V-HeFT I and V-HeFT II Trials—The Path to A-HeFT

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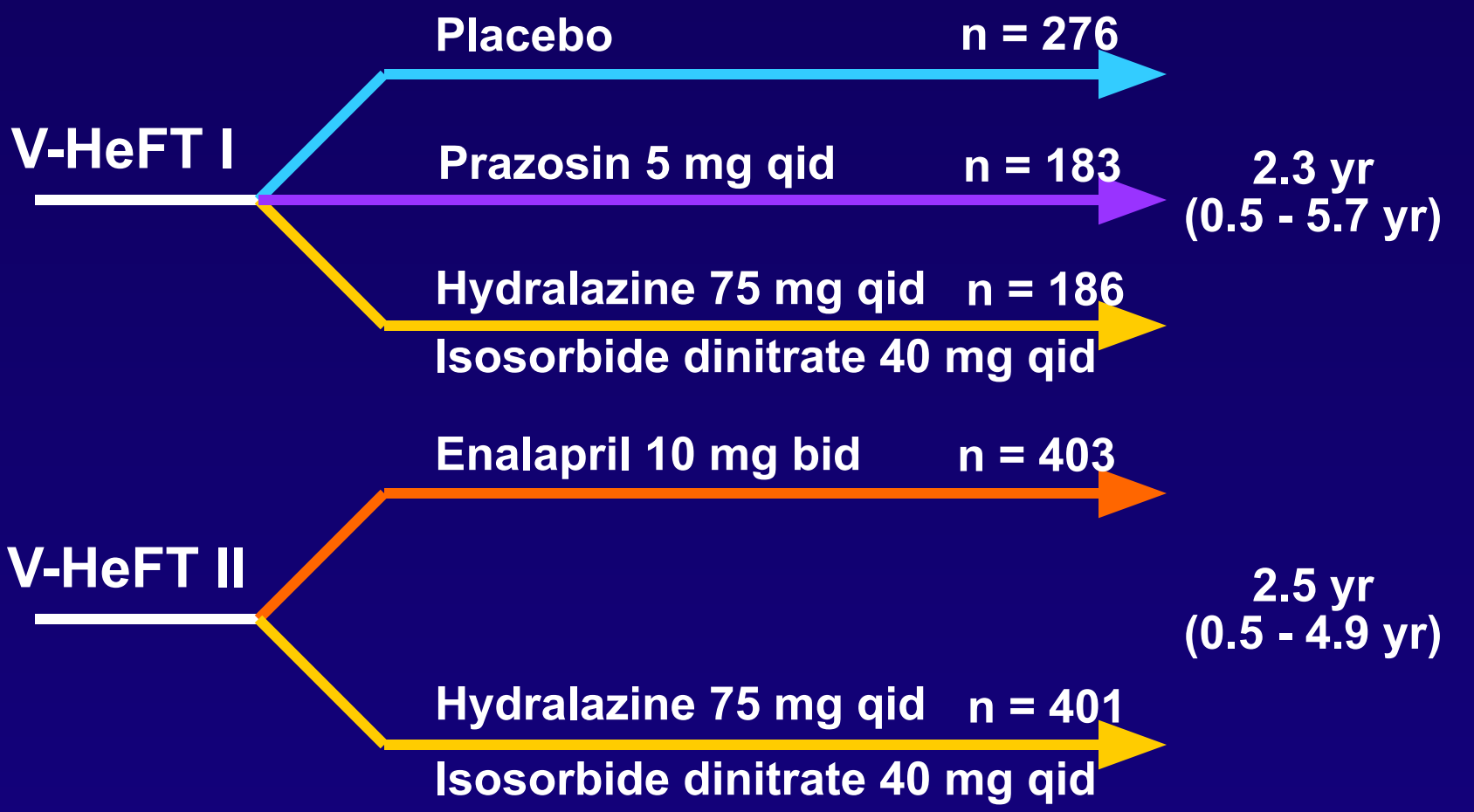
NITROMED

Major Entry Criteria
V-HeFT I and V-HeFT II

- **Inclusion criteria**
  - Men, 18 to 75 yr old
  - Heart failure ≥ 3 mo
  - Reduced exercise capacity (VO_2max < 25 mL/kg/min)
  - Symptomatic despite digitalis and diuretics
  - CT ratio > 0.55, LVEF < 0.45 or LVIDD > 2.7 cm/m^2
- **Exclusion criteria**
  - Hypertension requiring drugs other than diuretics
  - Angina requiring frequent or chronic nitrates
  - Use of beta-blockers or non-nitrate vasodilators
  - Myocardial infarction or cardiac surgery within 3 mo
  - Hypertrophic cardiomyopathy or significant valvular disease
  - Severe primary lung, liver, or kidney disease

Study Plan

V-HeFT I and V-HeFT II

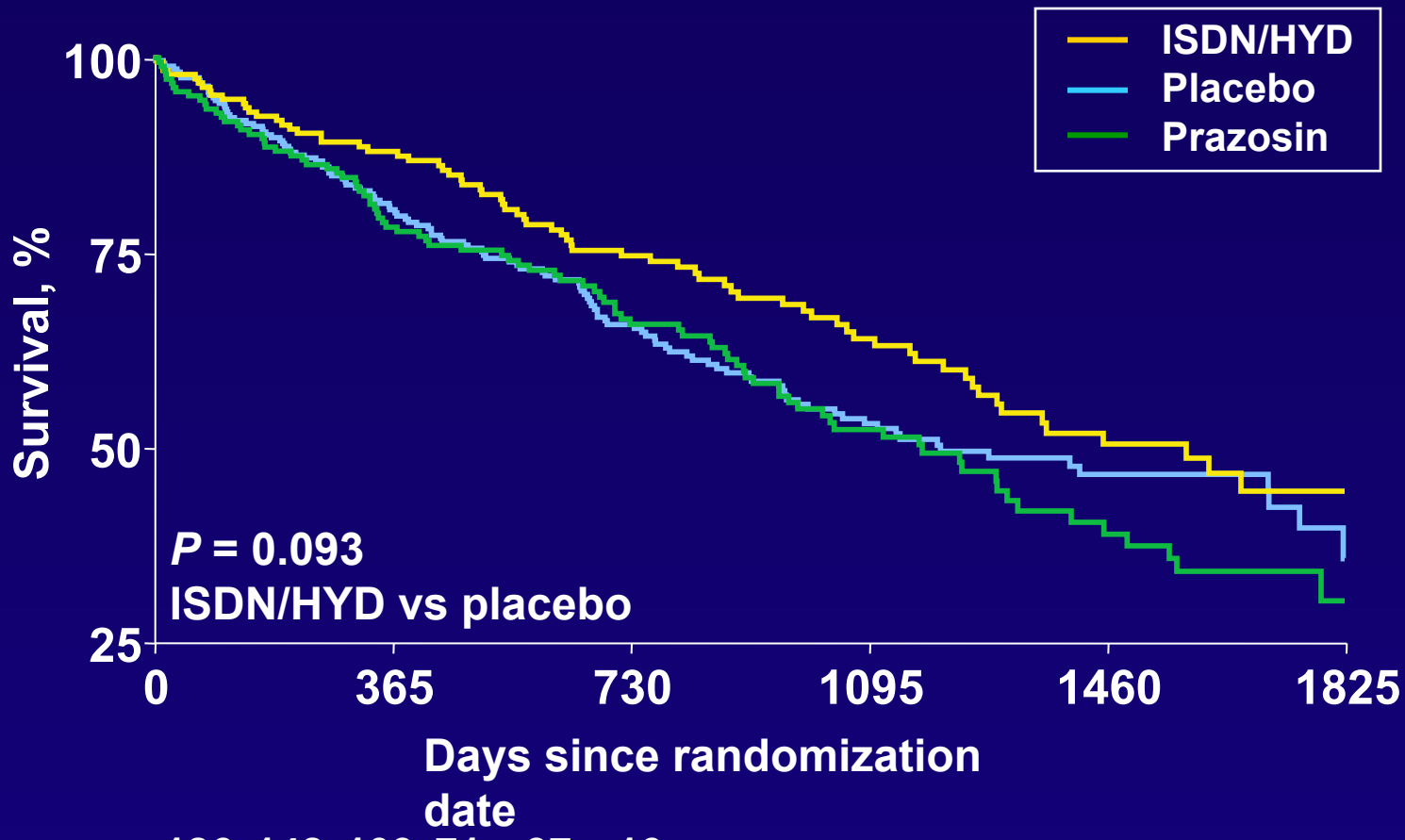


Study Endpoints
V-HeFT I and V-HeFT II

- Major endpoints
  - All-cause mortality during entire study
  - All-cause mortality at 2 yr
  - Number and duration of cardiovascular hospitalizations
  - Maximum oxygen consumption at peak exercise
  - Quality of life (V-HeFT II)

Survival in All Patients

V-HeFT I



date						
ISDN/HYD, n =	186	148	109	71	37	16
Placebo, n =	276	202	135	84	41	10
Prazosin, n =	183	135	94	58	27	7

Survival in All Patients

V-HeFT I

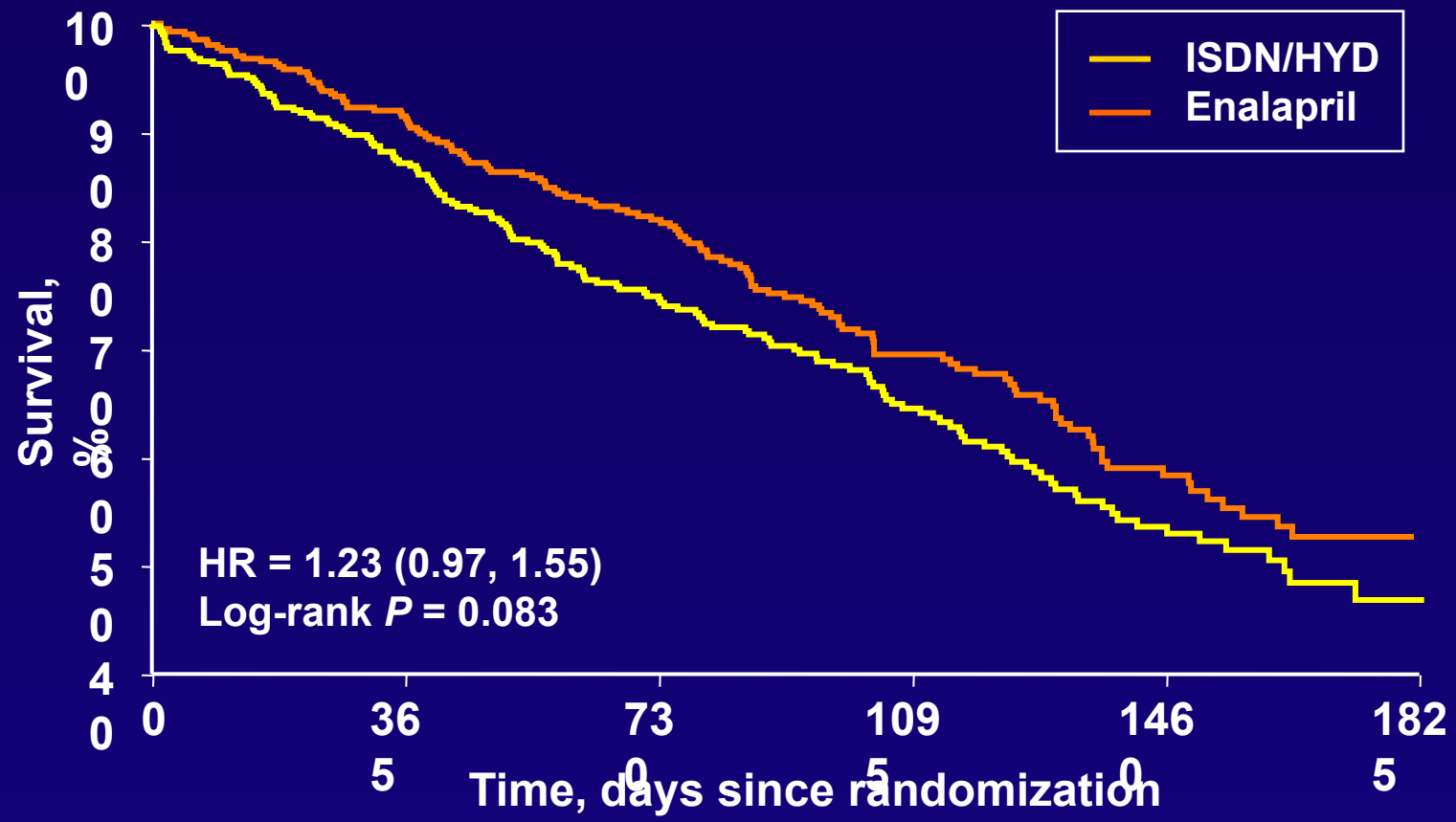
V-HeFT I, overall

Treatment	Placebo, n (%)	Drug, n (%)	Hazard ratio (95% CI)	Log-rank *P* value
ISDN/HYD	120 (44.0)	72 (38.7)	0.78 (0.58, 1.04)	0.093
Prazosin	120 (44.0)	91 (49.7)	1.11 (0.85, 1.46)	0.441

V-HeFT I, endpoint of 2 yr

Placebo, %	ISDN/HYD, %	*P* value
34.3	25.6	0.053

Survival in All Patients
V-HeFT II



ISDN/HYD,	n = 401	332	242	157	86	3
Enalapril,	n = 403	346	265	169	89	1

Survival in All Patients
V-HeFT II

V-HeFT II, overall

Enalapril n = 403	ISDN/HYD n = 401	Hazard ratio (95% CI)	Log-rank *P* value
132 (32.8%)	153 (38.2%)	1.23 (0.97, 1.55)	0.083

V-HeFT II, endpoint of 2 yr

Enalapril, %	ISDN/HYD, %	*P* value
18.0	25.0	0.016

Subgroup Analysis

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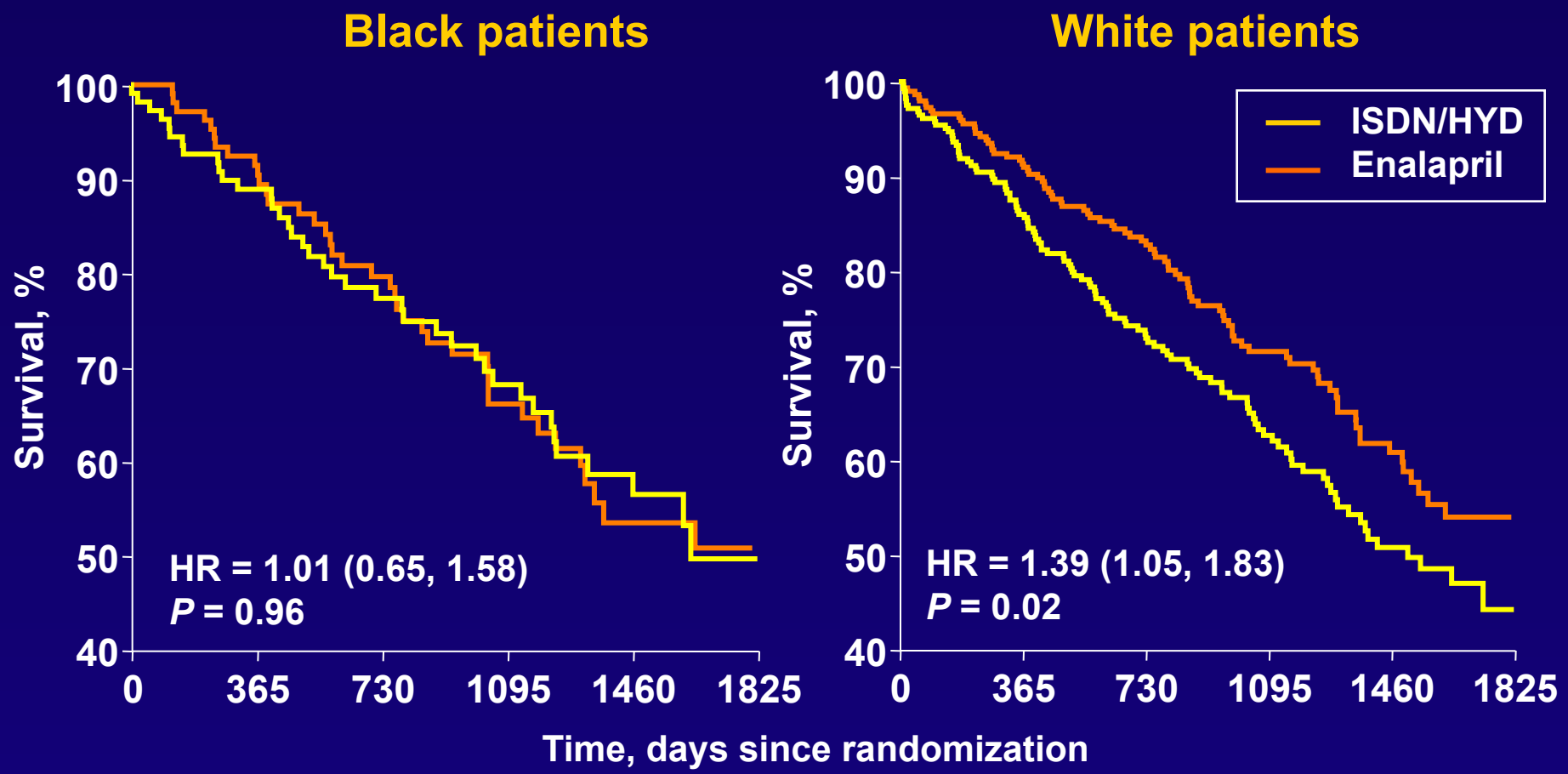
Survival in Black Patients and White Patients

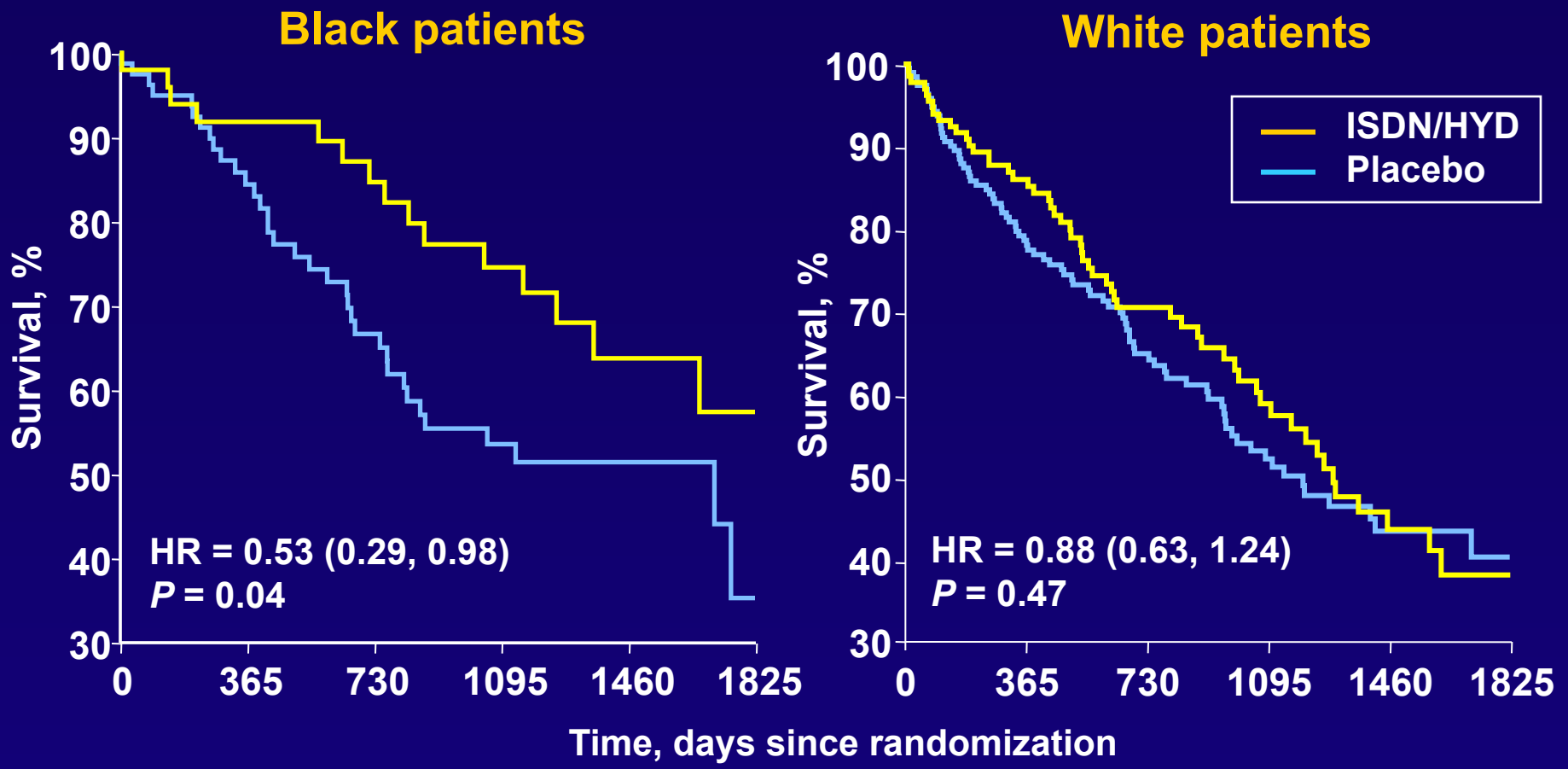
V-HeFT II



Patients, n												
ISDN/HYD	109	92	67	49	29	1	282	231	171	105	55	1
Enalapril	106	93	69	47	24	2	292	251	194	123	66	1

Survival in Black Patients and White Patients

V-HeFT I



Patients, n												
ISDN/HYD	49	43	36	28	16	8	132	102	71	42	22	9
Placebo	79	61	44	29	14	3	192	140	91	55	27	8

V-HeFT I—Conclusions (1)

- ISDN/HYD compared to placebo was associated with
  - A 22% lower risk of death overall ($P = 0.09$)
  - A 12% lower risk of death in white patients ($P = 0.47$)
  - A 47% lower risk of death in black patients ($P = 0.04$)

V-HeFT II—Conclusions (2)

- Enalapril compared to ISDN/HYD was associated with
  - A 23% lower mortality overall ($P = 0.08$)
  - A 39% lower mortality in white patients ($P = 0.02$)
  - No difference in mortality in blacks

From V-HeFT I and V-HeFT II to A-HeFT

- Based on V-HeFT I and V-HeFT II, a clinical study was needed to confirm the hypothesis that the ISDN/HYD combination benefits outcomes in black HF patients
- A-HeFT was designed as a prospective, placebo-controlled study with the objective of testing BiDil's effects on survival, heart failure hospitalizations, and quality of life in patients receiving contemporary therapy for heart failure