ONTARGET: The ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial

ACE-inhibitors (e.g. ramipril in the HOPE trial) reduces CV death, MI, stroke and HF hosp in those with CVD or DM in the absence of ventricular dysfunction or heart failure

ACE-inhibitors are not tolerated by 15% to 25% of patients

Will an ARB (telmisartan) be as effective and better tolerated?

Is the combination superior?

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Questions:

1. Is telmisartan “non-inferior” to ramipril?
2. Is the combination superior to ramipril?

Outcome:

1. Primary: CV death, MI, stroke, CHF hosp
2. Key secondary: CV death, MI, stroke (HOPE trial outcome)

Design:

Single blind run-in (n=29,019)

Randomized, double blind, double dummy study conducted in 733 centers in 41 countries (n=25,620)

56 months follow-up with 99.8% outcome ascertainment

ONTARGET Statistical Considerations

In HOPE the hazard ratio for ramipril v plac	: 0.77
40th percentile	: 0.794
Excess risk of placebo/ramipril	: 1.26
Half of above	: 1.13

For non-inferiority (Telmisartan v ramipril) the one-sided 97.5% CI should be below 1.13.

Assuming an annual event rate of 3.97%, 7800 patients per group followed for 4.5 yrs provides :

- -89% power for NI (T v R)
- -93% power superiority (T + R v R)

Total randomized: 25,620 in 18 months

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Study Medications Titration

Run-in (Single Blind)	
Day 1-3	Ram 2.5 mg + Tel Placebo
Day 4-10	Ram 2.5 mg + Tel 40 mg
Day 11-18	Ram 5.0 mg + Tel 40 mg
Randomization (Double Blind)	
2 weeks	Ram Placebo + Tel 80 mg
	Ram 5 mg + Tel Placebo
	Ram 5 mg + Tel 80 mg
Then	Full doses (Tel 80 mg daily,
	Ram 10 mg daily) for the 3 arms

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Reasons for Not Randomizing Patients

		%
Run-in Completed (n=29,018)		100
Not Randomized		11.71
Creatinine elevated	0.22	
Potassium elevated	0.77	
Persistent symptomatic hypotension	1.70	
Death	0.09	
Total Medical Reasons		2.78
Compliance <75%	3.87	
Other reasons	3.01	
Patient Decision	2.06	
Total Patient Reasons		5.93

ONTARGET Key Baseline Characteristics

	Ramipril	Telmisartan	Combination
N	8576	8542	8502
Age	66.4	66.4	66.5
% females	27.2	26.3	26.5
% CAD	74.4	74.5	74.7
% Stroke/TIA	21.0	20.6	20.9
% Diabetes	36.7	38.0	37.9
BP	141.8/82.1	141.7/82.1	141.9/82.1
Statins	61.0	62.0	61.8
Antiplatelet	80.5	81.1	81.1
β-blocker	56.5	56.9	57.4

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Change in BP (mmHg)

	Ramipril	Telmisartan	Combination
Systolic	-6.0	-6.9	-8.4
Diastolic	-4.6	-5.2	-6.0

Time to Permanent Discontinuation of Study Medication

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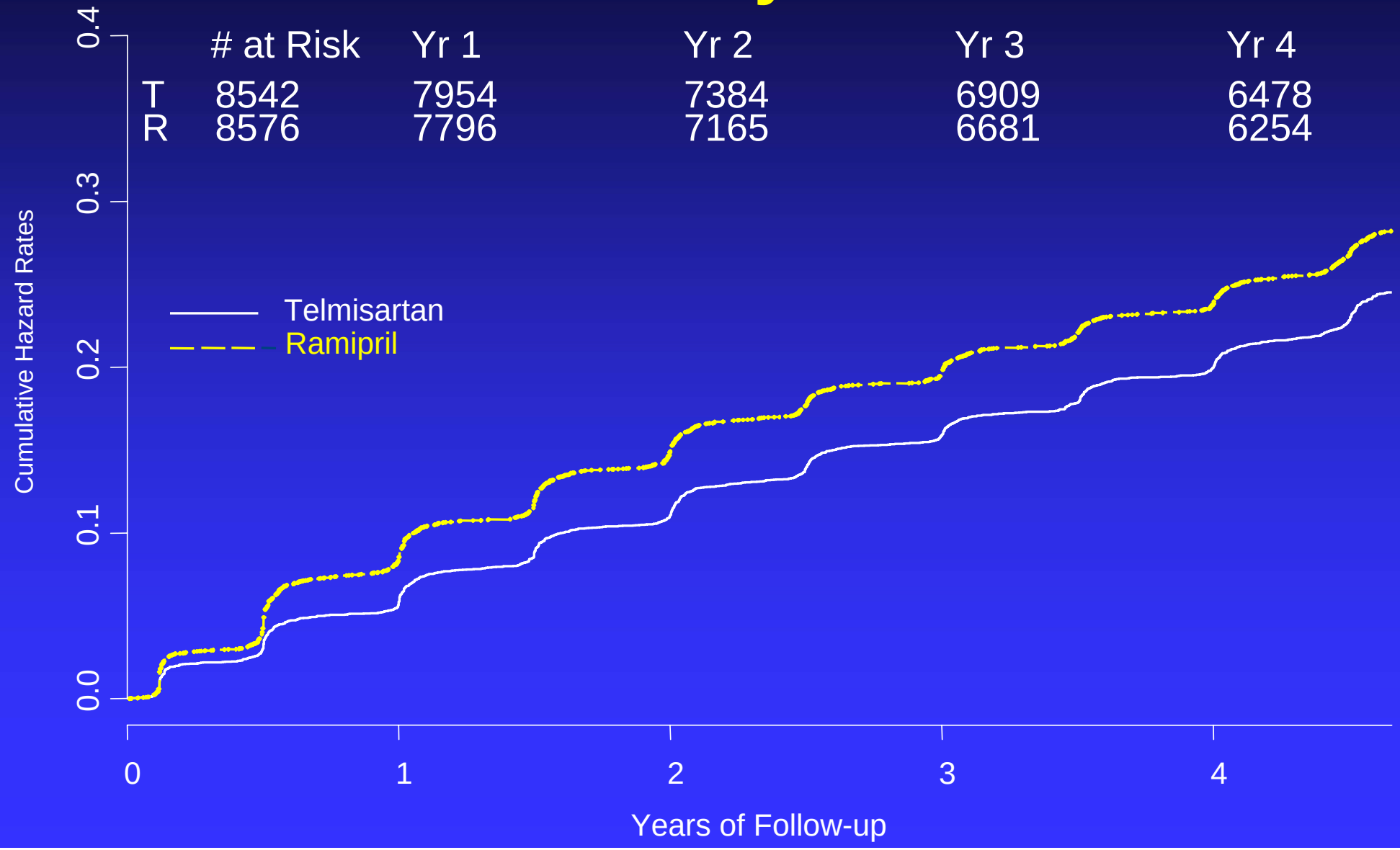
	# at Risk	Yr 1	Yr 2	Yr 3	Yr 4
T	8542	7954	7384	6909	6478
R	8576	7796	7165	6681	6254



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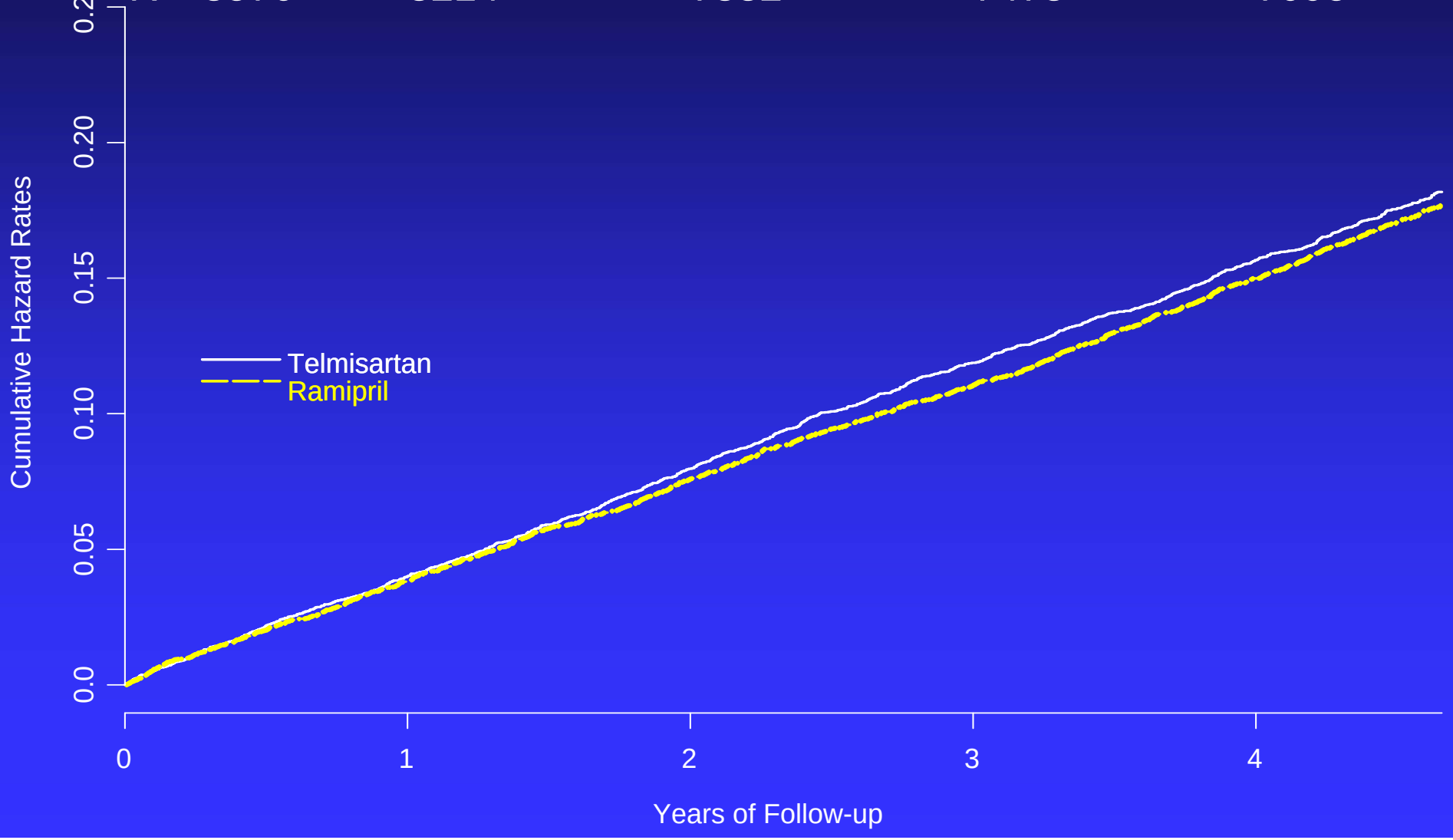
Reasons for Permanently Stopping Study Medications

	Ram	Tel	Tel vs. Ram	
	N=8576	N=8542	RR	P
Hypotension	149	229	1.54	0.0001
Syncope	15	19	1.27	0.4850
Cough	360	93	0.26	<0.0001
Diarrhea	12	19	1.59	0.20
Angioedema	25	10	0.40	0.0115
Renal Impairment	60	68	1.14	0.46
Any Discontinuation	2099	1962	0.94	0.02

ONTARGET Time to Primary Outcome

	# at Risk	Yr 1	Yr 2	Yr 3	Yr 4
T	8542	8176	7778	7420	7051
R	8576	8214	7832	7473	7095



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Primary Outcome & HOPE Primary Outcome

	Ram	Tel	Tel vs Ram	
	N (%)	N (%)	RR (95% CI)	P (non-inf)
N	8576	8542		
Primary Outcome				
CV Death, MI, Stroke, CHF Hosp	1412 (16.46%)	1423 (16.66%)	1.01 (0.94-1.09)	0.0038
(Adjusted for SBP)			1.02 (0.95-1.10)	0.0055
HOPE Primary Outcome				
CV Death, MI, Stroke	1210 (14.11%)	1190 (13.93%)	0.99 (0.91-1.07)	0.0009
(Adjusted for SBP)			0.99 (0.91-1.07)	0.0012

ONTARGET Non-Inferiority Comparison

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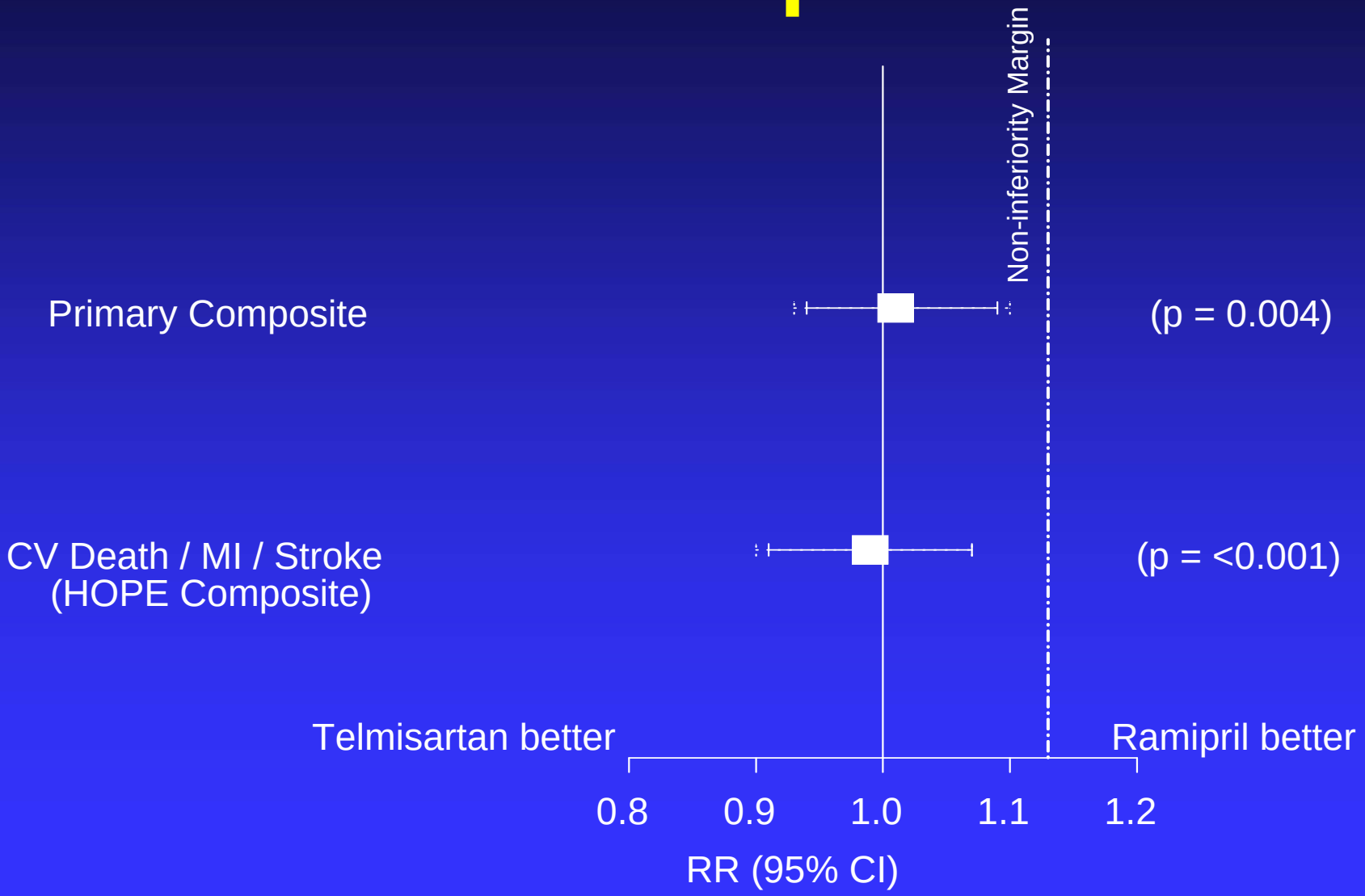

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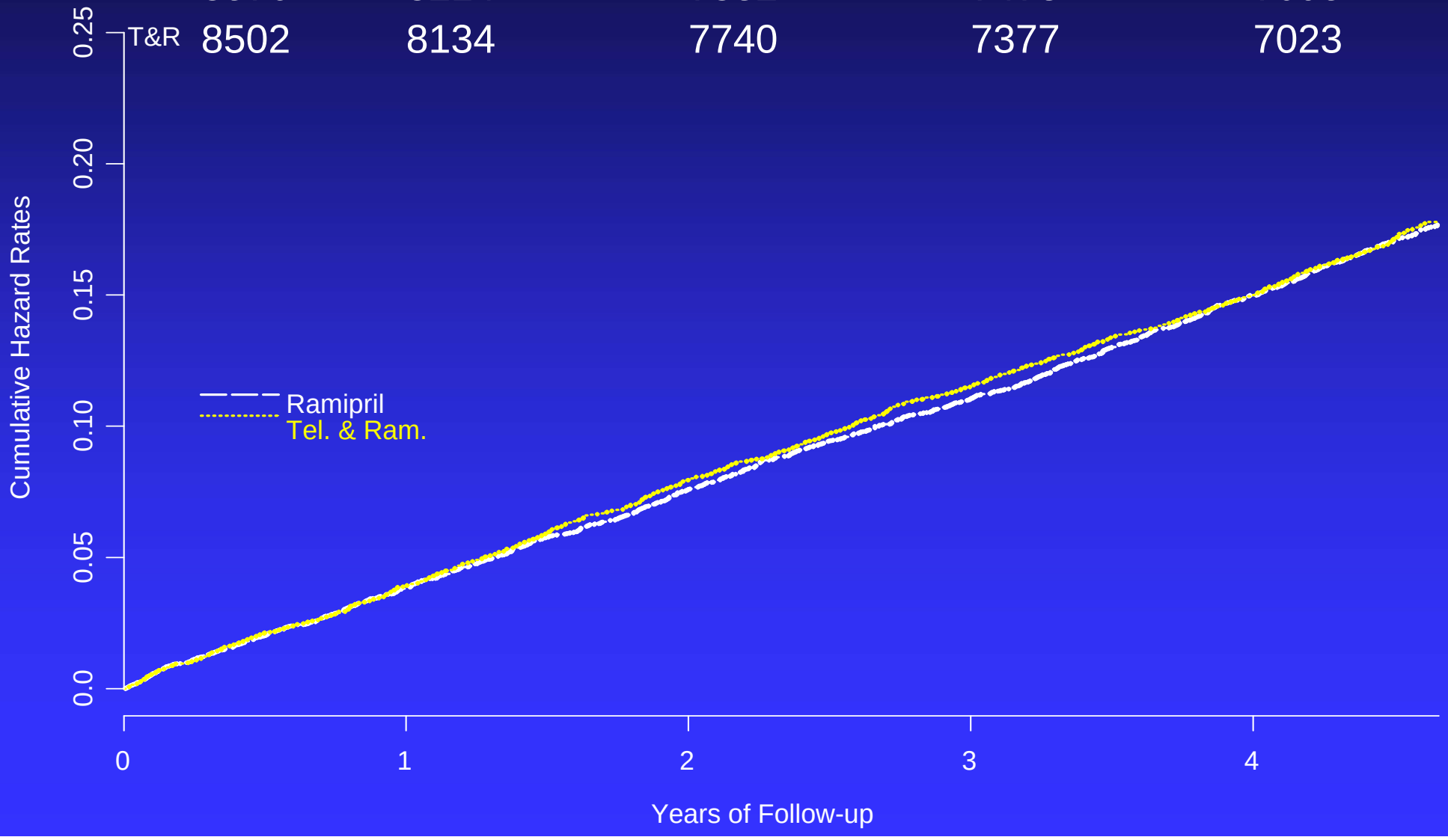
Time to Primary Outcome

	# at Risk	Yr 1	Yr 2	Yr 3	Yr 4
R	8576	8214	7832	7473	7095
T&R	8502	8134	7740	7377	7023



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Reasons for Permanently Stopping Study Medications

	Ram N=8576	Ram + Tel N=8502	Ram + Tel vs. Ram RR	P
Hypotension	149	406	2.75	<0.0001
Syncope	15	29	1.95	0.032
Cough	360	392	1.10	0.1885
Diarrhea	12	39	3.28	0.0001
Angioedema	25	18	0.73	0.30
Renal Impairment	60	94	1.58	0.0050
Any Discontinuation	2099	2495	1.20	<0.0001

Combination vs Ramipril

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Conclusions: Telmisartan vs. Ramipril (1)

1. Telmisartan is clearly “non-inferior” to ramipril
   - Primary composite outcome (p=0.0038)
   - HOPE primary outcome (p=0.001)
     Most (>90%) of the benefits of ramipril are preserved

2. Consistent results on a range of:
   - Secondary outcomes
   - Subgroups

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Conclusions: Telmisartan vs. Ramipril (2)

3. Sensitivity analysis using a per protocol approach confirms this

4. Telmisartan exhibits slightly superior tolerability
   - Less cough and angioneurotic edema
   - More mild hypotensive symptoms, but no difference in severe hypotensive symptoms, such as syncope

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Conclusions: Telmisartan plus Ramipril vs. Ramipril

1. Combination therapy does not reduce the primary outcome to a greater extent compared to ramipril alone

2. Higher rates of adverse events:
   - -hypotension related, including syncope
   - -renal dysfunction

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Implications

- Telmisartan is as effective as ramipril, with a slightly better tolerability.
- Combination therapy is not superior to ramipril, and has increased side effects.