Management of patients with cirrhosis and ascites

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Dall'epatite cronica alla cirrrosi epatica e le sue complicanze
Gorizia , 2 Febbraio 2006

MANAGEMENT OF PATIENTS WITH CIRRHOSIS

Survival in cirrhotic patients according to the presence of ascites

Author	1 year	2 years	5 years
NO ASCITES			
Gines P. (1987)	96 %	68 %	47 %
Fattovich (1997)	100 %	91 %	79 %
ASCITES			
Llach G. (1988)	56 %	49 %	25 %
Salerno F. (1993)	78 %	63 %	38 %
Gines P. (1996)	59 %	46 %	29 %
Angeli P. (1996)	68 %	58 %	38 %

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MANAGEMENT OF PATIENTS WITH CIRRHOSIS

FUNCTIONAL RENAL ABNORMALITIES IN CIRRHOSIS

Abnormality	Clinical consequence
• Sodium retention	• Ascites and edema
• Water retention	• Dilutional hyponatremia
• Renal vasoconstriction	• Hepatorenal syndrome

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Circulatory dysfunction in cirrhosis with ascites

Portal hypertension/liver failure

↓ Increased release of NO, CO and other vasodilators

Splanchnic arterial vasodilation

↓

Reduction of circulating volume

↓

Activation of systemic endogenous vasocontrictors

↓

Renal functional abnormalities

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Possible clinical scenario

- Uncomplicated ascites

- Complicated ascites

- Refractory ascites
- Hyponatremia
- Spontaneous bacterial peritonitis
- Hepatorenal syndrome

K. Moore et al. Hepatology 2003 ; 38 : 258-266.

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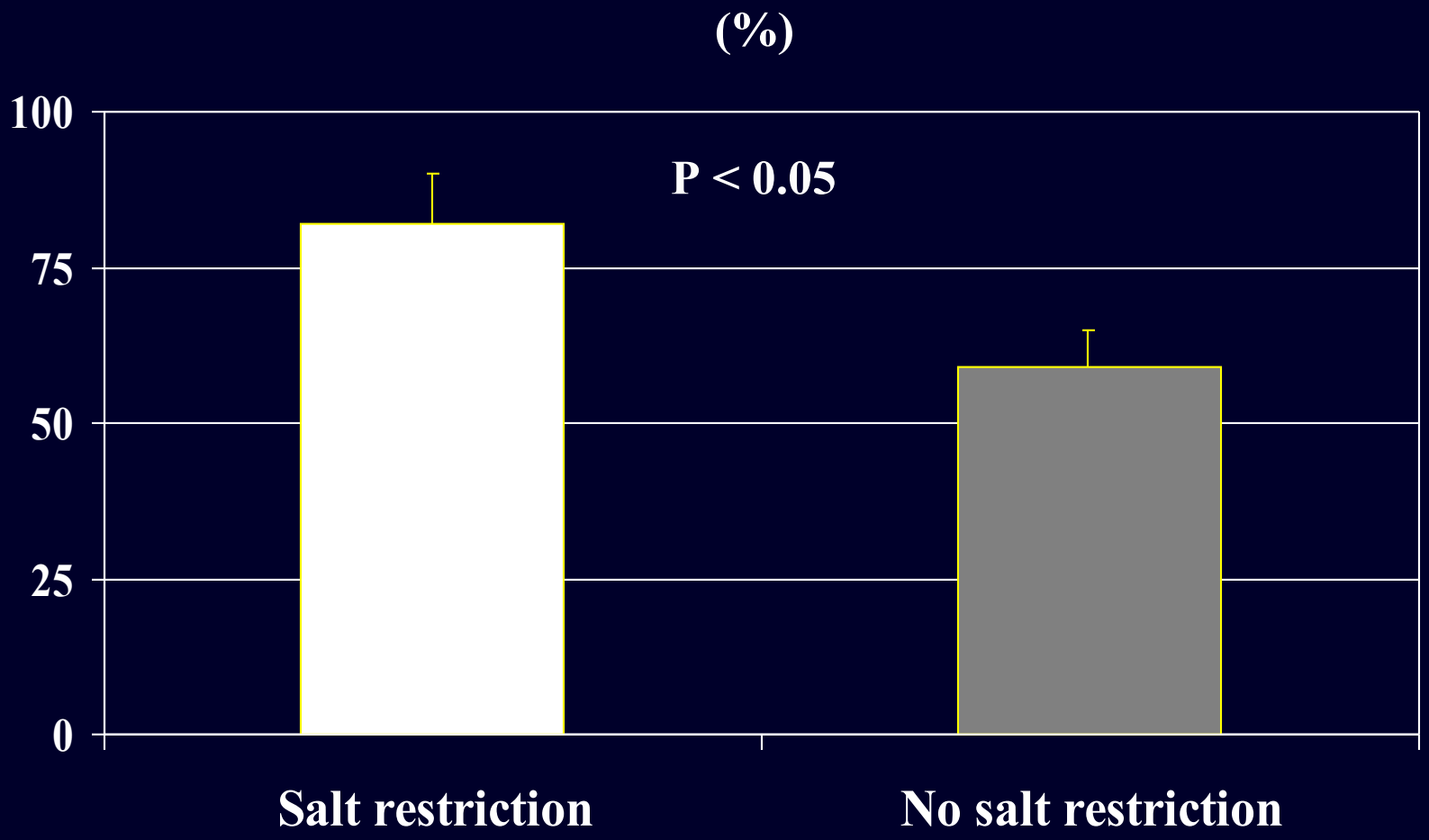
Treatment of uncomplicated ascites

GRADE OF ASCITES	TYPE OF TREATMENT
• Grade 1 or minimal ascite	• No treatment
• Grade 2 or moderate ascites	• Sodium resctriction and diuretics
• Grade 3 or massive ascites	• Paracentesis, sodium resctriction and diuretics

K. Moore, et al. Hepatology 2003 ; 38 : 258-266.

Effects of different sodium intakes on the response to high dose of spironolactone



A. Gauthier, et al. Gut 1986 ; 27 : 705-709.

Effects of different sodium intakes on the response to diuretics

	40 mmol/day	120 mmol/day
No diuretics	9.7 %	7.5 %
Response to potassium canrenoate (200 mg/day)	40,4 %	41,5 %
Response to potassium canrenoate (400 or 600 mg/day)	25,8 %	30,2 %
Response to potassium canrenoate (400 mg/day) plus furosemide (up to 100 mg/day)	17,7 %	13,2 %
No response to diuretics	4,8 %	5,7 %

M. Bernardi, et al. Liver 1993 ; 13 : 156-162.

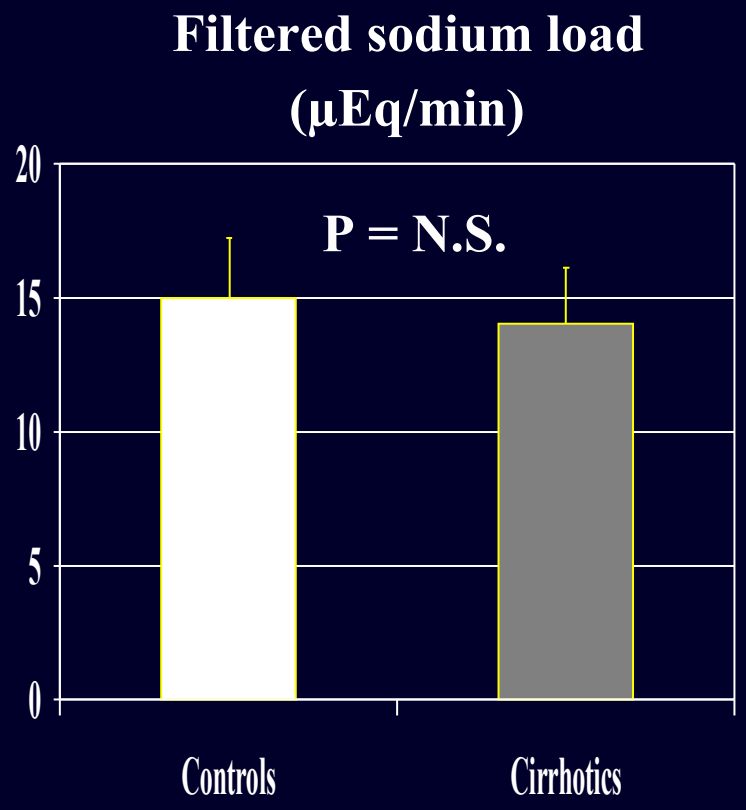
MANAGEMENT OF PATIENTS WITH CIRRHOSIS

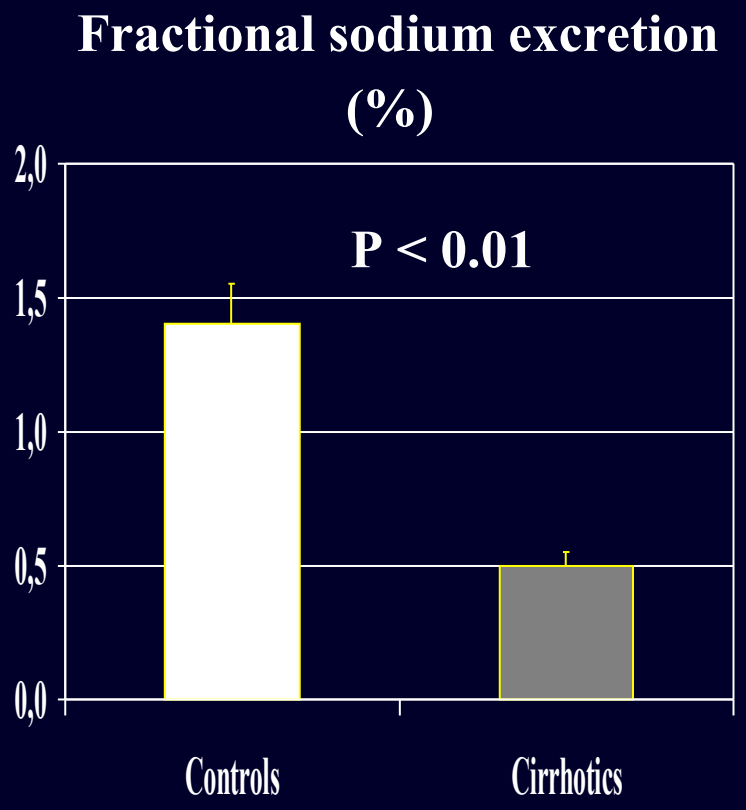
Dietary sodium restriction

- ✓ Dietary sodium intake should be moderately restricted to 90 mmol/day.
- ✓ There is no indication for a more severe salt restriction.
- ✓ The use of salt substitutes that contain potassium is contraindicated.
- ✓ There is no indication for the prophylactic use of salt resctriction in patients who have never had ascites.

K. Moore, et al. Hepatology 2003 ; 38 : 258-266.

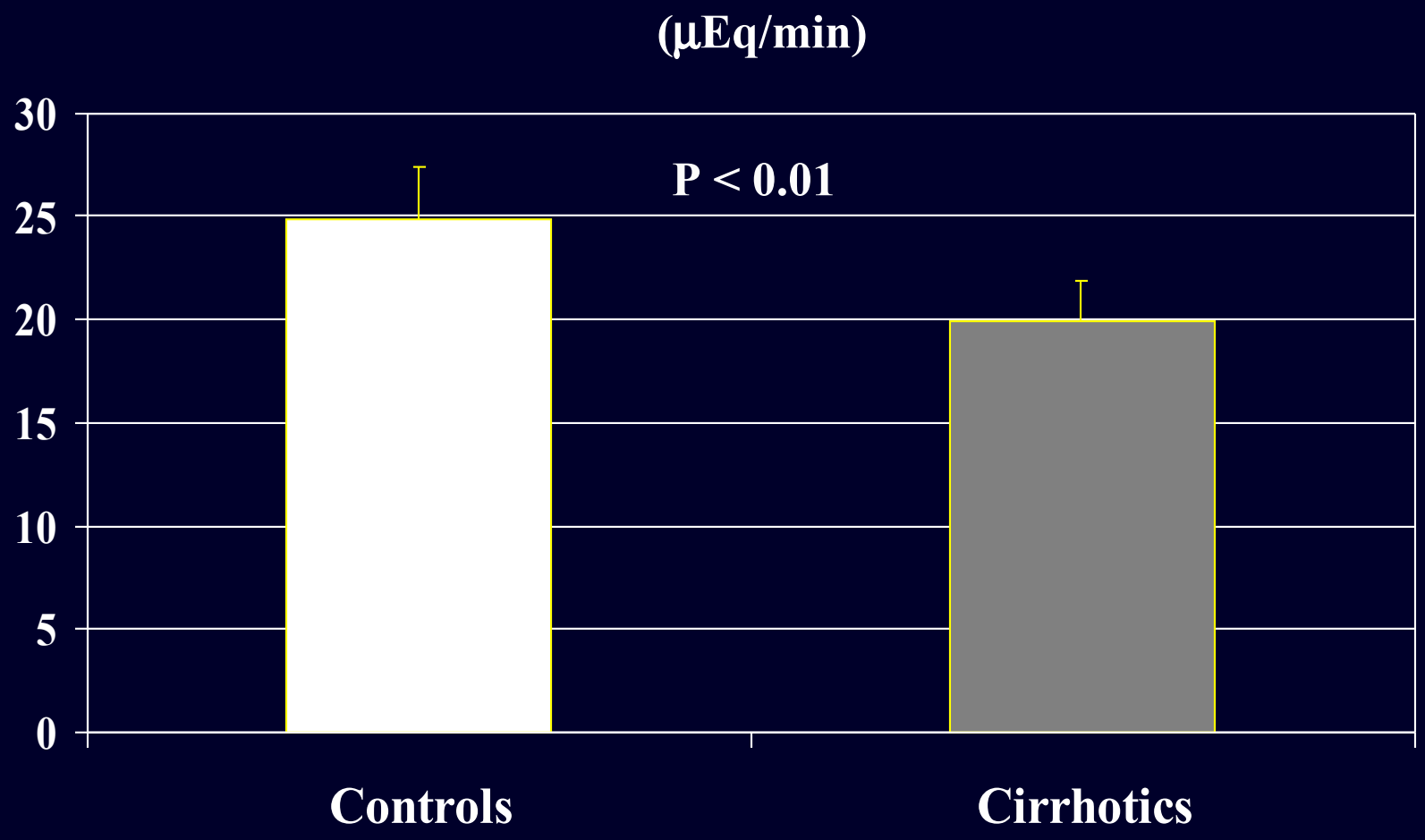
Pathophysiological mechanisms of renal sodium retention in cirrhosis





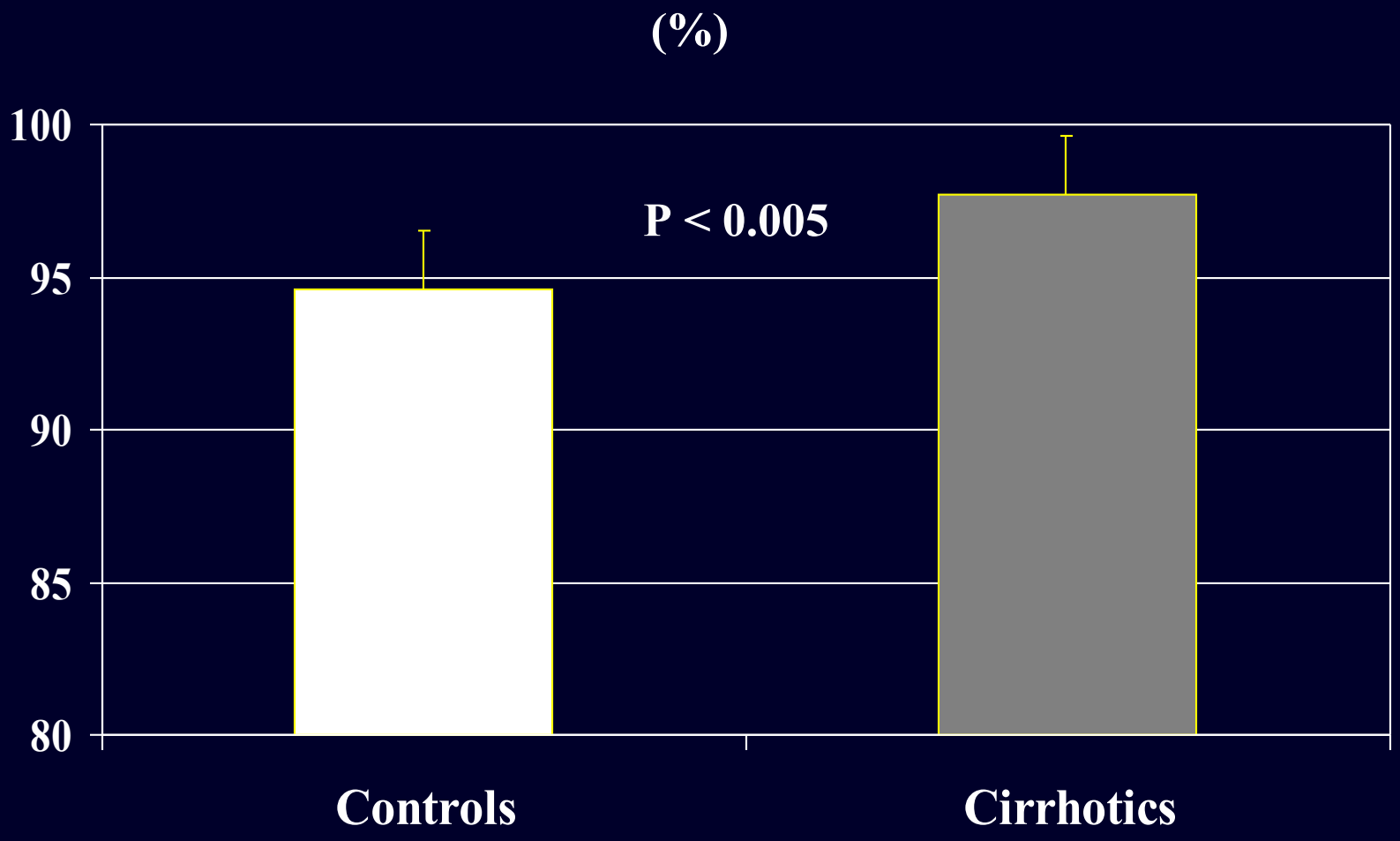
A. Gatta, et al. Hepatology 1991 ; 14 : 231-236.

Delivery of sodium to the distal tubule



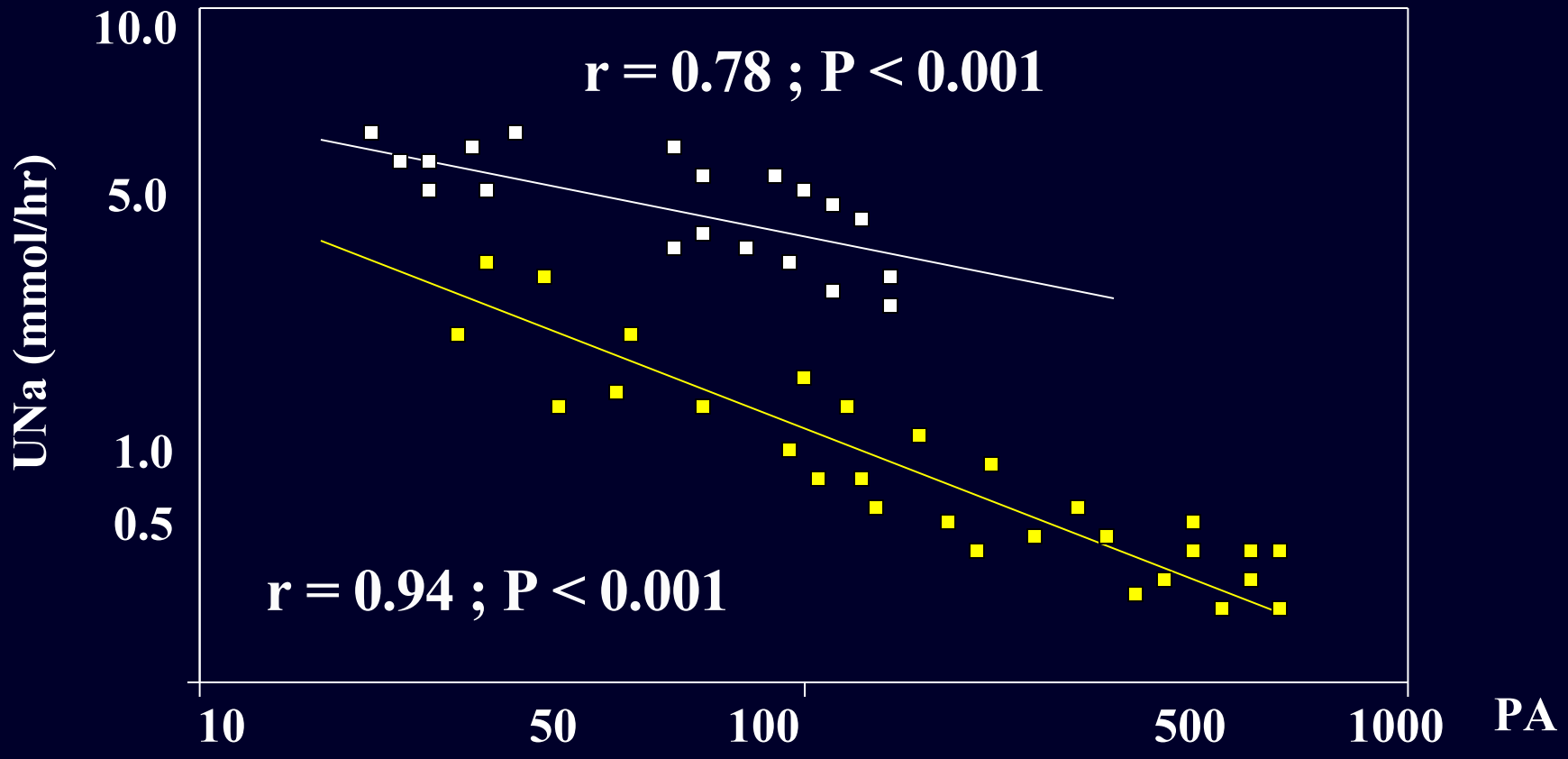
P. Angeli, et al. Eur. J. Clin. Invest. 1990 ; 20 : 111-117.

Fractional distal sodium reabsorption



P. Angeli, et al. Eur. J. Clin. Invest. 1990 ; 20 : 111-117.

Correlation between aldosteronemia (PA) and hourly urinary sodium excretion (UNa)



M. Bernardi, et al. Gut 1983 ; 24 : 761-766.

MANAGEMENT OF PATIENTS WITH CIRRHOSIS

Protocol design

Furosemide 80 mg/day

↓

Furosemide 160 mg/day

↓

Cross over to spironolactone in non responders

Spironolactone 150 mg/day

↓

Spironolactone 300 mg/day

↓

Cross over to furosemide in non responders

R.M. Perez-Ayuso, et al. Gastroenterology 1983 ; 84 : 961-968.

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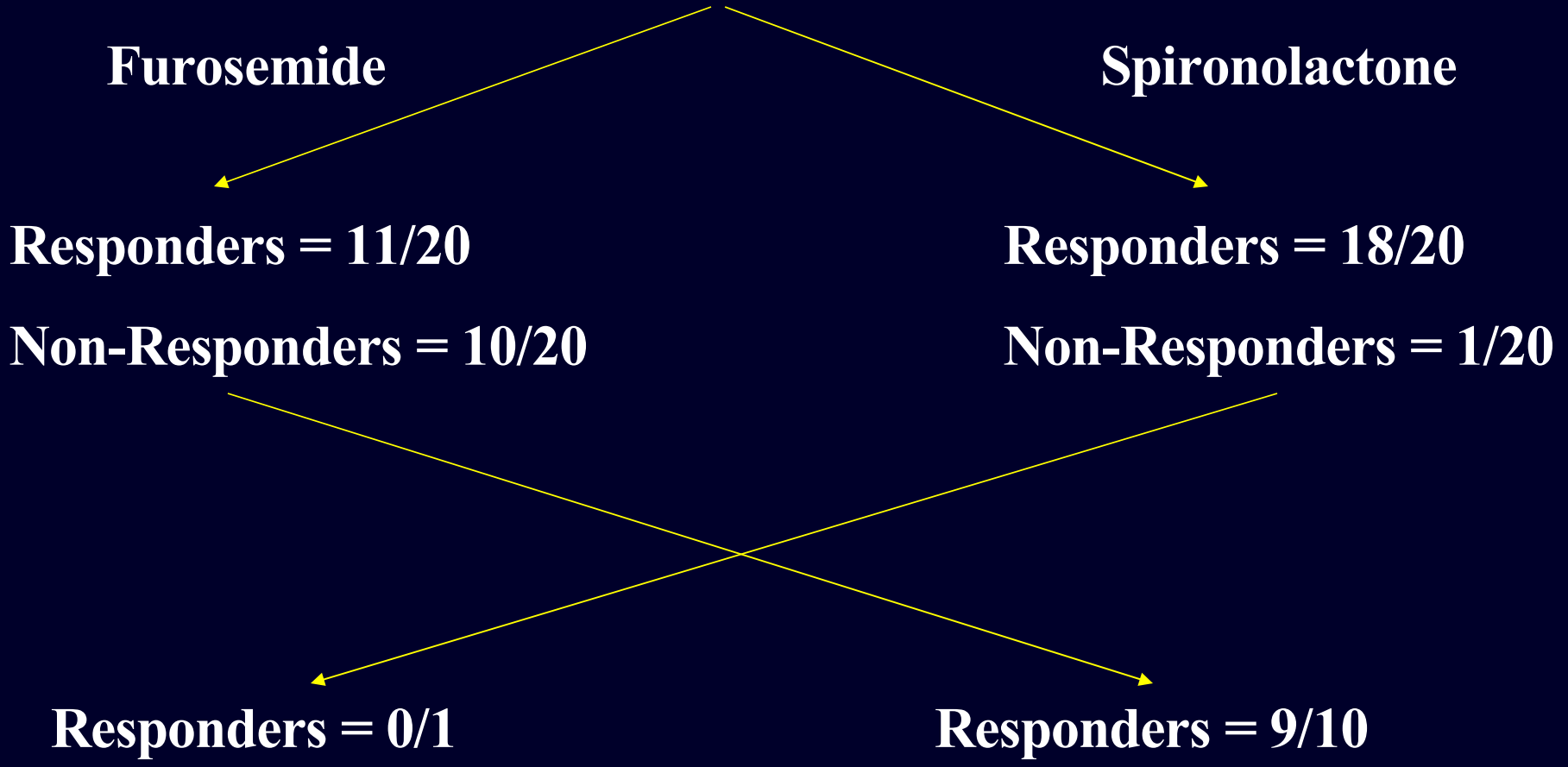
Enrolled patients n = 40



R.M. Perez-Ayuso, et al. Gastroenterology 1983 ; 84 : 961-968.

MANAGEMENT OF PATIENTS WITH CIRRHOSIS

Protocol design

Amiloride 20 mg/day

↓

Amiloride 40 mg/day

↓

Amiloride 60 mg/day

↓

Cross over to potassium canrenoate in non responders

Potassium canrenoate 150 mg/day

↓

Potassium canrenoate 300 mg/day

↓

Potassium canrenoate 500 mg/day

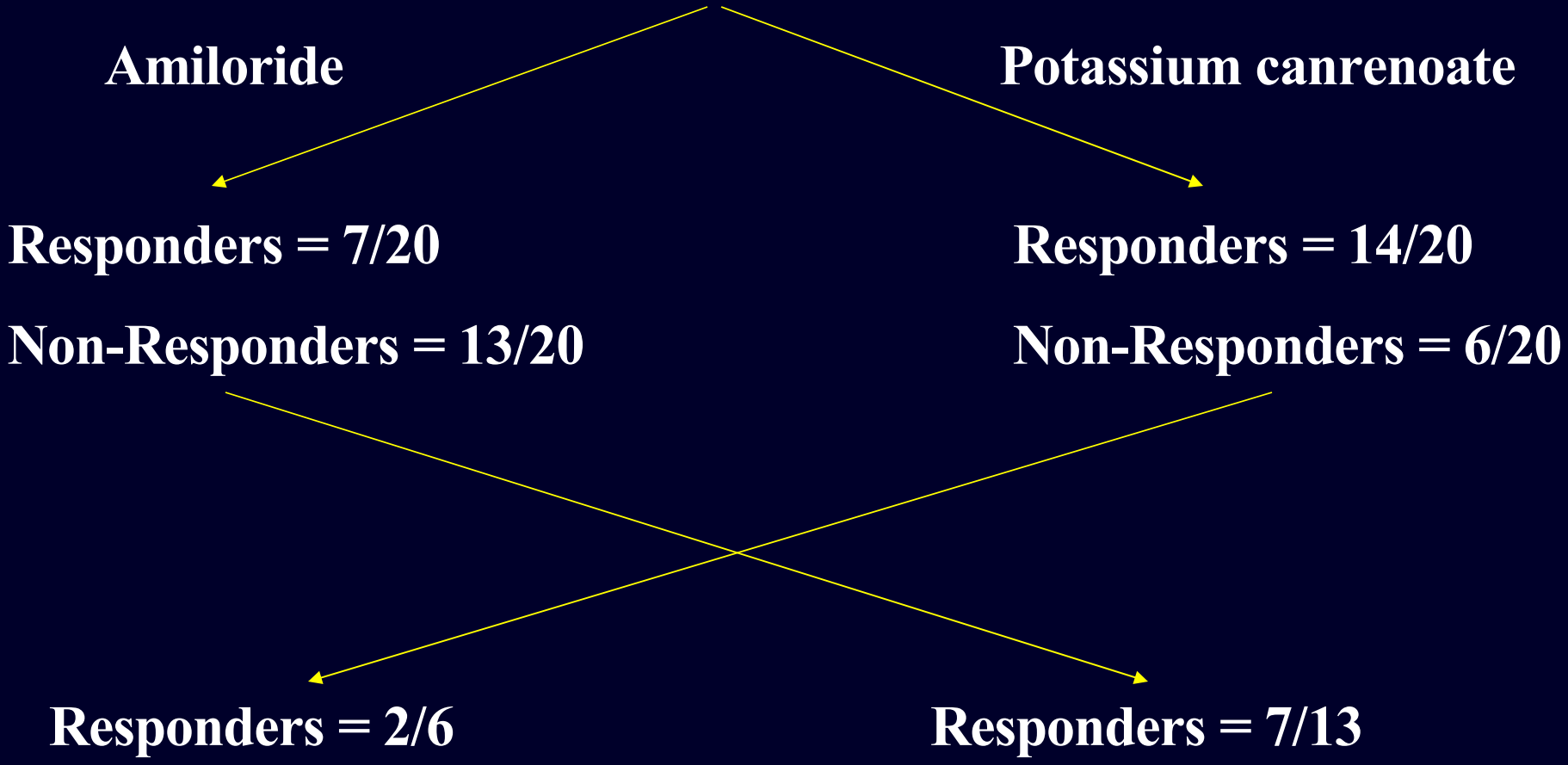
↓

Cross over to amiloride in non responders

P. Angeli, et al. Hepatology 1994 ; 19 : 72-79.

MANAGEMENT OF PATIENTS WITH CIRRHOSIS

Enrolled patients n = 40



P. Angeli, et al. Hepatology 1994 ; 19 : 72-79.

Diuretics (1)

- ✓ **The core diuretic should be an aldosterone antagonist and this should be given once *per* day with food.**
- ✓ **The aldosterone antagonist should be given at the initial dose of 100-200 mg/day. The diuretic dosage should be increased stepwise to a maximum of 400 mg/day in case of insufficient response.**
- ✓ **Other potassium sparing diuretic (amiloride) are indicated only in those patients with adverse effects due to the aldosterone antagonist.**

K. Moore, et al. Hepatology 2003 ; 38 : 258-266.

Diuretics (2)

- ✓ In clinical trials a loop diuretic was added (furosemide 20-40 mg/day) once a patient fails to respond to the aldosterone antagonist (sequential diuretic therapy).
- ✓ The initial dose of furosemide may be increased in a stepwise manner to a maximum of 160 mg/day.

K. Moore, et al. Hepatology 2003 ; 38 : 258-266.

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Enroled patients n = 51

Patients with spontaneous diuresis n = 6 (12%)

Patients that required diuretic therapy = 45 (88%)

Responders to spironolactone = 55 (56 %)

Responders to spironolactone and furosemide= 18 (40 %)

Patients with refractory ascites = 2 (4 %)

A. Gatta, et al. Hepatology 1991 ; 14 : 231-236.

MANAGEMENT OF PATIENTS WITH CIRRHOSIS

Open question

- ✓ **Should we go on with sequential diuretic treatment or introduce combined diuretic treatment (aldosterone antagonist and loop diuretic) from the beginning ?**

Comparison between spironolactone alone and spironolactone plus furosemide

Spironolactone 100-200 mg/day

↓ 4 days

Spironolactone 200-300 mg/day

↓ 4 days

Spironolactone 400 mg/day

↓ 4 days

Spironolactone 400 mg/day plus increasing doses of furosemide up to 160 mg/day

Spironolactone 100-200 mg/day plus furosemide 40-80 mg/day

↓ 4 days

Spironolactone 200-300 mg/day plus furosemide 80-120 mg/day

↓ 4 days

Spironolactone 400 mg/day plus furosemide 120-160 mg/day

J. Santos, et al. J. Hepatol. 2003 ; 39 : 187-192.

MANAGEMENT OF PATIENTS WITH CIRRHOSIS

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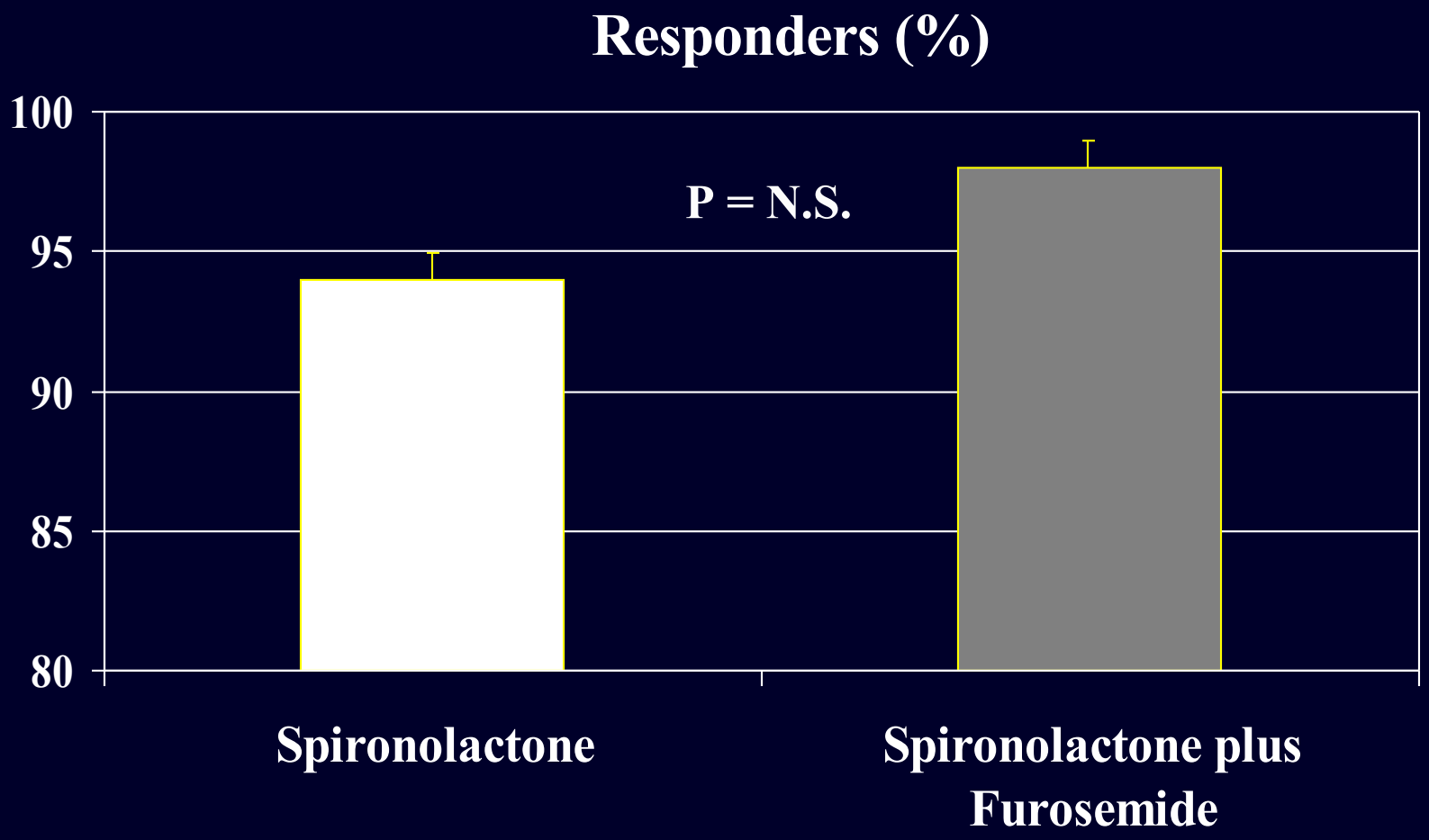

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MANAGEMENT OF PATIENTS WITH CIRRHOSIS

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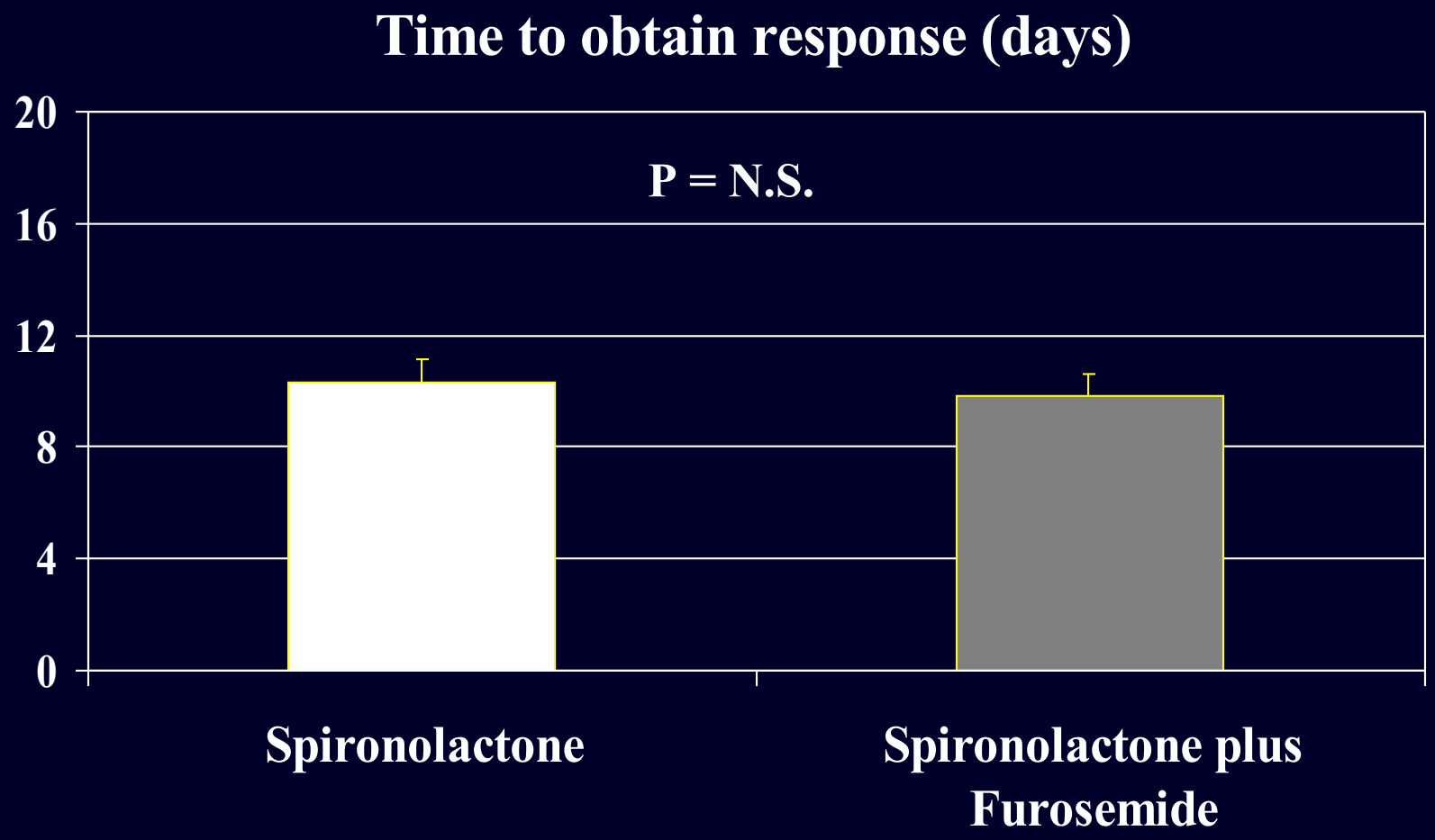

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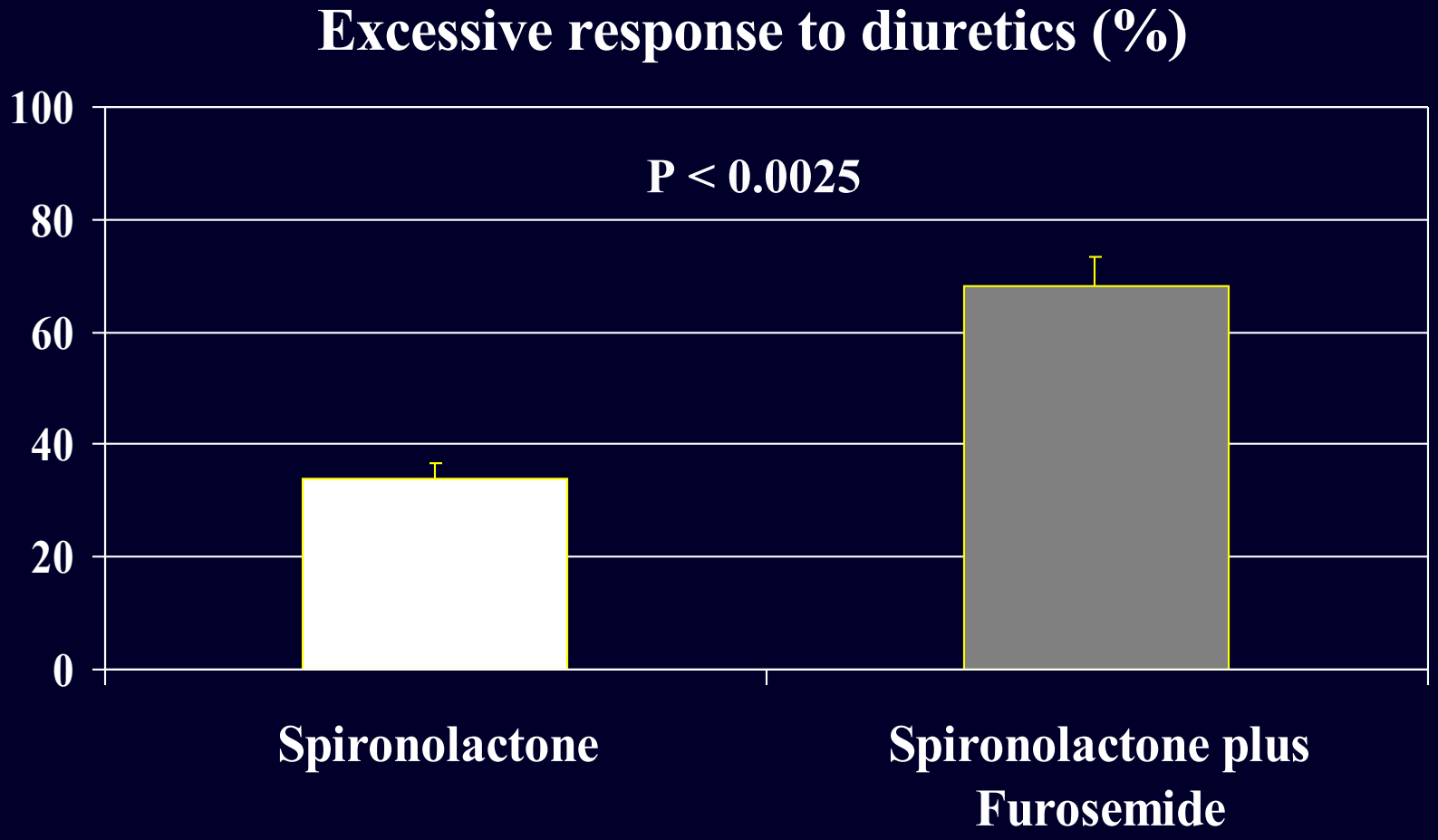


J. Santos, et al. J. Hepatol. 2003 ; 39 : 187-192.

Comparison between sequential versus combined diuretic treatment

Potassium canrenoate 200 mg/day

↓ 4 days

Potassium canrenoate 400 mg/day

↓ 4 days

Potassium canrenoate 400 mg/day plus furosemide 50/day

↓ 4 days

Potassium canrenoate 400 mg/day plus furosemide 100 mg/day

↓ 4 days

Potassium canrenoate 200 mg/day plus furosemide 50 mg/day

↓ 4 days

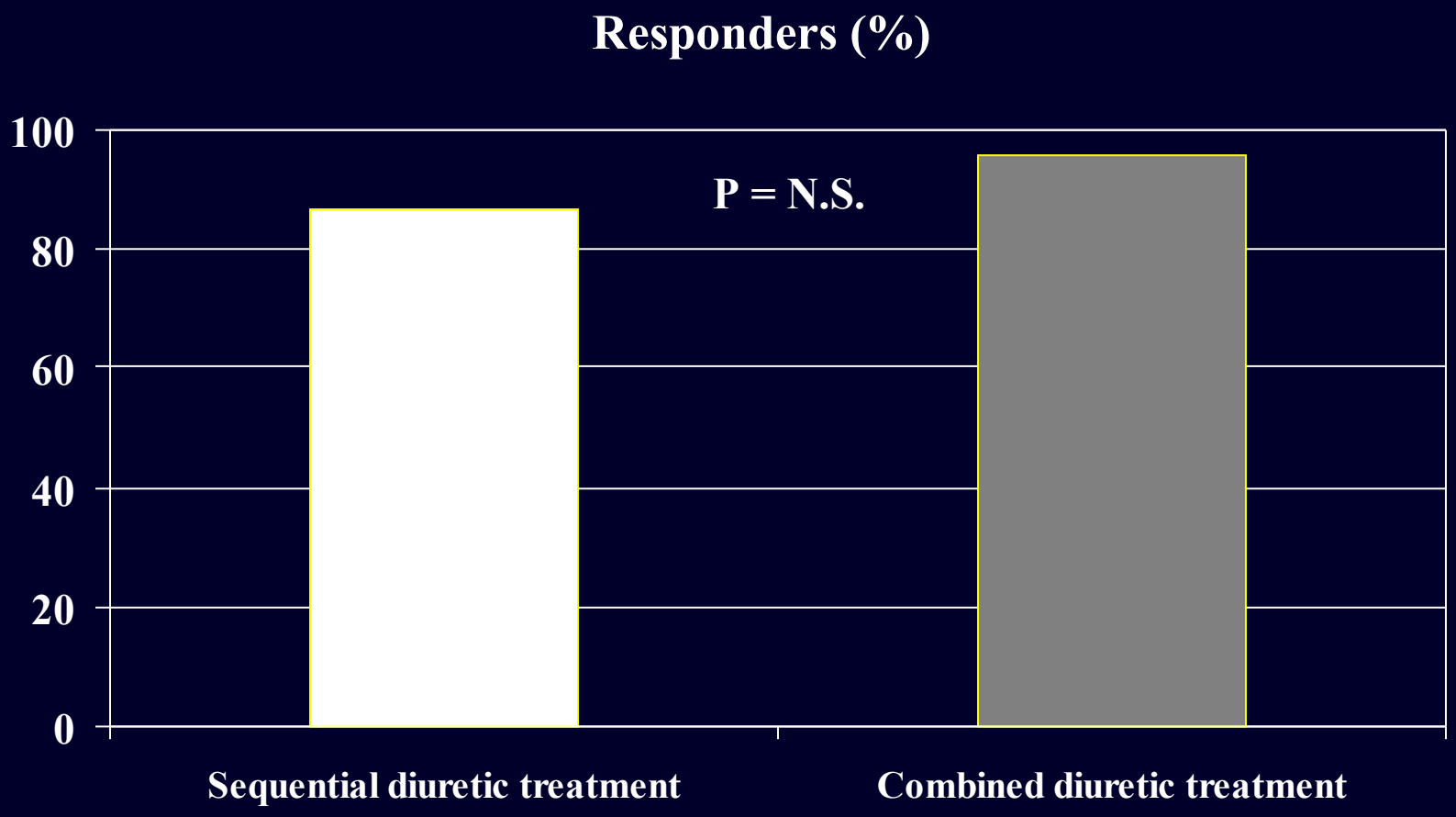
Potassium canrenoate 400 mg/day plus furosemide 100 mg/day

↓ 4 days

Potassium canrenoate 400 mg/day plus furosemide 150 mg/day

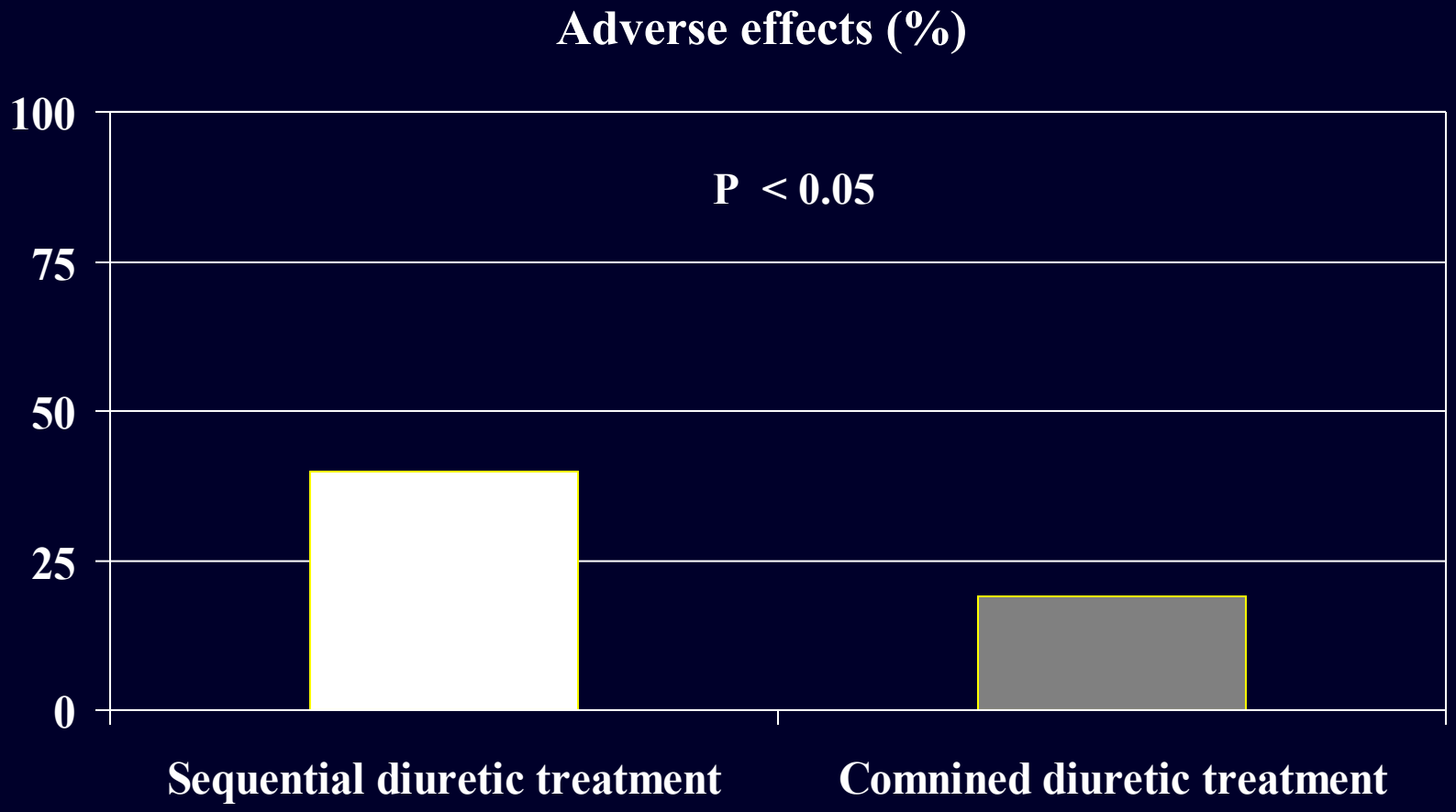
P. Angeli et al. AASLD 2005

Comparison between sequential versus combined diuretic treatment



P. Angeli et al. AASLD 2005

Comparison between sequential versus combined diuretic treatment



P. Angeli et al. AASLD 2005

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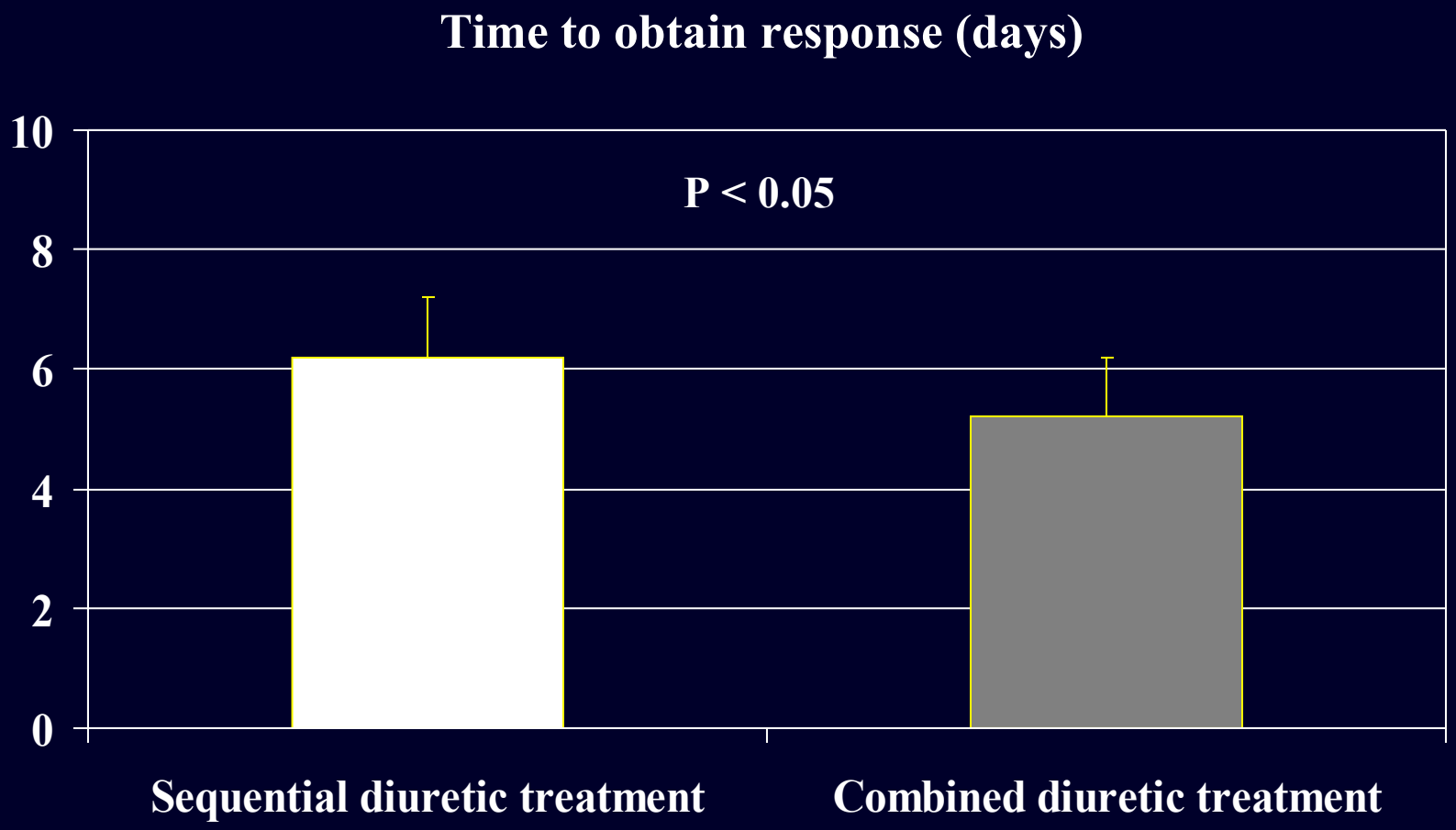
Comparison between sequential versus combined diuretic treatment

Types of adverse effects

	Sequential diuretic treatment (n = 49)	Combined diuretic treatment (n = 47)	*P*
Iperkaliemia	9	3	< 0.05
Ipokaliemia	1	0	N.S.
Iponatremia	6	2	N.S.
Insufficienza renale	6	7	N.S.
Encefalopatia	4	1	N.S.

P. Angeli et al. AASLD 2005

Comparison between sequential versus combined diuretic treatment



P. Angeli et al. AASLD 2005

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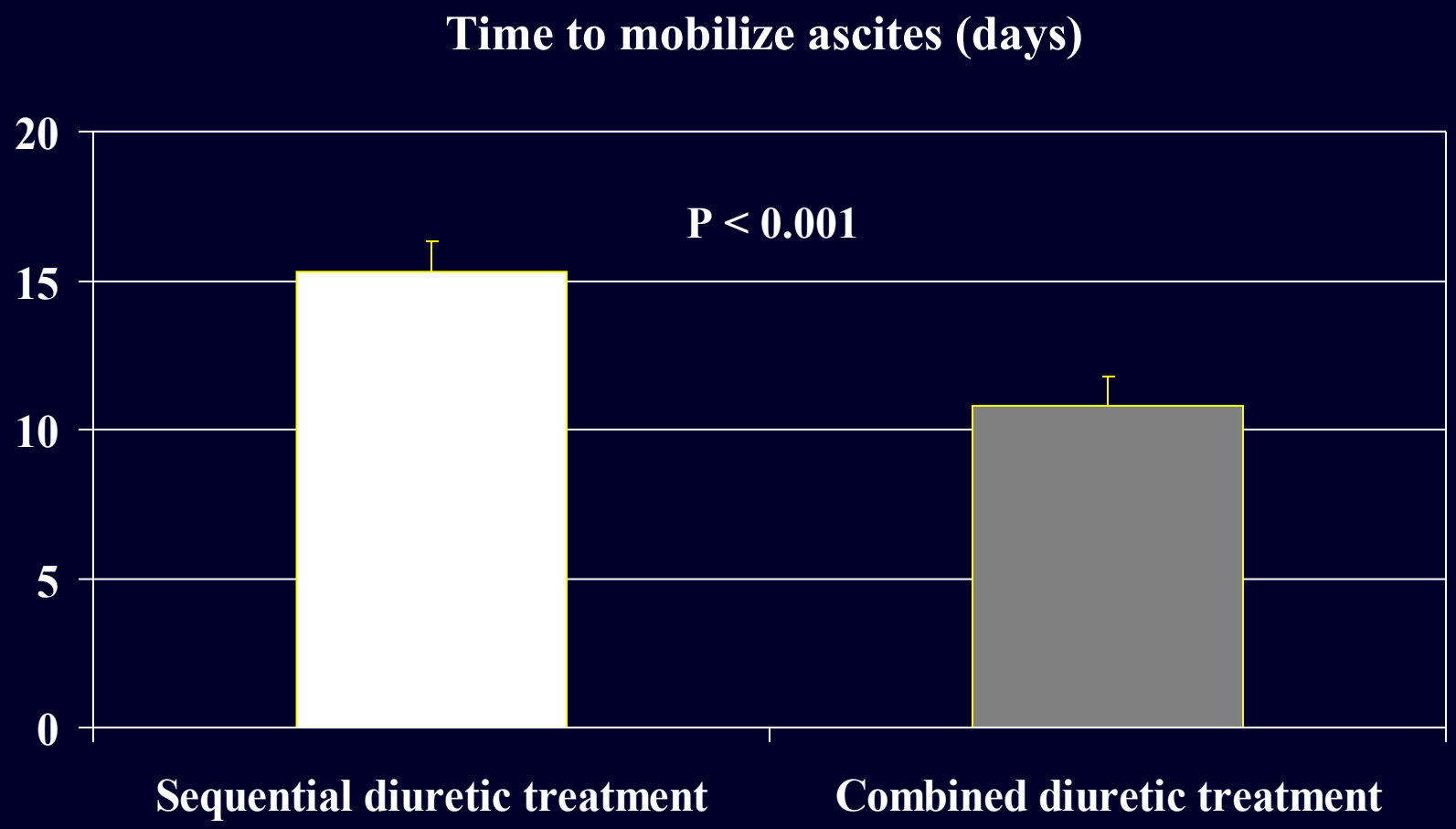
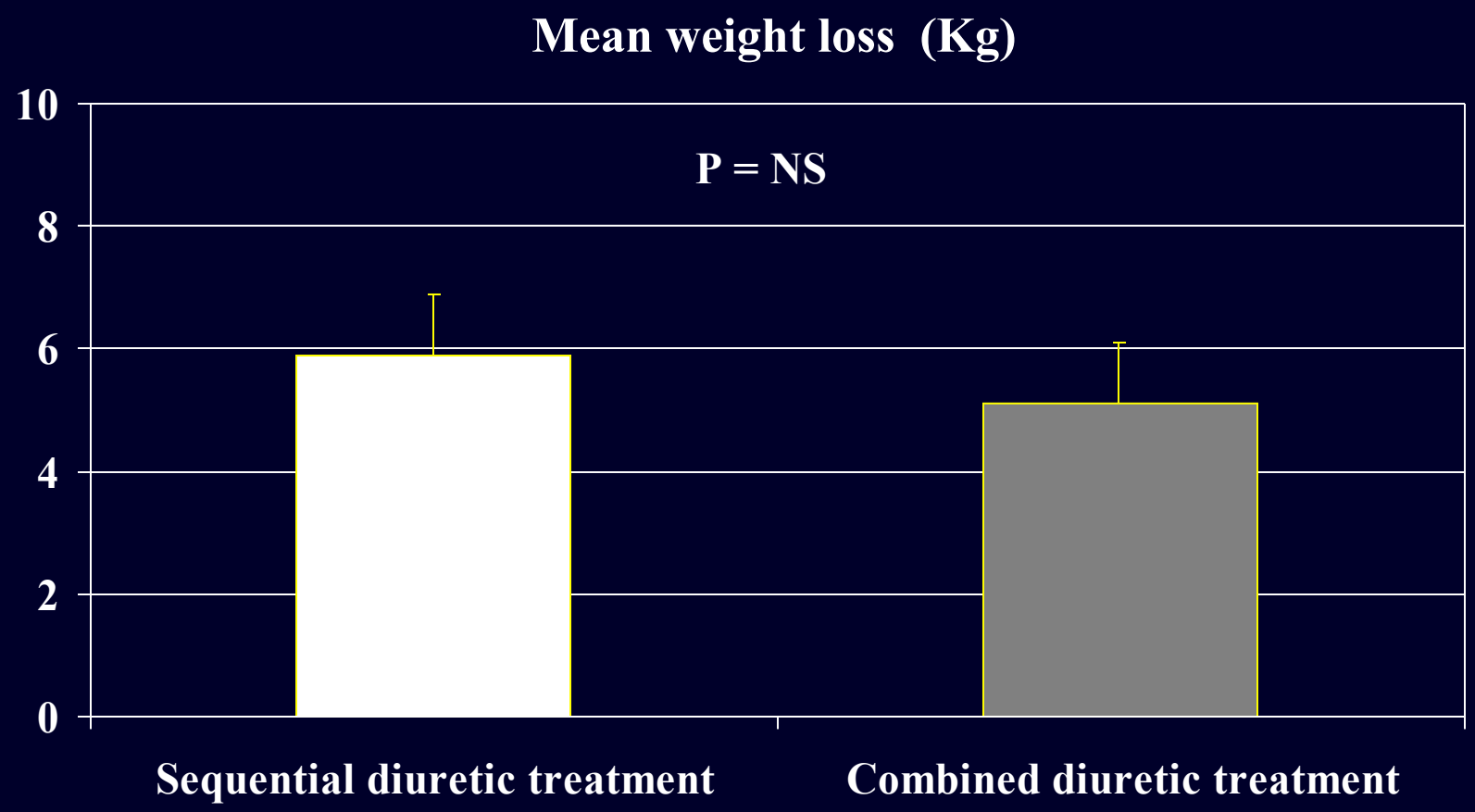


P. Angeli et al. AASLD 2005

Comparison between sequential versus combined diuretic treatment



P. Angeli et al. AASLD 2005

Diuretics (3)

- ✓ **Diuretic dosage should be increased stepwise if there is an insufficient response as defined by a weight loss < 1 Kg in the first week or < 2 Kg every week thereafter until fluid balance is achieved.**
- ✓ **The safe upper limit of weight loss is contentious. Most experts agree that the diuretic dosage should be adjusted to achieve a maximum rate of weight loss < 500 gr/day in patients without peripheral edema or < 1 Kg in those with peripheral edema.**

K. Moore, et al. Hepatology 2003 ; 38 : 258-266.

Diuretics (4)

- ✓ **Diuretics are contraindicated or should be stopped in patients with:**
  - **Severe hyponatremia (serum sodium < 125 mmol/l)**
  - **Progressive renal impairment**
  - **Worsening hepatic encephalopathy**
  - **Incapacitating muscle cramps**
  - **Hypokalemia (serum K < 3.5 mmol/l) stop furosemide**
  - **Hyperkalemia (serum K > 6.0 mmol/l) stop aldosterone antagonist.**

K. Moore, et al. Hepatology 2003 ; 38 : 258-266.

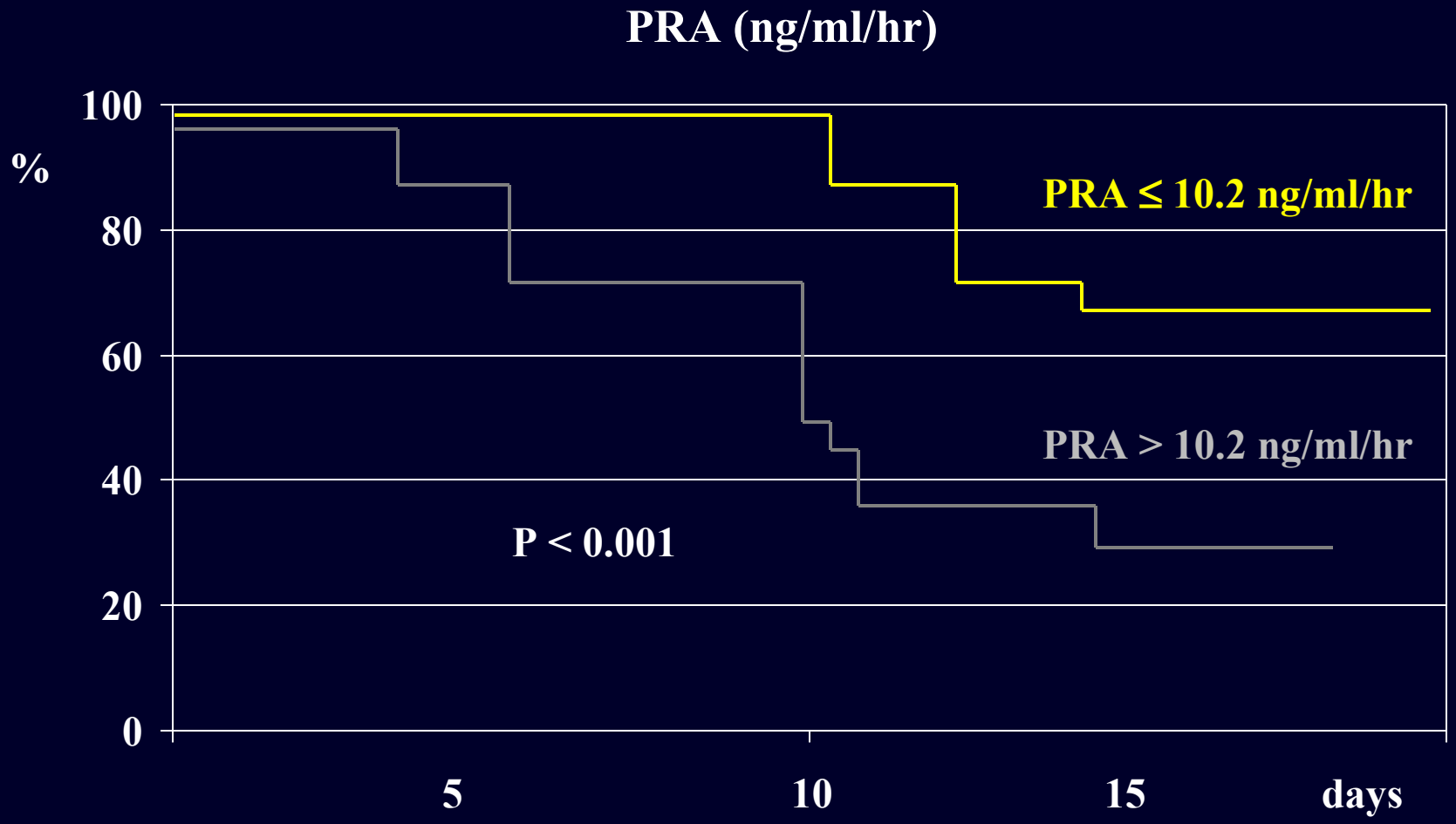
Features of patients who devloped adverse effects to diuretic treatment

Baseline parameters

	with adverse effects (n = 40)	without adverse effects (n = 56)	*P*
Plasma renin activity (ng/ml/h)	19.7±2.7	8.8±1.3	< 0.001
Plasma aldosterone (pg/ml)	713.2±217.4	207.1±44.2	< 0.01
Distal delivery of preurine (ml/min)	12.4±2.2	21.7±2.1	< 0.005

P. Angeli et al. AALSD 2005

Probability to be free from adverse effects during diuretic treatment according to plasma renin activity



P. Angeli et al. AALSD 2005

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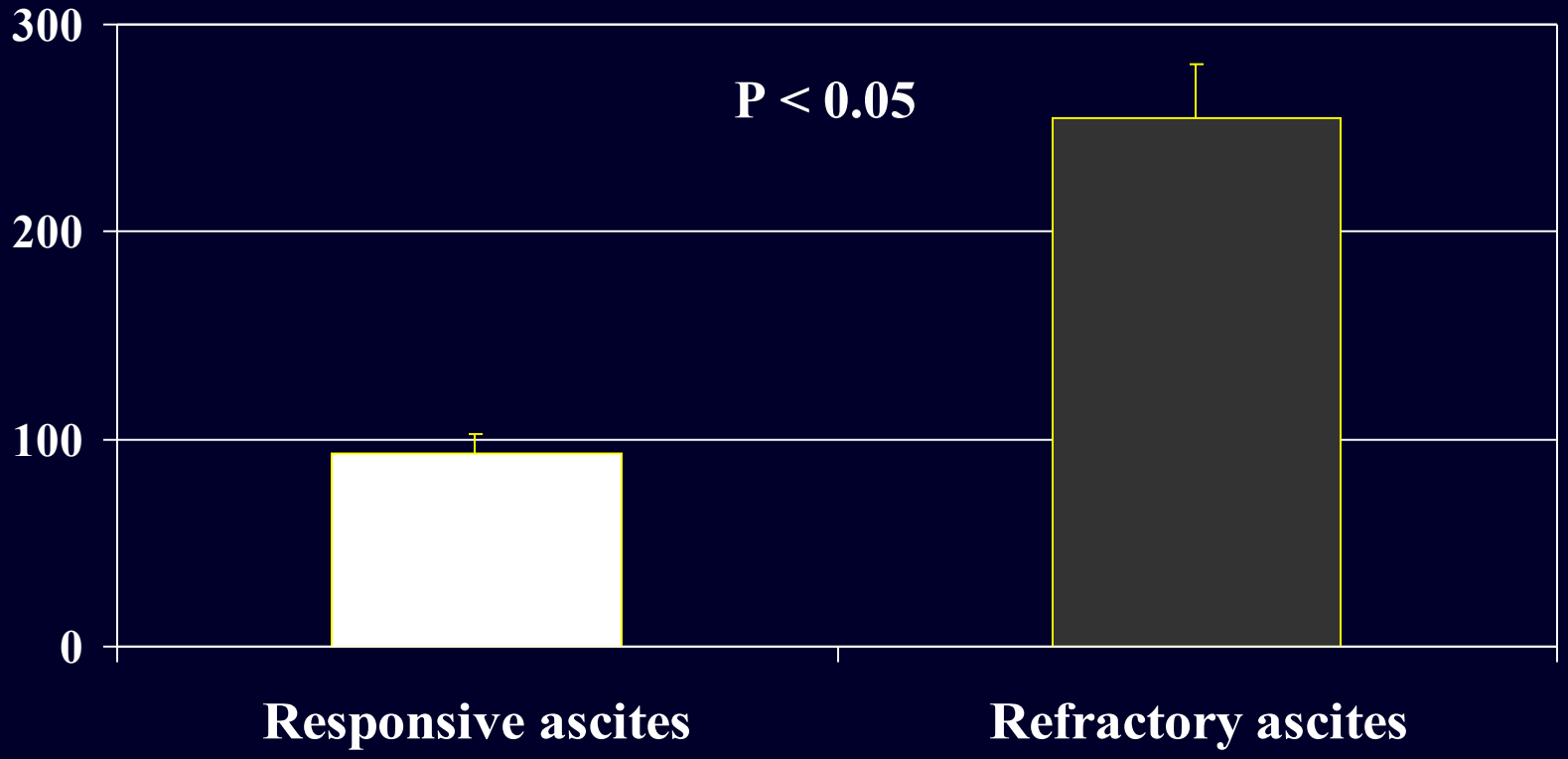
Subtypes of refractory ascites

- **Diuretic-resistant ascites:** ascites that cannot be mobilized or he early recurrence of which cannot be prevented because od a lack of response to dietary sodium restriction and intensive diuretic therapy.
- **Diuretic-intractable ascites:** ascites that cannot be mobilized or the early recurrence of which cannot be prevented because of the development of diuretic-induced complications that preclude the use of an effective diuretic regimen.

V. Arroyo et al. Hepatology 1996 ; 23 : 165-176.

Plasma renin concentration (pg/ml) in cirrhotic patients with responsive or refractory ascites



I. Colle et al. Eur. J. Gastroenterol. Hepatol. 2001 ; 13 : 251-256.

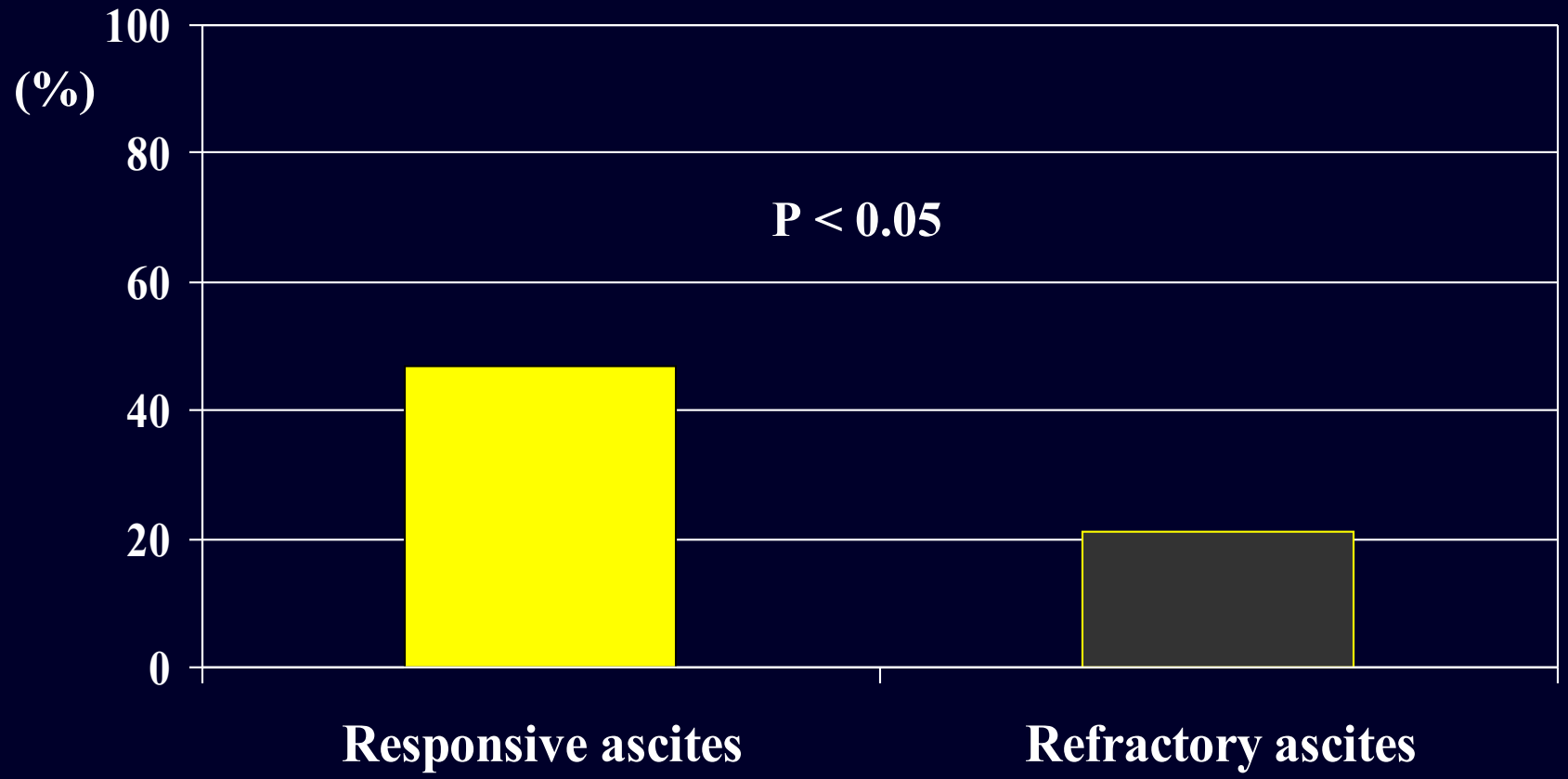
MANAGEMENT OF PATIENTS WITH CIRRHOSIS

Factors that may affect the efficacy of diuretics

- Inadequate sodium intake
- Excessive physical activity
- Drugs (NSAIDs, vasodilators)
- Bacterial infections

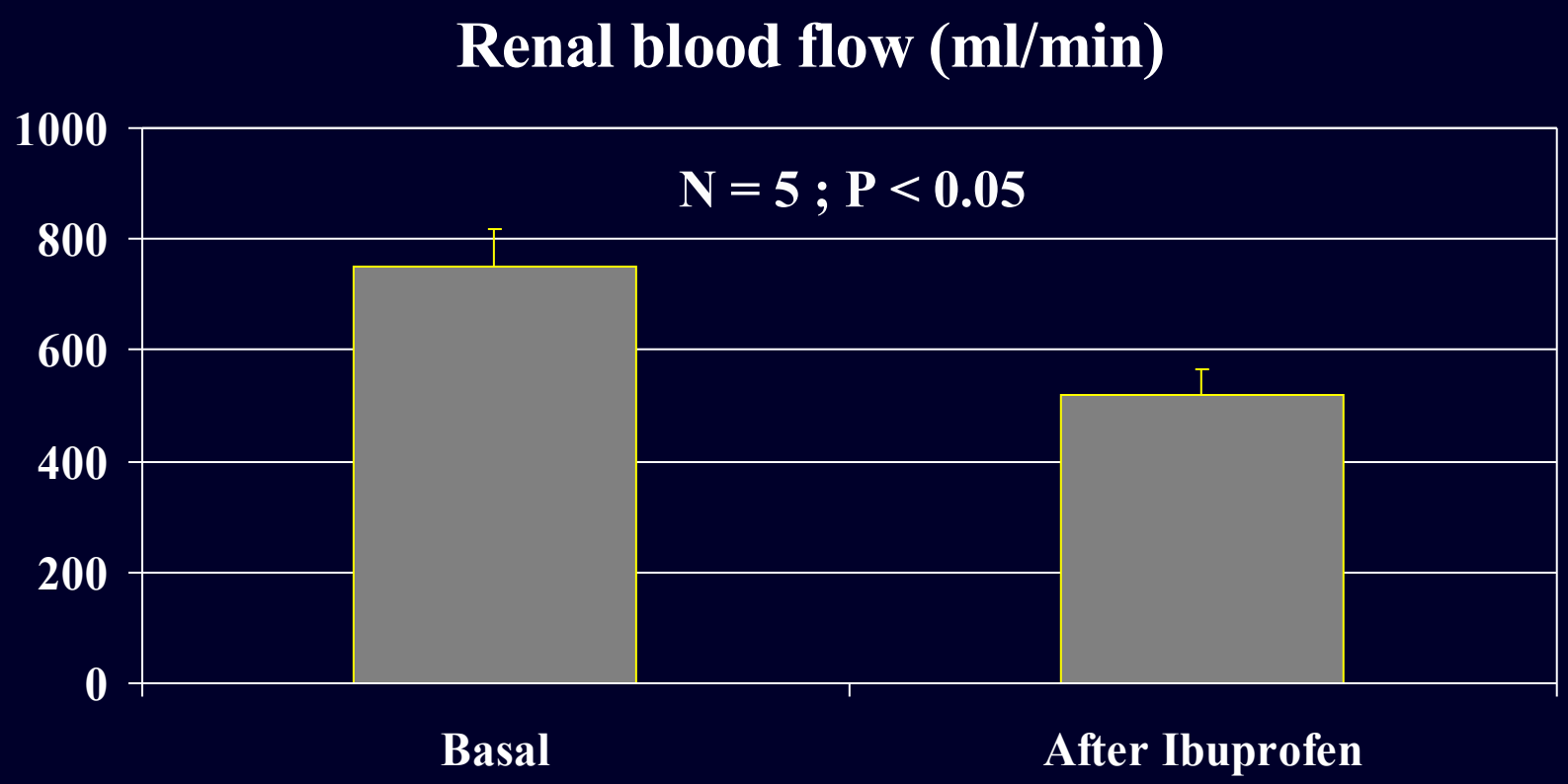
V. Arroyo et al. Hepatology 1996 ; 23 : 165-176.

Prevalence of no compliance to reduced sodium intake among cirrhotic patients with asccites according to the response to diuretic therapy



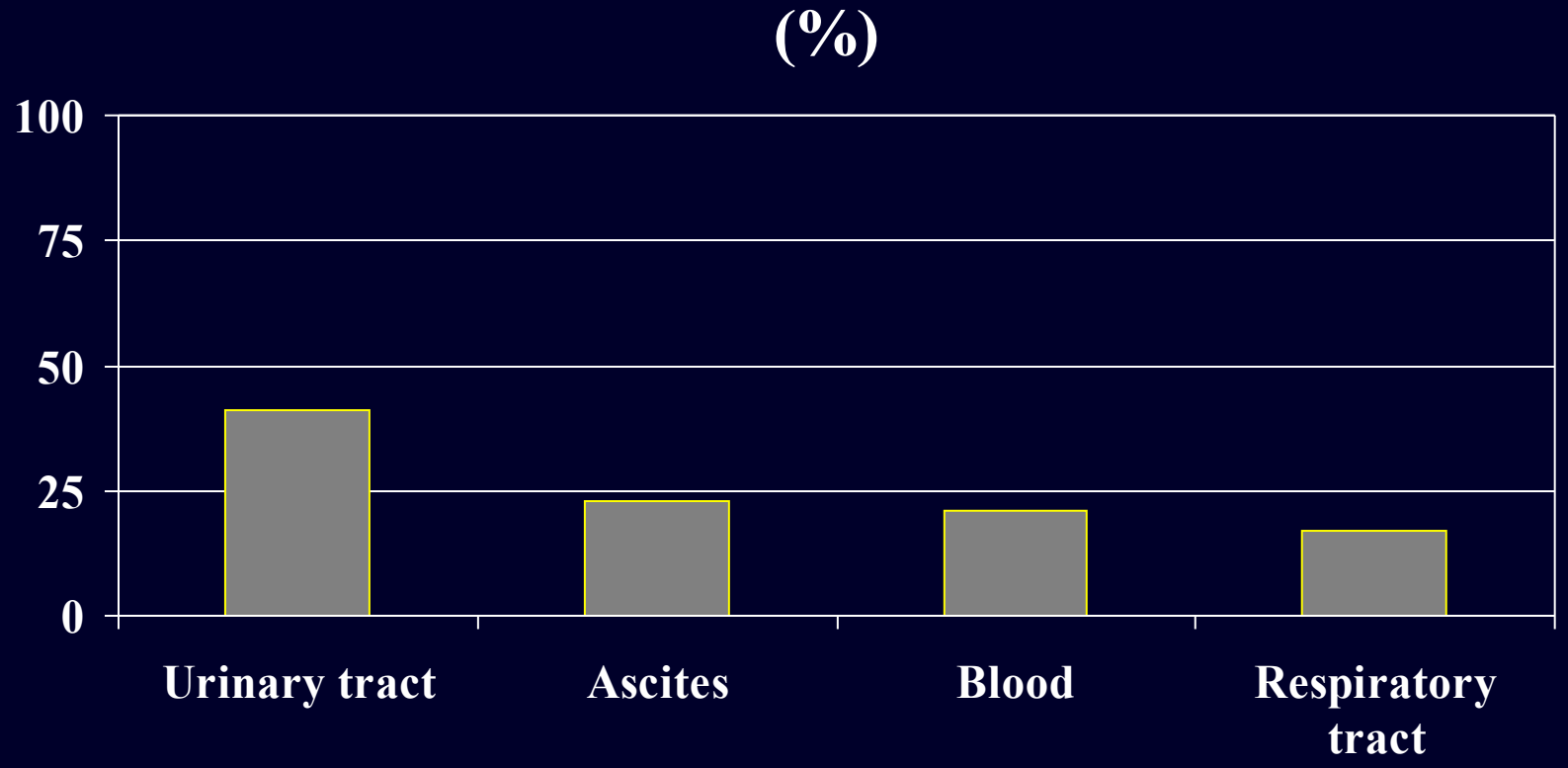
P. Angeli et al. 2005

Acute effects of Ibuprofen on renal blood flow in cirrhotic patients with ascites



G. Laffi et al. Gastroenterology 1986 ; 90 : 182-187.

Sites of infections in cirrhotic patients



M. Borzio et al. Digest. Liver Dis. 2001 ; 33 : 41-48.

MANAGEMENT OF PATIENTS WITH CIRRHOSIS

Diagnosis of spontaneous bacterial peritonitis in cirrhotic patients

Sensitivity, specificity, positive (PPD) and negative predictive value (NPV) of the reagent strip test of ascitic fluid to diagnose of spontaneous bacterial peritonitis

Variable	RS + ≥ 3	Value (95% CI)	RS + ≥ 2	Value (95% CI)
Sensitivity	51/57	0.89 (0.81-0.97)	55/57	0.96 (0.92-1)
Specificity	170/171	0.99 (0.98-1)	152/171	0.89 (0.84-0.94)
PPV	51/52	0.98 (0.94-1)	55/74	0.74 (0.64-0.84)
NPV	170/176	0.97 (0.94-0.99)	152/154	0.99 (0.97-1)
Accuracy	221/228	0.97 (0.95-0.99)	207/228	0.91 (0.87-0.94)

J. Castellote, et al. Hepatology 2003 ; 37 : 893-896.

Conclusions

- In our hands the combination “ab initio” of an aldosterone antagonist and furosemide is the most safe and cost/effective option in the diuretic treatment of moderate ascites in patients with cirrhosis.
- Patients with high baseline plasma renin activity levels should be carefully monitored for adverse effects during the diuretic treatment.
- Factors which may interfere with diuretic action may be carefully excluded before defining ascites as refractory.