

# **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?**

# ONTARGET

## 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 40 countries (n=25,620)

56 months follow-up with 99.8% outcome ascertainment

# Statistical Considerations

In HOPE the hazard ratio for ramipril v plac	:	0.77
40 <sup>th</sup> 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

## 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
$\beta$ -blocker	56.5	56.9	57.4

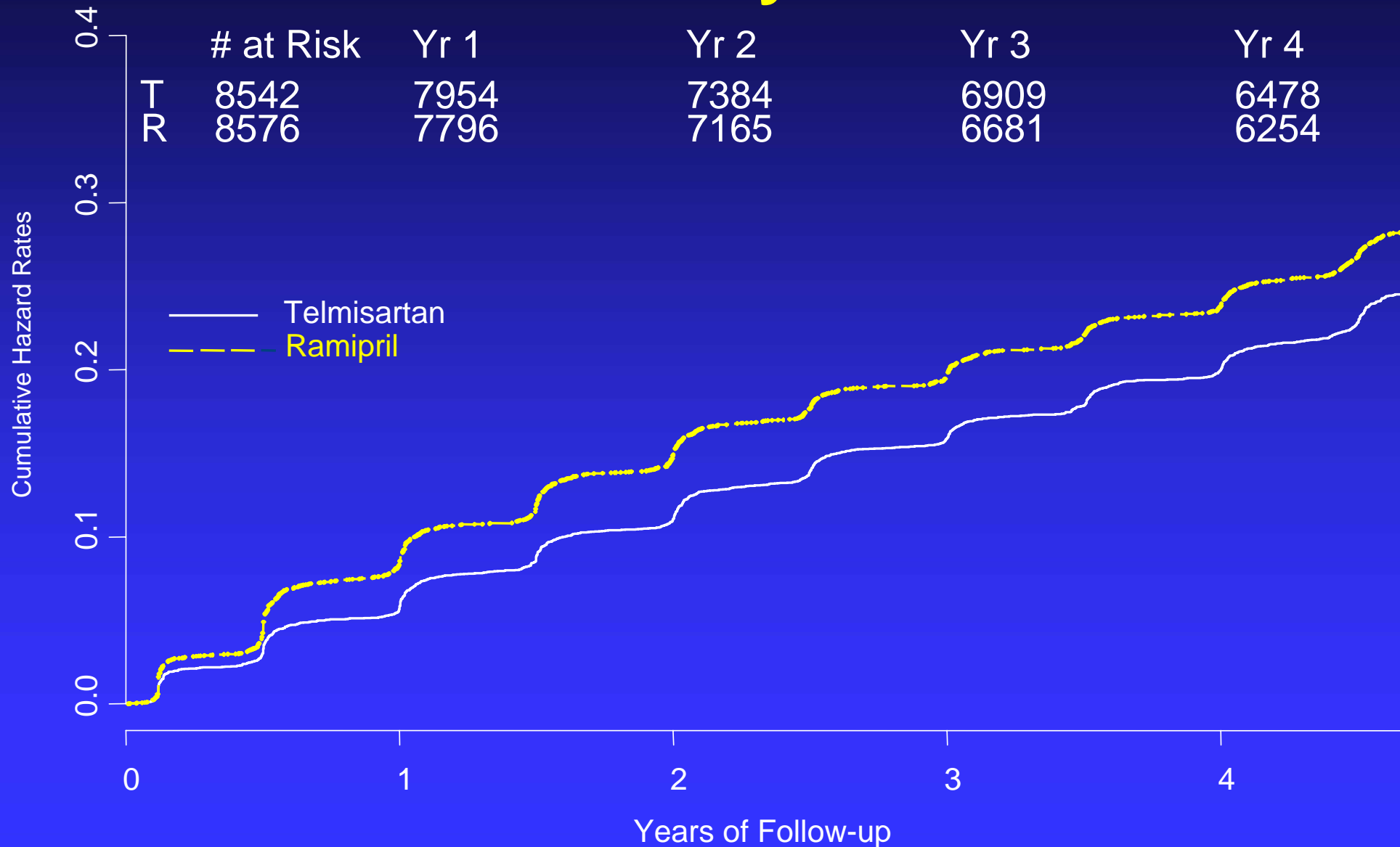
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## Change in BP (mmHg)

	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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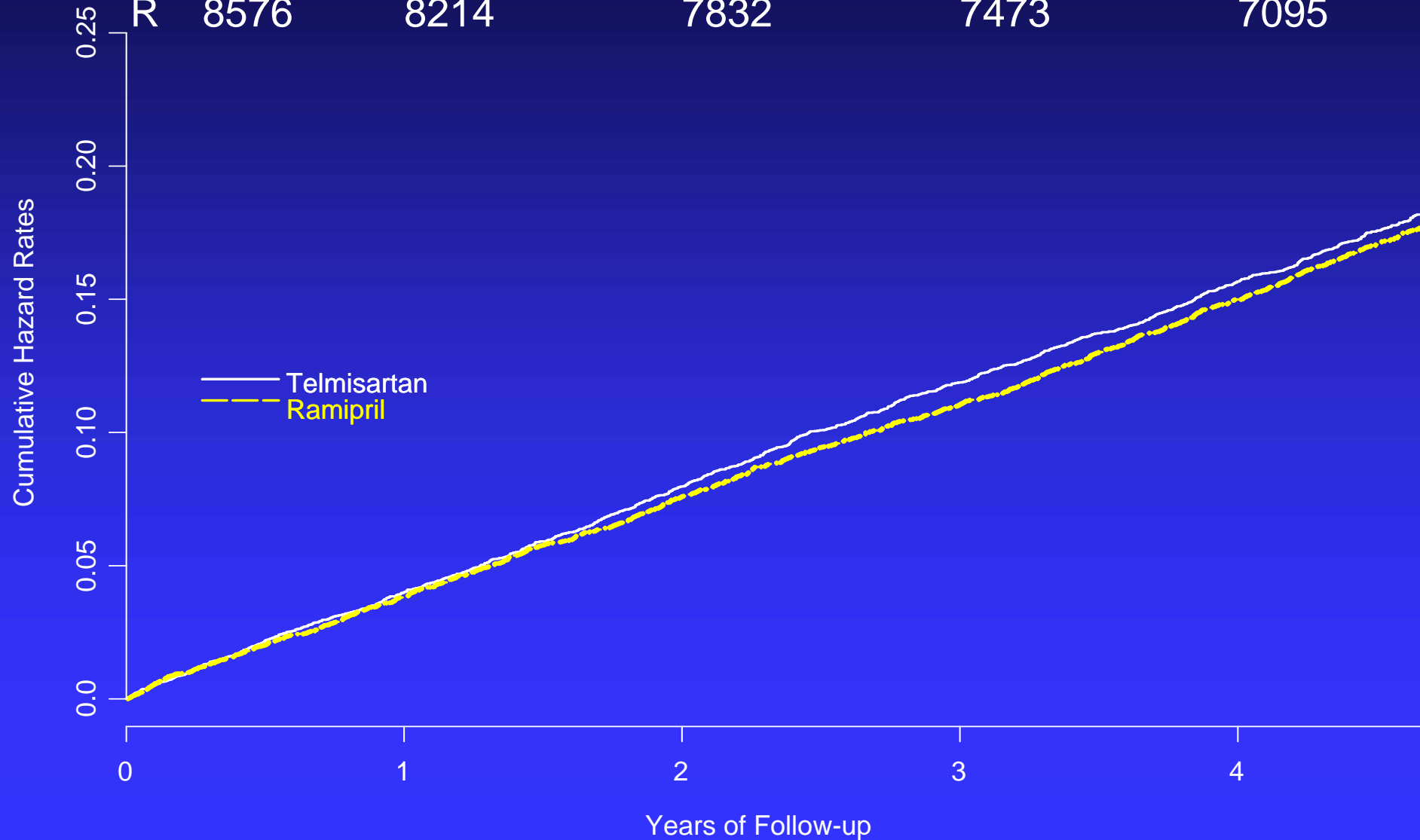
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# Reasons for Permanently Stopping Study Medications

	Ram N=8576	Tel N=8542	Tel vs. Ram	
			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

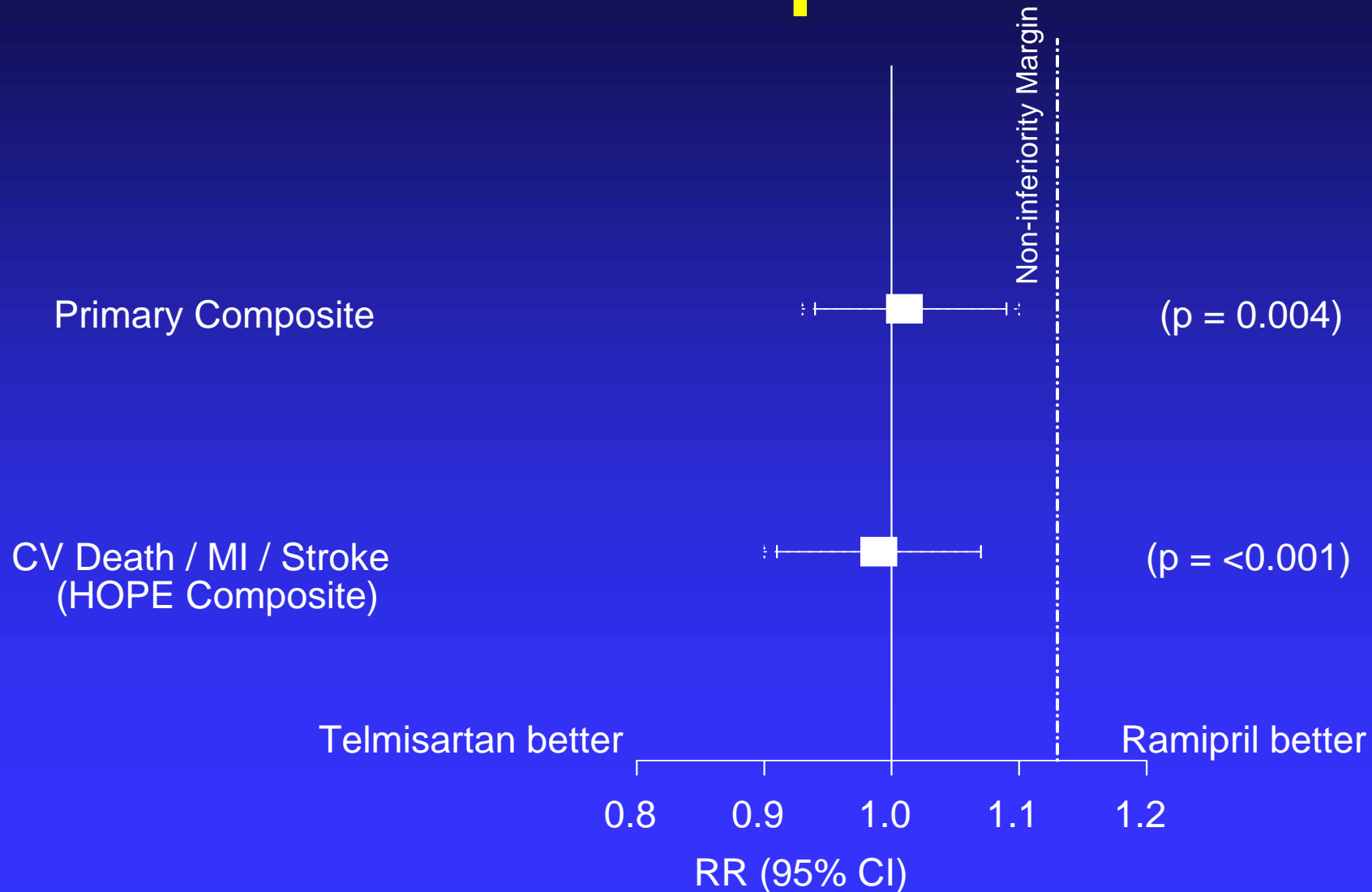
## Primary Outcome

	Ram	Tel	Tel vs Ram	
	N (%)	N (%)	RR (95% CI)	P (non-inf)
N	8576	8542		
<u>Primary Outcome</u>				
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
<u>HOPE Primary Outcome</u>				
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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## Comparison



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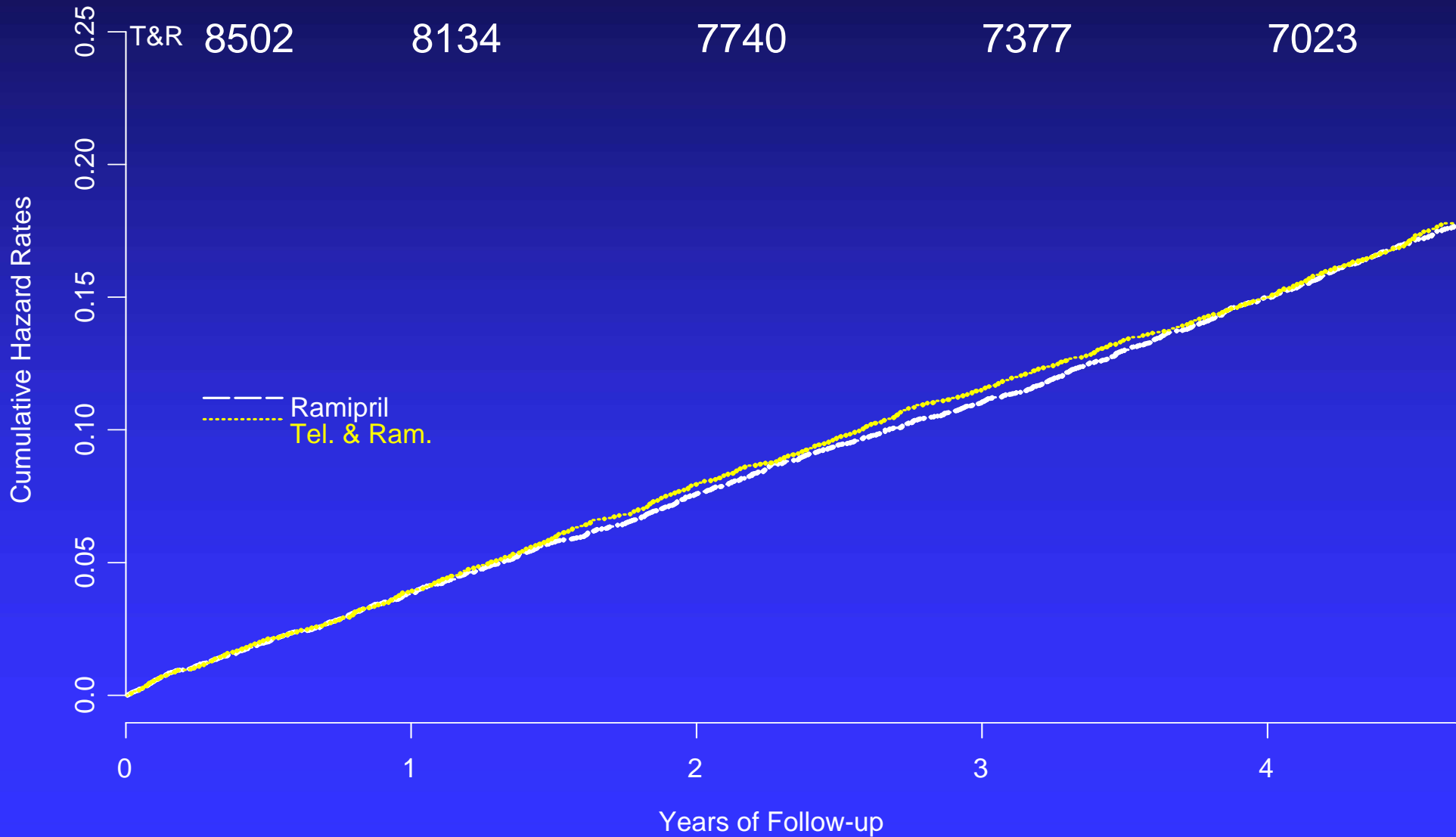
# **Combination vs Ramipril**

# ONTARGET **Time to Primary Outcome**

# at Risk    Yr 1                      Yr 2                      Yr 3                      Yr 4

R    8576                      8214                      7832                      7473                      7095

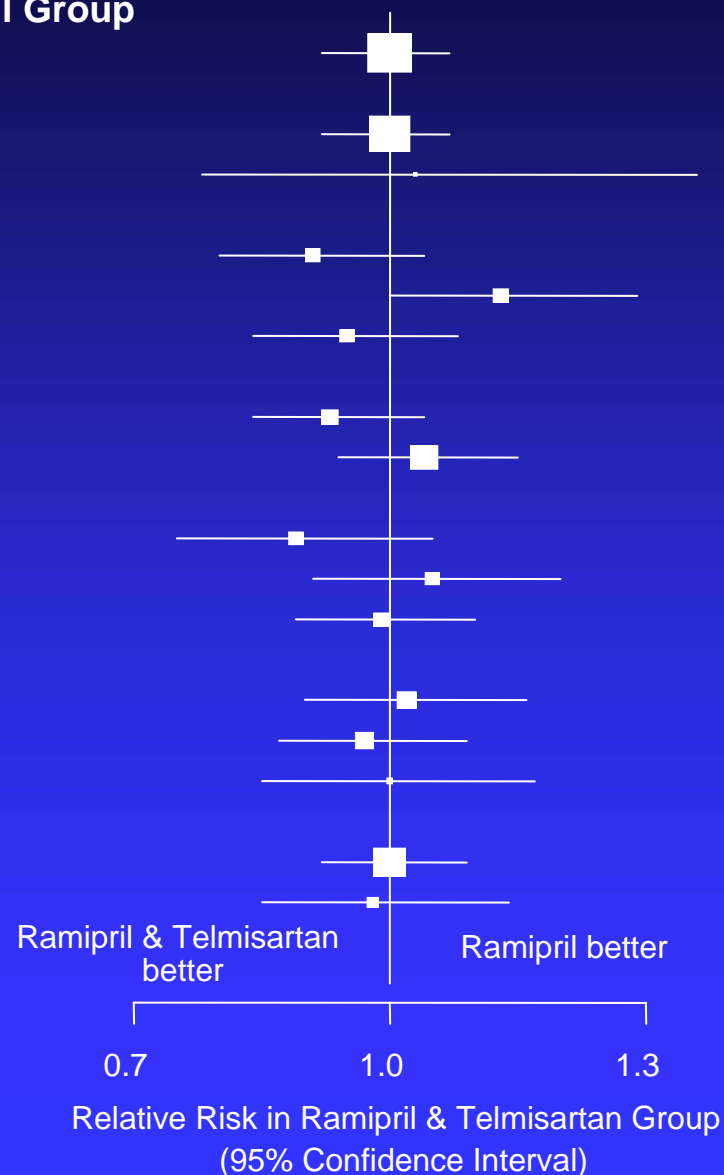
T&R 8502                      8134                      7740                      7377                      7023



# Tel + Ram v Ram: Pre-specified Subgroups

## ONTARGET

	No. of Patients	Incidence of Primary Outcome in Ramipril Group
Primary Composite	17078	16.4
Hx of CVD	15589	16.7
No Hx of CVD	1484	13.1
SBP ≤ 134	5714	16.2
134 < SBP ≤ 150	6019	14.9
SBP > 150	5329	18.3
Diabetes	6364	20.6
No Diabetes	10709	14.0
HOPE Low Risk Score	5637	10.4
HOPE Medium Risk Score	5596	15.0
HOPE High Risk Score	5845	23.8
Age < 65	7362	13.0
65 ≤ Age < 75	7177	17.2
Age ≥ 75	2539	24.1
Male	12497	16.7
Female	4581	15.7



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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

# Conclusions: Telmisartan vs. Ramipril (1)

1. Telmisartan is clearly “non-inferior” to ramipril, with most ( 95-100%) of the benefits preserved
2. Consistent results on a range of:
  - Secondary outcomes
  - Subgroups

# Conclusions: Telmisartan vs. Ramipril (2)

**3. Telmisartan exhibits slightly superior overall tolerability:**

- **Less cough and angioneurotic edema**
- **More mild hypotensive symptoms, but no difference in severe hypotensive symptoms, such as syncope**

# Conclusions: Telmisartan plus Ramipril vs. Ramipril

1. Combination therapy does not reduce the primary outcome to a greater extent compared to ramipril alone and has higher adverse events.

# Implications

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

# Acknowledgments

- Patients
- National coordinators and Project office staff at McMaster Univ, Hamilton, Canada.
- Sponsor: Boehringer-Ingelheim

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**Reserve**

# T v R: Pre-specified Subgroup Analysis

## ONTARGET

	No. of Patients	Incidence of Primary Outcome in Ramipril Group
Primary Composite	17118	16.4
Hx of CVD	15627	16.7
No Hx of CVD	1486	13.1
SBP < 134	5704	16.2
134 - 150	6042	14.9
> 150	5352	18.3
Diabetes	6390	20.6
No Diabetes	10723	14.0
HOPE Risk Score Low	5709	10.4
Medium	5664	15.0
High	5745	23.8
Age < 65	7319	13.0
65 - 75	7310	17.2
> 75	2489	24.1
Male	12537	16.7
Female	4581	15.7

