IDNT
Irbesartan Diabetic Nephropathy Trial

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IDNT
Hypotheses

Interruption of the renin-angiotensin system with irbesartan has renoprotective effects in patients with type 2 diabetic nephropathy *independent of blood pressure lowering*

- **Irbesartan would be superior to placebo (primary comparison)**
- **Irbesartan would be superior to amlodipine (secondary comparison)**

IDNT: Primary Endpoint

Time to a composite of:

- **Doubling of baseline serum creatinine**
- **End-stage renal disease (defined as renal transplantation, need for dialysis, or serum creatinine ≥ 6.0 mg/dL)**
- **Death (all cause mortality)**

IDNT: Secondary Endpoint

Time to a composite of:

- Cardiovascular death
- Non-fatal myocardial infarction
- Hospitalization for heart failure
- Permanent neurological deficit attributed to stroke
- Above-the-ankle amputation

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Major Study Entry Criteria

- Age 30 to 70 years
- Type 2 diabetes
- SeSBP $>$ 135 mmHg and/or SeDBP $>$ 85 mmHg, or receiving antihypertensive medication
- 24-hour urine protein excretion $\geq$ 900 mg
- Serum creatinine level 1.0 - 3.0 mg/dL in women; 1.2 - 3.0 mg/dL in men
- No known non-diabetic renal disease
- No recent cardiovascular events
- Serum potassium inside of normal range
- BMI $<$ 45 kg/m^2

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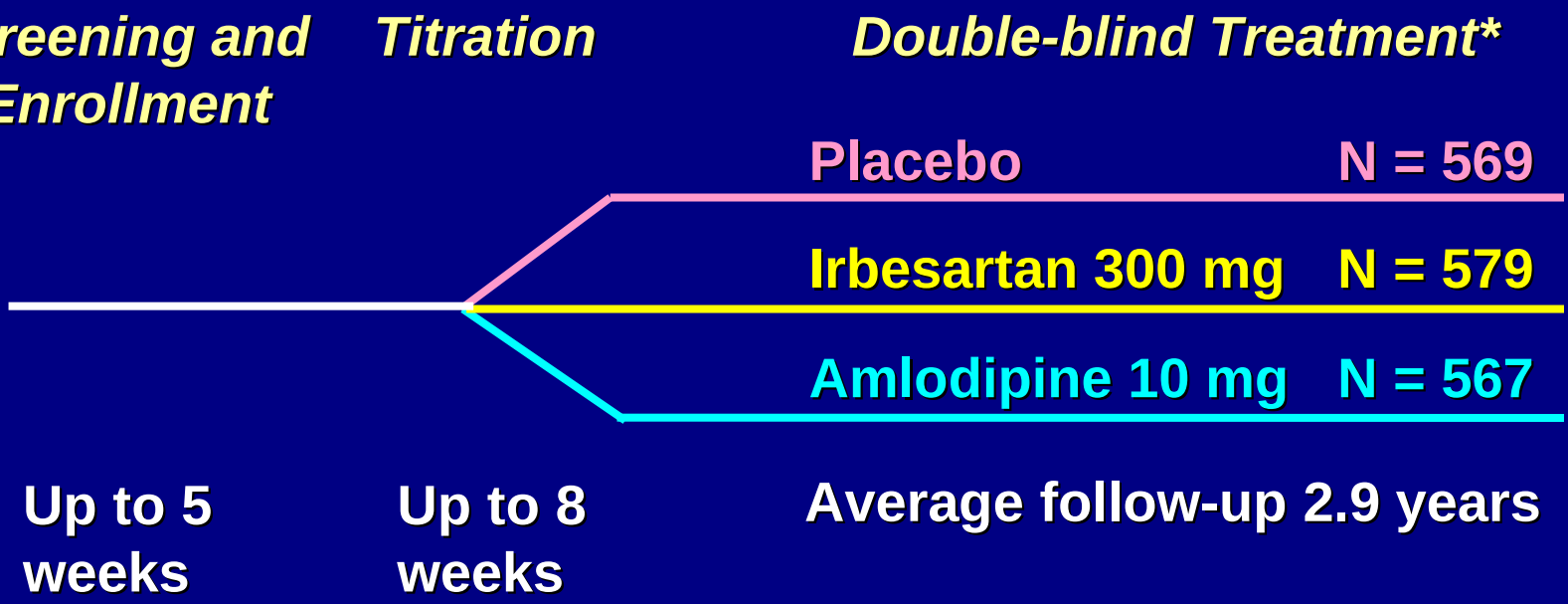
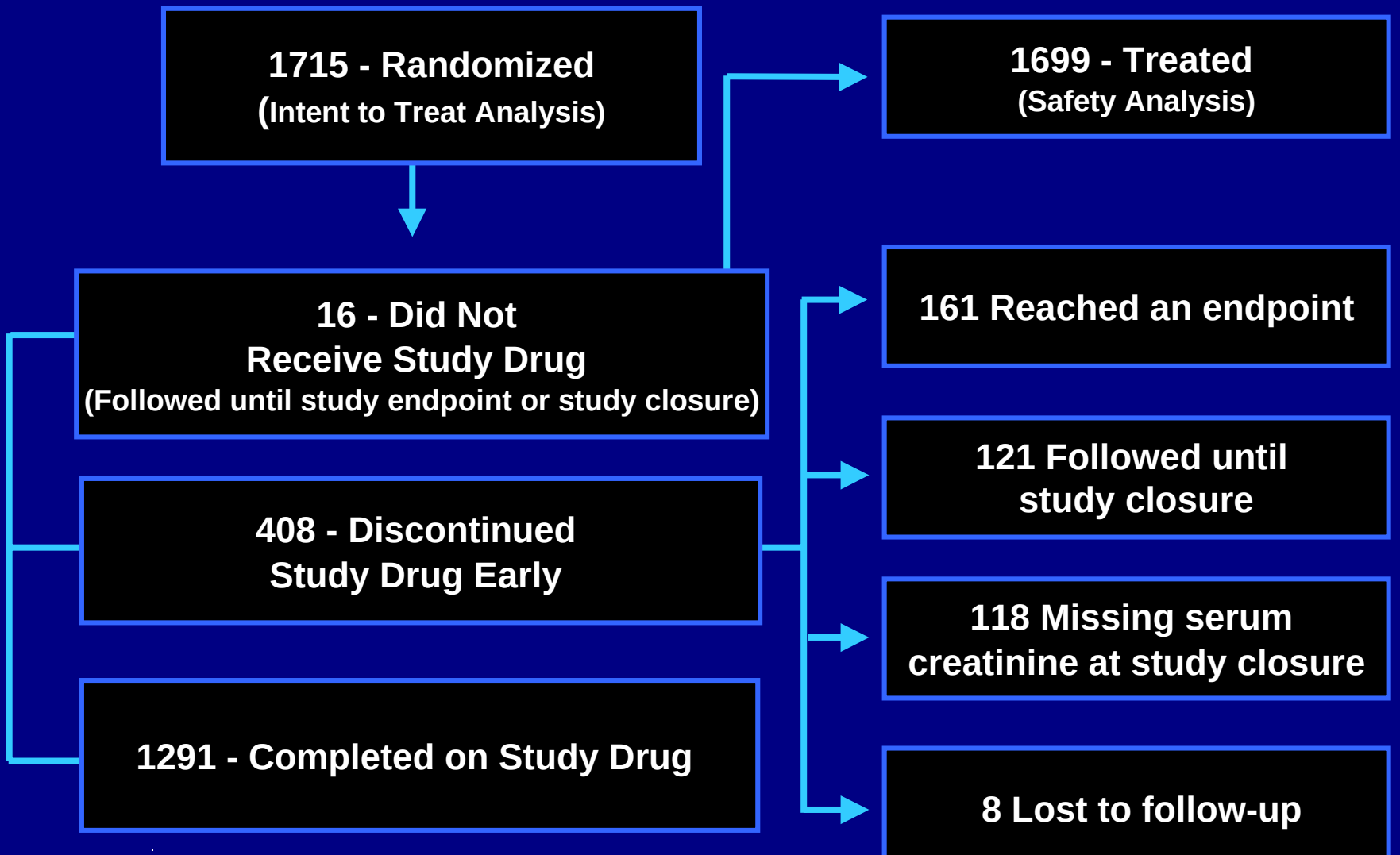
Study Design



*Target blood pressure: SeSBP ≤ 135 mmHg and/or SeDBP ≤ 85 mmHg

IDNT: Subject Disposition



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Baseline Characteristics of all Randomized Subjects*

	Placebo	Irbesartan	Amlodipine
N	569	579	567
Age (yr)	58.3	59.3	59.1
Male (%)	70.8	65.3	63.3
Race - White (%)	72.9	75.6	68.6
BMI (kg/m^2)	30.5	31.0	30.9
Known Duration of Diabetes (yr)	15.0	15.5	13.9
HbA_{1c} (%)	8.2	8.1	8.2
Serum Creatinine (mg/dl)	1.7	1.7	1.7
Creatinine Clearance (mL/min 1.73 m^2)	57.7	56.3	59.3
Urine Protein (g/24h)†	3.1	3.1	2.9
Blood Pressure (mmHg)	158/87	161/87	159/87

* Mean values
† Geometric mean

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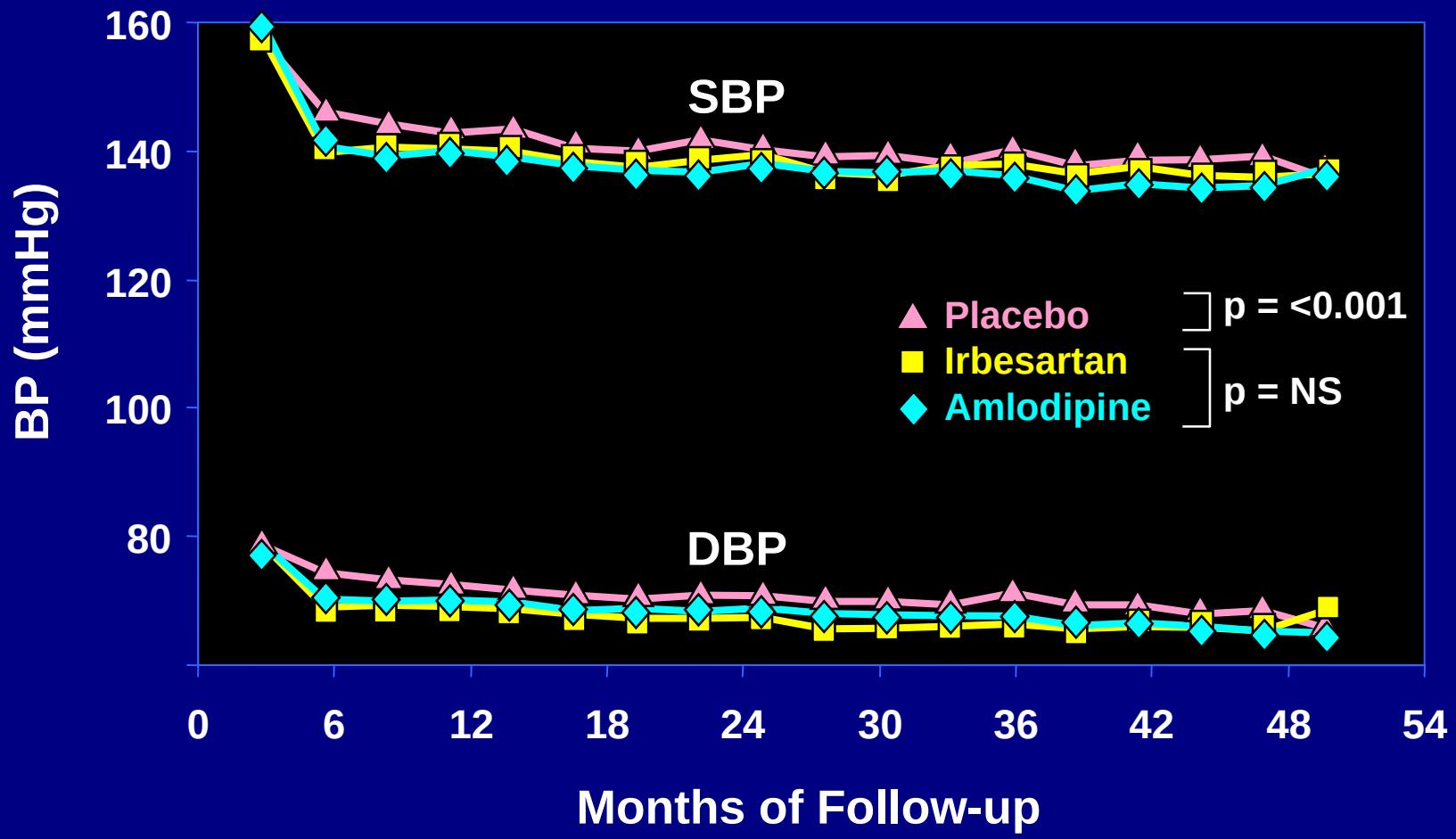
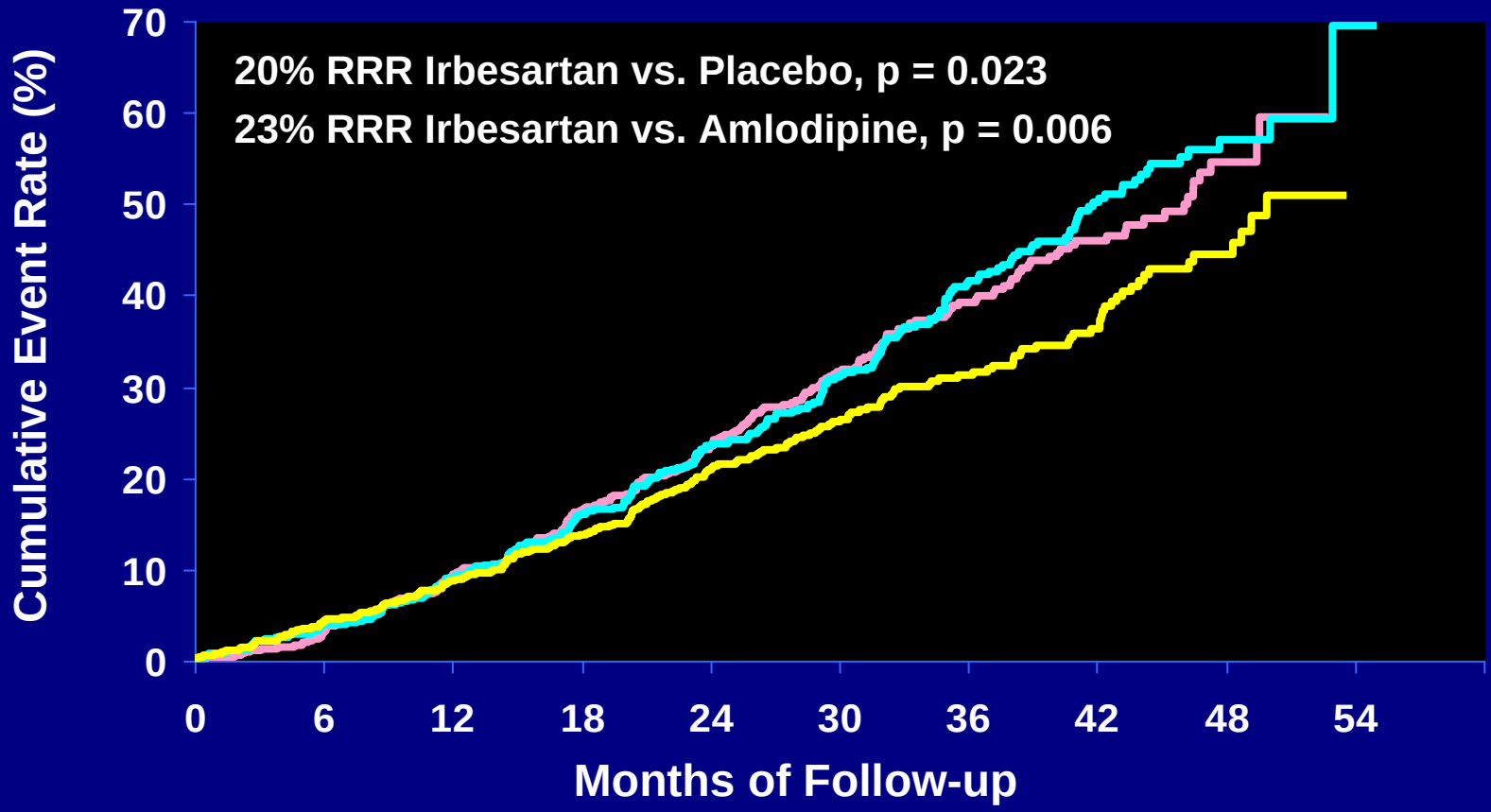
Mean Systolic (SBP) and Diastolic Blood Pressure (DBP) Throughout the Study



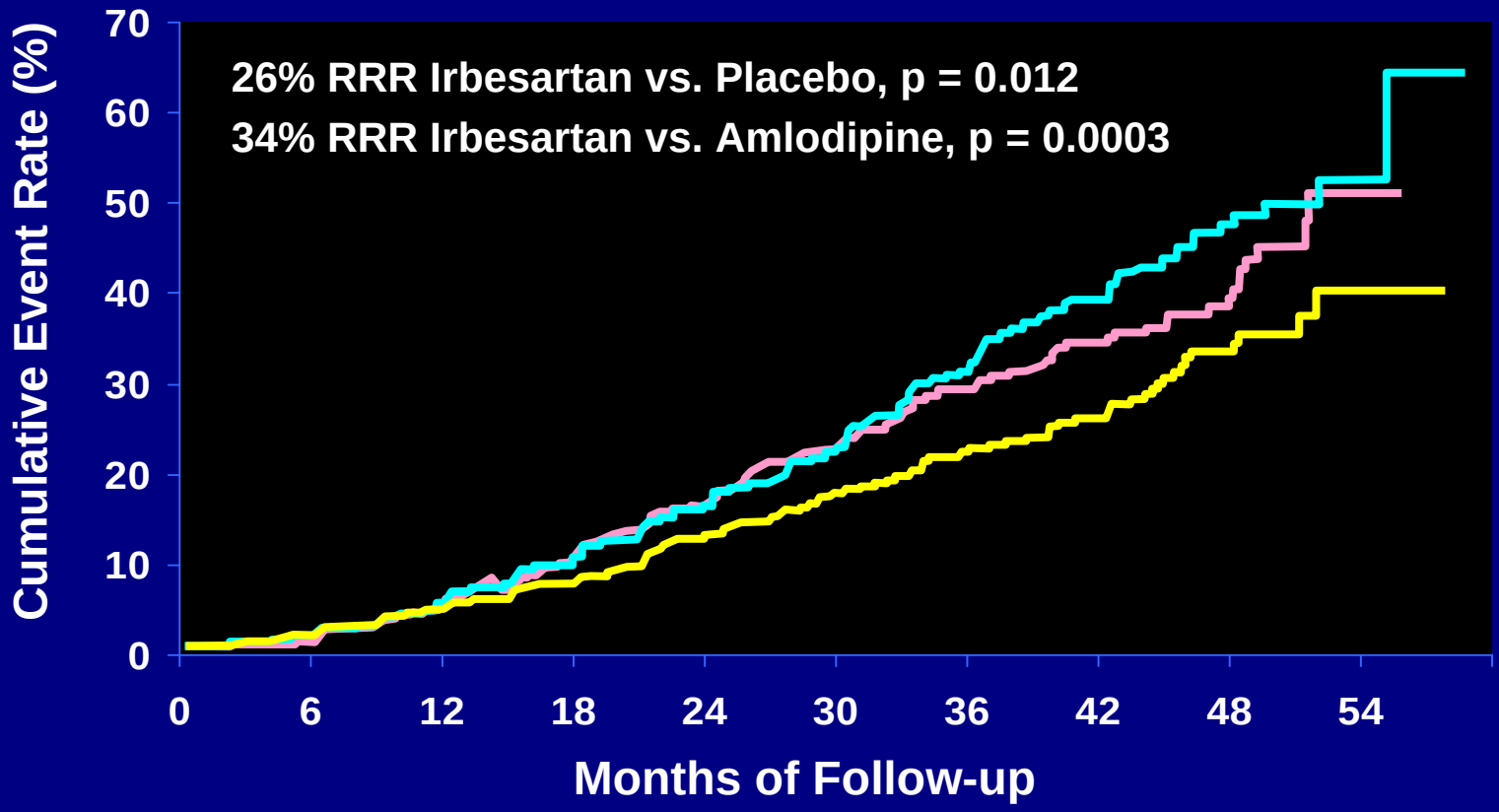
IDNT: Primary Endpoint – Time to Doubling of Serum Creatinine, ESRD, or Death



No. at Risk

Placebo	569	552	515	474	407	289	194	126	59	4
Irbesartan	579	556	528	497	409	308	219	151	69	5
Amlodipine	567	544	513	479	399	299	200	132	51	9

IDNT: Renal Outcome Endpoints – Doubling of Serum Creatinine or ESRD

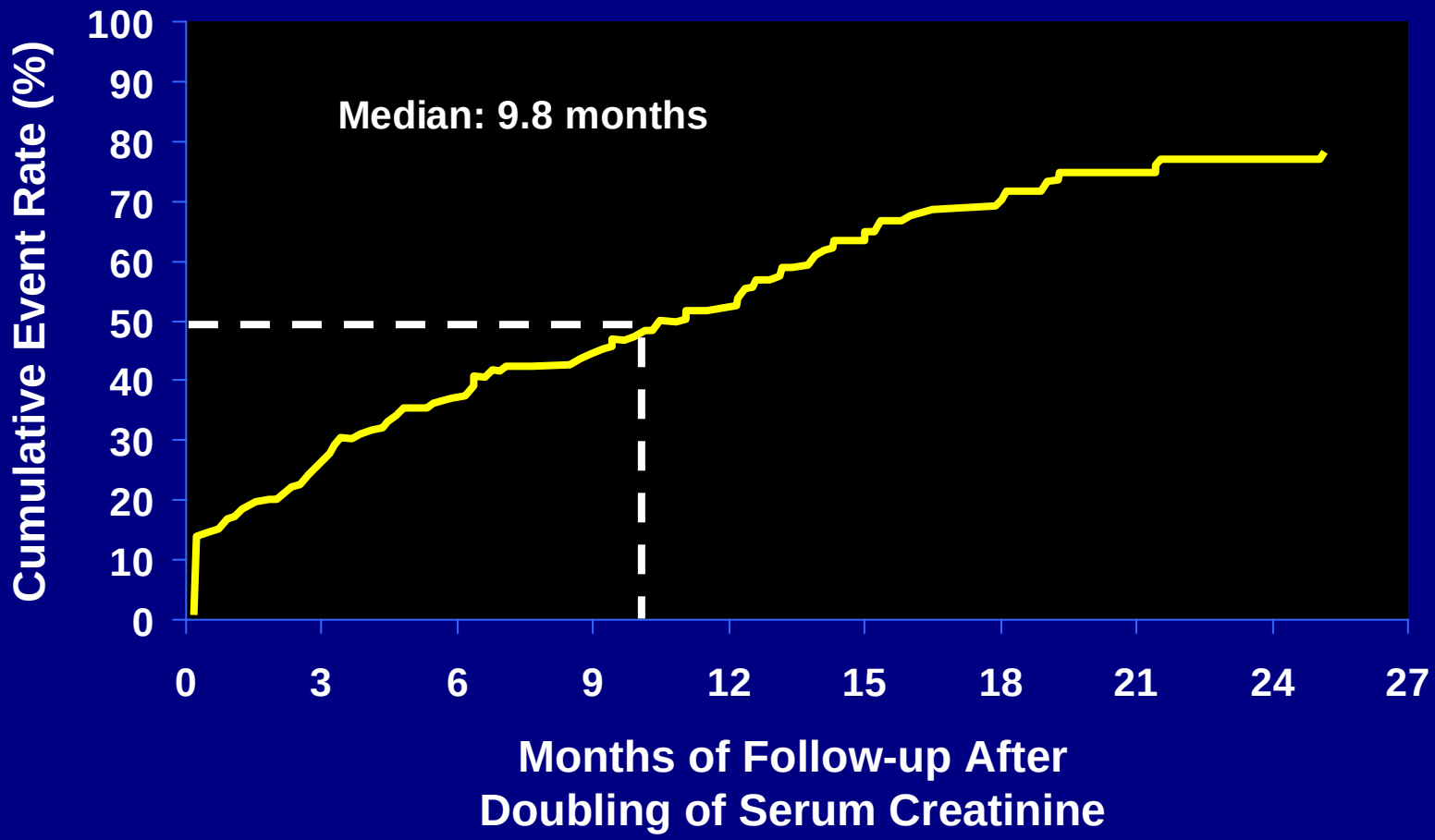


No. at Risk

Placebo	569	544	508	470	399	284	192	126	59	4
Irbesartan	579	549	519	489	403	305	217	149	69	5
Amlodipine	567	539	506	475	394	296	197	127	51	9

IDNT: Time to the Development of ESRD After Doubling of Serum Creatinine

Figure S.10.1D



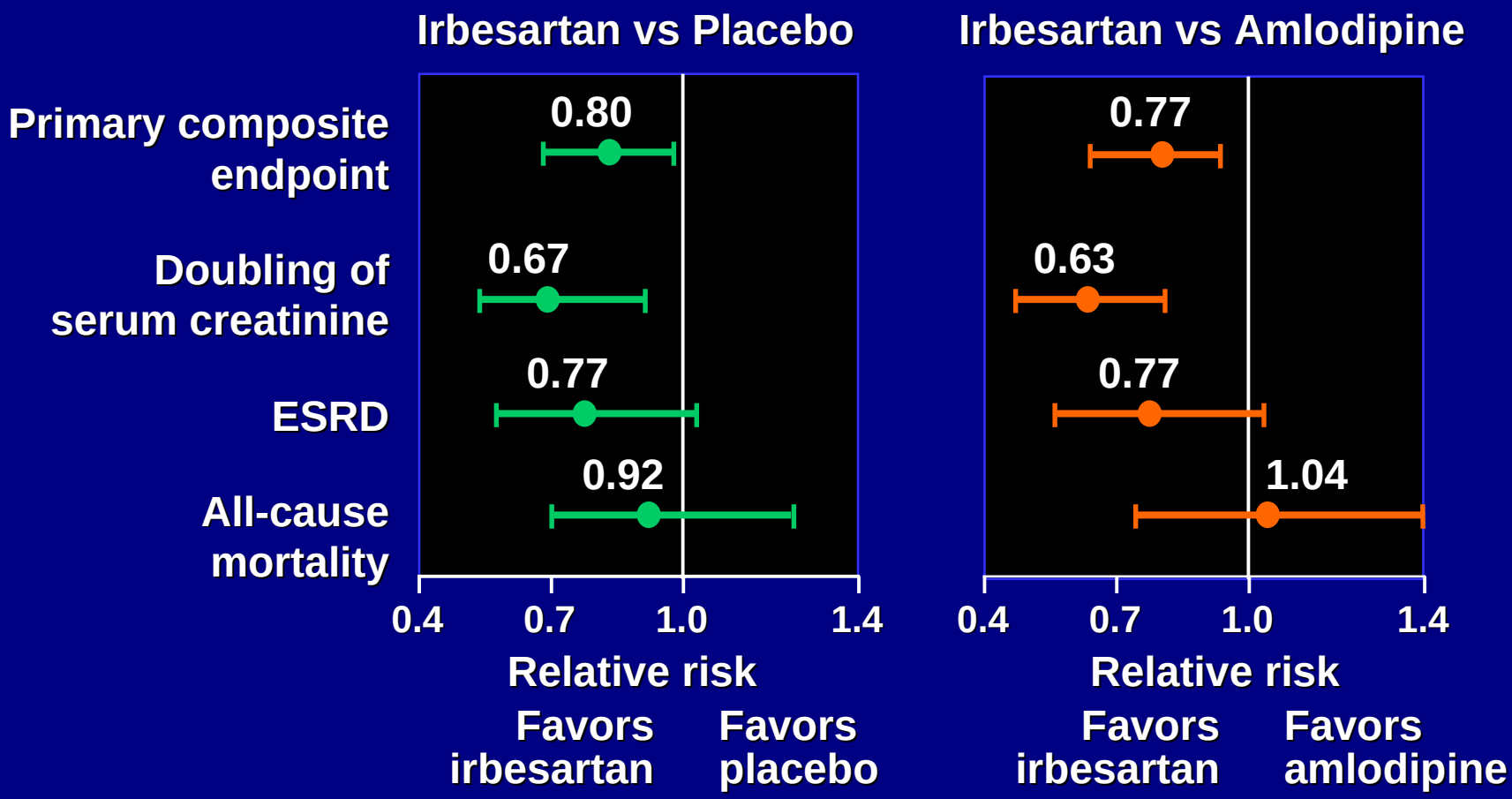
Dataset: 377 Randomized Subjects

IDNT: Dialysis or Transplantation

Endpoint	Number (%) of Subjects		
	Serum Creatinine Doubled* N = 322	Serum Creatinine ≥ 6.0 mg/dL N = 71	No Serum Creatinine Event N = 1,322
Dialysis or Transplantation	133 (41.3)	59 (83.1)	69 (5.2)

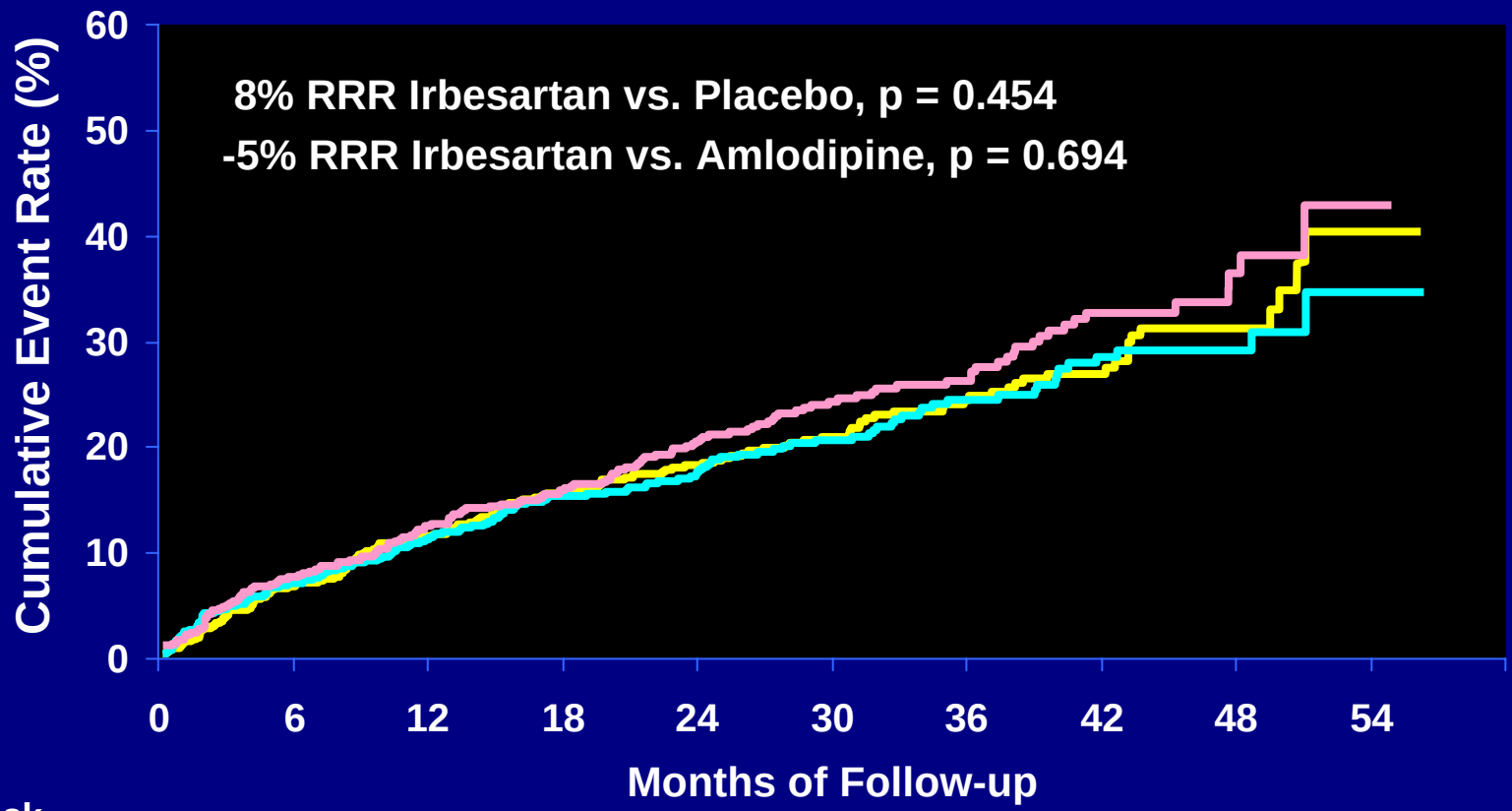
* Excludes 55 subjects who also had serum creatinine ≥ 6.0 mg/dL on same day

IDNT: Primary Endpoint Analysis – Composite and Components*



* Total incidence counts all occurrence of each individual components event.

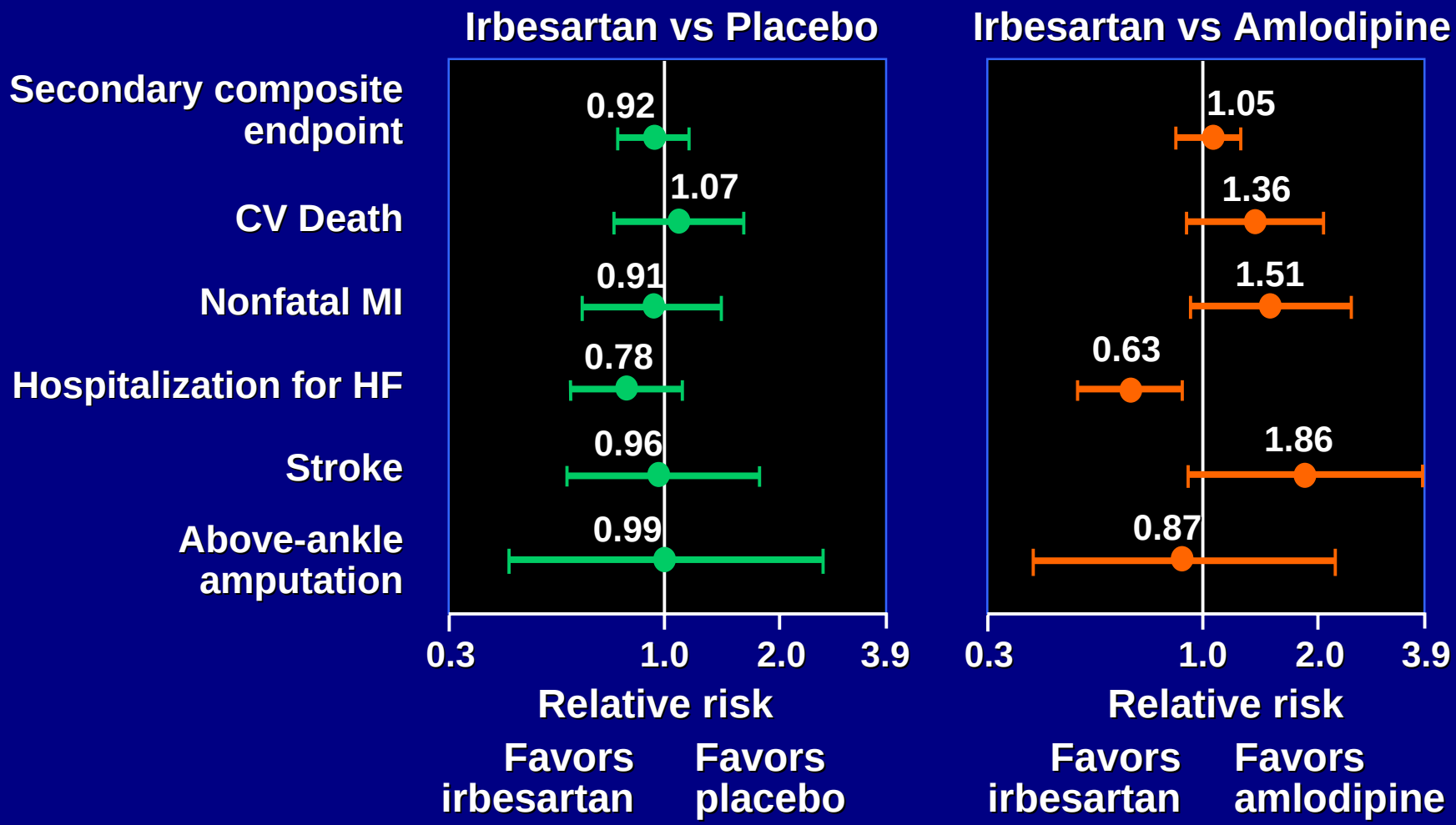
IDNT: Secondary Endpoint – Time to Composite of CV Disease



No. at Risk

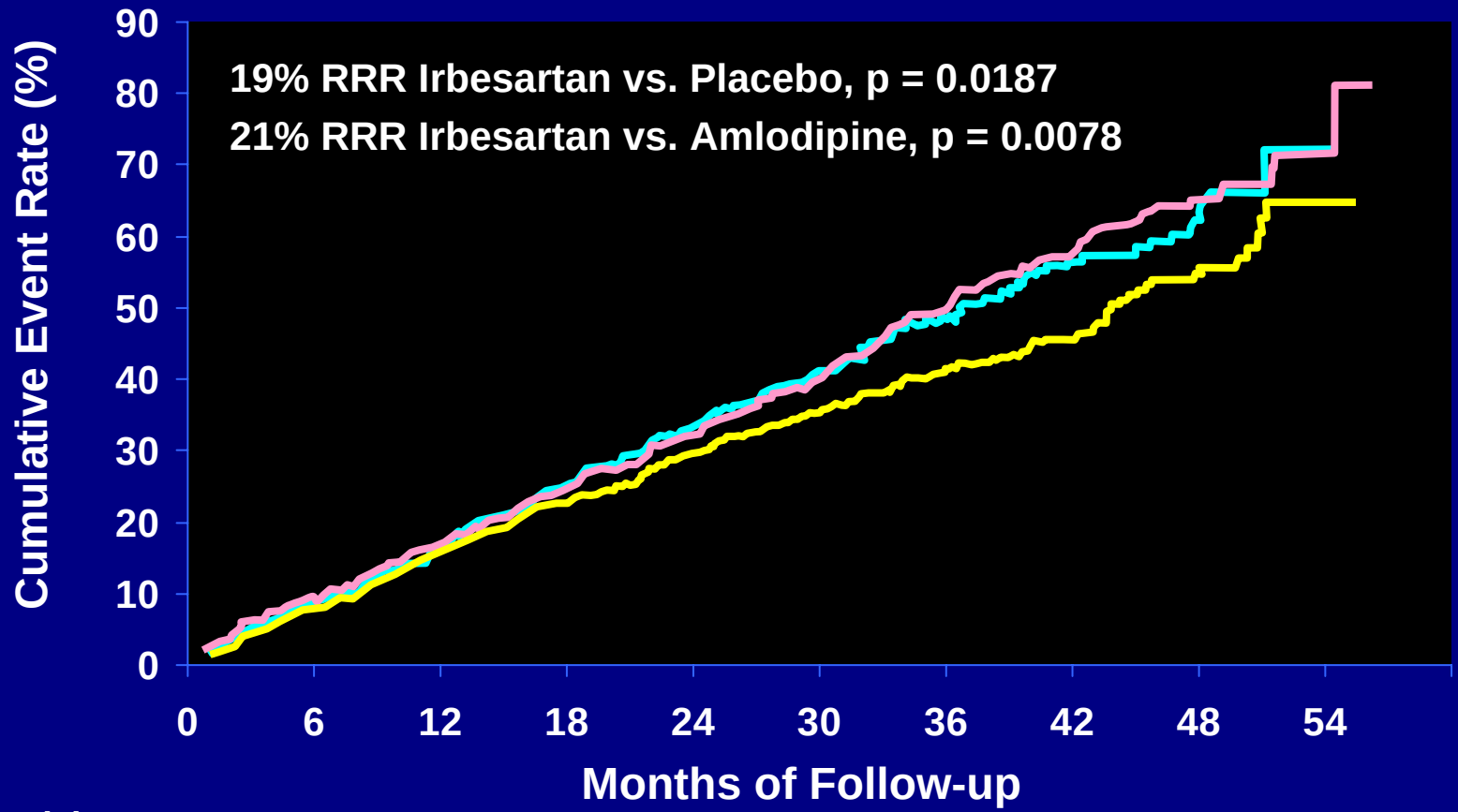
Placebo	569	519	477	433	365	264	175	113	49	2
Irbesartan	579	529	486	449	378	286	198	137	63	4
Amlodipine	567	515	476	434	368	268	186	126	47	7

IDNT: Secondary Endpoint Analysis – Composite and Components*



* Total incidence counts all occurrences of each individual component event.

IDNT: Combined Primary and Secondary Composite Endpoints



No. at Risk

Placebo	569	520	470	416	346	245	159	96	40	2
Irbesartan	579	528	482	437	355	265	183	125	51	2
Amlodipine	567	513	470	423	349	247	159	104	39	6

IDNT: Safety Profile

	Number (%) of Subjects		
	Placebo N = 563	Irbesartan N = 577	Amlodipine N = 559
Adverse Events (AEs)	524 (93.1)	540 (93.6)	526 (94.1)
Serious Adverse Events (SAEs)	363 (64.5)	358 (62.0)	361 (64.6)
Discontinuations due to an AE	36 (6.4)	43 (7.5)	44 (7.9)
Deaths	90 (16.0)	86 (14.9)	79 (14.1)

IDNT: Adverse Events of Special Interest Resulting in Discontinuation of Study Drug

	Number (%) of Subjects		
	Placebo N = 563	Irbesartan N = 577	Amlodipine N = 559
Hyperkalemia	2 (0.4)	12 (2.1)	3 (0.5)
Inability to Control Blood Pressure	17 (3.0)	9 (1.6)	3 (0.5)
Edema	7 (1.2)	4 (0.7)	14 (2.5)
Orthostatic Symptoms*	3 (0.5)	3 (0.5)	3 (0.5)
Early Rise in Serum Creatinine	1 (0.2)	0 (0.0)	0 (0.0)

*Includes dizziness, orthostatic dizziness and orthostatic hypotension

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Summary

- Irbesartan reduced the risk for progression of advanced diabetic nephropathy
  - 20% reduction in the primary endpoint compared with placebo
  - 23% reduction in primary endpoint compared with amlodipine
- Benefits of irbesartan were in addition to blood pressure reduction alone
- Irbesartan was generally safe and well tolerated

IRMA 2

IRbesartan MicroAlbuminuria in Type 2 Diabetic Subjects

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