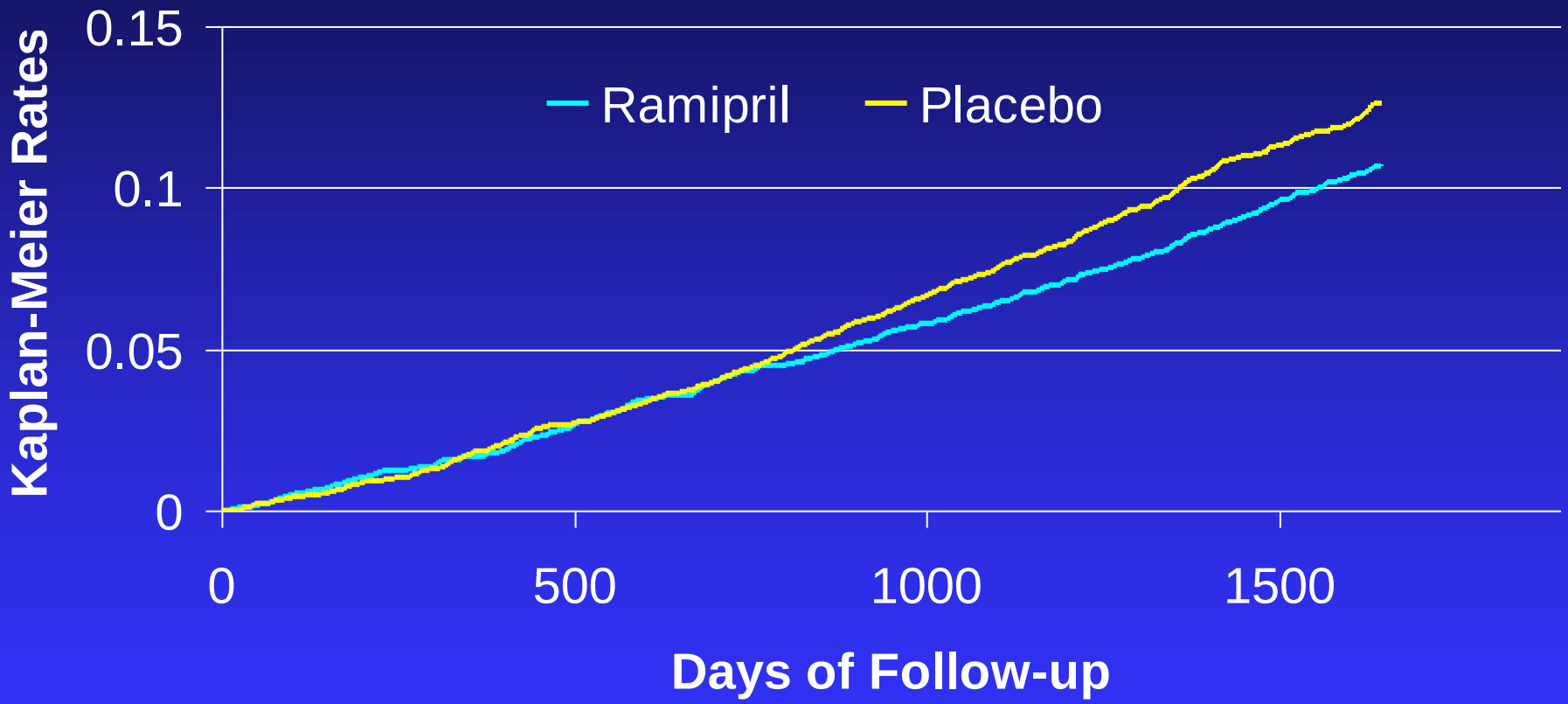
CV Death - Ramipril vs Placebo



RR=0.74 (0.64-0.87)

p<0.001

All Deaths - Ramipril vs Placebo



RR=0.84 (0.75-0.95) p=0.0053

Causes of Death: Ramipril vs Placebo

	Ramipril		Placebo	
	N	%	N	%
CV	282	6.1	377	8.1
MI	186	4.0	219	4.7
Stroke	17	0.4	44	1.0
CHF	24	0.5	27	0.6
Documented Arrhythmia	6	0.1	7	0.2
Other CV	49	1.1	80	1.7
Non-CV	200	4.3	192	4.1

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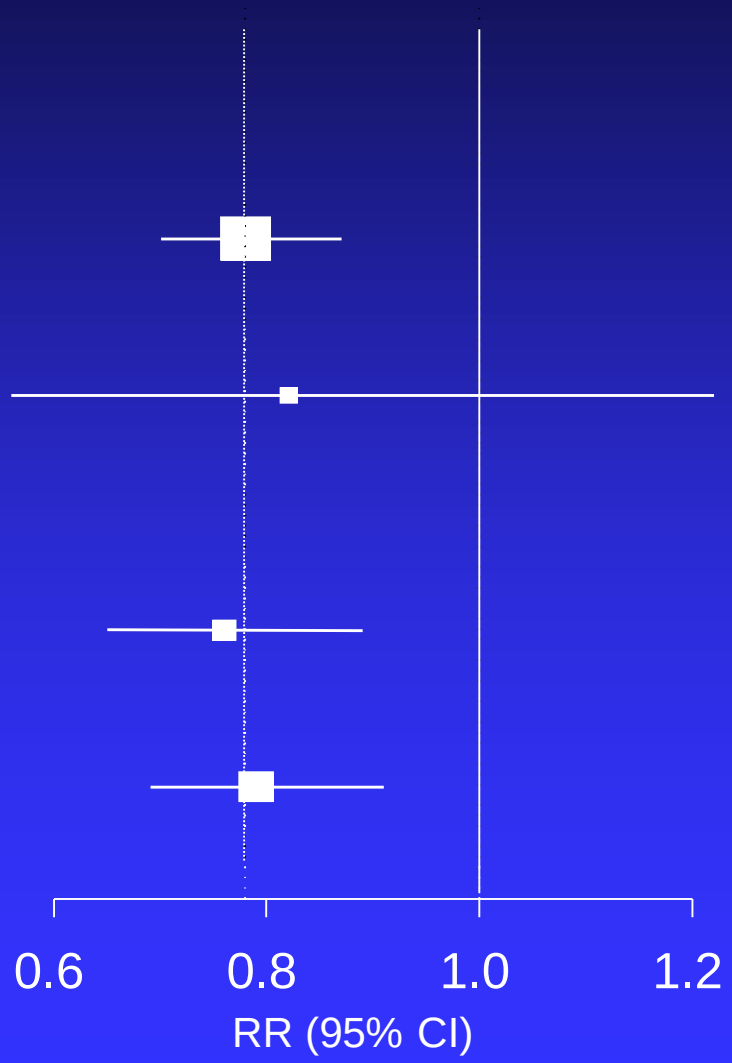
Primary Endpoint by Vitamin E – Ramipril vs Placebo

	Ram	Plac	RR	95% CI	p
Placebo Vit E	13.5	17.3	0.76	0.66-0.89	<0.001
Active Vit E	14.5	18.2	0.79	0.68-0.91	<0.001
Overall	14.0	17.8	0.78	0.70-0.86	<0.001

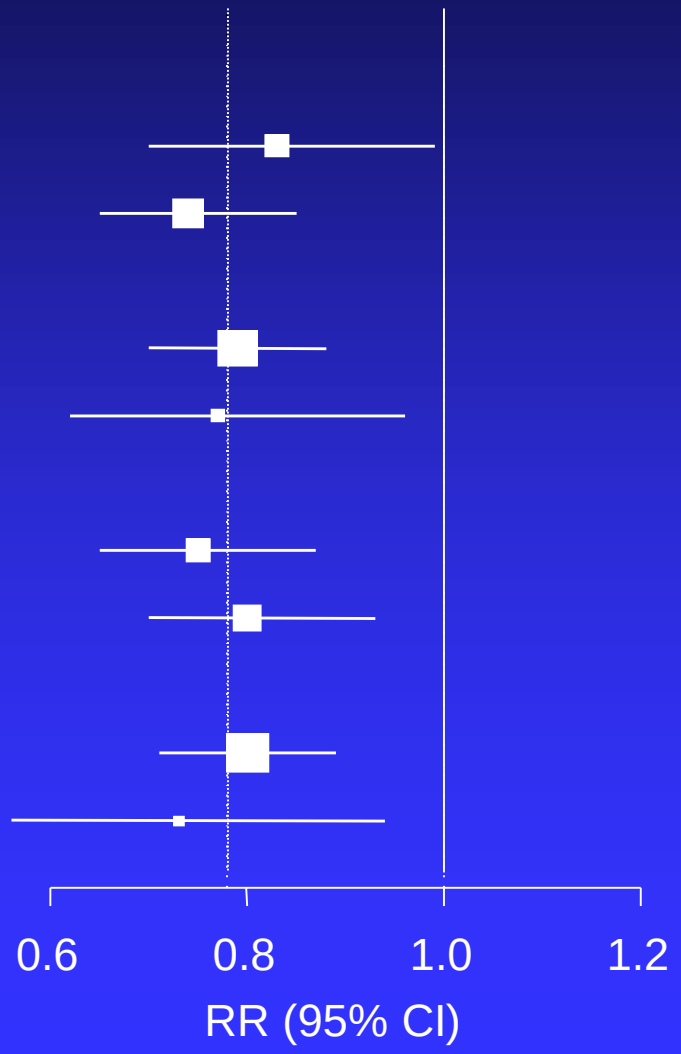
Prespecified Subgroups - Ramipril vs Placebo

	N	Plac%	Interaction p
CVD+	8160	18.7	0.88
CVD-	1137	10.1	
Diabetes+	3578	19.8	0.66
Diabetes-	5719	16.5	



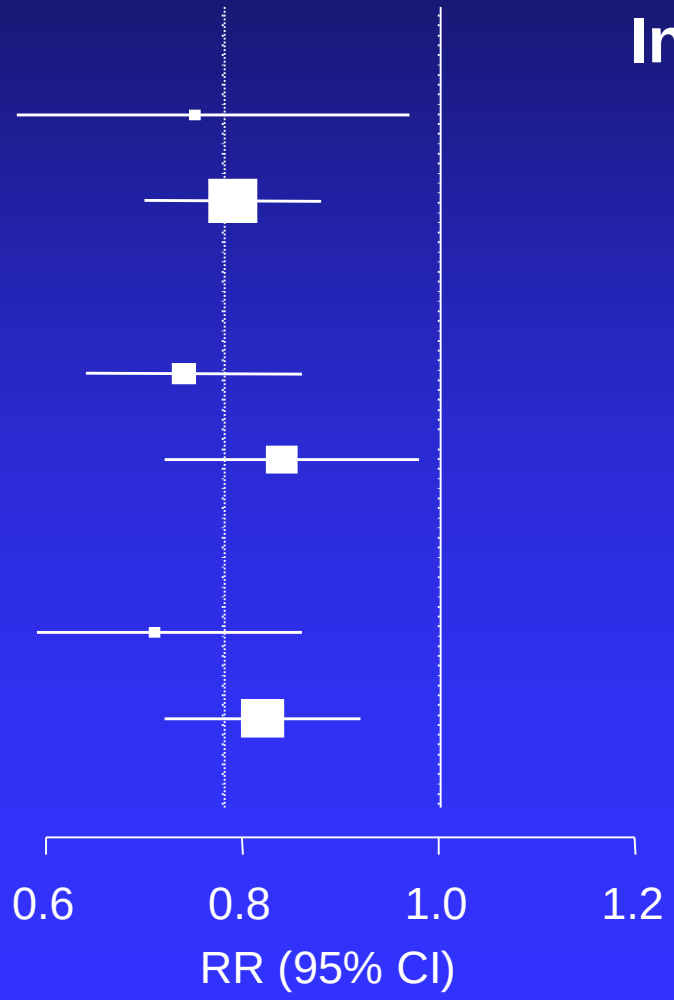
Other Subgroups of Prior Stated Interest: Ramipril vs Placebo

	N	Plac%	Interaction p
Age <65	4169	14.2	0.33
Age 65+	5128	20.7	
Male	6817	18.8	0.79
Female	2480	14.8	
HTN+	4355	19.4	0.47
HTN-	4942	16.3	
CAD+	7477	18.5	0.50
CAD-	1820	14.2	



Other Subgroups of Prior Stated Interest: Ramipril vs Placebo

	N	Plac%	Interaction p
CerebroVD+	1013	25.9	0.72
CerebroVD-	8284	16.7	
PVD+	3828	22.4	0.26
PVD-	5469	14.4	
MA+	1963	26.3	0.25
MA-	7334	15.4	



Secondary Outcomes

	Ramipril N=4645 N(%)	Placebo N=4652 N(%)	RR (95% CI)	p-value
Revascularization	743(16.0)	854(18.4)	0.85(0.77-0.94)	0.0014
Hosp for UA	554(11.9)	567(12.2)	0.97(0.87-1.09)	0.64
with ECG changes	175(3.8)	181(3.9)	0.96(0.78-1.19)	0.72
Hosp for HF	141(3.2)	161(3.5)	0.87(0.69-1.09)	0.22

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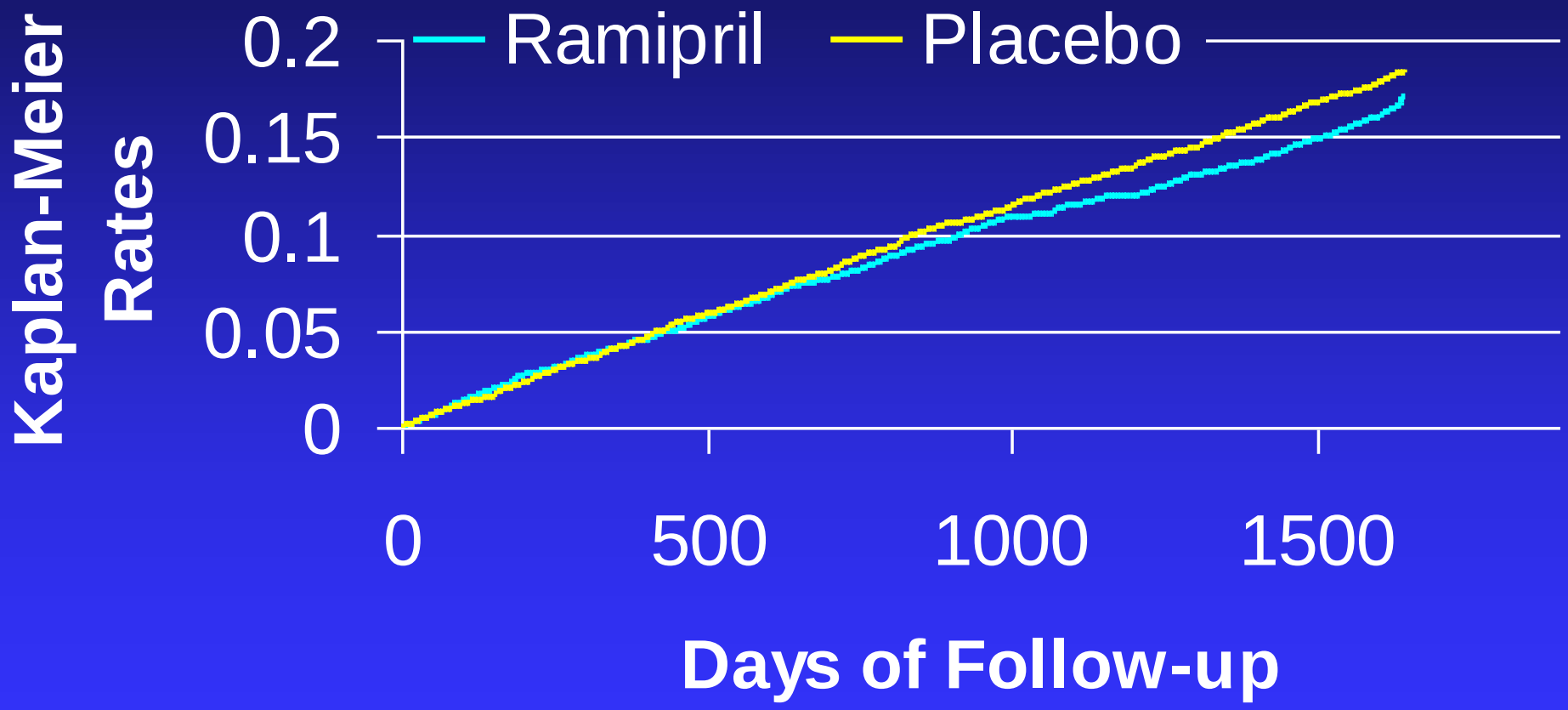
Other Outcomes

	Ramipril N=4645 N(%)	Placebo N=4652 N(%)	RR (95% CI)	p-value
Complic Related to DM	303(6.5)	356(7.7)	0.85(0.73-0.99)	0.038
Heart Failure	417(9.0)	534(11.5)	0.77(0.68-0.87)	<0.001
Cardiac Arrest	37(0.8)	59(1.3)	0.62(0.41-0.94)	0.02
Worsening Angina	1107(23.8)	1222(26.3)	0.88(0.82-0.96)	0.003
New Diagnosis of DM	102(3.6)	155(5.4)	0.66(0.51-0.85)	<0.001

Revascularization - Ramipril vs Placebo



RR=0.85 (0.77-0.94) p=0.0014

Revascularization Type - Ramipril vs Placebo

	Ramipril N=4645 N(%)	Placebo N=4652 N(%)	RR (95% CI)	p-value
Any Revascularization	**743(16.0)**	**854(18.4)**	**0.85(0.77-0.94)**	**0.0014**
PTCA/CABG	580(12.5)	688(14.8)	0.83(0.74-0.92)	
Non-Coronary*	191(4.1)	213(4.6)	0.89(0.73-1.08)	

* Peripheral Angioplasty/Surgery, Limb Amputation, Carotid Endarterectomy, Other

Evolution of Trials of Heart Failure with ACE-I

TRIALS	% ACE-I with CHF/↑symptoms	Type of Pt	Benefit
HOPE	60%	Preserved EF + vascular dis/diabetes	HF prevented
SOLVD-P	40%	Low EF alone	HF & HF Hosp prevented
SOLVD- T	20%	Low EF + CHF(II/III)	HF hosp & mortality reduced
CONSENSUS	<10%	Class IV CHF	Mortality reduced

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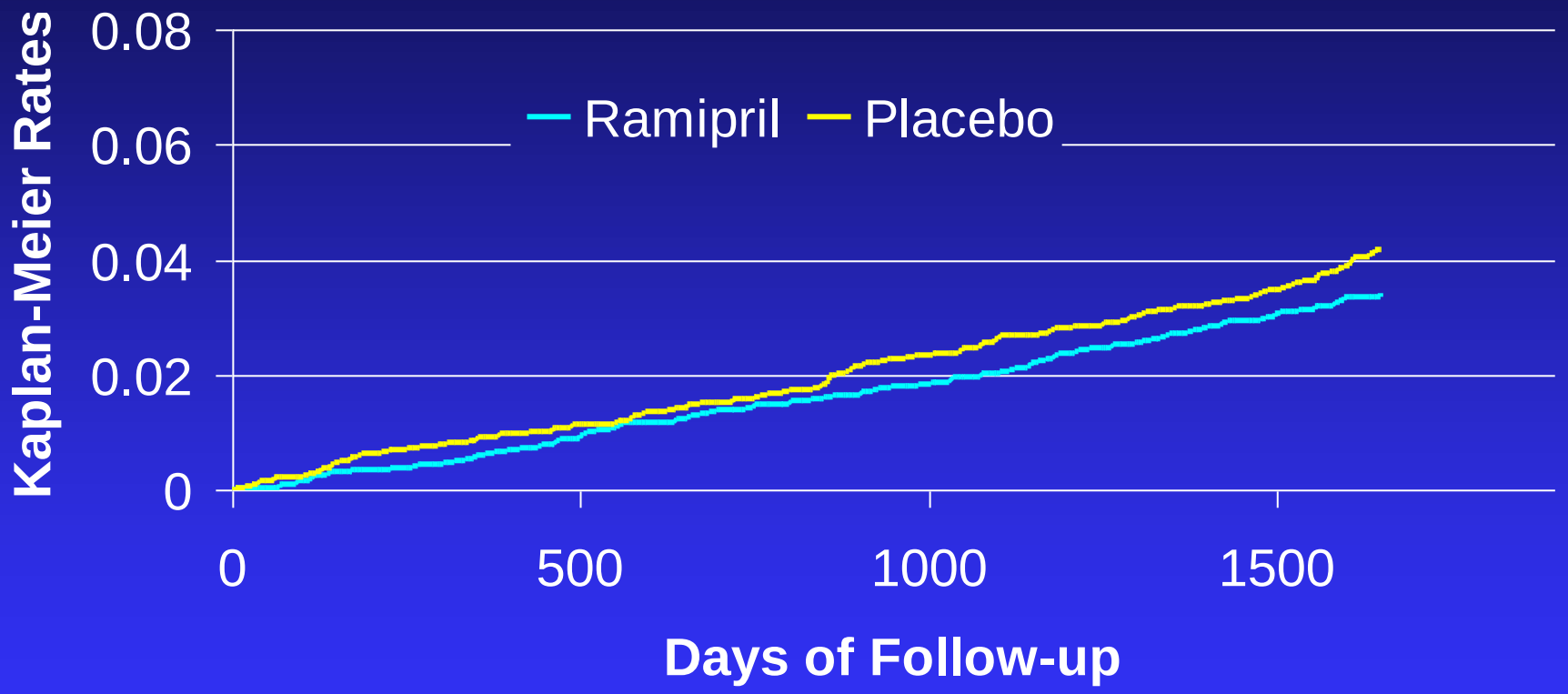
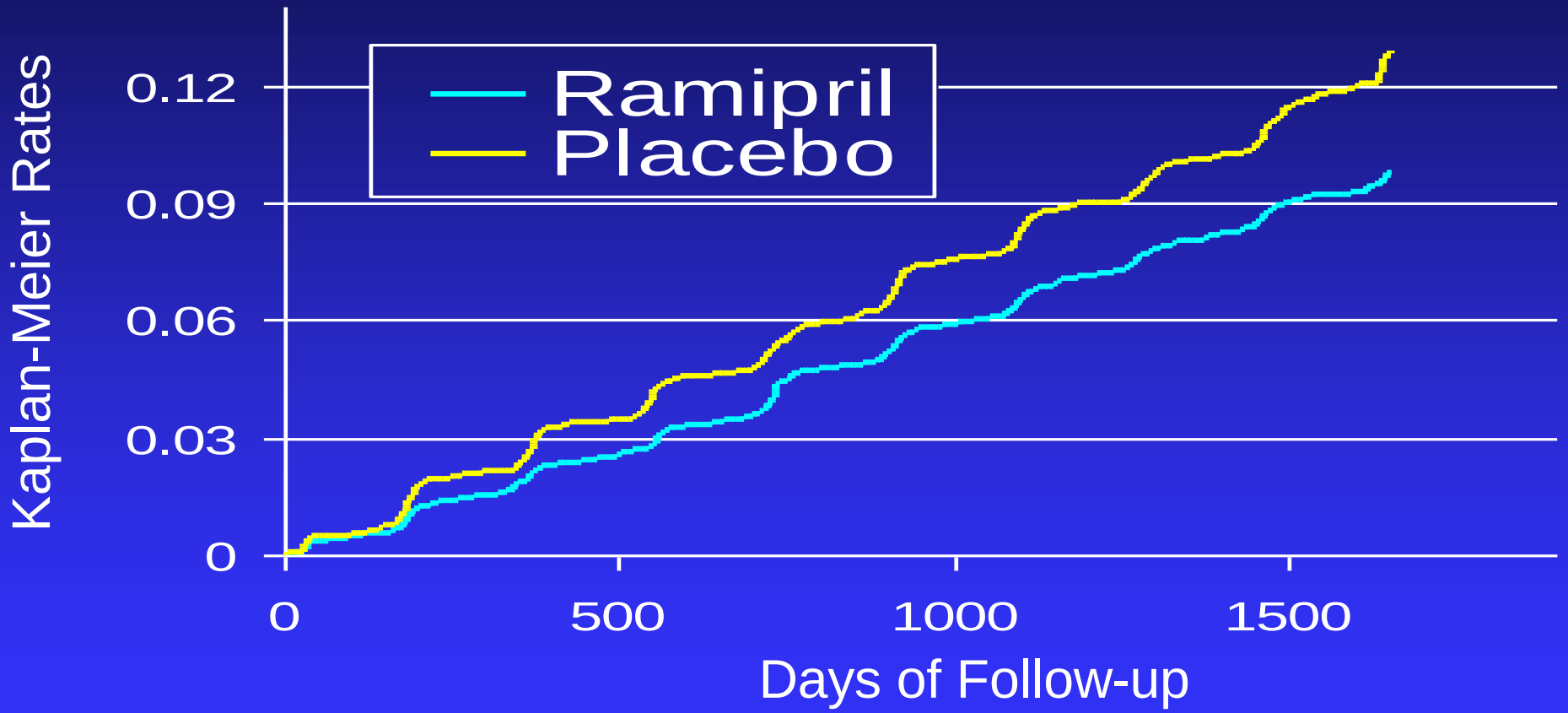
CHF Hospitalization - Ramipril vs Placebo



RR=0.87 (0.69-1.09) p=0.22

All CHF - Ramipril vs Placebo



RR=0.77 (0.68-0.87) p<0.001

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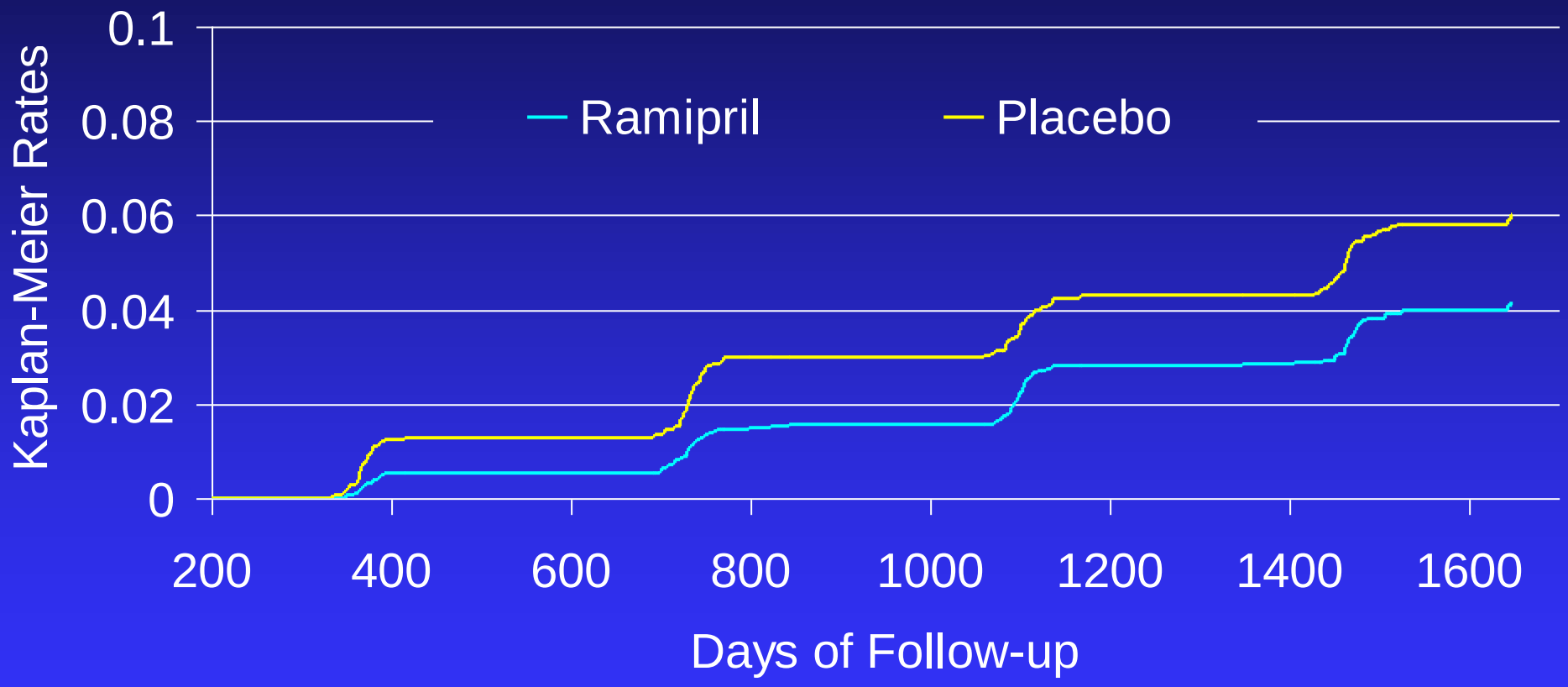
All Heart Failure - Ramipril vs Placebo

	Ramipril N=4645 N(%)	Placebo N=4652 N(%)	RR (95% CI)	p-value
All HF	417(9.0)	534(11.5)	0.77(0.68-0.87)	<0.001
Open ACE-I For HF	240(5.2)	327(7.0)	0.72(0.61-0.85)	<0.001
Hosp HF	141(3.2)	161(3.5)	0.87(0.69-1.09)	0.22
HF Death	24(0.52)	27(0.58)	0.88(0.51-1.53)	0.66
CV Death + All HF	624(13.4)	807(17.4)	0.76(0.69-0.84)	<0.001
CV Death + HF Hospitalization	383(8.3)	491(10.6)	0.77(0.68-0.88)	<0.001

Development of DM: Ramipril vs Placebo



RR=0.66 (0.51-0.85) p<0.001

Development of DM and DM Medications

	Ramipril (N=2837)		Placebo (N=2883)	
	N	%	N	%
New DM	102	3.6	155	5.4
Oral Agents	53	1.9	101	3.5
Insulin	5	0.2	1	0.0
Both	1	0.0	3	0.1
Diet Alone	43	1.5	50	1.7

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Ramipril vs Placebo
Patients with Documented normal EF
[N= 4775; mean 0.59 (SD 0.11)]

	Ramipril N=2381	Placebo N=2394	
	N(%)	N(%)	RR (95% CI)
Primary Outcome (MI/Stroke/CV Death)	332(13.9)	451(18.8)	0.73(0.63-0.84)
CV Death	123(5.2)	181(7.6)	0.68(0.54-0.85)
MI	254(10.7)	337(14.1)	0.75(0.63-0.88)
Stroke	69(2.9)	102(4.3)	0.67(0.50-0.91)
All Heart Failure	206(8.7)	257(10.7)	0.79(0.66-0.95)
Revascularization	475(20.0)	565(23.6)	0.82(0.72-0.92)

Mean Change in Blood Pressure - Ramipril vs Placebo

	Baseline Value (mmHg)	1 Month Δ	2 Year Δ	End Δ
Arm Systolic BP				
Ramipril	138.50	-5.51	-3.32	-2.19
Placebo	138.85	-1.69	0.00	0.40
Arm Diastolic BP				
Ramipril	78.91	-2.73	-2.86	-3.13
Placebo	78.92	-0.56	-1.01	-2.05

Mortality reductions in HOPE vs prior trials of anti-hypertensive treatment vs control

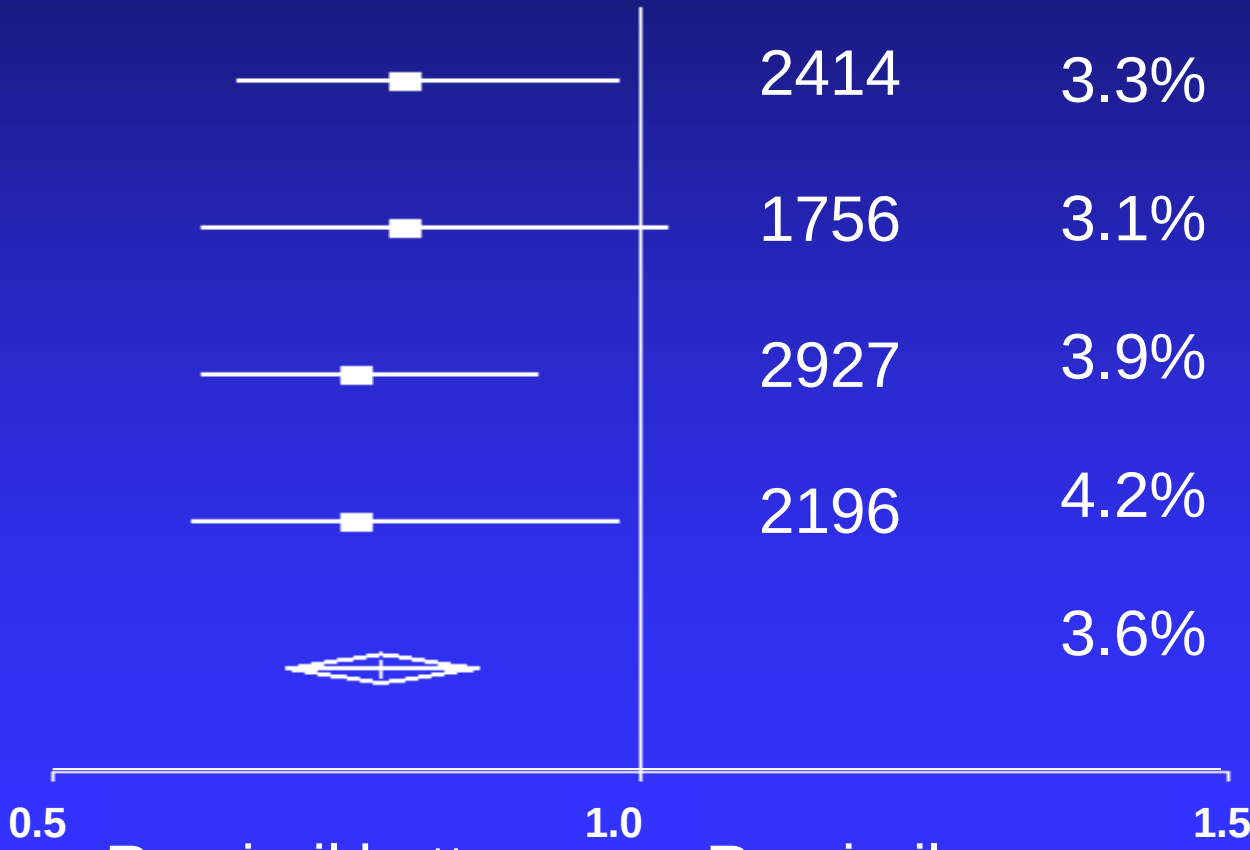
10-15 mmHg↓ in SBP (based upon trials) → 40% ↓ Stroke

→ 15% ↓ MI

	Expected from Epi Studies	Achieved in HOPE
3.3mmHg↓ in SBP	13% ↓ Stroke	32% ↓
	5% ↓ MI	20% ↓

Risk of CV Death / MI / Stroke by DBP

Quartiles	Usual BP	RR with 95% CI	N	Abs. Risk Reduction
≤70	71		2414	3.3%
71-79	75		1756	3.1%
80-85	79		2927	3.9%
86+	85		2196	4.2%
Overall				3.6%



P for trend=0.64

Risk of CV Death / MI / Stroke by SBP

Quartiles	Usual BP	RR with 95% CI	N	Abs. Risk Reduction
≤124	125		2281	2.7%
125-139	134		2465	2.5%
140-150	142		2438	2.0%
151+	153		2110	7.9%
Overall				3.6%

P for trend=0.06

Ramipril better

Ramipril worse

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Treatment Effect and Adjustment for Change in Systolic and Diastolic BP as Time-dependent Covariates

Outcome	Unadjusted RR(95%CI)	Adjusted RR(95%CI)
Primary	0.78(0.70-0.86)	0.78(0.71-0.87)
MI	0.80(0.70-0.90)	0.77(0.65-0.91)
Stroke	0.68(0.56-0.84)	0.72(0.58-0.89)
CV Death	0.74(0.64-0.87)	0.77(0.65-0.91)

Treatment Effect and Adjustment for Change in Systolic and Diastolic BP as Time-dependent Covariates

Outcome	Unadjusted RR(95%CI)	Adjusted RR(95%CI)
Primary	0.78(0.70-0.86)	0.78(0.71-0.87)

Events Prevented per 1,000 Patients Treated

	No. Prev. per 1,000 treated	Corr. for 20% noncompl.
No. Deaths	18	23
MI	16	20
Stroke	9	11
Total Events	43(NNT=23)	
No. People with above	36(NNT=28)	

Events Prevented per 1,000 Patients Treated

	No. Prev. per 1,000 treated	Corr. for 20% noncompl.
No. Deaths	18	23
MI	16	20
Stroke	9	11
Revasc	26	33
CHF	26	33
Cardiac Arrest	5	6
Diab Comp	12	15
New Diab	16	20
Total Events	128(NNT= 8)	
No. People with above	59(NNT=17)	

Conclusions: Ramipril vs Placebo(1/2)

There is convincing evidence that Ramipril prevents:

- **CV death, MI and stroke**
- **Need for revascularization**

These benefits are consistently observed in a very broad range of high risk patients and in addition to other effective therapies

Conclusions: Ramipril vs Placebo(2/2)

Additional observations:

Significant reductions in

- Any heart failure
- New diagnosis of diabetes
- Nephropathy

The only adverse event is a 5% excess of cough