Der Patient mit erhöhten Leberwerten

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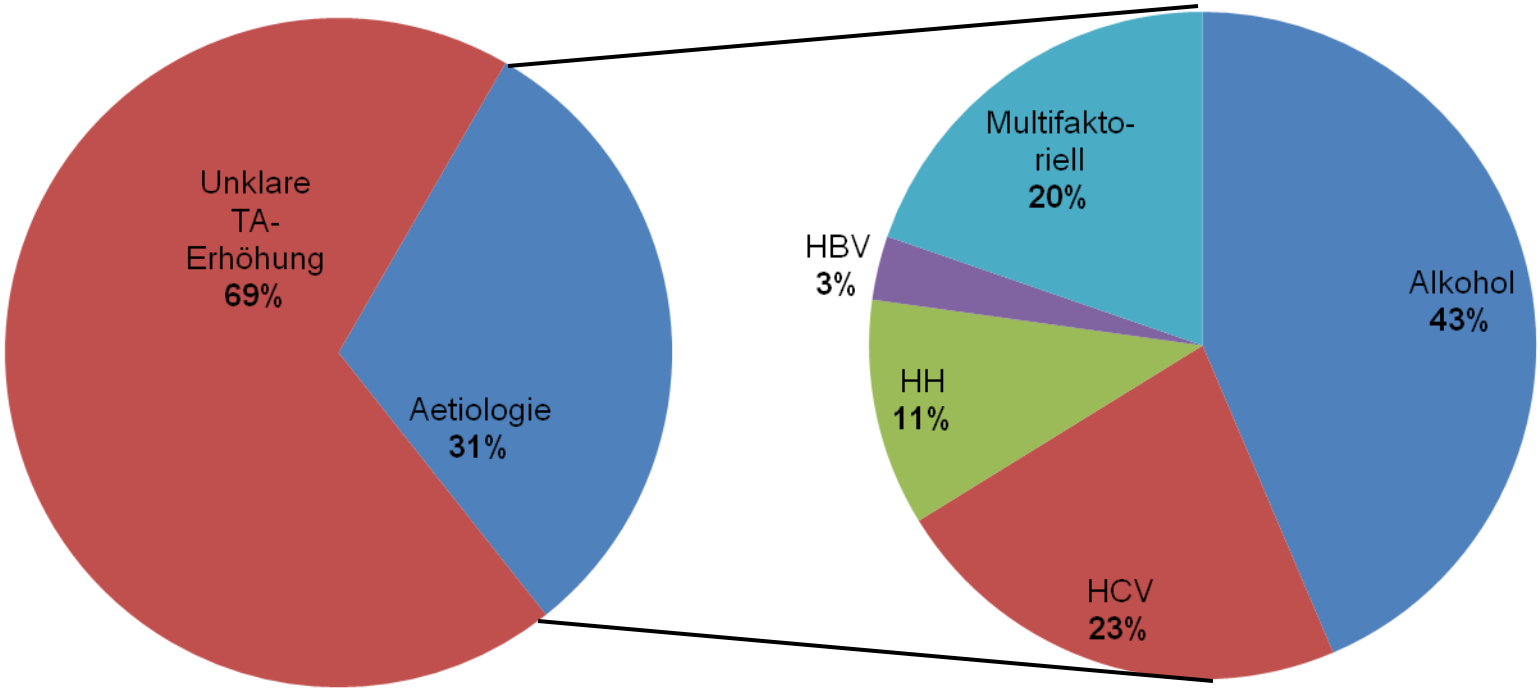
Prävalenz und Aetiologie erhöhter Leberwerte

7,9%



Clark. Am J Gastroenterol 2003;98:960

Herr E.B. 39.Lj, Kaufmann

- **JL:**
- Check-Up
- Asymptomatisch
- **PA:**
- Arterielle Hypertonie seit 2 Jahren
- TE/AE in Kindheit

Herr E.B. 39.Lj, Kaufmann

- **Medikamente:**
- ACE-Hemmer
- **Alkohol:**
- Nicht täglich (ca 40g/Woche)
- **Nikotin:**
- Nihil
- **Sozialanamnese:**
- Verheiratet, 3Kinder

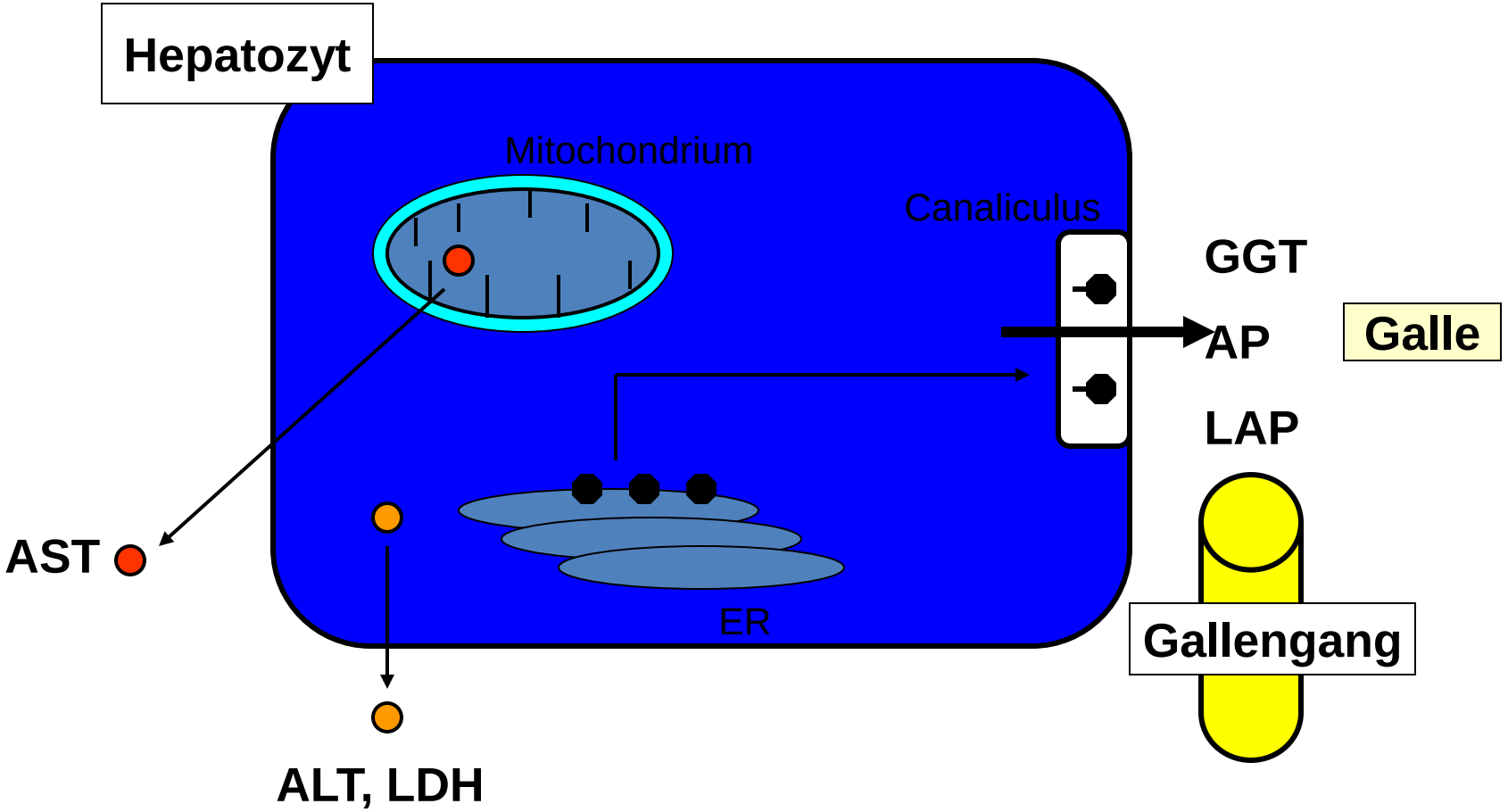
Herr E.B. 39.Lj, Kaufmann

- **Status:**
- Guter AEZ, 95kg, 178cm,
- BD 135/75mmHg, HF 72/min
- Herz, Lunge, Abdomen sowie übriger Status kursorisch iO

Herr E.B. 39.Lj, Kaufmann

- **Labor:**
- GOT(AST) 40 (<33 U/l)
- GPT(ALT) 101 (< 32 U/l)
- GGT 75 (<32 U/l)
- AP 79 (35-115 U/l)

„Ursprung“ der Leberwerte



Screening-Test:Transaminasen

- Freisetzung bei hepatozellulärem Schaden
- 2 Formen:
  - AST:
    - Nicht-spezifisch für Leber: Herz, Skelettmuskel, Niere, Hirn, Pankreas, Lunge, Lc und Ec
    - HWZ 17h
  - ALT:
    - Spezifischer: erhöht bei Myopathien
    - HWZ 47h

Screening-Test:Transaminasen

- Freisetzung bei hepatozellulärem Schaden
- 2

Keine Korrelation zwischen Höhe Transaminasen und

-Ausmass Leberzellschaden

- Prognose

- HWZ 17h

Normale Transaminasen schliessen Leberschaden nicht aus

AST/ALT-Quotient (De-Ritis)

- > 2:
  - Typisch für alkoholische Lebererkrankung
  - Falls AST >500:
    - Andere Ursache als Alkohol
  - Keine C2-Anamnese→suggestiv für ZI
- <1:
  - zB NAFLD, HCV etc

Sorbi D. Am J Gastroenterol 1999;94:1018

Screening-Test:Alkalische Phosphatase

- Vorkommen:
  - Leber (Gallencanaliculus), Knochen
  - Weniger in Darm, Plazenta
- HWZ 7d
- Erhöhung:
  - Hepatobiliär:
    - GG-Obstruktion, PBZ, PSC
    - Leberinfiltration, ZI, Hepatitis
    - Medikamente
  - Nicht-Hepatisch:
    - Knochenerkrankung, NI, HI, TU
    - SS, Adoleszenz
    - Nikotin

Screening-Test: GGT

- Vorkommen:
  - Leber, Niere, Pankreas, Darm, Prostata
- Enzyminduktion:
  - Alkohol
  - Medikamente (Phenytoin, Barbiturate, Kontrazeptiva, Warfarin, Steroide,….)
- HWZ 7-10d
- Erhöht auch bei:
  - DM, Hyperthyreose, rA, COPD

Screening-Test: GGT

- Vorkommen:

Prädiktiver Wert für hepatobiliäre Pathologie nur 32%

>30% Patienten mit normaler GGT trotz mehr als 80g Alkohol/d

- HWZ 7-10d
- Erhöht auch bei:
  - DM, Hyperthyreose, rA, COPD

Bilirubin

- Produkt des Hämoglobinabbaus
- Indirektes Bilirubin:
  - Hämolyse, M.Meulengracht, Hämatomresorption, ineffektive Erythropoese
- Direktes Bilirubin:
  - = konjugiert = wasserlöslich
  - GG-Obstruktion, Cholestase, ZI, Hepatitis
  - An Albumin gebunden
  - HWZ 17-20d

Schweregrad?
Albumin

- Synthese in Leber
- Vermindert:
  - Leberzirrhose
  - Malnutrition
  - Kataboler Stoffwechsel (Trauma, Sepsis,…)
  - Nephrotisches Syndrom
  - Malabsorption
- HWZ 19-21d

Schweregrad?
INR

- Leber produziert div. Gerinnungsfaktoren (Fibrinogen=Faktor I, Faktor II, V, VII, IX, X)
- Lebersynthesestörung → INR hoch
  - Faktor VII mit kürzester HWZ
  - Faktor VIII normal (tief bei DIC)
  - Faktor V tief (Normal bei Vitamin K-Mangel)

Hepatitisches vs. Cholostatisches Muster

Test	Cholostatische Erkrankung	Hepatozellulärer Schaden
GOT	normal bis +	++ bis +++
GPT	normal bis +	++ bis +++
Alk. Ph‘ase	++ bis +++	normal bis +
GGT	++ bis +++	normal bis +
Bili	normal bis +++	normal bis +++

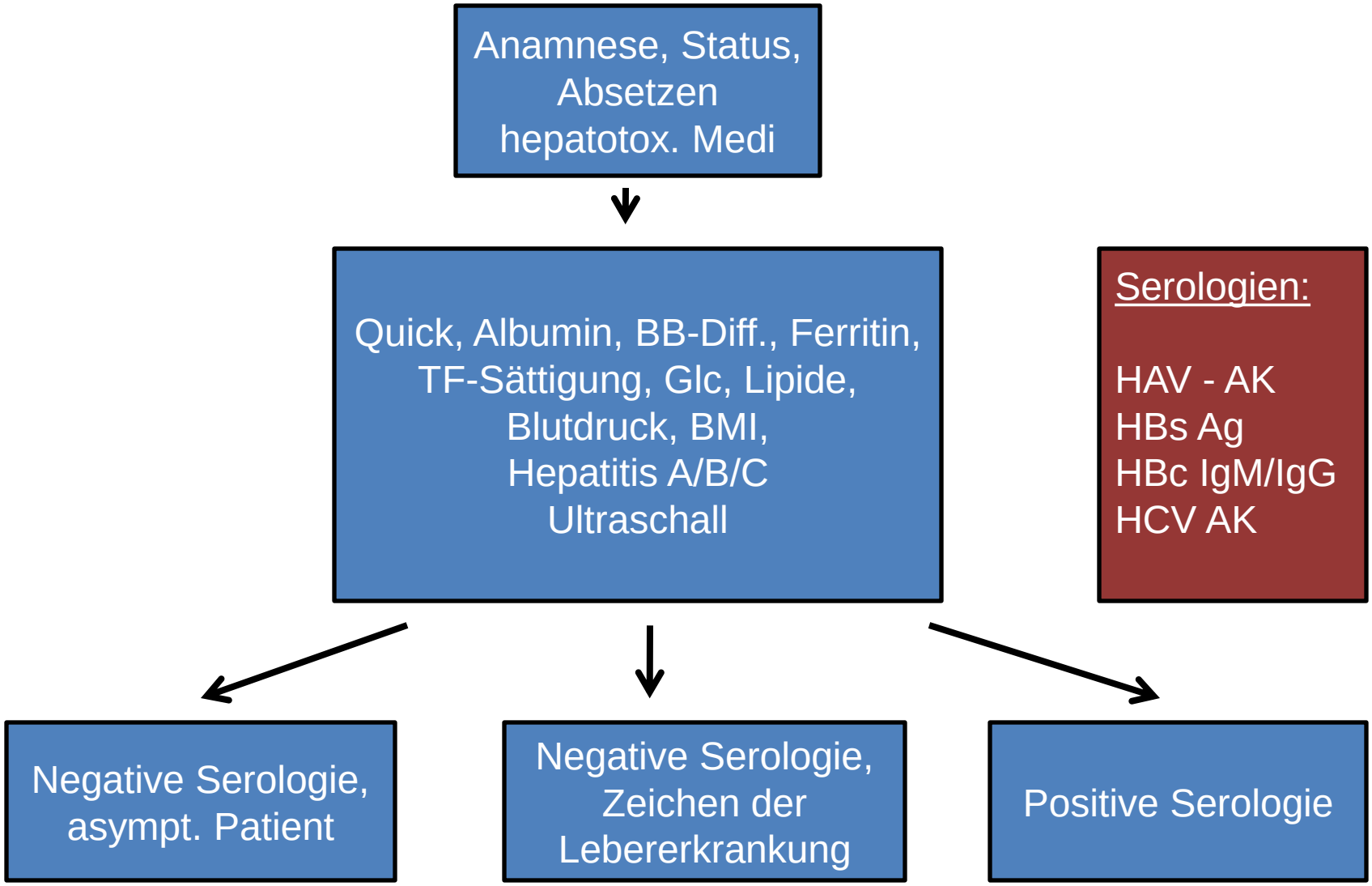
Herr E.B., 39.Lj, Kaufmann

- **Kontrolle nach 2 Monaten:**
- **Labor:**

GOT	51	(<33 U/l)
GPT	87	(< 32 U/l)
GGT	71	(< 32 U/l)
AP	80	(< 115 U/l)

?

Transaminasen <5f erhöht



Negative Abklärung Symptome/Zeichen Leberkrankheit

Ultraschall
ANA, SMA-AK, tTG-IgA, (Coeruloplasmin), Antitrypsin

+

Leberbiopsie

Herr E.B., 39.Lj, Kaufmann

Labor:

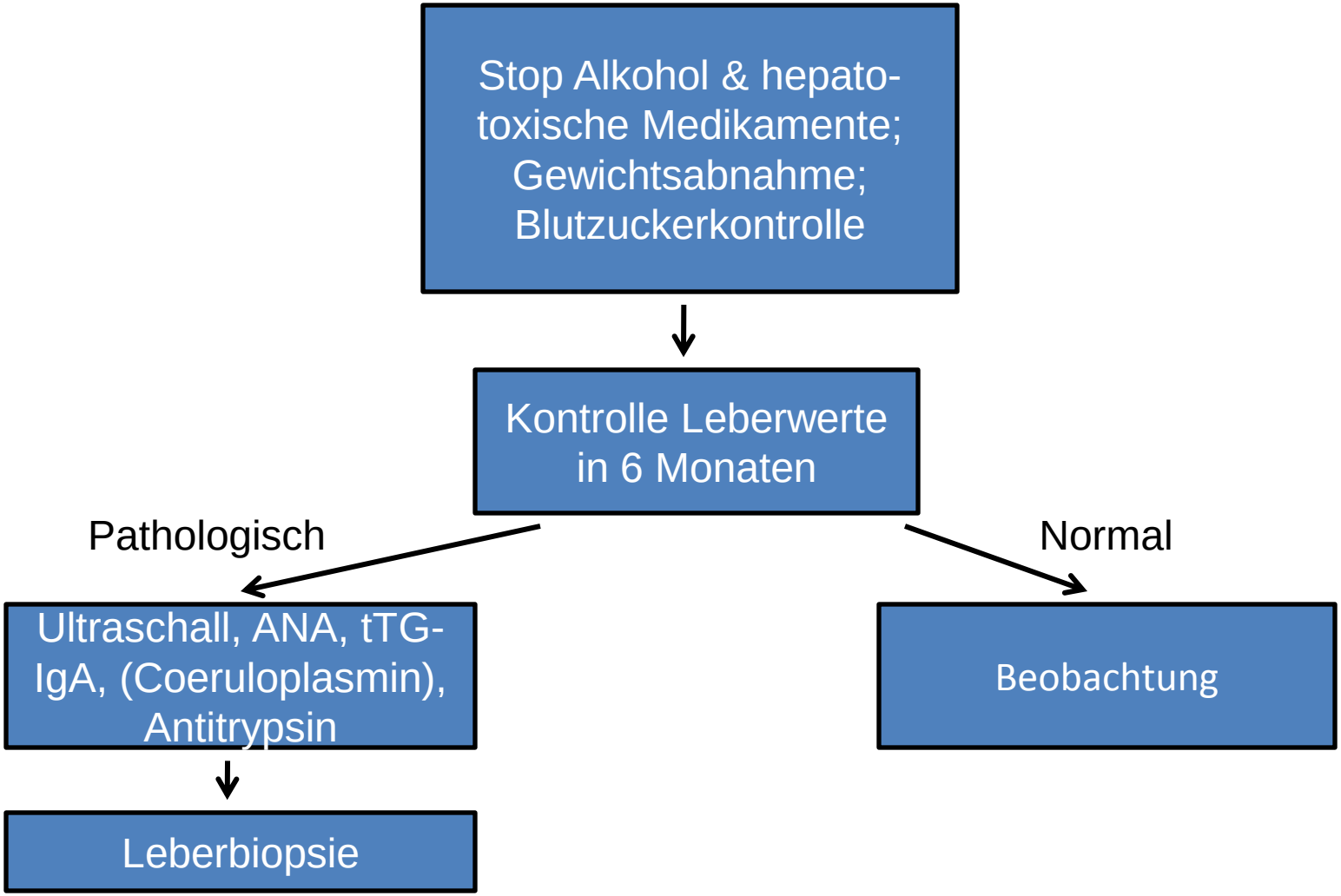
-**Quick:**	91%
-**Albumin:**	45g/l
-**BZ:**	5,8mmol/l
-**Cholesterin:**	4,1
-**BB:**	Hb 14,8g/dl; normochrom, normozytär
-**Ferritin:**	461ug/l
-**TF-Sättigung:**	32%
-**HBs-Ag/HBc-AK:**	negativ
-**HCV-AK:**	negativ

?

Ultraschall:

Keine Zirrhose

Negative Abklärung asymptomatischer Patient

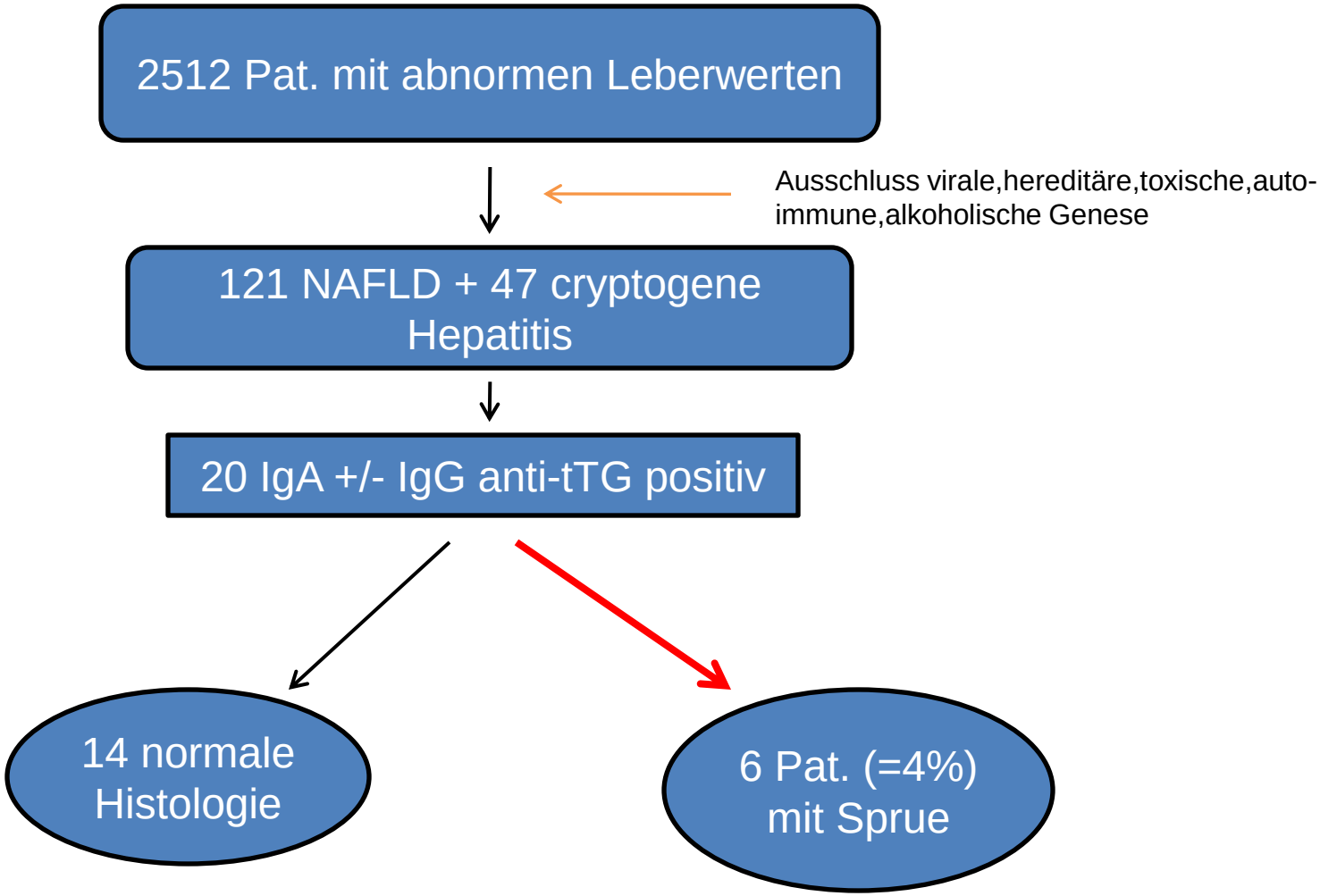


Sprue und Leber

Serie	Pat.zahl	abnorme TA (%)	Besserung mit Therapie (%)
Hagander	**75**	**39**	**100**
Jacobsen	**132**	**47**	**75**
Bodé	**50**	**19**	**?**
Bardella	**158**	**42**	**95**
Novacek	**178**	**40**	**89**
Mugica	**20**	**40**	**?**

Duggan J. Aliment Pharmakol Ther 2005;21:515

Erhöhte Leberwerte & Sprue



Lo Iacone. Am J Gastroenterol 2005;100:2472

Herr E.B., 39.Lj, Kaufmann

Labor nach 6 Monaten:

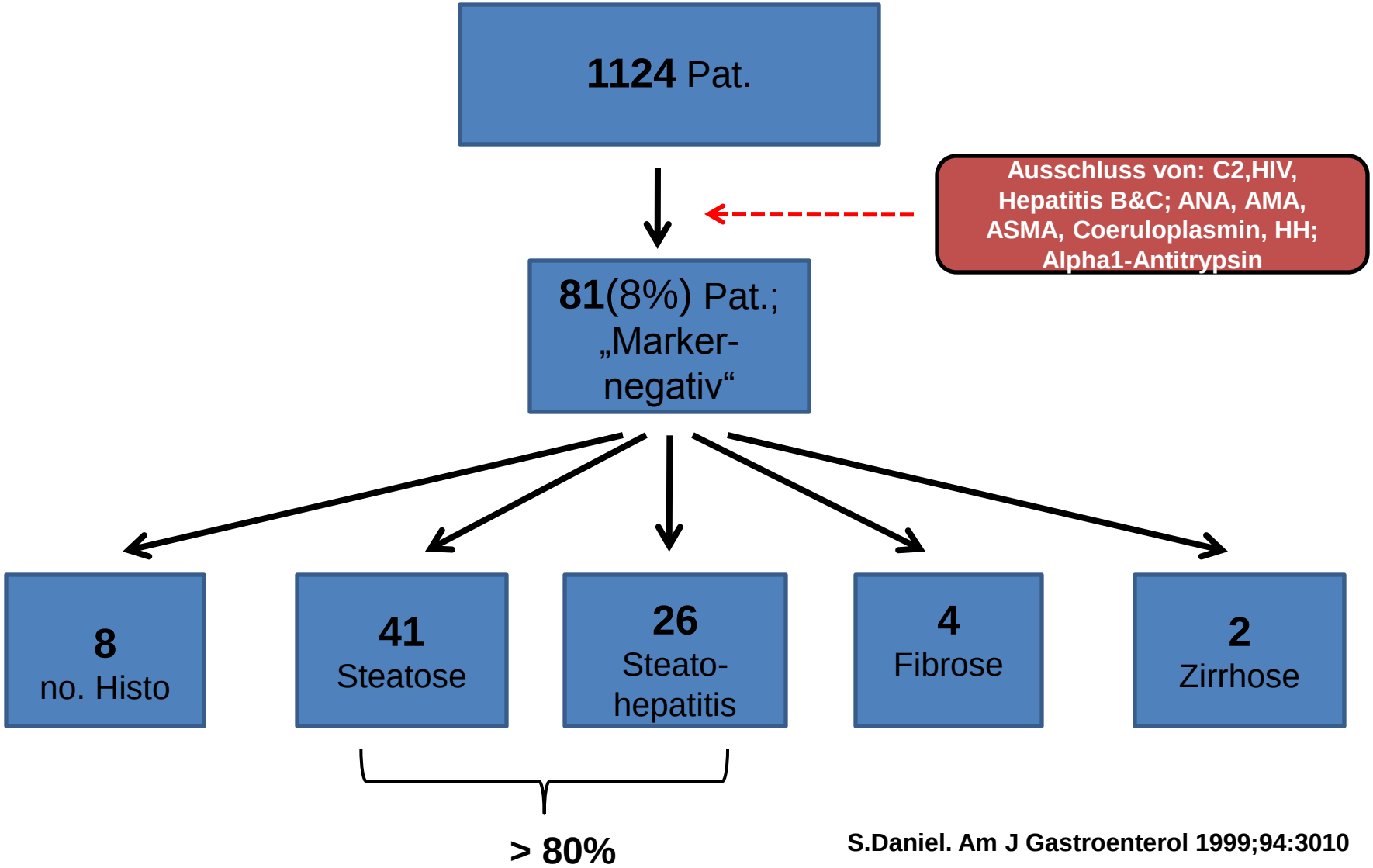
-Quick:	88%
-GOT	45 U/l
-GPT	67 U/l
-AP	84 U/l
-tTG-IgA:	normal
-ANA:	negativ
-Coeruloplasmin:	normal
-Alfa1-Antitrypsin:	negativ

Diagnose?

NAFLD

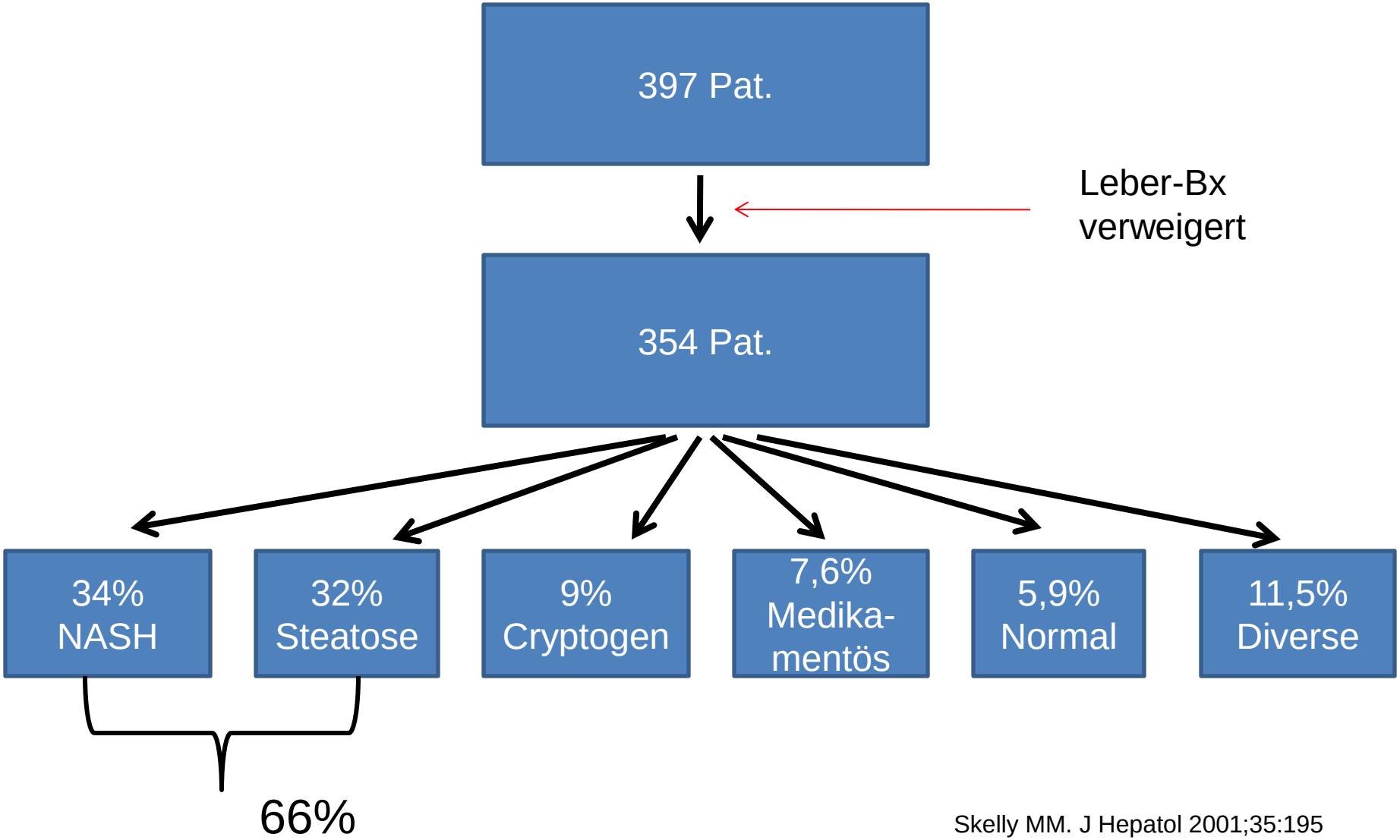
Nichtalkoholische Fettlebererkrankung

Unklar erhöhte TA



S.Daniel. Am J Gastroenterol 1999;94:3010

Unklar erhöhte TA



Skelly MM. J Hepatol 2001;35:195

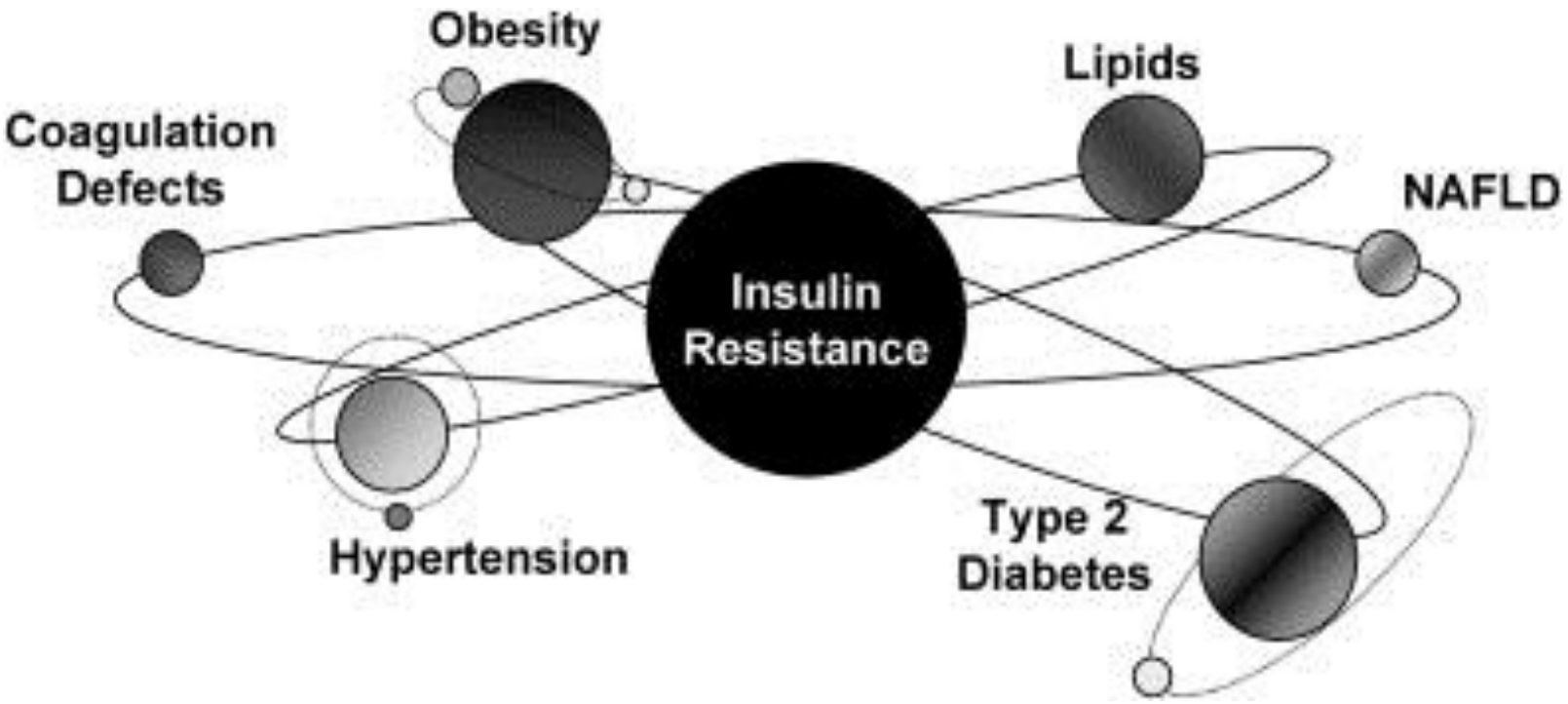
NAFLD

- **<u>Dionysos-Study:</u>**
  - Prävalenz ca 20%
- Risikofaktoren:
  - Adipositas
  - Hyperglycämie
  - Hyperinsulinämie
  - Hypertonie
  - Hypertriglycerinämie

} **Metabol. Syndrom**

Bellentani S. Hepatology 1994;20:1442
Bedogni G. Hepatology 2005;42:44

NAFLD und metabol. Syndrom



Marchesini G. Clin Liver Dis 2007;105-117

Insulinresistenz: HOMA-Index

(Homeostasis model assessment)

HOMA= ((Nüchterninsulin (umol/ml)x Nüchternglucose (mmol/l))/22,5

>3 ist pathologisch

Klinik

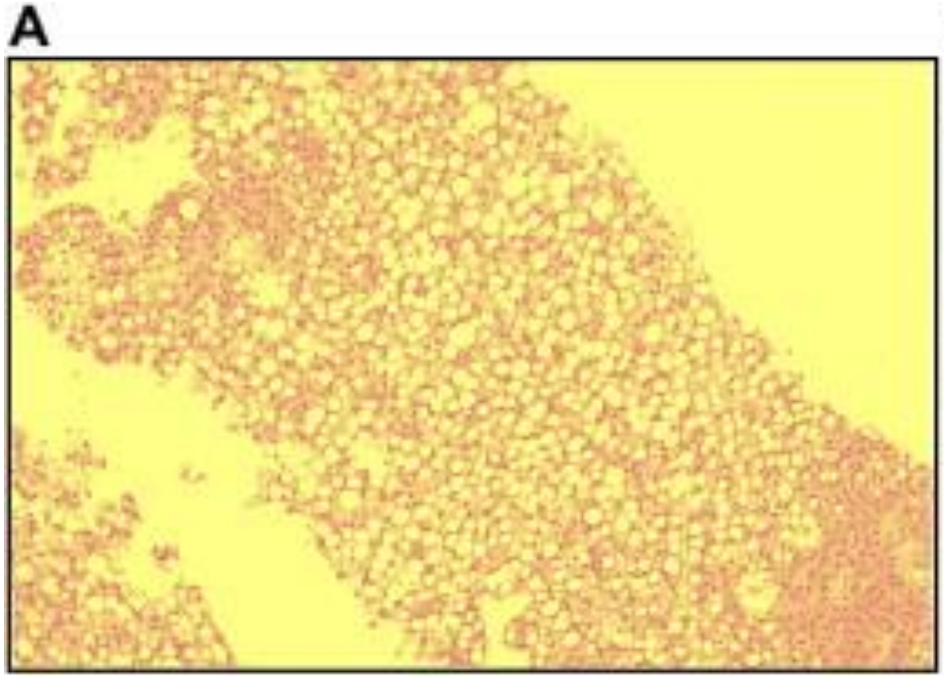
Evt. Müdigkeit

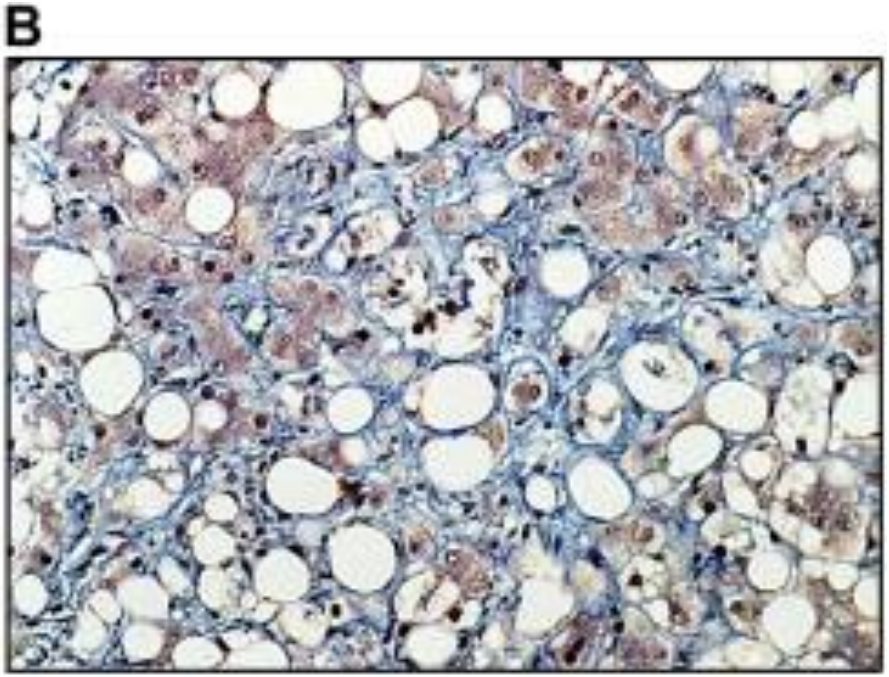
Hepatomegalie

Erhöhte TA

„Bright“ liver im Ultraschall

Histologie=Diagnose





Steatosis

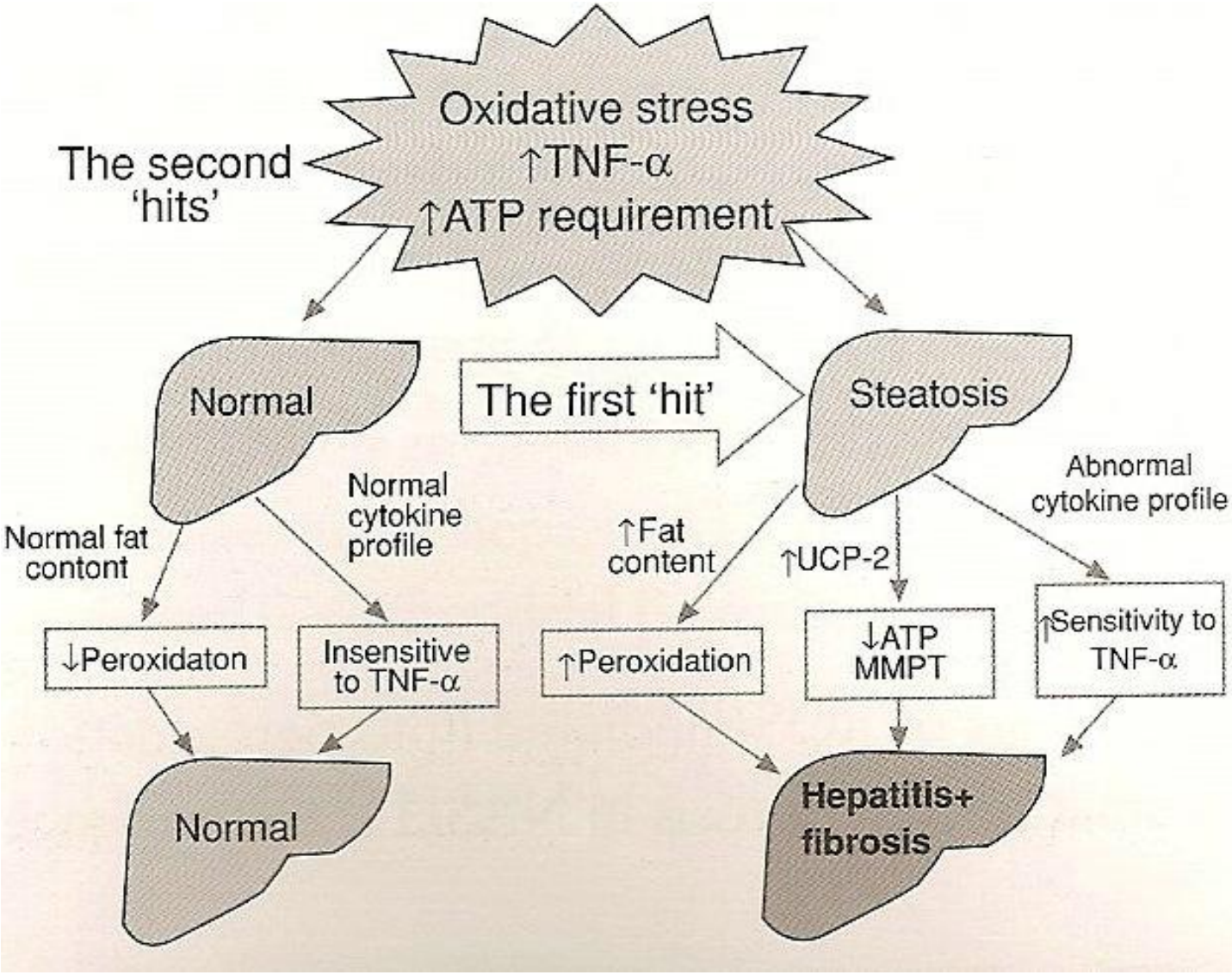
Steatohepatitis

Nicht-Invasive Marker

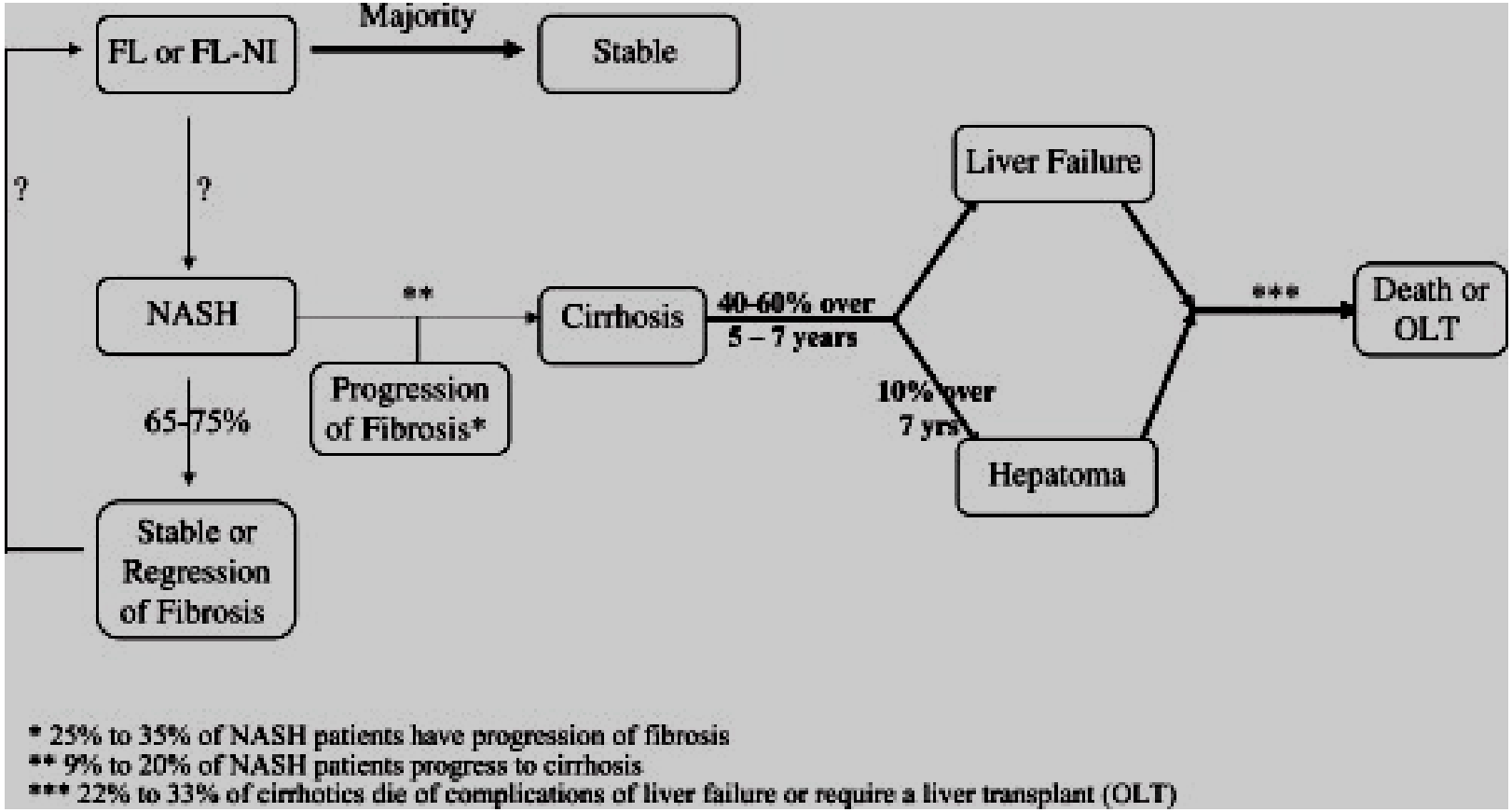
	Serum-Biomarker	Bildgebung	Atemtest
Fibrosis	BARD score Fibrotest NAFLD fibrosis score ELF/OELF Hyaluronsäure	Fibroscan MR-Elastography MR-Spektroskopy	Acetone (C13) methacetin (C13) ketoisocaproate Ethanol
Oxidat. stress	TBARS Oxidized-LDL Total antioxidant response Total lipid peroxide levels		
Hepatocyte apoptosis	CK-18 fragment		
Inflammation	TNF-Alfa/adiponectin ratio hsCRP IL-6 CC-chemokine ligand-2		

Vuppalanchi R. Hepatology 2009;49:306

NAFLD/NASH

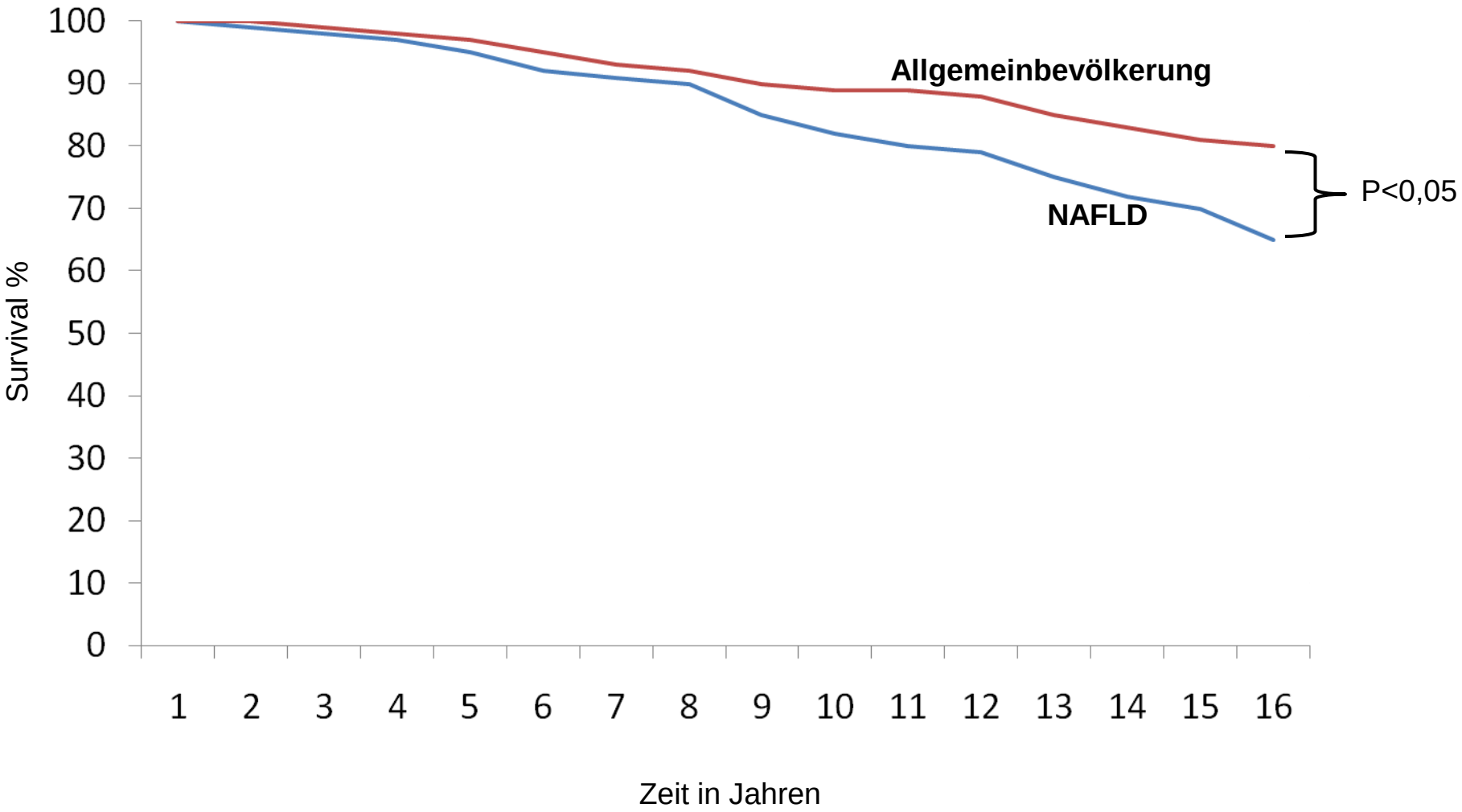

Oxidative stress
↑TNF-α
↑ATP requirement
The second 'hits'
Normal
The first 'hit'
Steatosis
Normal fat contont
Normal cytokine profile
↑Fat content
↑UCP-2
Abnormal cytokine profile
↓Peroxidaton
Insensitive to TNF-α
↑Peroxidation
↓ATP MMPT
↑Sensitivity to TNF-α
Normal
Hepatitis+ fibrosis

Verlauf NAFLD



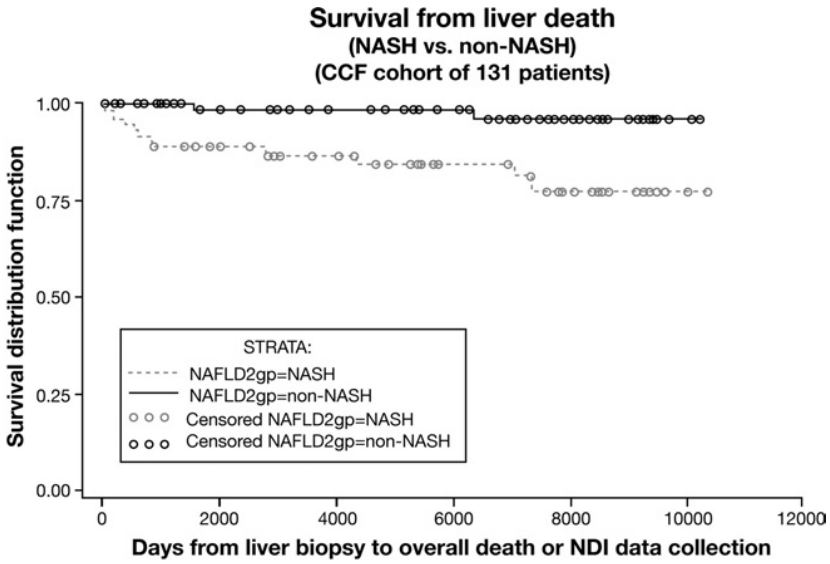
Adams LA. J Hepatol 2005;42:132

Prognose NAFLD



Adams L. Gastroenterol 2005;129:113

Prognose Steatose vs NASH

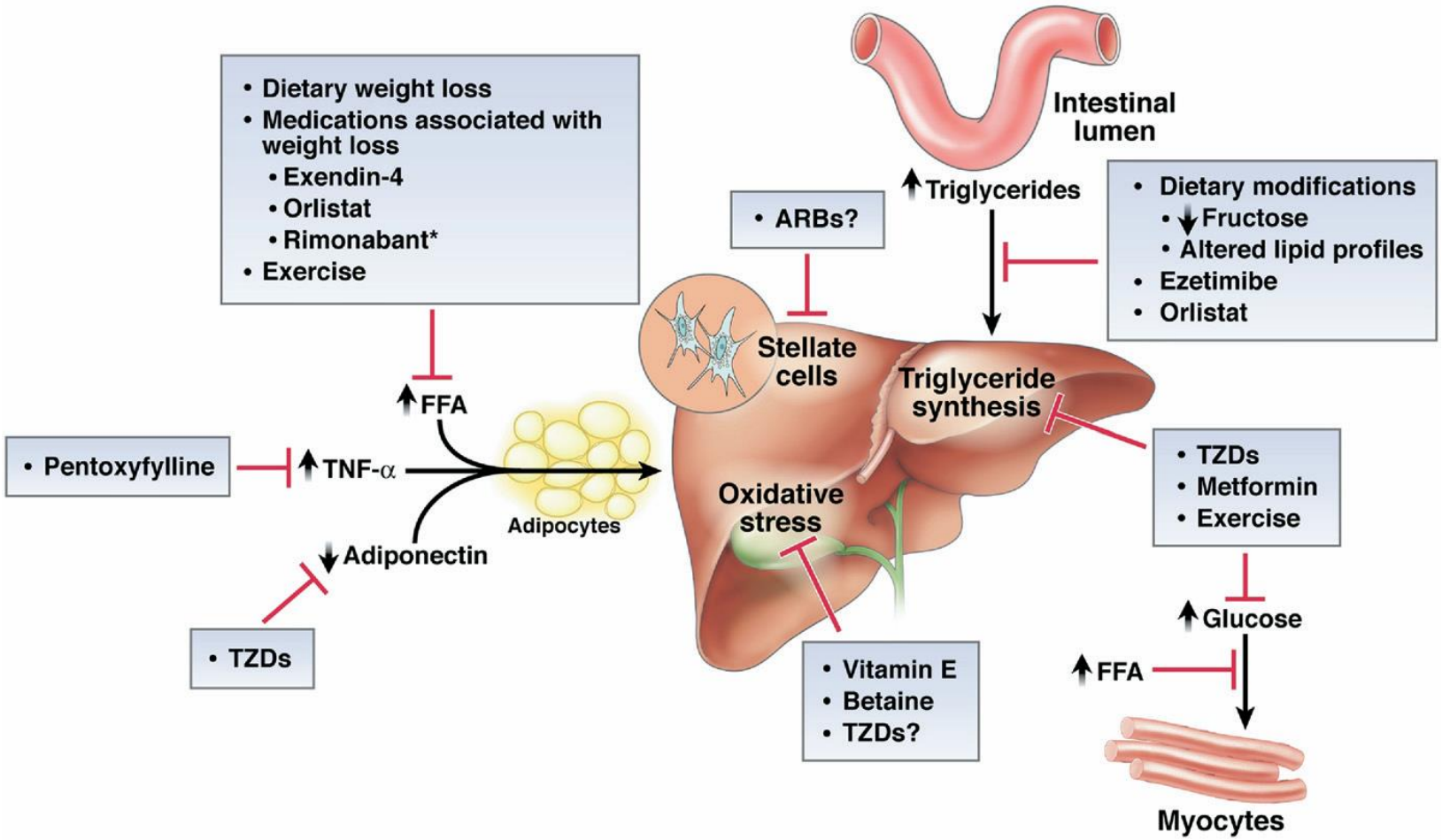


Causes of Mortality

Causes of death	Count	%
Coronary artery disease	22	12.7
Malignancy	14	8.1
Liver-related mortality (including hepatocellular carcinoma)	12	6.9
Complications of type 2 diabetes	5	2.9
Other causes of death (infection, lung disease, and so forth)	18	10.4
Unknown	7	4.0

Rafiq N. Clin Gastroenterol Hepatol 2009;2:234

Potentielle Therapieansätze



Gastroenterology 2008;134:1682

Therapie

Gewichtsabnahme:

Diät:

ausgewogene Kost
low-glycemic, low fat
vermehrt Gemüse/Früchte

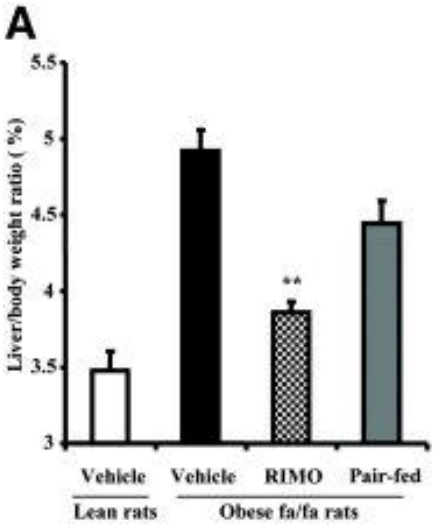
Bewegung:

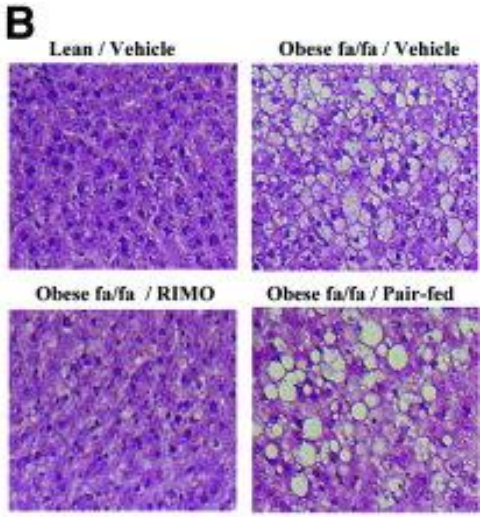
5-7x/ Woche
mässige Anstrengung
je 30-45 Min.

Medikamente:

Orlistat (wenig Daten)
Rimonabant?
Glucagon-like protein-1-receptor agonist?

Rimonabant



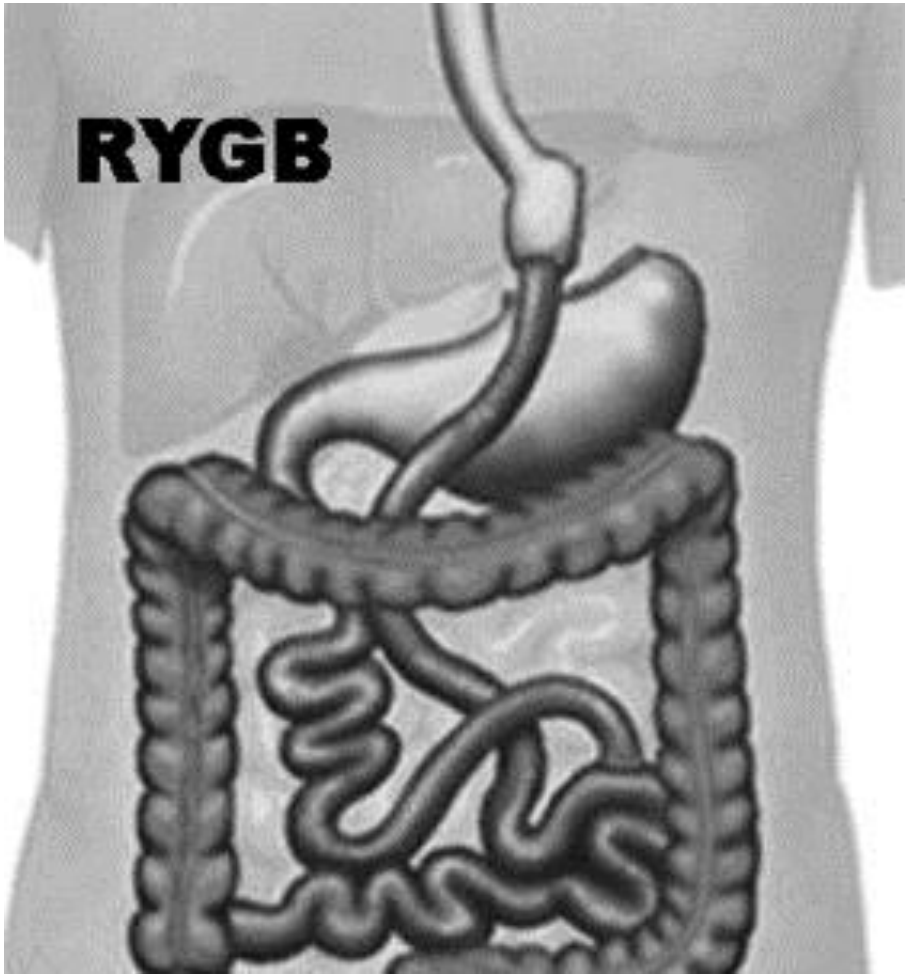


C

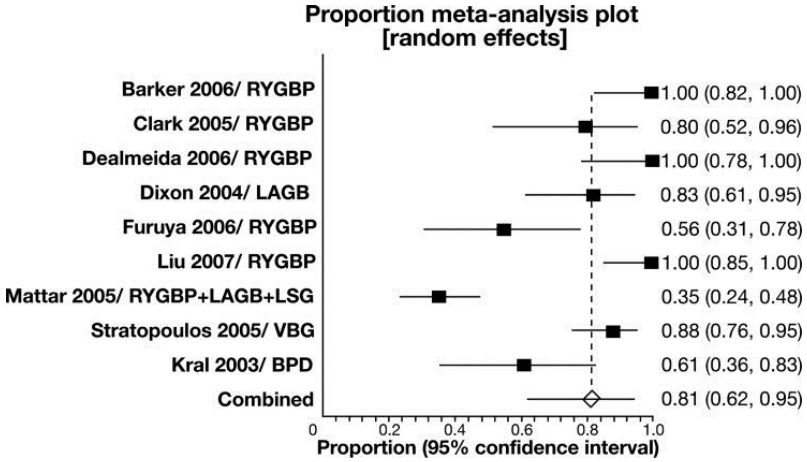
	ALT (U/L)	GGT (U/L)	ALP (U/L)
Lean / Vehicle	59.20 ± 8.97	0.09 ± 0.09	246 ± 10.28
Obese fa/fa / Vehicle	119.58 ± 6.23	10.67 ± 2.52	351 ± 14.43
Obese fa/fa / RIMO	86.78 ± 6.69 **	2.50 ± 0.91 **	290 ± 7.45 **
Obese fa/fa / Pair-fed	121.01 ± 9.60	7.18 ± 1.03	358 ± 15.62

Gary-Bobo M. Hepatology 2007;46:122

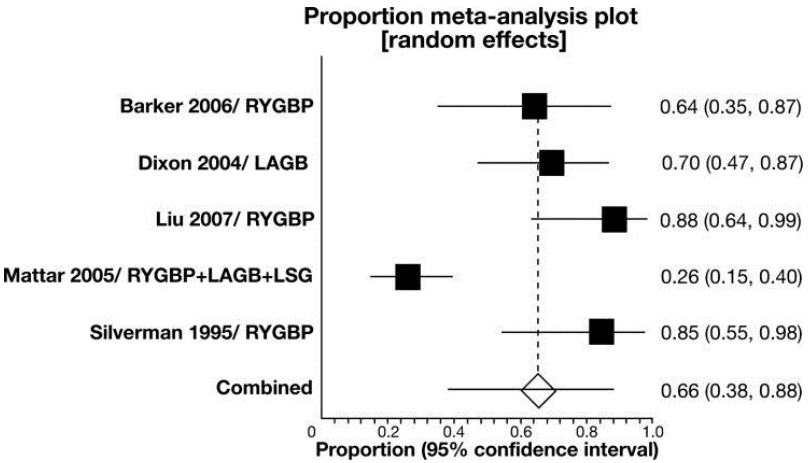
Therapie



Bariatrische Chirurgie



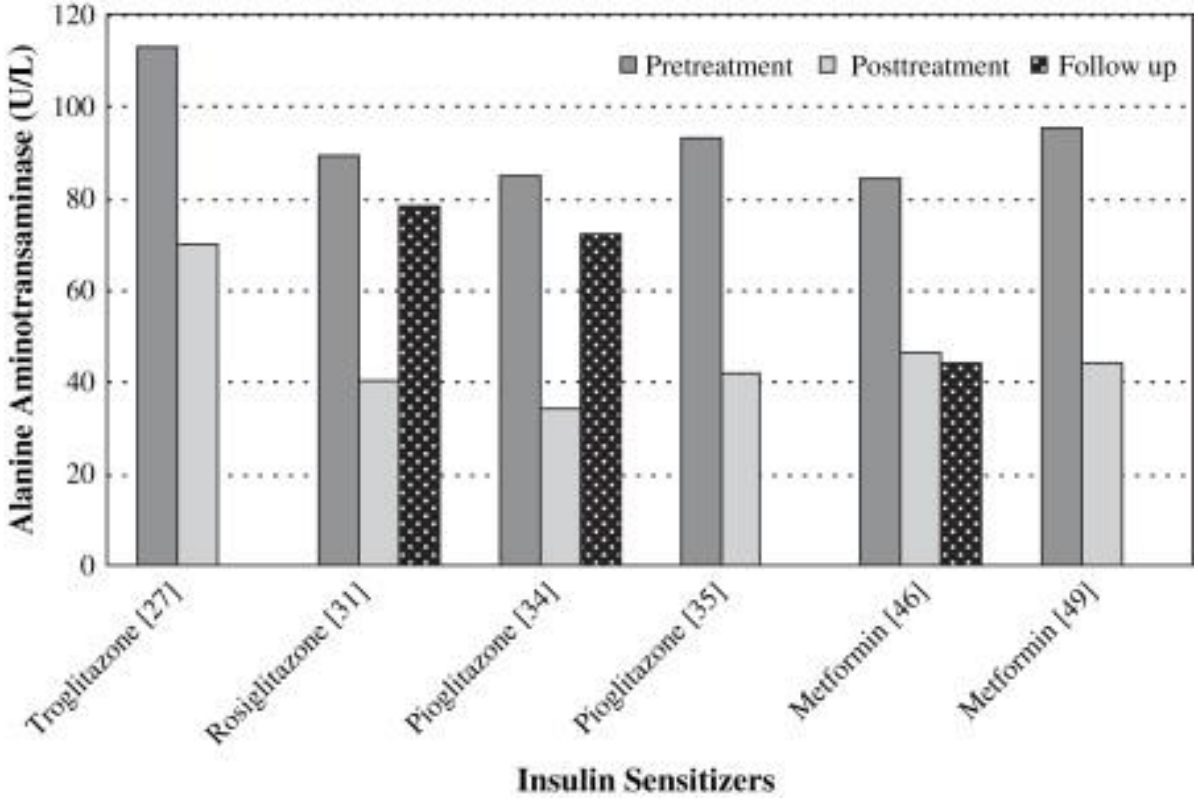
Steatohepatitis



Fibrose

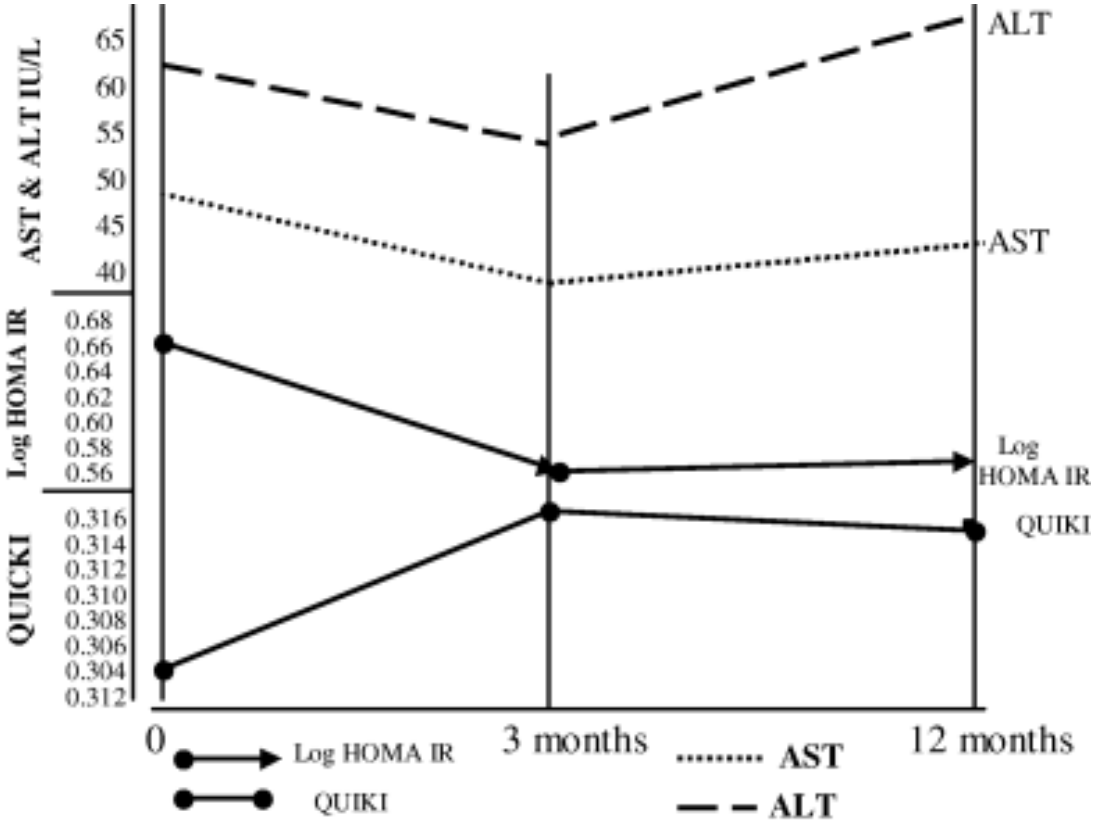
Mummadi et al. Clin Gastroenterol Hepatol 2008;6:1396

Therapie: Insulinsensitizer



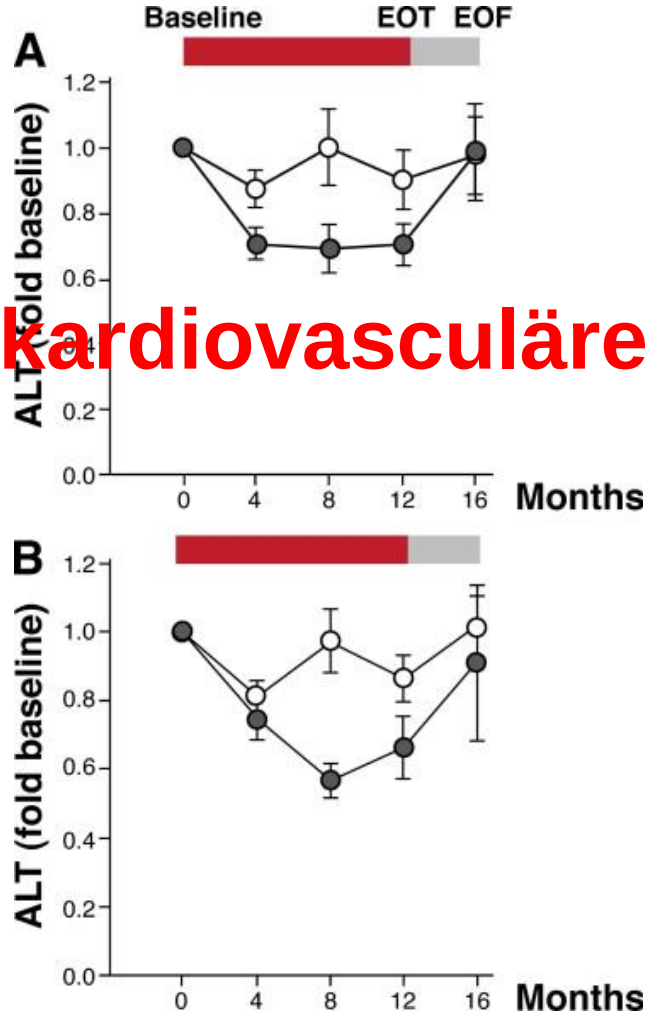
Kadayifci A. Clin Liver Dis 2007:119

Metformin



Nair S. Aliment Pharmacol Ther 2004;20:23

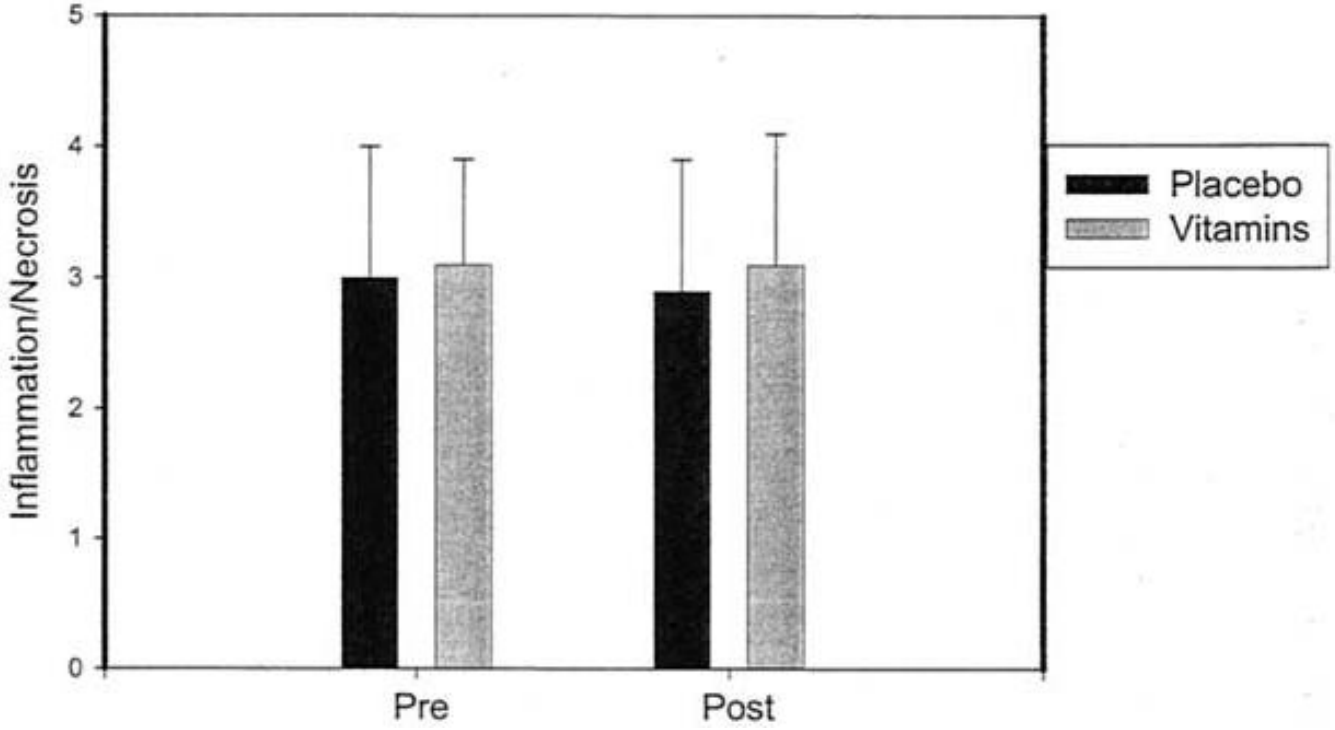
Thiazolidine



! Erhöhtes kardiovasculäres Risiko !

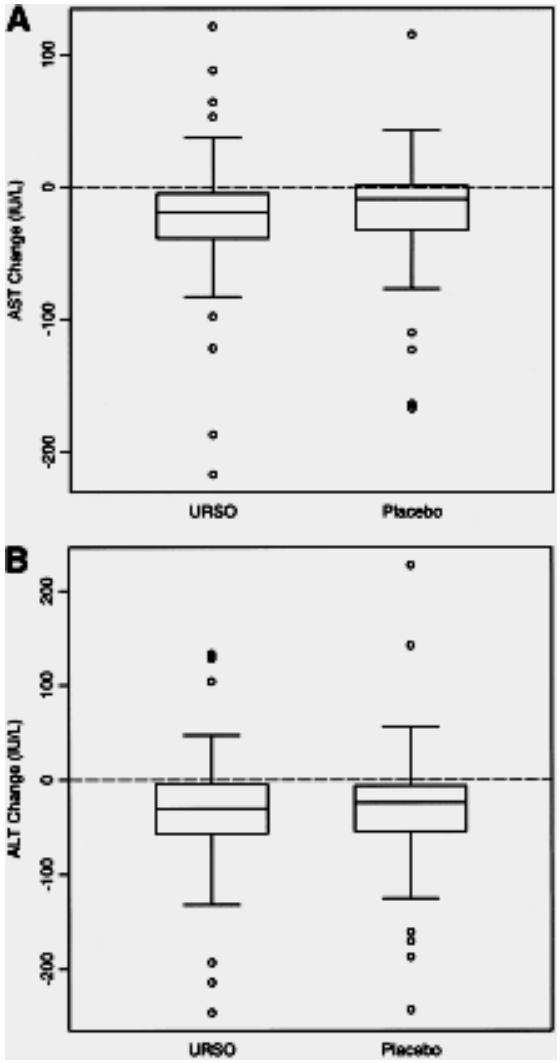
Neuschwander-Tetri BA. Hepatology 2003;38:1008

Antioxidantien



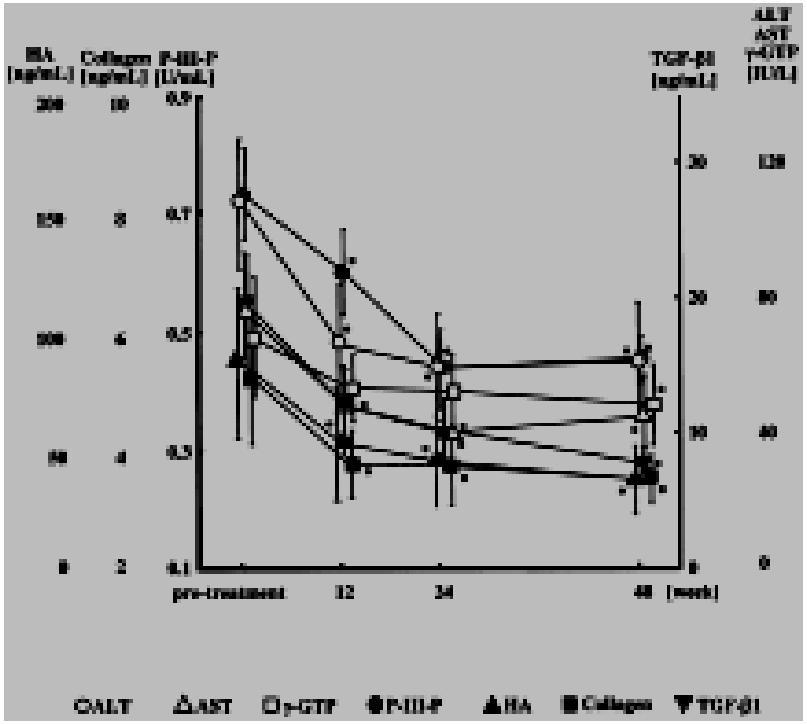
Harrison SA. Am J Gastroenterol 2003;98:2485

Ursodeoxycholsäure



Lindor KD. Hepatology 2004;39:770

AT-II-Antagonisten



Yokohama S. Hepatology 2004;40:1222

Therapie

Metformin vs Vit. E vs Placebo	Phase III, Multicenter RCT
Pioglitazon vs Metformin vs Placebo	Phase III, Multicenter RCT
Omega-3-Fettsäuren	Phase II, Pilotstudie
Orlistat	Phase III, Multicenter
Silymarin	Phase II, Multicenter RCT
Rimonabant	Phase IIb, Multicenter RCT
Pentoxiphyllin	Phase II, Pilotstudie
SAM	Phase II, Pilotstudie
Eisendepletion	Phase II, Pilotstudie

Hepatopathie und Statine

Baseline ALT	Week	Pravastatin	Placebo	p
NAFLD				
Normale ALT	12	5/45(11%)	3/40(7,5%)	0,6575
	36	5/45(11%)	4/40(10%)	0,9849
Erhöhte TA	12	3/58(5,2%)	4/61(6,6%)	0,7203
	36	4/58(6,9%)	8/61(13,1%)	0,2316
Chron. Hepatitis				
Normale ALT	12	0/17(0%)	1/16(6,3%)	0,3173
	36	0/17(0%)	1/16(6,3%)	0,3173
Erhöhte TA	12	0/11(0%)	1/27(3,7%)	0,3833
	36	1/27(3,5%)	5/27(18,5%)	0,3810
Alle Teilnehmer				
Normale TA	12	5/73(7,1%)	6/68(8,8%)	0,5675
	36	5/73(7,1%)	7/68(10,3%)	0,3700
Erhöhte TA	12	4/87(4,6%)	5/92(5,4%)	0,7363
	36	7/87(8%)	13/92(14,1%)	0,2098

! PROBLEMLOS !

Lewis J.Hepatology 2007;46:1453

Cholesterinsenker

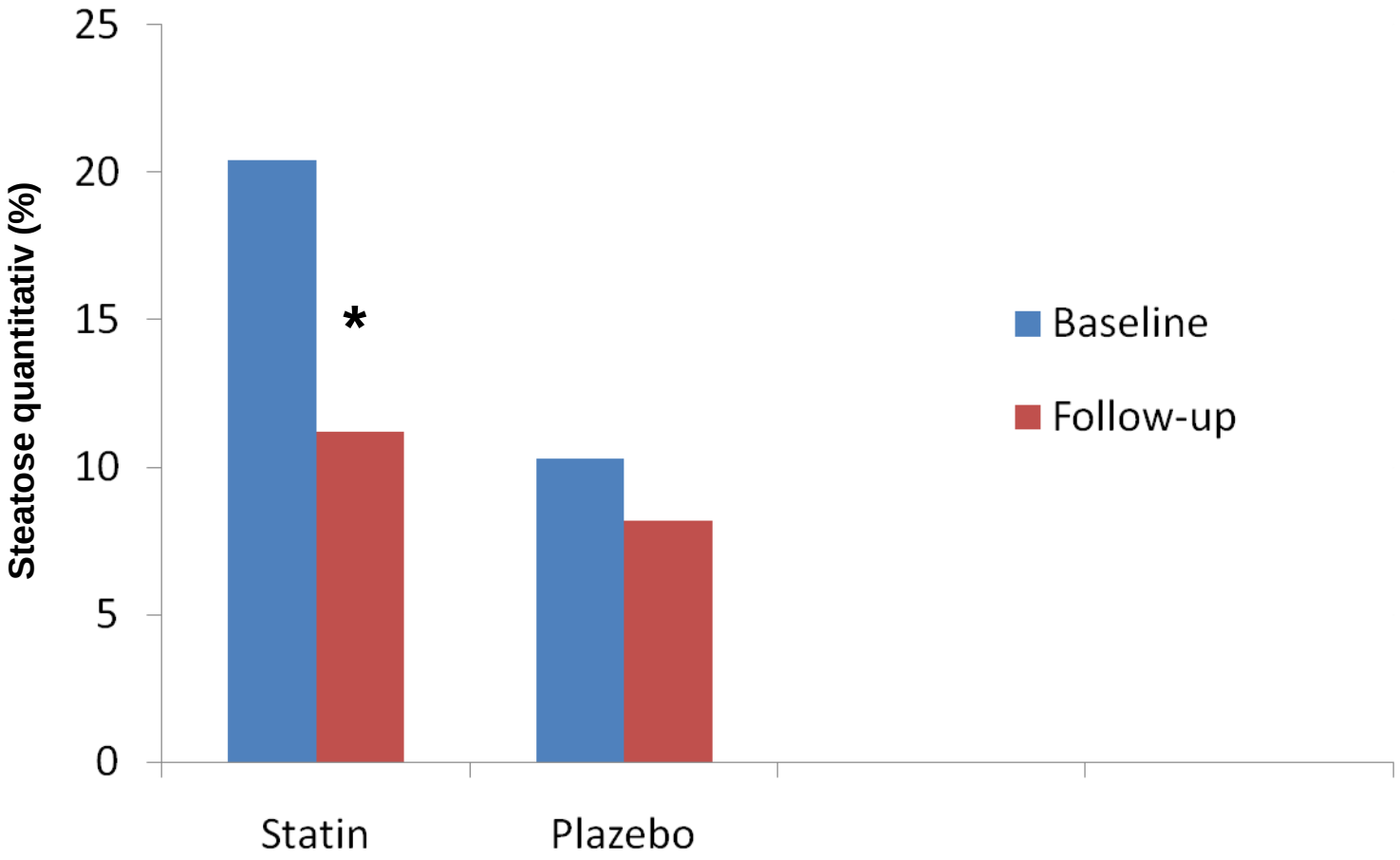
Box 1. Summary of recommendations of the liver expert panel to the National Lipid Association on statin safety

- Asymptomatic increases in aminotransferases are a class effect of statins, and they do not indicate liver dysfunction.
- Liver failure causing death or hospitalization or requiring liver transplantation is very rare from statins.
- Current evidence does not support routine monitoring of liver enzyme levels and liver biochemistries in patients receiving statins.
- Presence of chronic liver disease and Child's A cirrhosis should not be considered a contraindication for statin use.
- Current evidence supports the use of statins to treat hyperlipidemia in patients who have nonalcoholic fatty liver disease and nonalcoholic steatohepatitis.

From Vuppalanchi R, Chalasani N. Statins for hyperlipidemia in patients with chronic liver disease: are they safe? Clin Gastroenterol Hepatol 2006;4(7):838–9; with permission. Copyright © 2006, American Gastroenterological Society.

Sidhart S. Clin Liver Dis 2007;11:597

Statine und Leberhistologie



Ekstedt M. J Hepatol 2007;47:135

TAKE-Home Message NAFLD

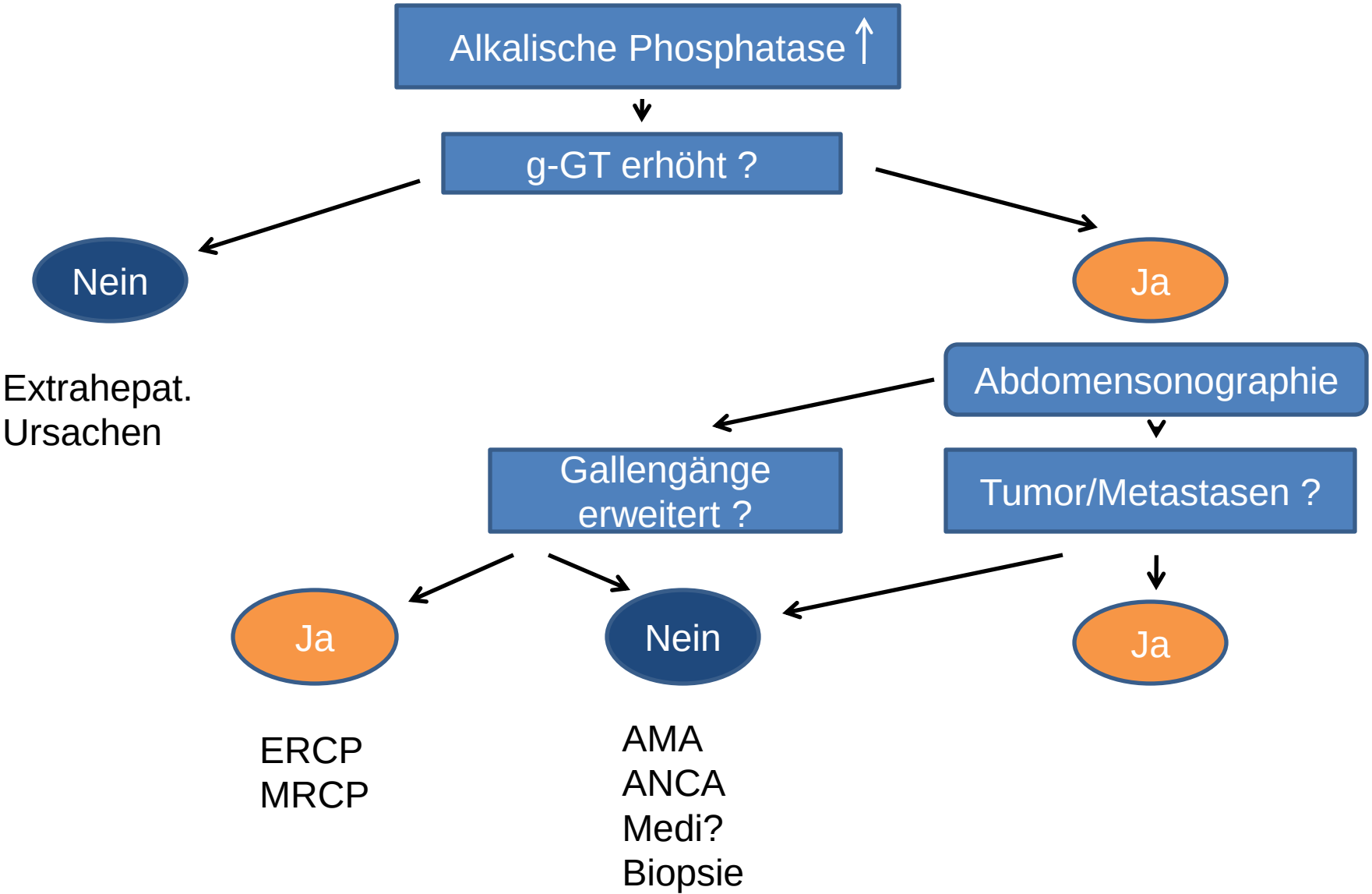
- häufigste Ursache einer chronischen Hepatopathie weltweit
- Insulinresistenz/Teil des metabolischen Syndromes
- Krankheitprogression und erhöhte Mortalität
- Ausschlussdiagnose
- Randomisierte Studien zur Therapie fehlen

Frau M.B., 61.Lj, Hausfrau

- **PA:**
  - St.n. AE und TE
- **JL:**
  - Seit Monaten anhaltende Müdigkeit und neu Pruritus
- **SA:**
  - Kein Alkohol-/Nikotinabusus
  - Keine Medikamente

Frau M.B., 61.Lj, Hausfrau

- **Status:**
  - Kardiopulmonal kompensiert
  - Xanthelasmen ?
  - Hepatomegalie
- **Labor:**
  - BB normal, CRP 7mg/dl
  - GOT 51U/l(<33), GPT 54U/l (<32), gGT 112U/l(<32)
  - AP 321U/l (<115)

Cholestase

Maier KP. Praxis 2005;94:139