TREATMENT OF

PRIMARY BILIARY CIRRHOSIS (PBC)

URSO not indicated

Therapy for PBC
Difficulties

- Etiology is uncertain
- Therapies are based on ideas regarding pathogenesis
- Present medical therapies have a limited effect

- Advanced cases: Liver transplantation may be the only option

Pathogenetic features of Primary Biliary Cirrhosis (PBC)

- Immuno-inflammatory destruction of small intrahepatic bile ducts
- ”The florid duct lesion”
- Progressive cholestasis
- Cirrhosis
- Liver failure

Ursodeoxycholic acid (UDCA)

- UDCA is hydrophilic bile acid, constituting in man only 1-3% of biliary bile acids.
- UDCA is less hepatotoxic than other bile acids.
- By administering UDCA orally the concentration of UDCA in bile increases and the bile becomes less toxic.
- This may reduce the tissue damaging effects of bile leaking from damaged bile ducts.

RCTs of Ursodeoxycholic acid (UDCA)

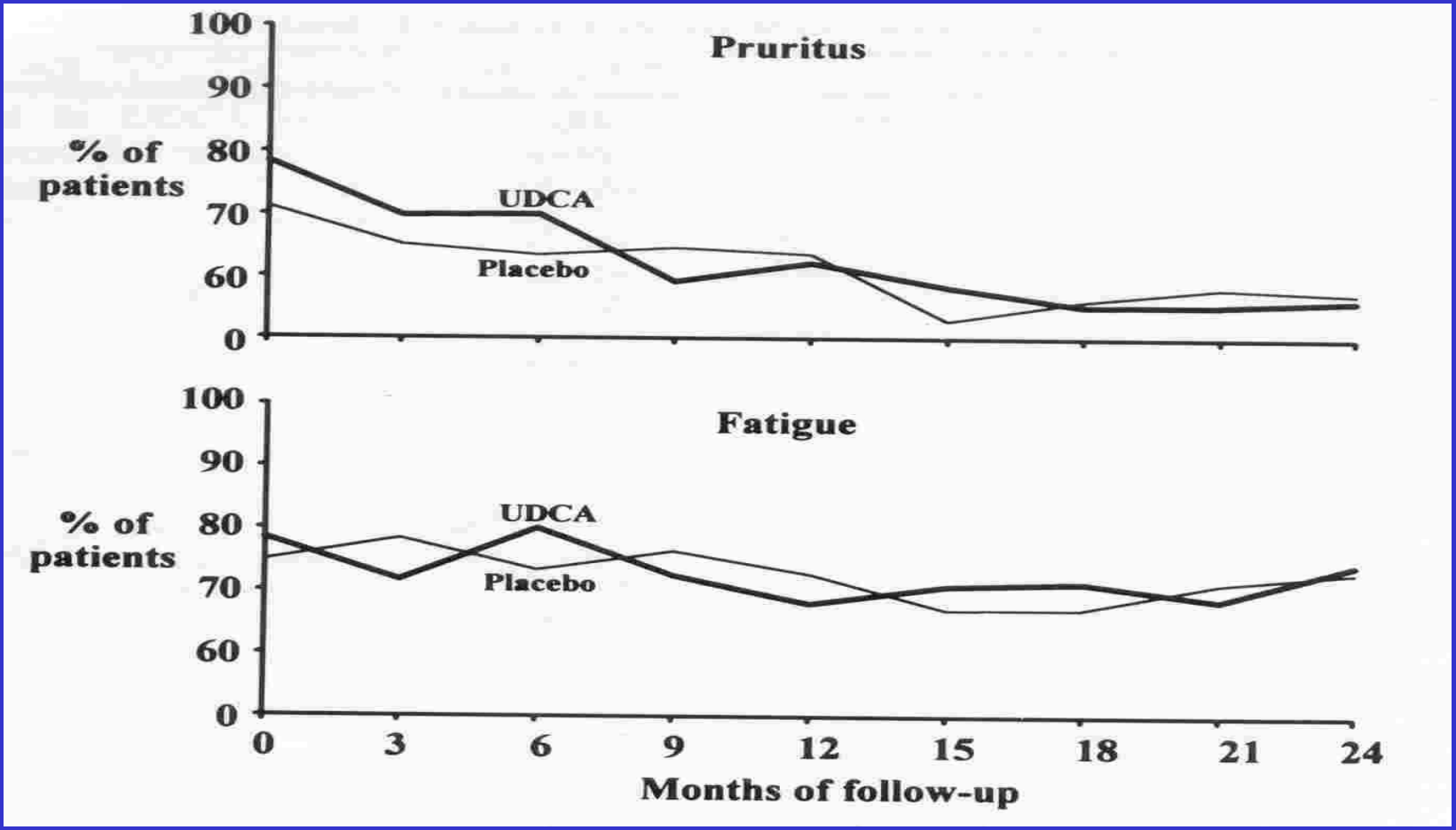
Cochrane Database Syst Rev. 2002;(1):CD000551

- UDCA (8-15 mg/kg/day) for 3 months to five years.
- 16 RCTs against placebo (n=15) or no intervention (n=1) in 1422 patients.
- UDCA significantly ($P<0.05$) reduced ascites, jaundice, serum bilirubin and liver enzymes.
- UDCA had no significant effects on mortality, liver transplantation, mortality or liver transplantation, pruritus, fatigue, s-albumin, prothrombin time, quality of life, liver histology, or portal pressure.

Effect of UDCA on Pruritus and Fatigue

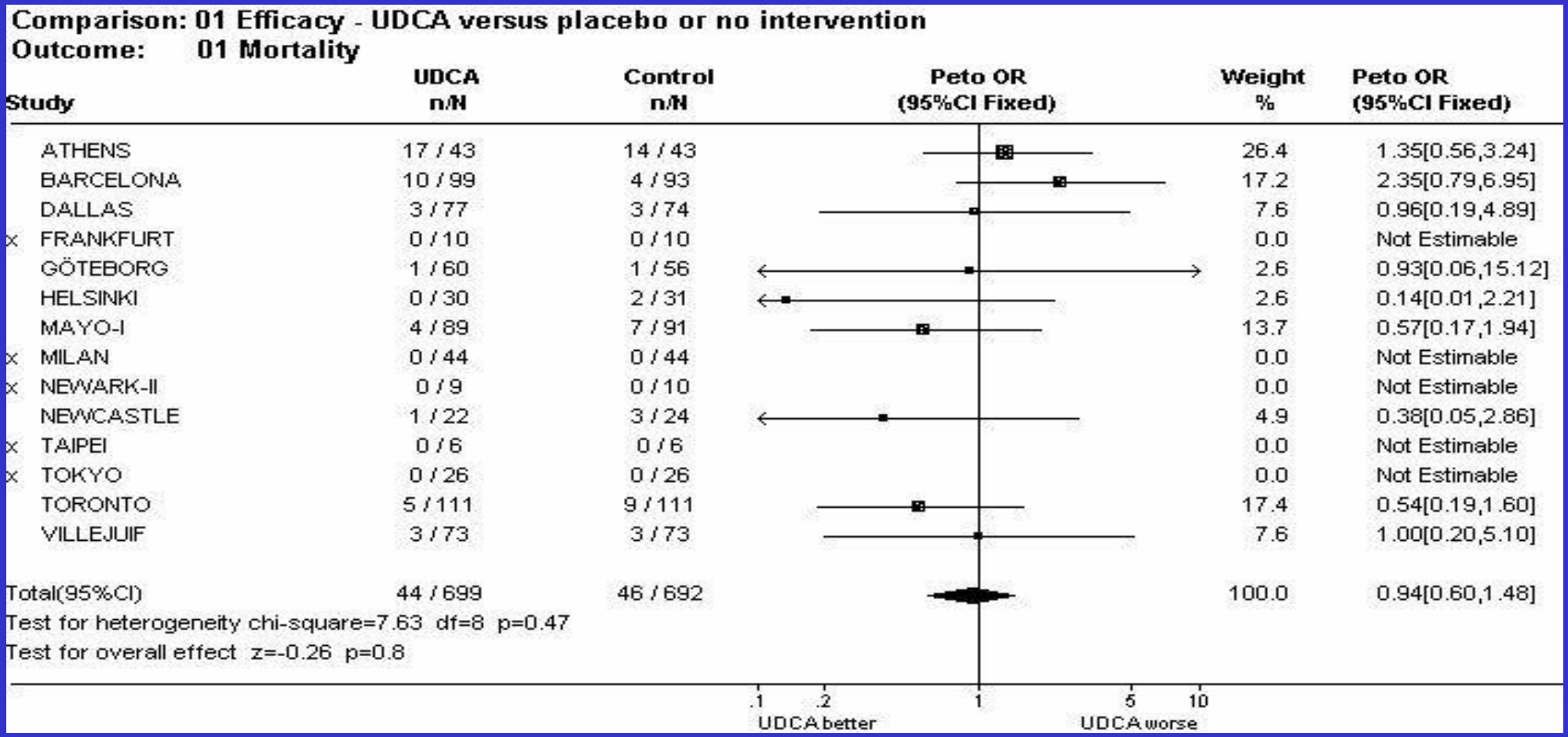
Heathcote J et al. Hepatology 1994;19:1149-56.

UDCA (14 mg/kg/day) 111 pts. Placebo 111 pts.



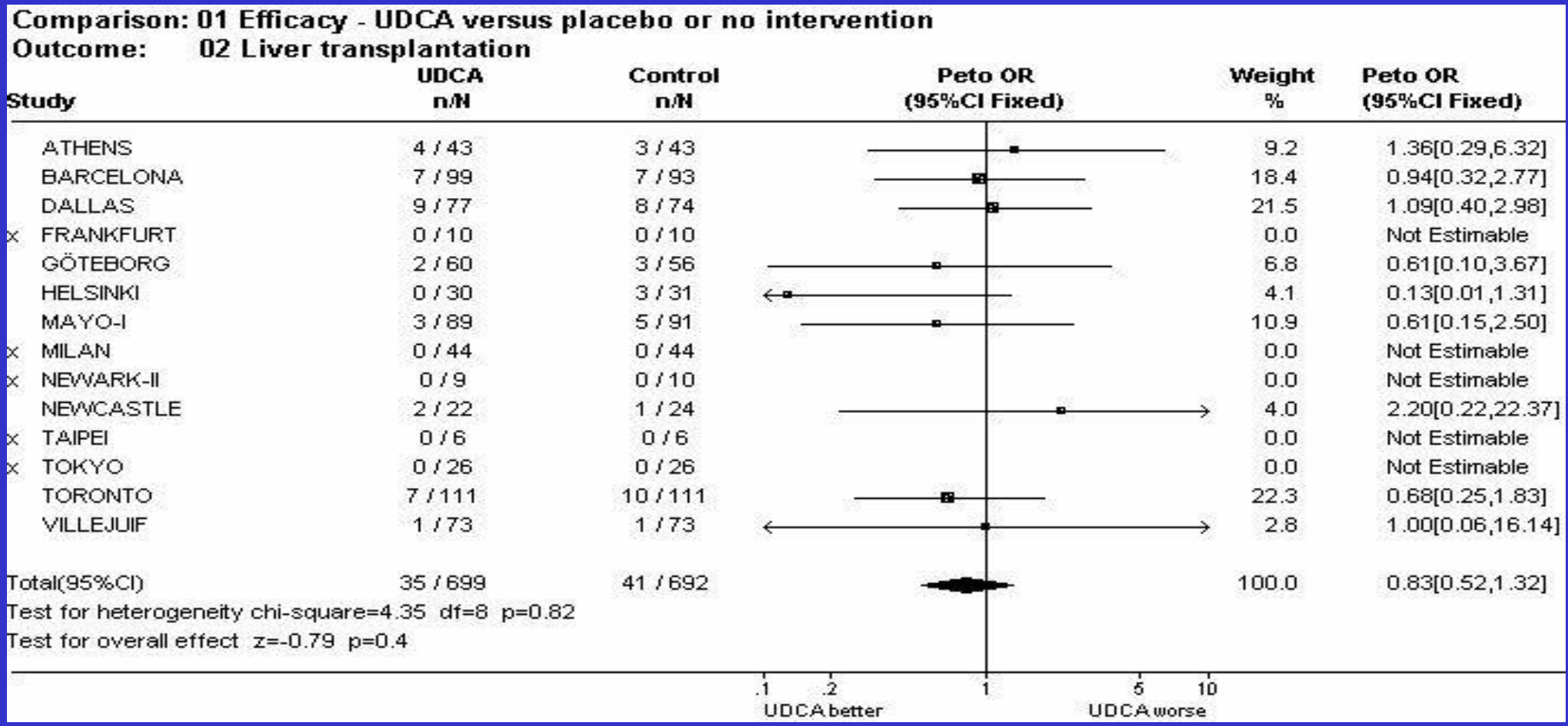
PBC: The effect of UDCA on mortality

Cochrane Database Syst Rev. 2002;(1):CD000551



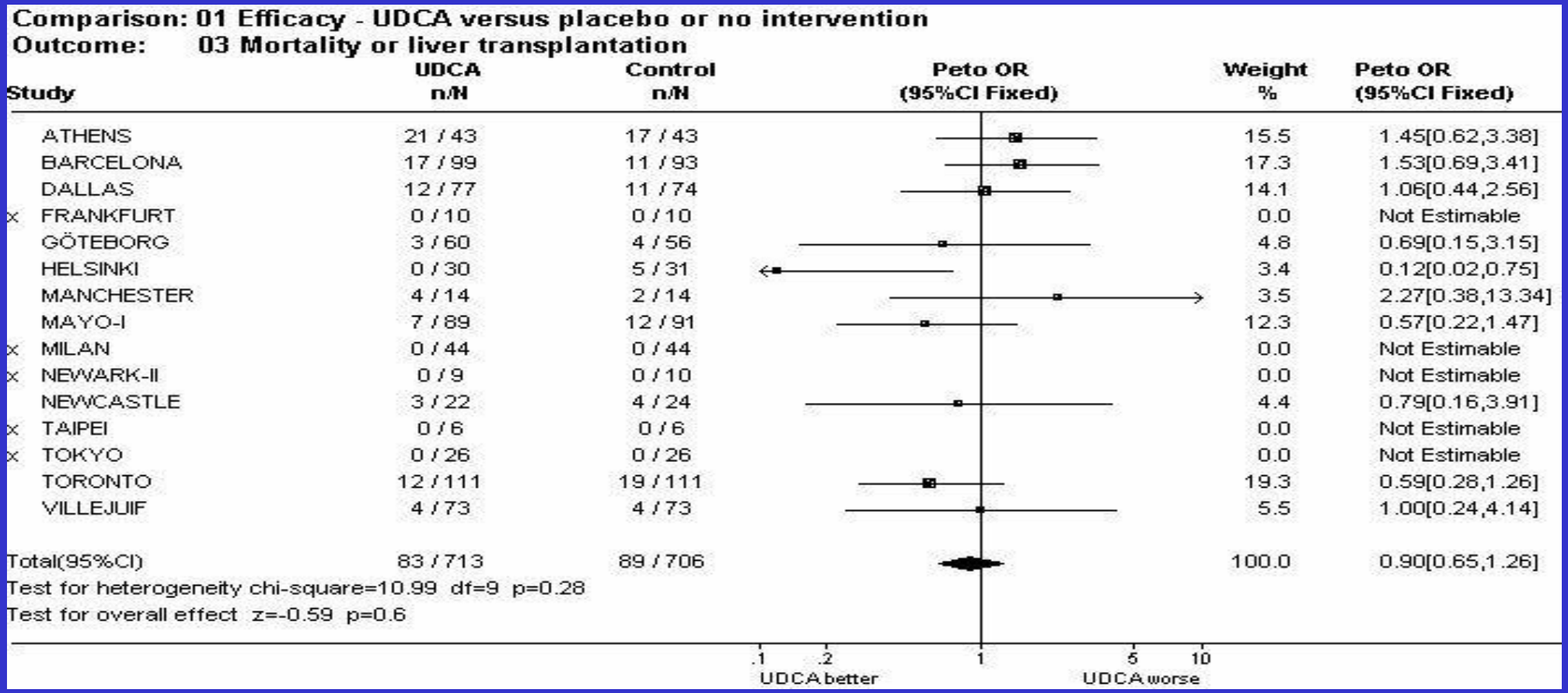
PBC: Effect of UDCA on transplantation

Cochrane Database Syst Rev. 2002;(1):CD000551



PBC: Effect of UDCA on mortality or transplantation

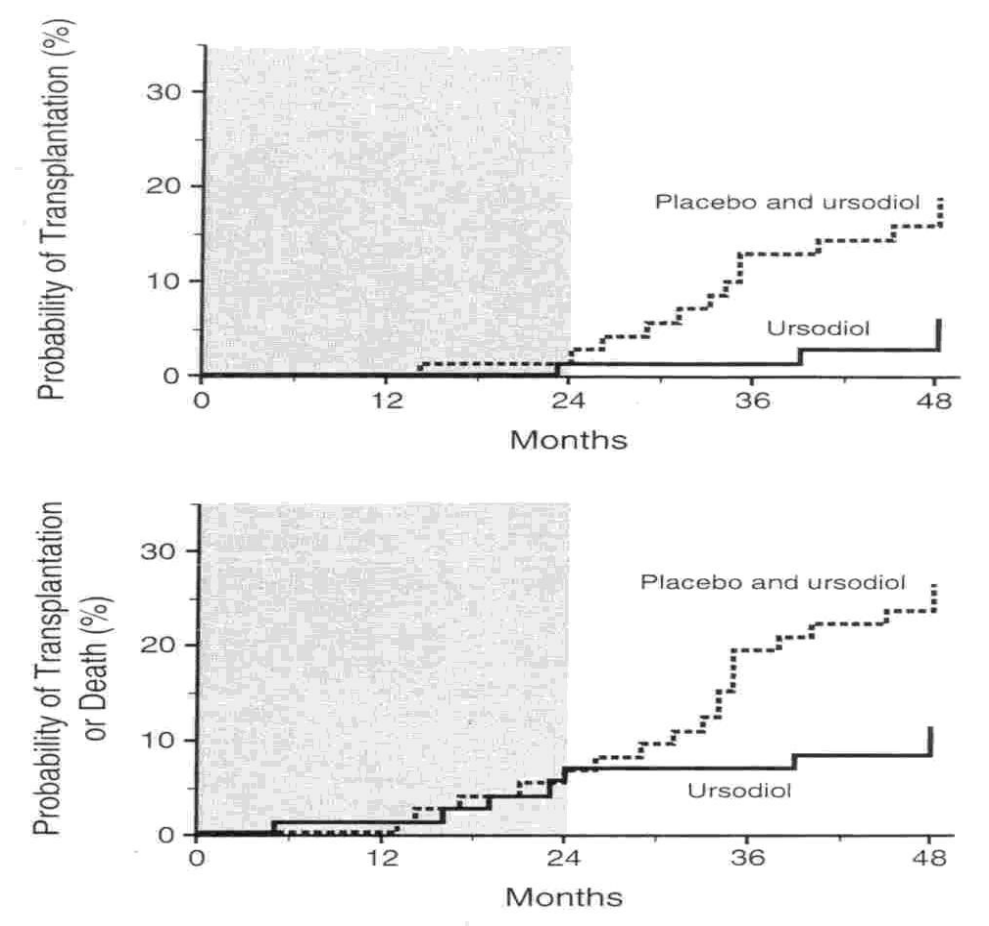
Cochrane Database Syst Rev. 2002;(1):CD000551



RCT with the most marked effect of UDCA

Poupon R et al. N Engl J Med 1994;330:1342-7.

Placebo: 72 pts. UDCA (13-15 mg/kg/day): 73 pts.

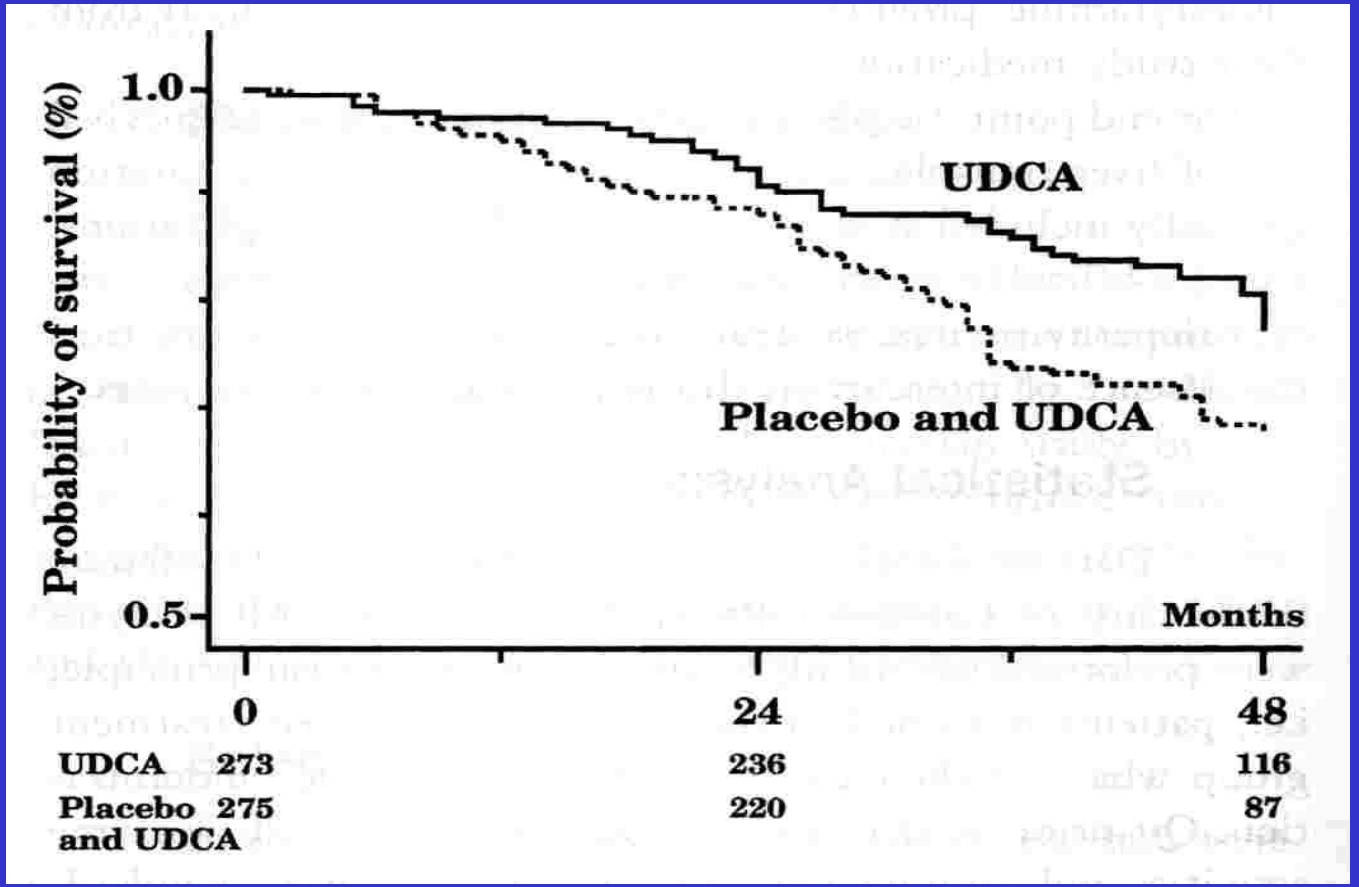


The excess endpoints in the placebo group occurs after ”cross-over”, i.e. **during** UDCA therapy.

The excess endpoints are transplantations, not deaths.

”Cross-over” from Placebo to UDCA after 2 years

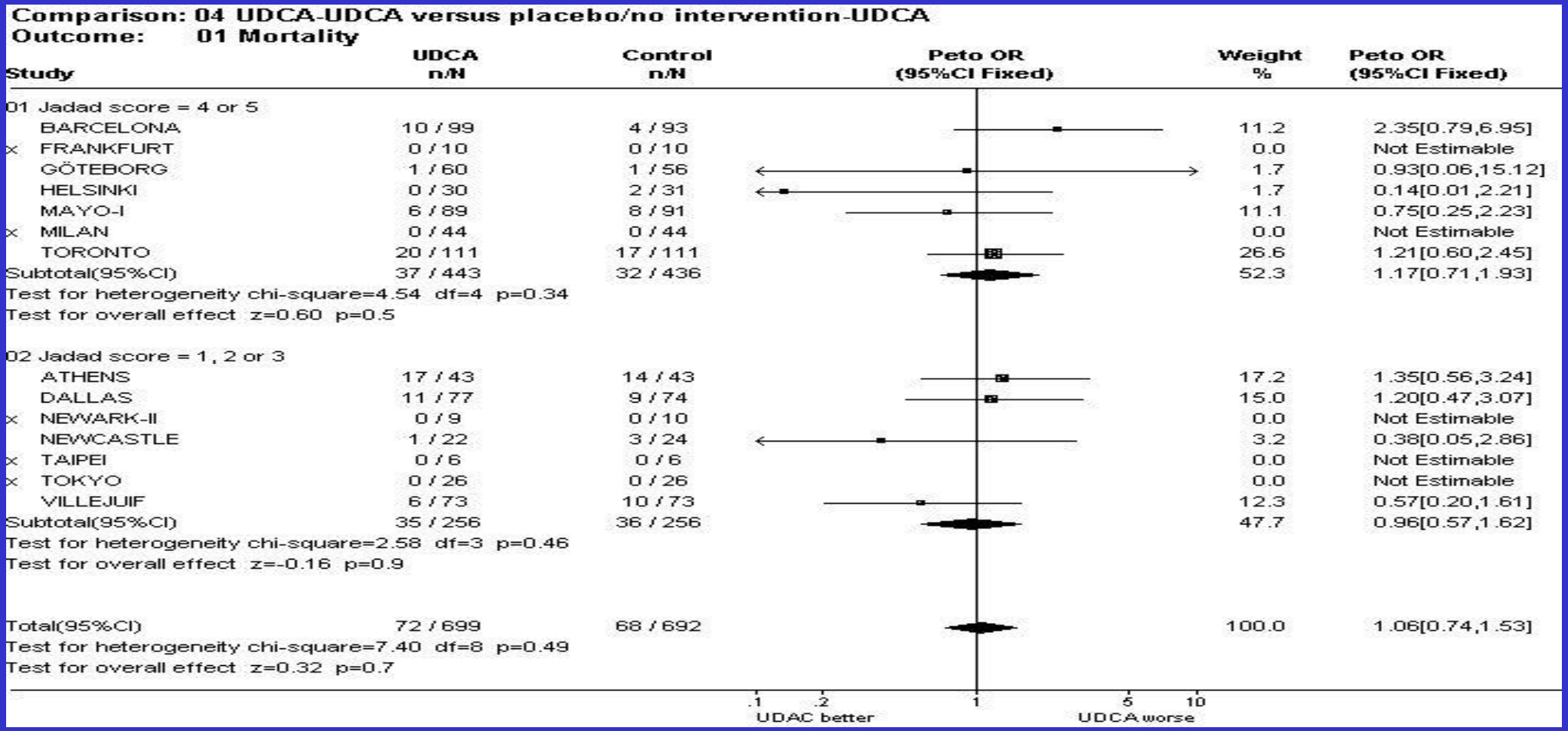
Poupon R et al. Gastroenterology 1997;113:884-90.



The excess endpoints in the Placebo group occurs *during* UDCA treatment

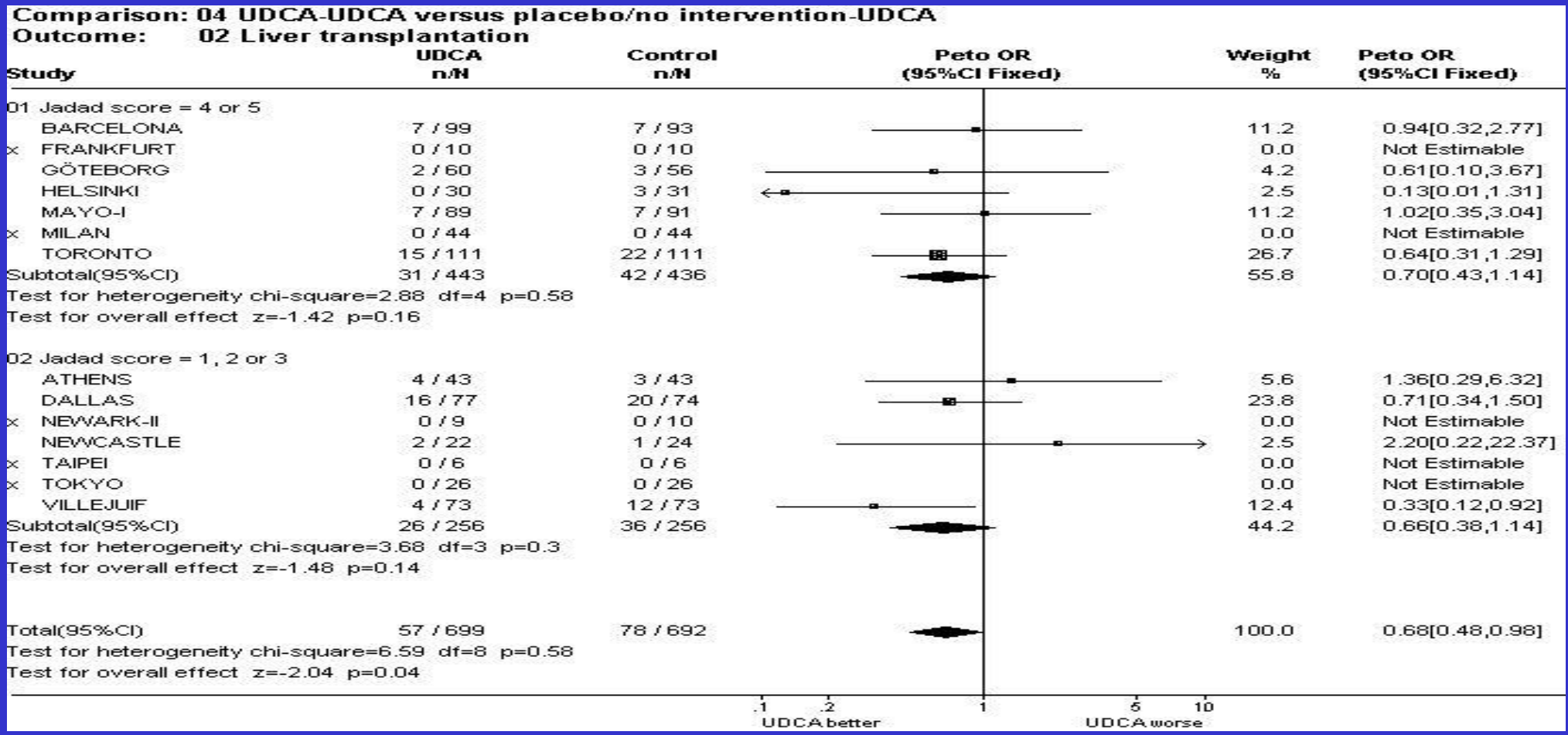
PBC: The effect of UDCA on mortality including ”cross-over” data

Cochrane Database Syst Rev. 2002;(1):CD000551



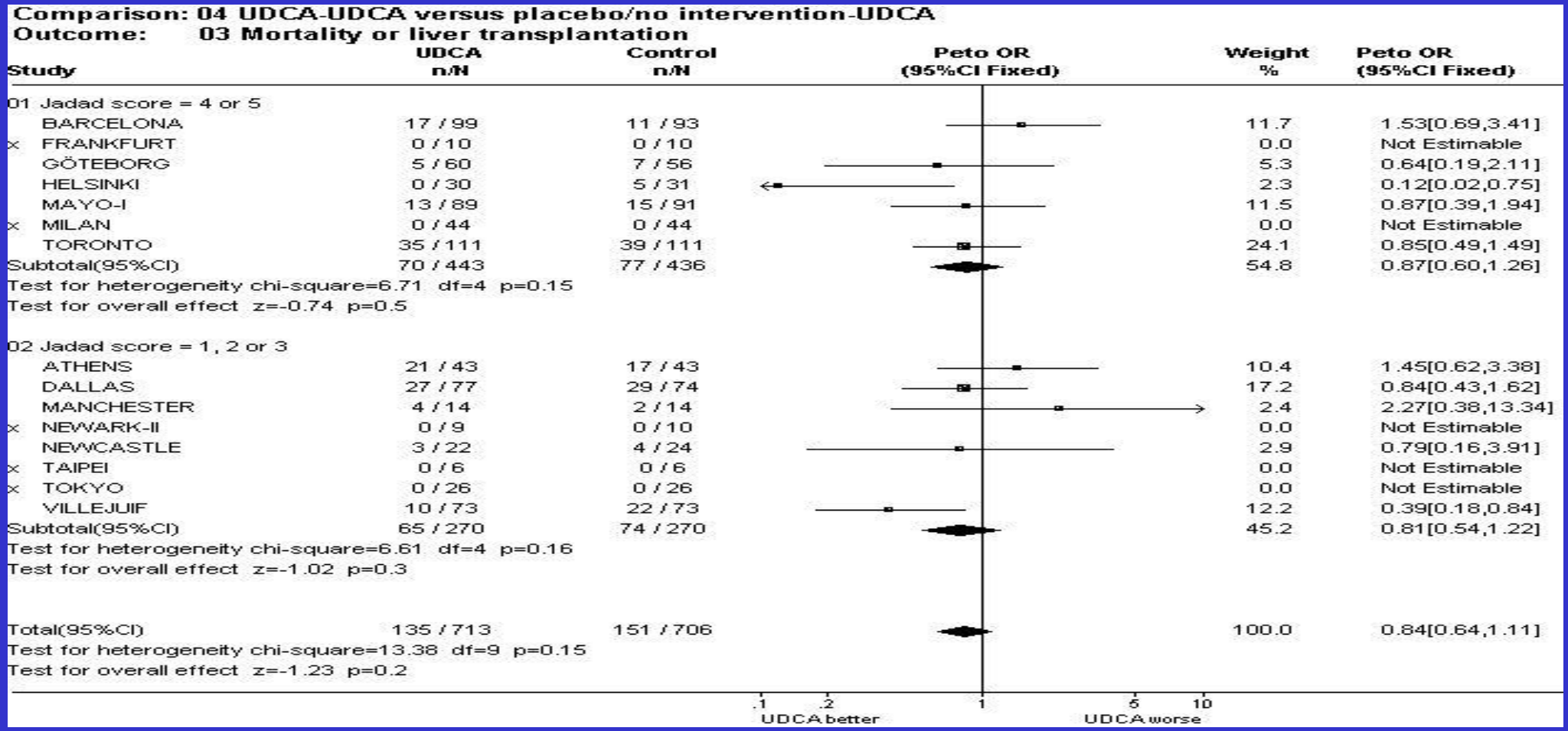
PBC: Effect of UDCA on transplantation including "cross-over" data

Cochrane Database Syst Rev. 2002;(1):CD000551



PBC: Effect of UDCA on mortality or transplantation including ”cross-over” data

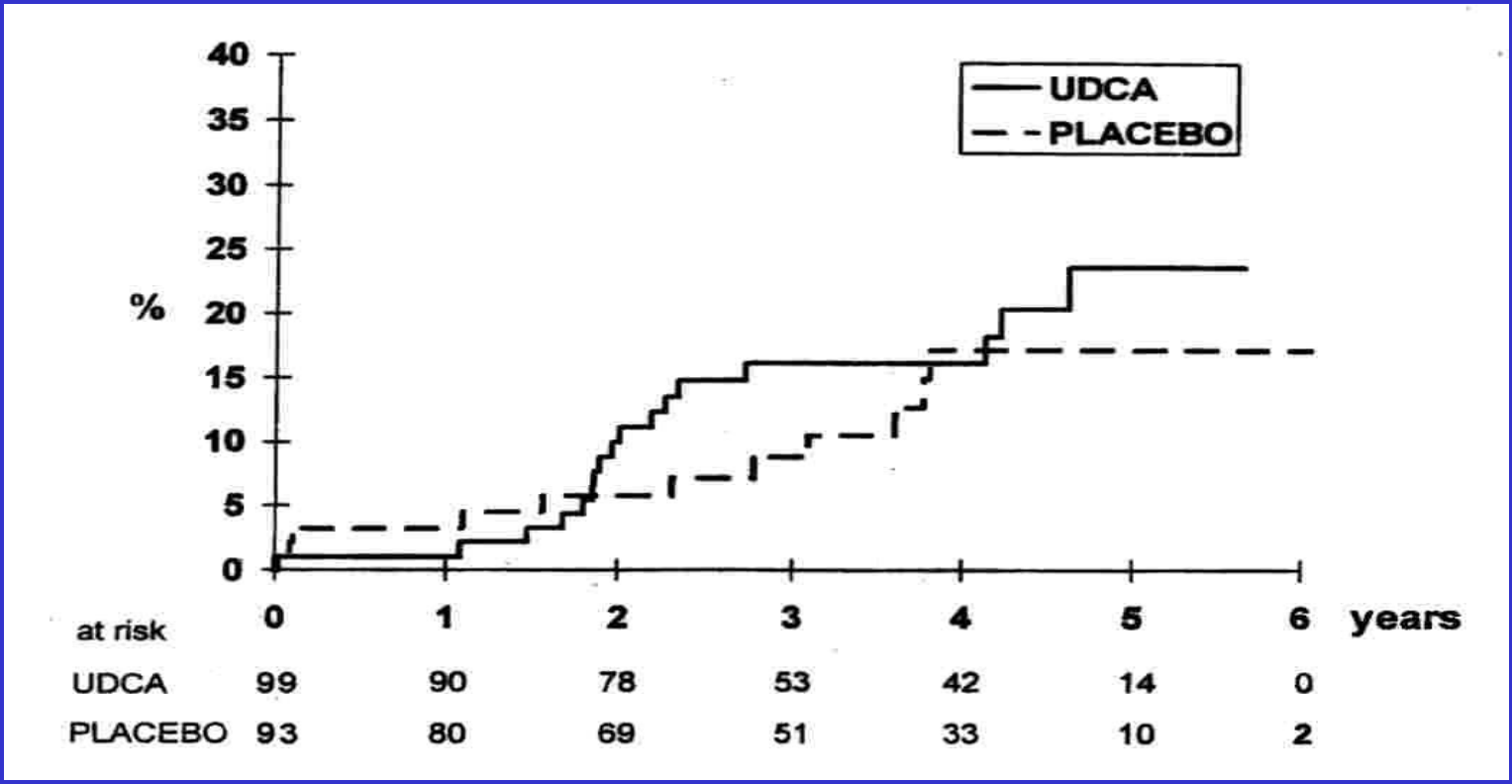
Cochrane Database Syst Rev. 2002;(1):CD000551



Long term UDCA therapy. Effect on mortality or liver transplantation (1)

Pares A et al. J Hepatol 2000; 32: 561-66.

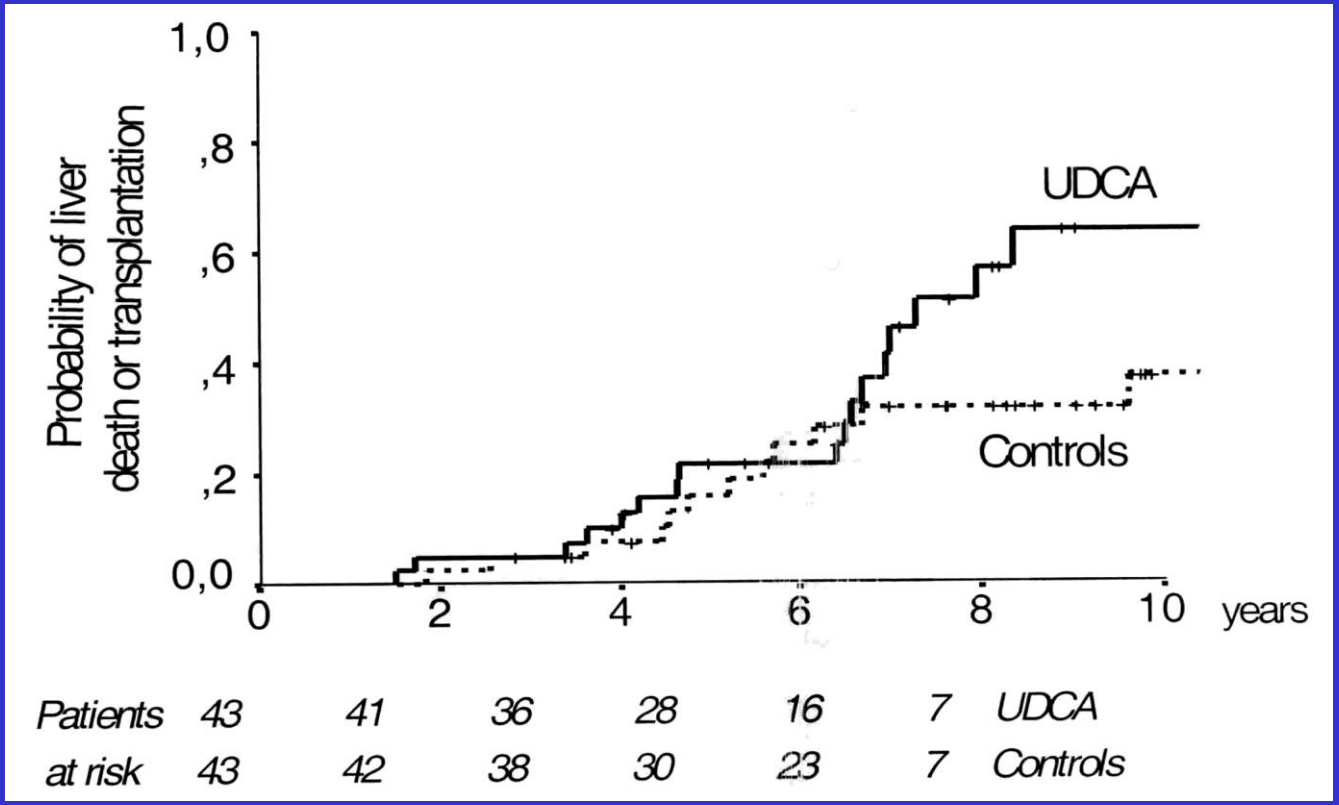
UDCA dose: 14-16 mg/kg/day



Long term UDCA therapy. Effect on mortality or liver transplantation (2)

Papatheodoridis G et al. Am J Gastroent 2002 (in press)

UDCA dose: 12 -15 mg/kg/day



Medical therapies for primary biliary cirrhosis (PBC) tested in RCTs.

Therapy	Number of patients in RCT(s)	Effect
Cyclosporin A	390	+
Azathioprine	281	+
Prednisolone[1]	66	+
Prednisone + Azathioprine[1]	50	+
Budesonide[1]	39	+
Chlorambucil	24	+
Malotilate	101	(+)
Ursodeoxycholic acid (UDCA) (standard dose)	1422	((+))
Colchicine[2]	493	((+))
D-penicillamine	635	-
Methotrexate	99	-
Thalidomide	18	-

PBC: Azathioprine 1-2 mg/kg/day

- **Heathcote** (Gastroenterology 1976;70:656-60)
  22 patients AZA (2 mg/kg/day)
  23 untreated controls

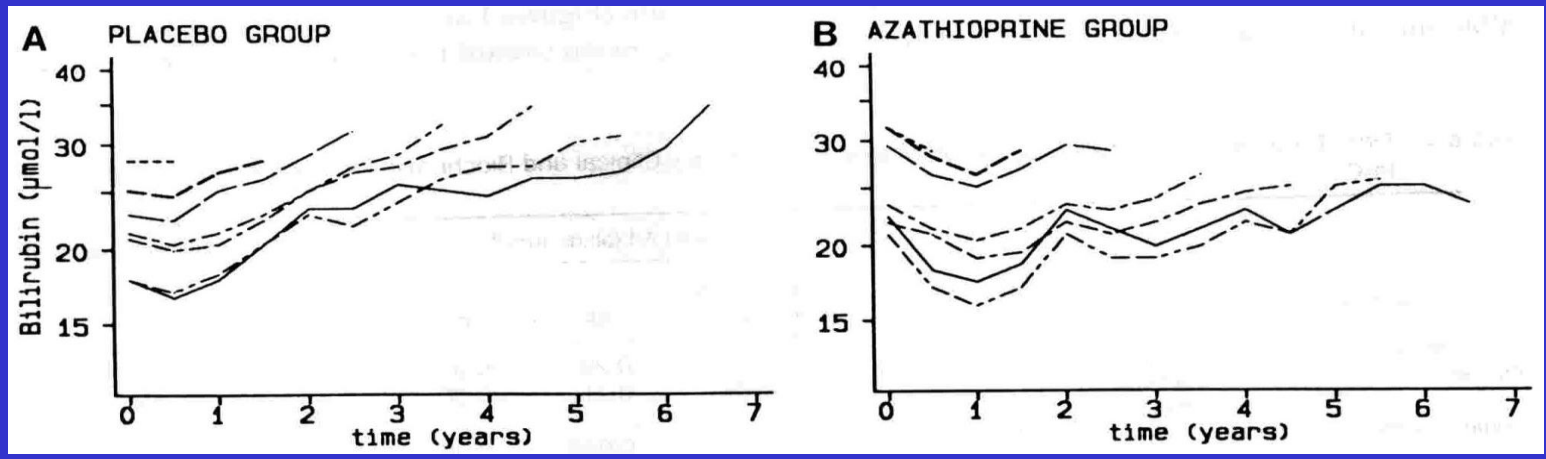
- **Multinational study** (Gastroenterology 1985;89:1084-91)
  124 patients AZA (1 mg/kg/day)
  112 patients placebo

- AZA initially improved symptoms and biochemical tests.
- AZA significantly improved survival in the large study
- Side effects 10% more frequent during AZA.

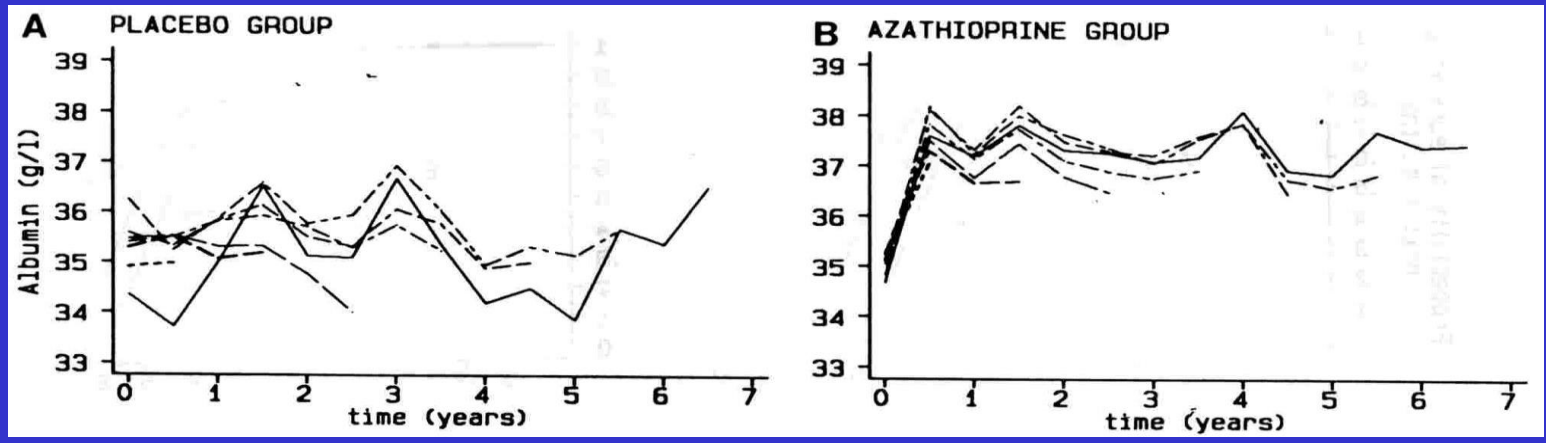
PBC: Effect of Azathioprine

Gastroenterology 1993;105:1865-76

Bilirubin:



Albumin:



PBC: Glucocorticosteroids

A: Mitchison (J Hepatol 1992; 15;336-44)
36 patients **Prednisolone** (30-10 mg/day) vs. placebo for 3 years.

B: Leuschner (J Hepatol 1996;25:29-57)
30 patients: **Prednisolone** (10 mg/day) vs. placebo for 9 months. (All on UDCA)

C: Leuschner (Gastroenterology 1999;117:918-25)
39 patients: **Budesonide k** (9 mg/day) vs. placebo for 2 years. (All on UDCA)

Steroid had significantly beneficial effect on "overall hepatic assessment" (hepatic deaths, doubling of bilirubin, >6 g/l reduction in albumin, new symptoms of portal hypertension and occurrence of cirrhosis) (prednisolone 21% placebo 65%) (A), biochemistry and histology (B and C). No significant adverse effect was found on bone mineral content.

PBC: Prednisone + Azathioprine

Wolfhagen FH . (J Hepatol 1998; 29:736-42)

50 patients treated for 1 year (all received UDCA).

Prednisone (30-10 mg/day) plus Azathioprine (50 mg/day) vs. Placebo

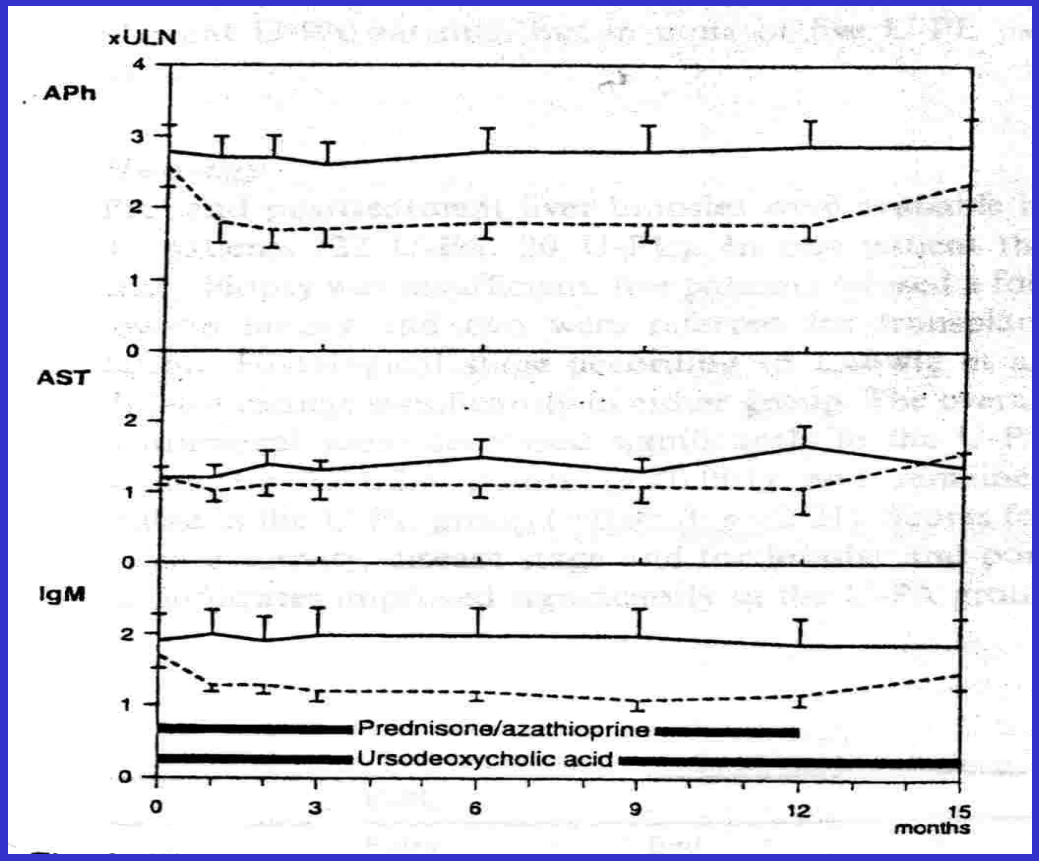
Prednisone + azathioprine led to

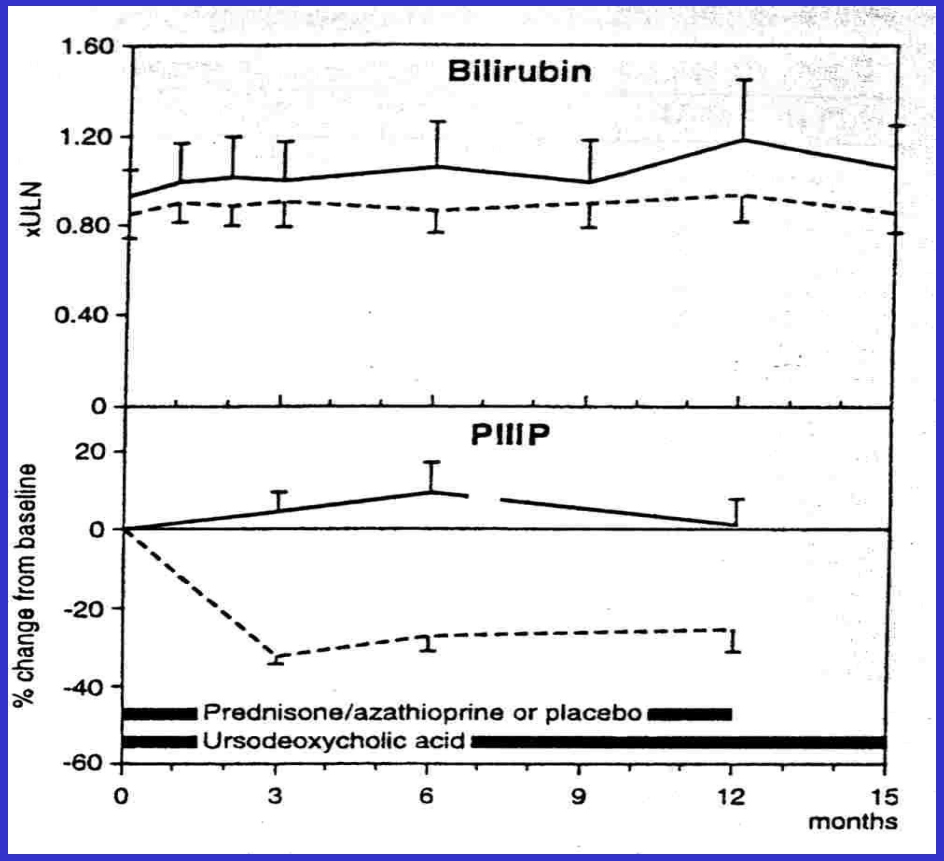
- Less pruritus
- A greater fall in enzymes and IgM
- Less histological disease activity
- Less progression of the histological stage

PBC: Prednisone + Azathioprine

Wolfhagen FH (J Hepatol 1998; 29:736-42)

Pred + Aza + UDCA: dotted line UDCA alone: solid line

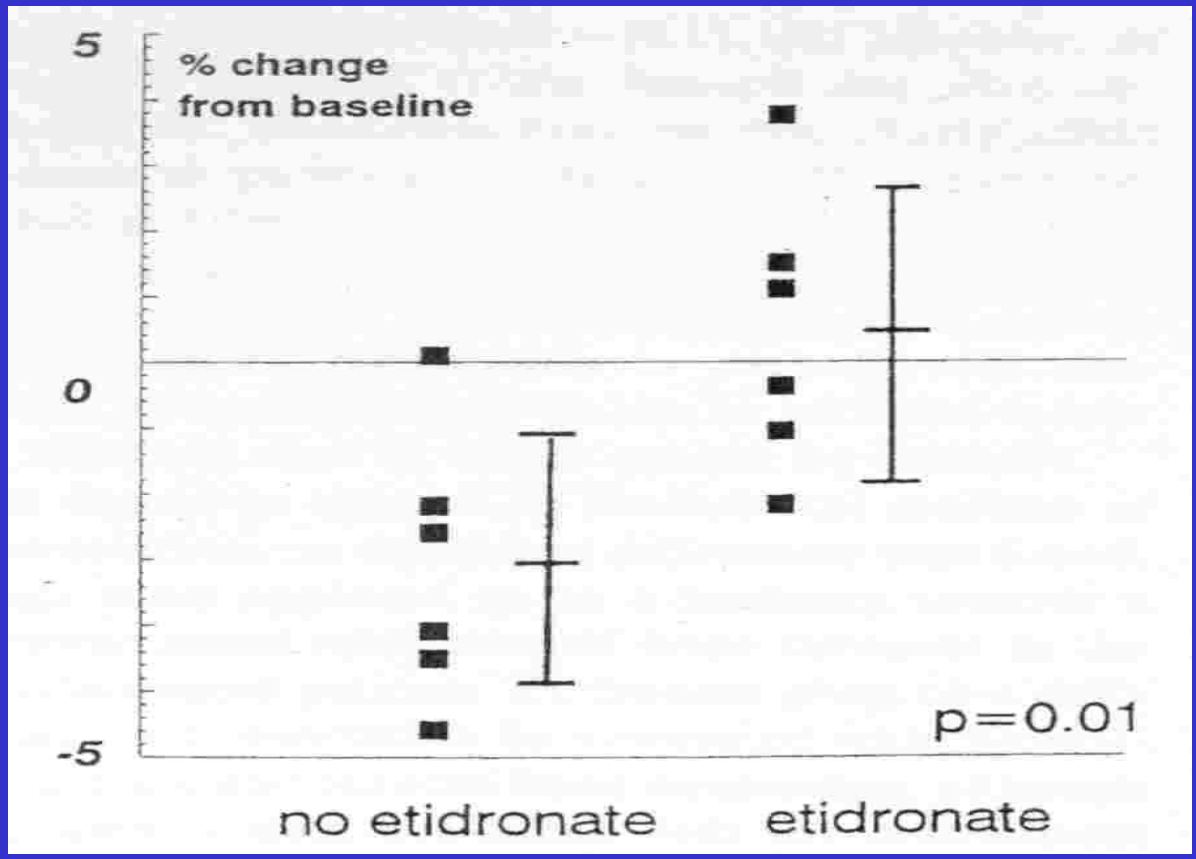




PBC Bone Loss: Etidronate (400 mg/day 2 of 11 weeks)

Wolfhagen J Hepatol 1997;26:325-30

1 year RCT. All patients received prednisone (~10 mg/day)



Conclusion

- Despite significant effects on some – mainly biochemical - variables, UDCA has no significant beneficial effect on symptoms, mortality or the need for liver transplantation.
- Other effective (immunosuppressive) therapies (including azathioprine and glucocorticosteroids) should not be withheld from the patients.
- However, more effective therapies are needed.
- Better understanding of the etiology is important.
- Gene-technology may be a valuable tool.