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Chronic Liver Disease Foundation

Treatment of Overt Hepatic Encephalopathy: Focus on Outpatient Management

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Program Disclosure

- This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the sponsorship of Purdue University College of Pharmacy and the Chronic Liver Disease Foundation. Purdue University School of Pharmacy is accredited by the ACCME to provide continuing medical education for physicians.

- This program is supported by an educational grant from Salix Pharmaceuticals.

Educational Objectives

- Explain the importance of secondary prophylactic therapy following an overt episode of hepatic encephalopathy
- List current treatment options used to prevent recurrent episodes of hepatic encephalopathy and discuss factors influencing choice of therapy

Incidence of Overt Hepatic Encephalopathy

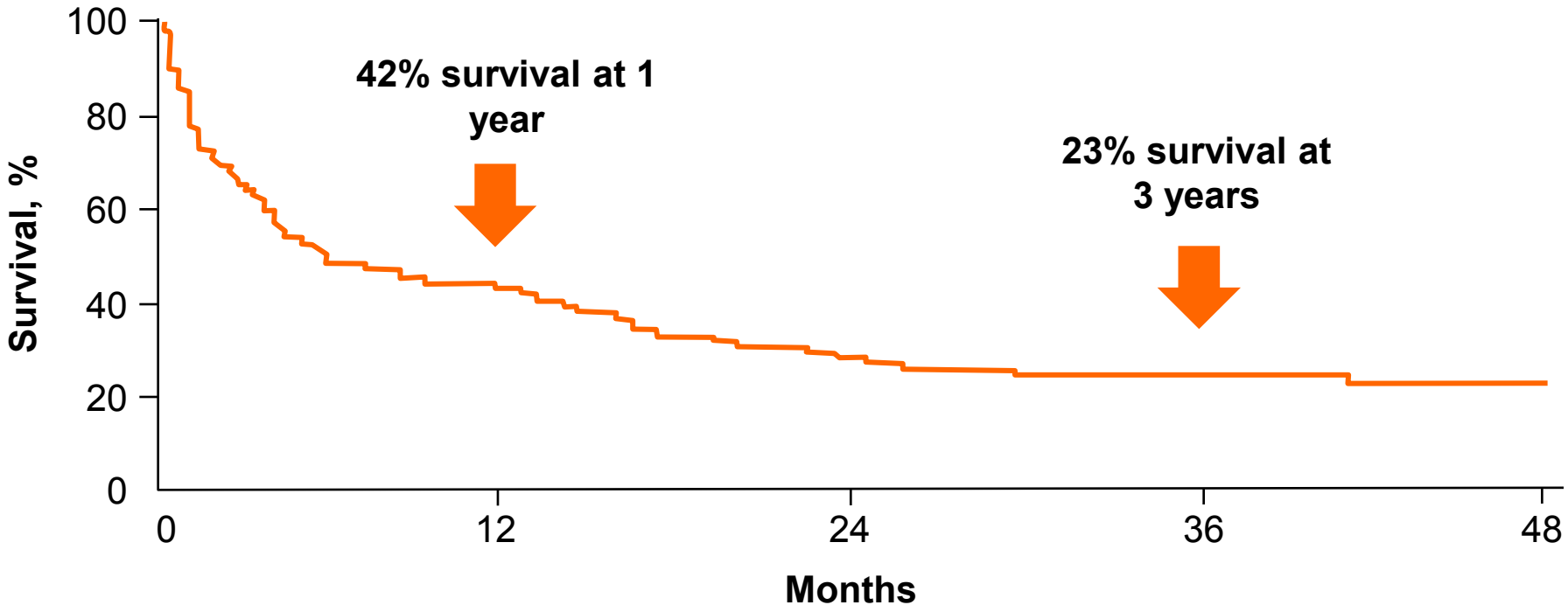
- Overt hepatic encephalopathy (OHE) occurs in:
  - 30% to 45% of cirrhotic patients
  - 10% to 50% of patients with TIPS

TIPS = transjugular intrahepatic portosystemic shunt.

Poordad FF. *Aliment Pharmacol Ther.* 2006;25(Suppl 1):3-9.

Overt HE is Associated with a Poor Prognosis

- <50% survival at 1 year after diagnosis of HE; <25% survival at 3 years1



Bustamante et al. *J Hepatol.* 1999;30:890-895.

Cognitive Impairment Associated with OHE May Not Be Reversible

- Traditional concept: Most OHE events are potentially reversible
  - Patients who regain consciousness and survive a severe HE event typically ***seem*** to return to their baseline level of cognitive functioning with supportive care, or with disaccharides, or with rifaximin
  - A subset of patients with OHE continue to suffer with symptoms and are classified as chronic persistent HE that may not be reversible with medical therapy
- Neuropathologic characteristics found in brains of patients with HE at autopsy suggest that the concept of complete reversibility requires more in-depth analysis

Persistence of Cognitive Impairment after OHE

	Prior OHE* (n=32)	No OHE (n=131)	*P* value
NCT-A	65	44	0.02
NCT-B	146	102	0.01
DST	32	45	<0.0001
LTT time	130	100	0.02
LTT errors	49	31	0.1
SDT	86	74	0.2
BDT	13	34	<0.0001
Lures	16	15	0.6
Weighted lures	31	18	0.01
Targets	77%	92%	0.001

*Median 2 episodes, all on lactulose

Bajaj JS et al. *J Hepatol* 2012;56(Suppl 2):S242.

Current Treatment Options for HE

Drug Name	Drug Class	Indication
Lactulose	Poorly absorbed disaccharide	• Decrease blood ammonia concentration • Prevention and treatment of • portal-systemic encephalopathy
Rifaximin	Non-aminoglycoside semi-synthetic, nonsystemic antibiotic	Reduction in risk of OHE recurrence in patients ≥ 18 years of age
Neomycin	Aminoglycoside antibiotic	Adjuvant therapy in hepatic coma
Metronidazole	Synthetic antiprotozoal and antibacterial agent	**Not approved for HE**

Adapted from:
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/GastrointestinalDrugsAdvisoryCommittee/UCM201081.pdf. Accessed 10/22/12, and http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022554lbl.pdf. Accessed 10/22/12.

Proposed Terminology for Prophylactic Treatment of HE

- Treating patients with covert HE to prevent development of a first episode is referred to as primary prophylaxis of HE
- Preventing recurrence of HE in patients who had a previous episode of HE is referred to as secondary prophylaxis of HE

Sharma BC et al. *Gastroenterology.* 2009;137:885-891.

OHE Treatment Goals: Focus on Secondary Prophylaxis

- Acute episode of HE
  - Treatment of precipitating factors
  - Improvement in mental status
  - Evaluation for liver transplant
- Out-patient management after an episode of HE
  - Prevention of recurrent episodes of HE
  - Improvement of daily functioning
  - Evaluation for liver transplant

Bajaj JS. *Aliment Pharmacol Ther.* 2010;31:537-547.

Secondary Prophylactic Therapy Following Overt Episode(s) of HE

- After an episode of overt HE has resolved, patients with cirrhosis should remain on prophylactic therapy for an indefinite period of time or until they undergo liver transplantation
- Goals of therapy: To prevent recurrent episodes of HE and to ensure a reasonable quality of life

Adapted from Prakash R, Mullen KD. *Nat Rev Gastroenterol Hepatol.* 2010;7:515-525.

Most Patients are Not Receiving Prophylactic Therapy to Prevent Recurrence

- Subset of national claims for medical and hospital activity, Jan 2009 to Dec 20011, ICD-9 code 572.2 and filled prescriptions for rifaximin, lactulose, or rifaximin + lactulose

	2009	2010	2011
Eligible Patients Identified (n)	13,623	15,529	16,328
Patients with Inpatient Claims (%)	89.2%	87.8%	86.4%
Patients Receiving Ongoing Treatment (%)	39.7%	37.7%	36.1%

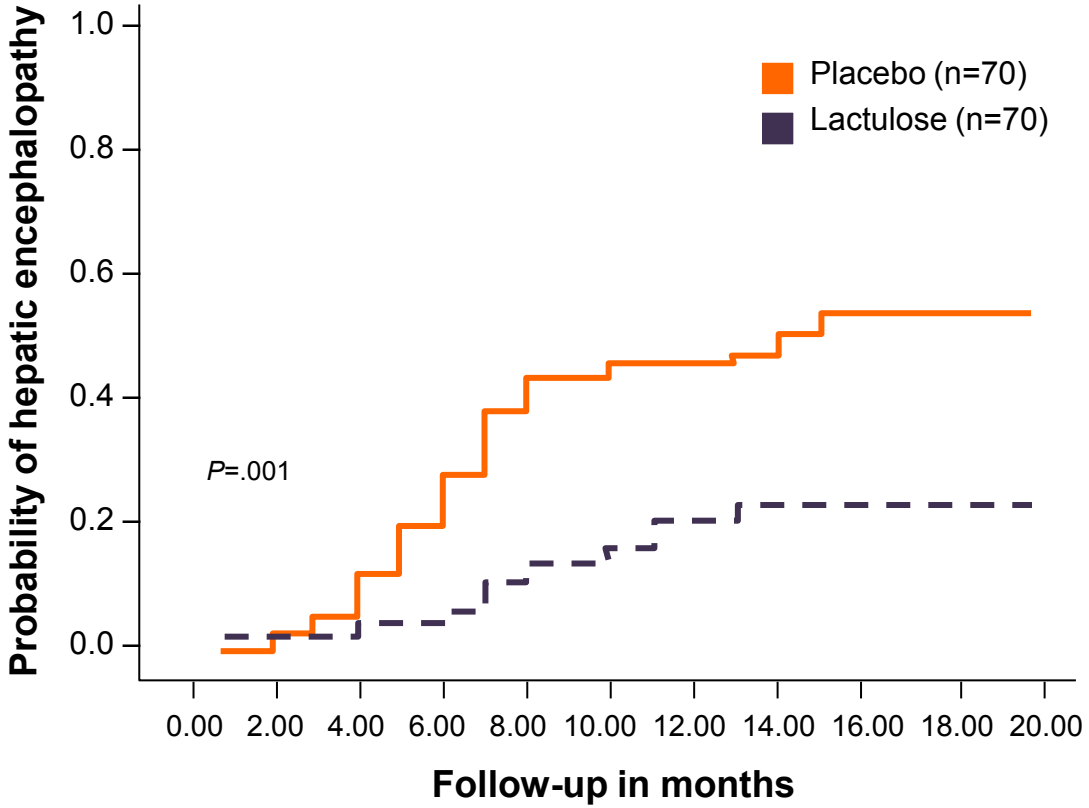
Neff GW et al. Abstract 1612. Poster presentation at The Liver Meeting® 2012, Boston, MA, November 12, 2012.

Secondary Prophylaxis of OHE: Lactulose vs Placebo

- Open-label randomized controlled trial
- Consecutive cirrhotic patients who recovered from HE randomized to receive lactulose (n=70) or placebo (n=70)
- Primary end point was development of OHE
- Median follow-up of 14 months (range 1-20 months)

Sharma BC, et al. *Gastroenterology.* 2009:137:885-891.

Probability of Developing HE in Patients Receiving Prophylactic Lactulose vs Placebo



Patients at risk*											
Lactulose	61	60(1)	59(2)	58(3)	51(8)	45(9)	38(11)	28(12)	10(12)	7(12)	1(12)
Placebo	64	62(1)	59(4)	50(13)	37(24)	33(27)	28(27)	19(29)	13(30)	8(30)	4(30)

*Values in parentheses indicate the cumulative number of subjects who developed HE.

Sharma BC, et al. *Gastroenterology.* 2009:137:885-891.

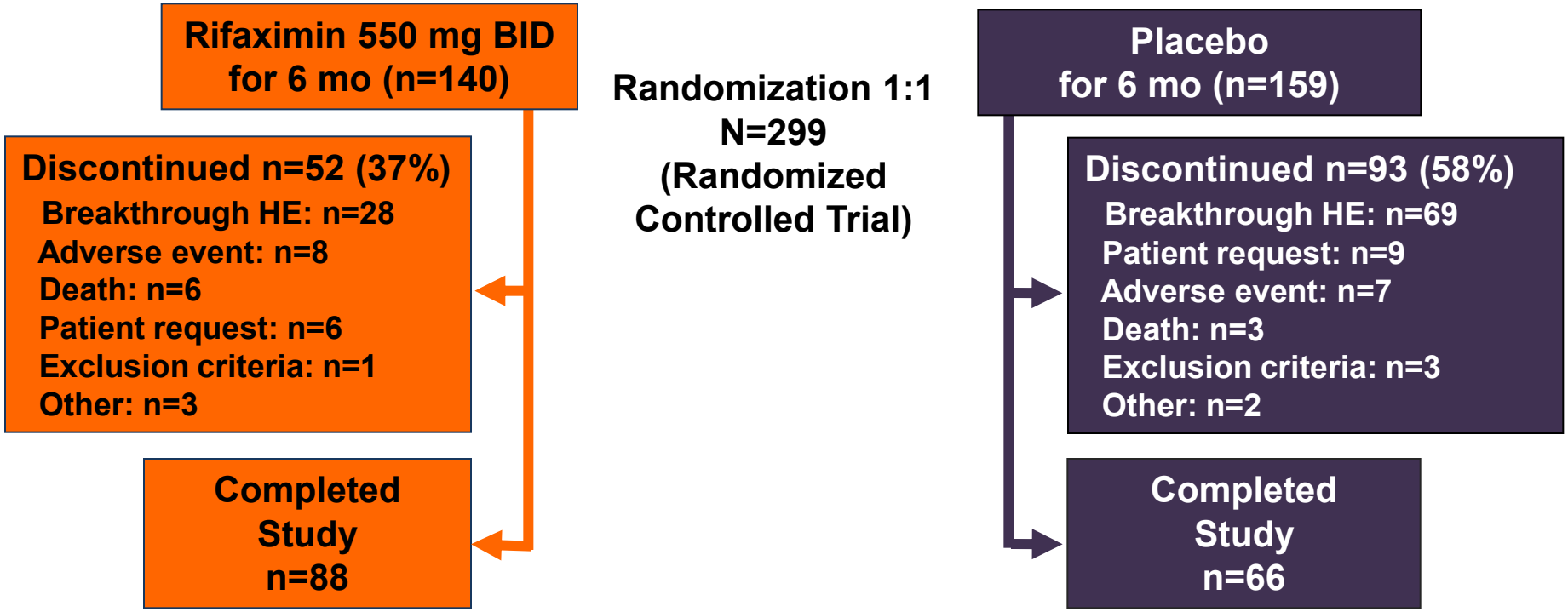
Side Effects in Patients Receiving Prophylactic Lactulose vs Placebo

	Lactulose (n=61)	Placebo (n=64)
Diarrhea	14 (23%)	---
Abdominal bloating	6 (10%)	---
Distaste to lactulose	8 (13%)	---
Constipation	---	10 (16%)

- All patients could tolerate and remained compliant to lactulose therapy

Sharma BC, et al. *Gastroenterology.* 2009:137:885-891.

Secondary Prophylaxis of HE: Rifaximin vs Placebo



Bass NM, et al. *N Engl J Med.* 2010;362:1071-1081.

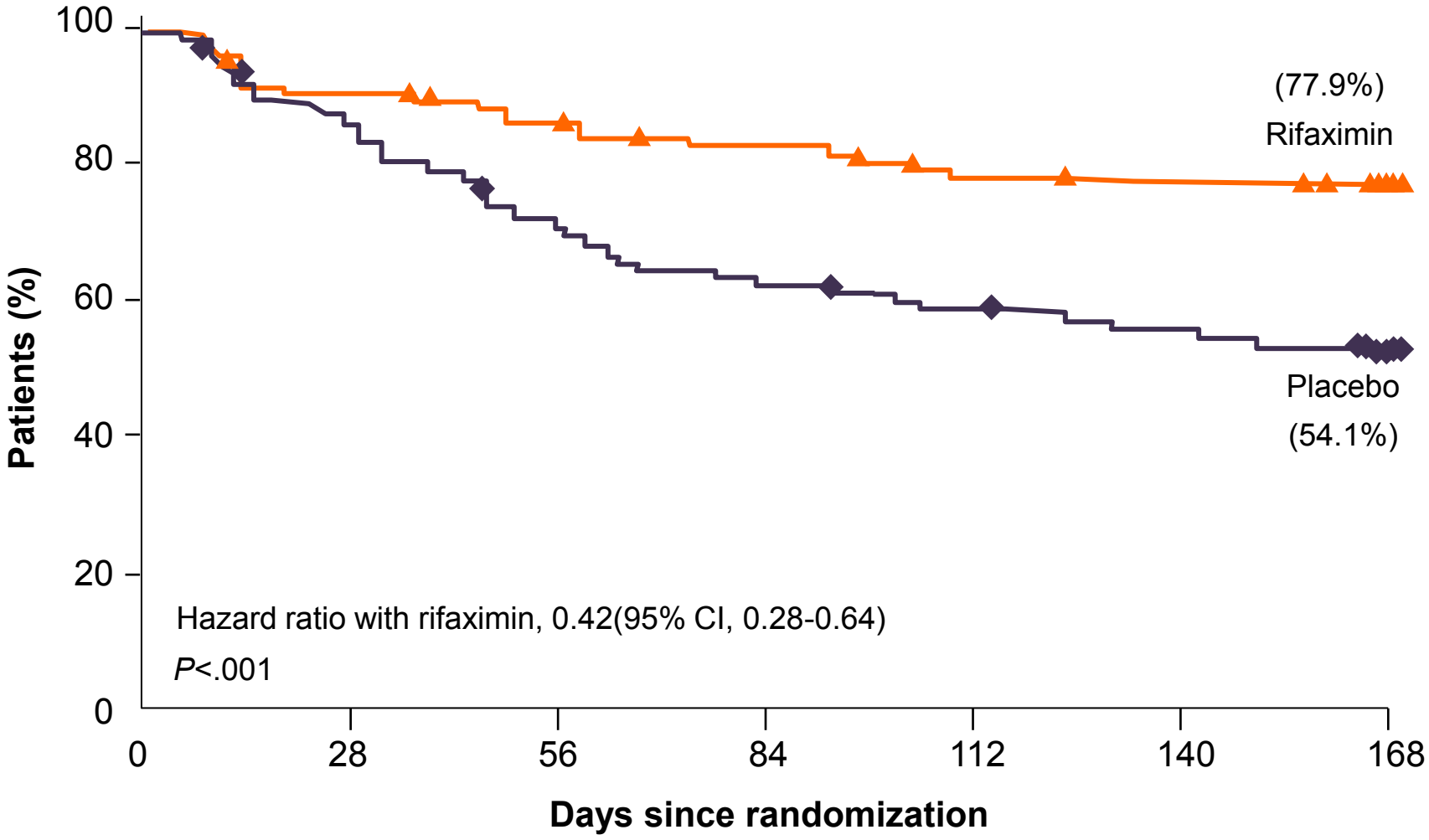
Rifaximin Treatment in HE: Lactulose Use at Baseline and During Study

	Rifaximin (n=140)	Placebo (n=159)
Lactulose use at baseline — n (%)*	128 (91.4)	145 (91.2)
Lactulose use during study — n (%)*	128 (91.4)	145 (91.2)

*During the study, 3 patients who had been receiving lactulose discontinued the therapy and another 3 patients started lactulose (1 in the rifaximin group and 2 in the placebo group).

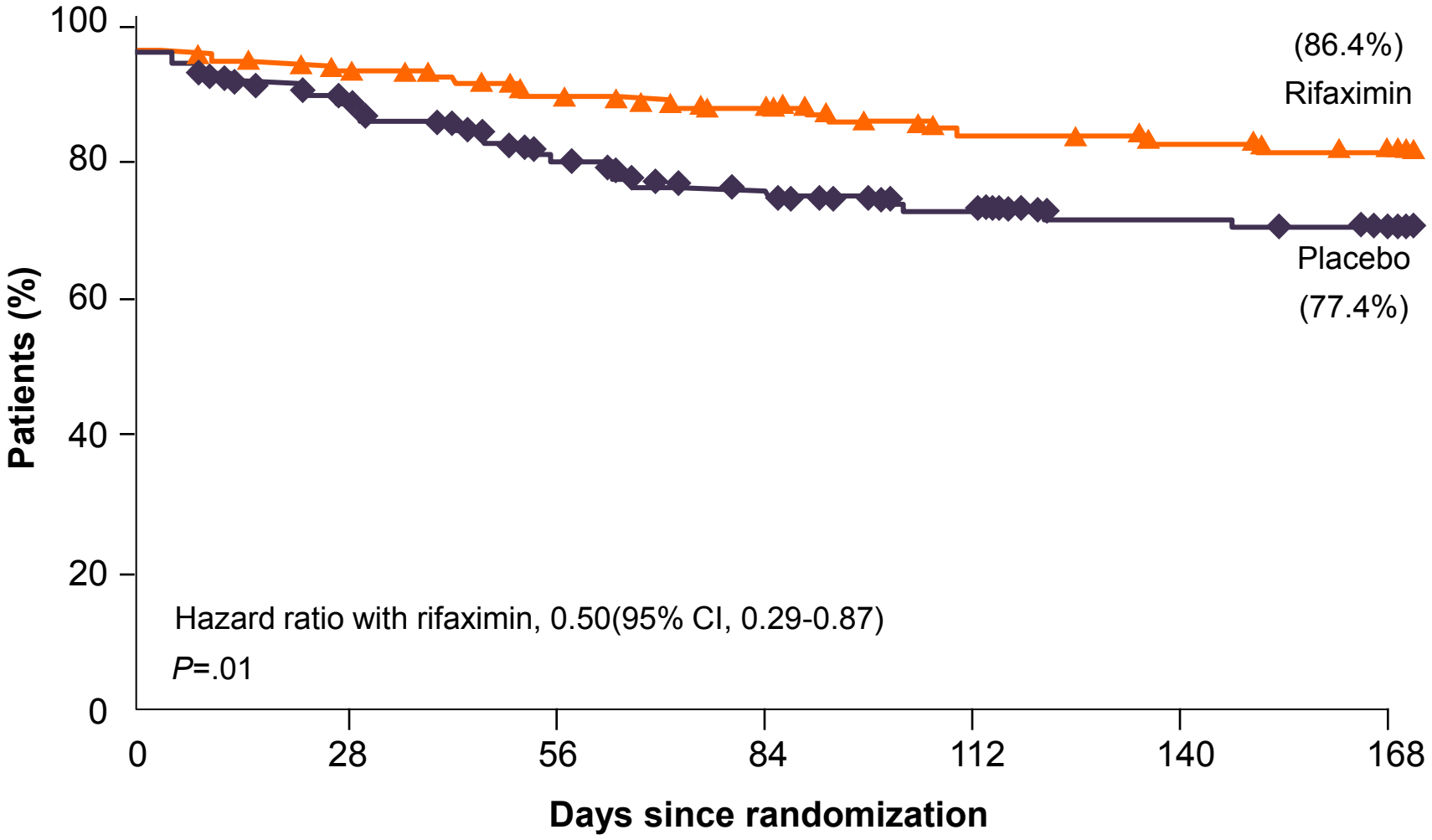
Bass NM, et al. *N Engl J Med.* 2010;362:1071-1081.

Rifaximin Treatment in HE: Time to First Breakthrough Episode (Primary End Point)



Bass NM, et al. *N Engl J Med*. 2010; 362(12):1071-1081.

Rifaximin Treatment in HE: Time to First HE-Related Hospitalization (Secondary End Point)



Bass NM, et al. *N Engl J Med*. 2010; 362(12):1071-1081.

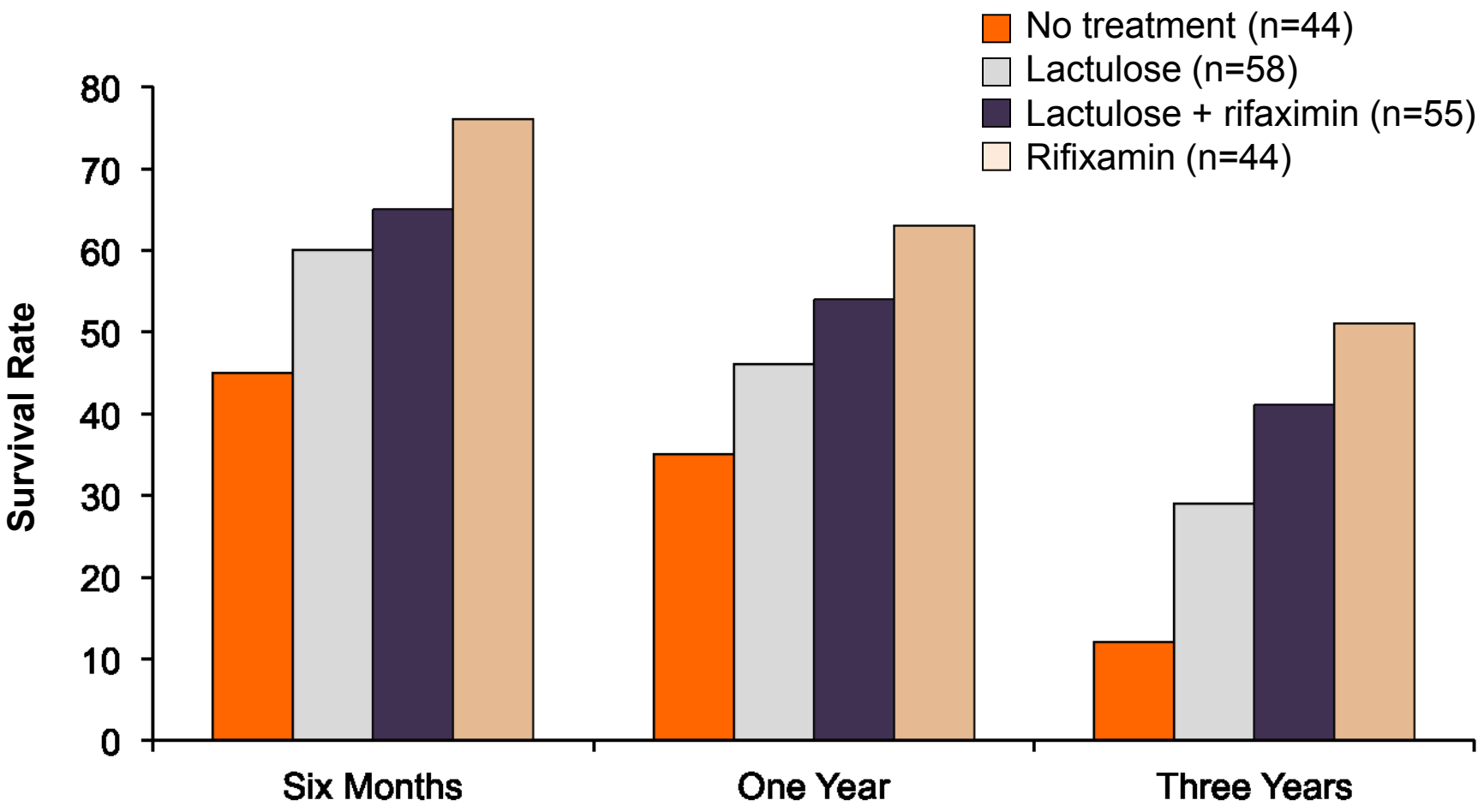
Rifaximin and HE: Side Effects Similar to Placebo

- The incidences of adverse events did not differ significantly between the two study groups (P>.05 for all comparisons)

	Adverse Events Reported in ≥10% of Patients in Either Study Group	
Event, n (%)	**Rifaximin (n=140)**	**Placebo (n=159)**
Any event	112 (80.0)	127 (79.9)
Nausea	20 (14.3)	21 (13.2)
Diarrhea	15 (10.7)	21 (13.2)
Fatigue	17 (12.1)	18 (11.3)
Peripheral edema	21 (15.0)	13 (8.2)
Ascites	16 (11.4)	15 (9.4)
Dizziness	18 (12.9)	13 (8.2)
Headache	14 (10.0)	17 (10.7)

Bass NM, et al. *N Engl J Med.* 2010;362:1071-1081.

Survival Rates Vary Depending on Treatment Choice



Neff GW et al. Abstract P927. Poster presentation at the 2012 ACG Annual Scientific Meeting and Postgraduate Course, Las Vegas, NV, October 22, 2012.

Changing Treatment Paradigm

- Subset of national claims for medical and hospital activity, Jan 2009 to Dec 20011, ICD-9 code 572.2 and filled prescriptions for rifaximin, rifaximin + lactulose, or lactulose

	2009	2011
Received rifaximin alone (%)	3.9%	13.2%
Received rifaximin + lactulose (%)	8.1%	8.8%
Received lactulose alone (%)	27.9%	14.1%

Neff GW et al. Abstract 1612. Poster presentation at The Liver Meeting® 2012, Boston, MA, November 12, 2012.

Treatment of Overt Hepatic Encephalopathy: Conclusions

- OHE occurs in 30% to 45% of cirrhotic patients
- OHE is associated with a poor prognosis; <50% survival at 1 year after diagnosis of HE
- Cognitive impairment after an OHE episode may be persistent
- Once an episode of overt HE has resolved, patients with cirrhosis should remain on prophylactic therapy with lactulose or rifaximin to prevent recurrence
  - Most patients, however, are not receiving prophylactic therapy
- Treatment choice may affect survival