How to improve long term outcome after liver transplantation?

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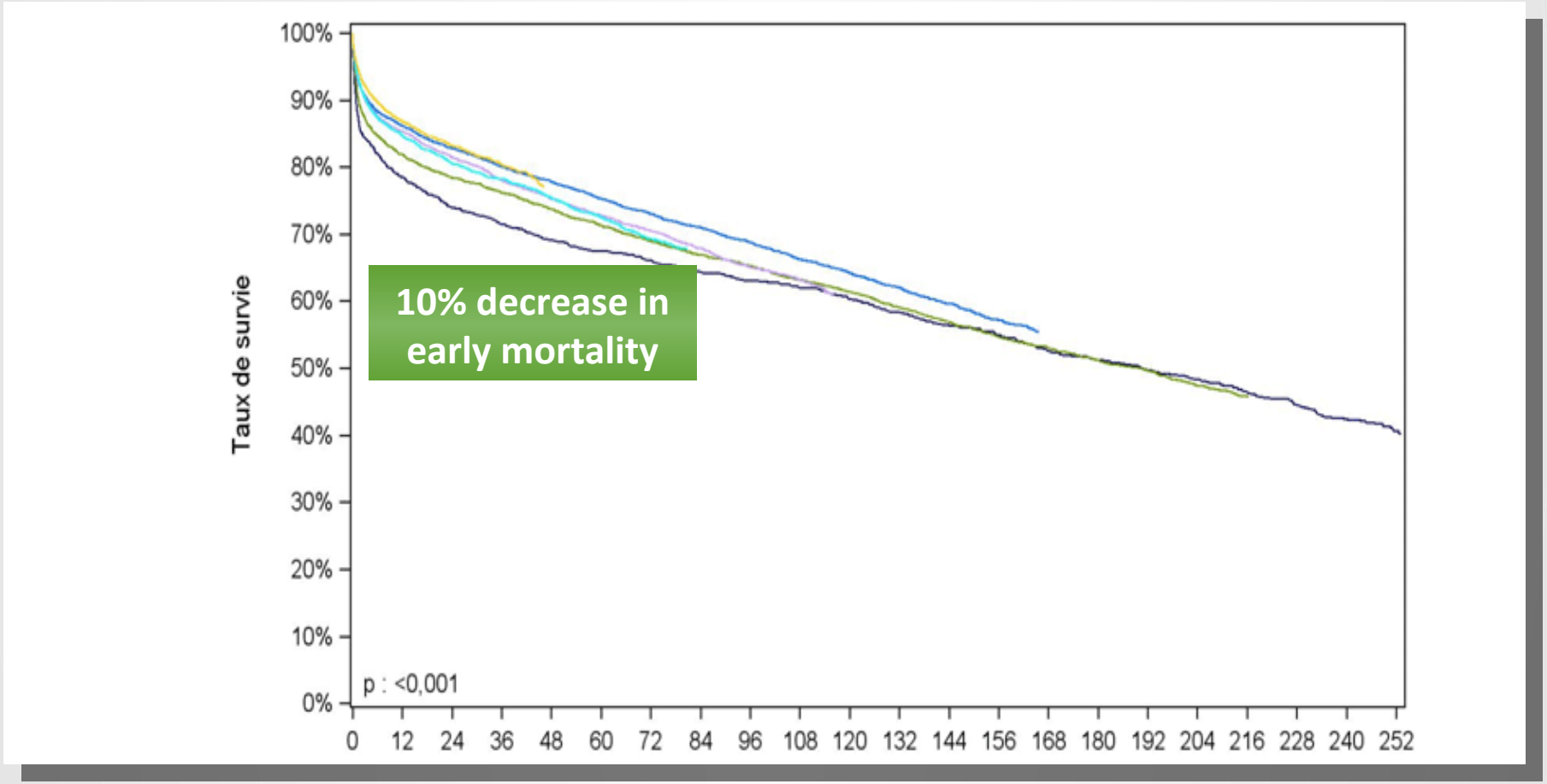
Long term outcome after liver transplantation in France 1994-2014

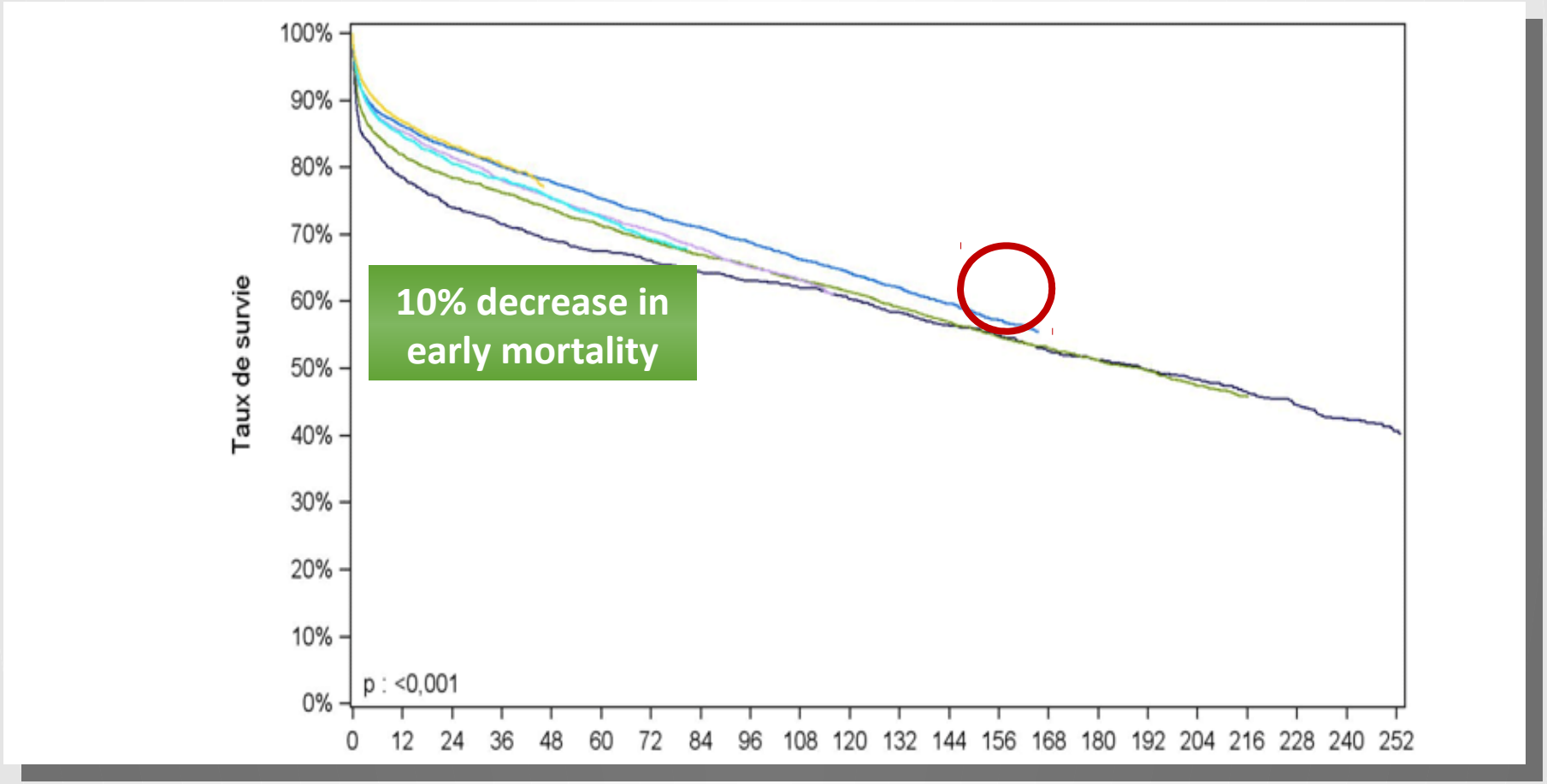


Data from Agence de la Biomédecine (www.agence-biomedecine.fr)

Decreased mortality: reasons for improvements

- Better selection of candidates
- Better preparation for transplantation
- Improvements in surgical techniques
- Improvement in procurement and preservation solutions
- Improvements in immunosuppression
- Better post-operative care
  - Earlier management of infection
  - Management of acute kidney injury…

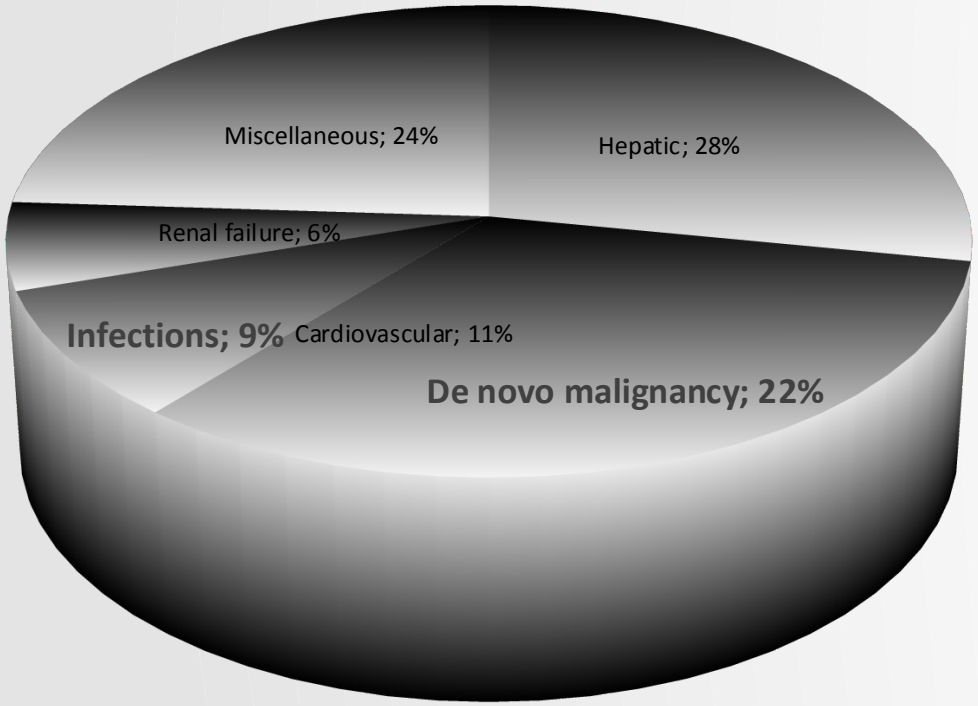
Long term outcome after liver transplantation in France 1994-2014



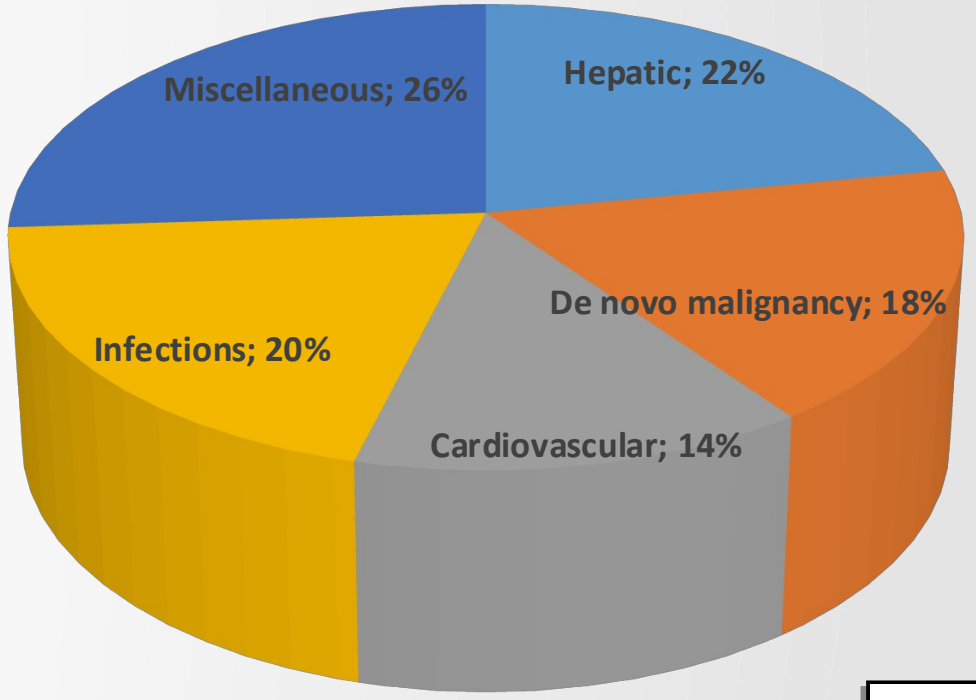
Data from Agence de la Biomédecine (www.agence-biomedecine.fr)

Causes of late mortality: mainly unrelated to the liver

United States

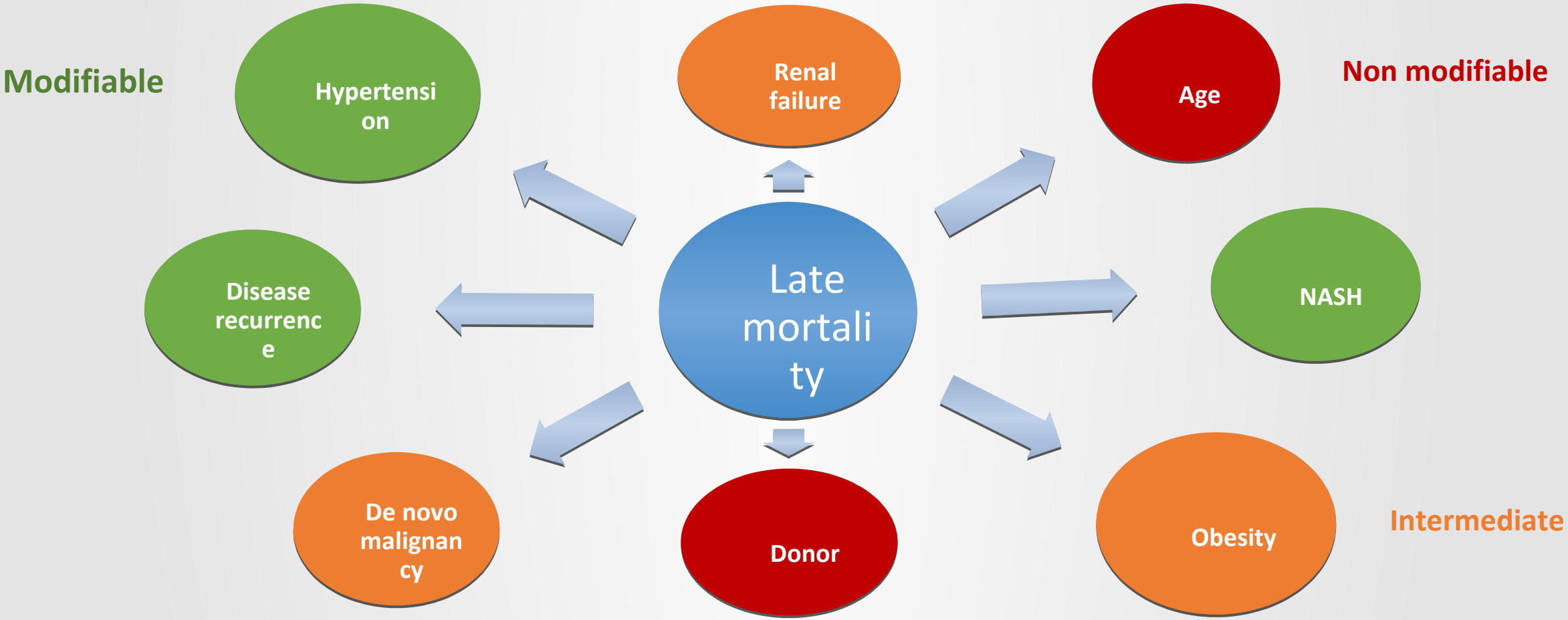


Europe



Watt KD et al. American Journal of Transplantation 2010; 10: 1420.
Rubin A et al. Transplant International 2013; 26: 740.

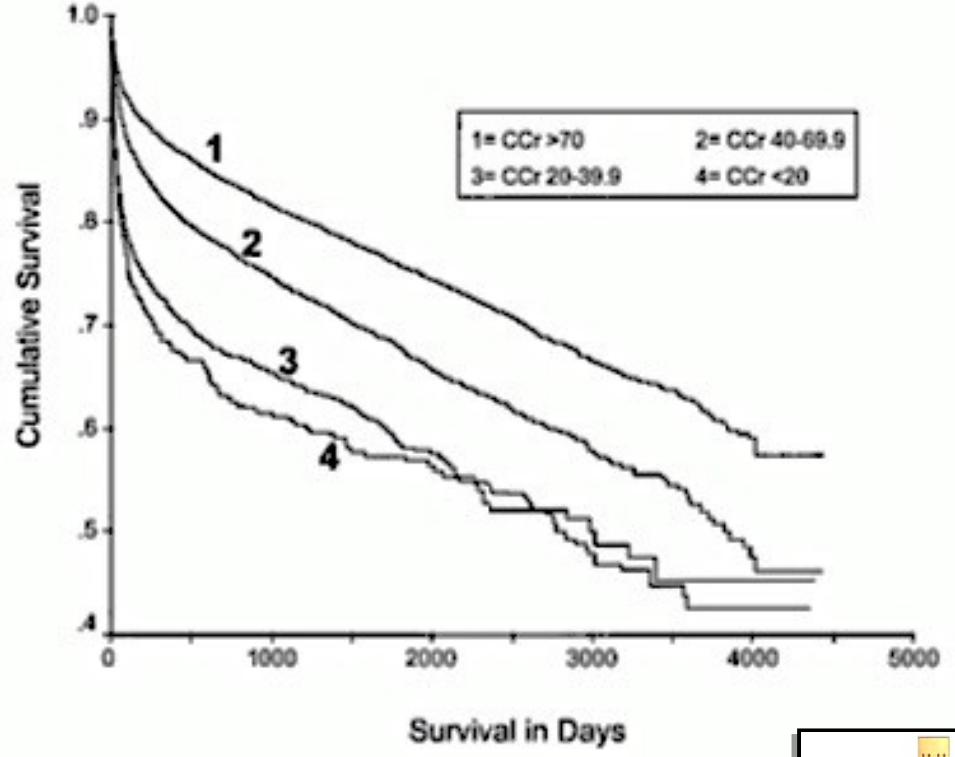
Late mortality in liver transplantation: multifactorial



Expected trends in liver transplantation

- More patients with NASH
  - More comorbidities
  - Cardiovascular risk
- Less patients with HCV cirrhosis
- Older age at transplantation
- More patients with impaired renal function
  - Impact of the MELD score

Post-transplant survival according to pre-transplant creatinine clearance

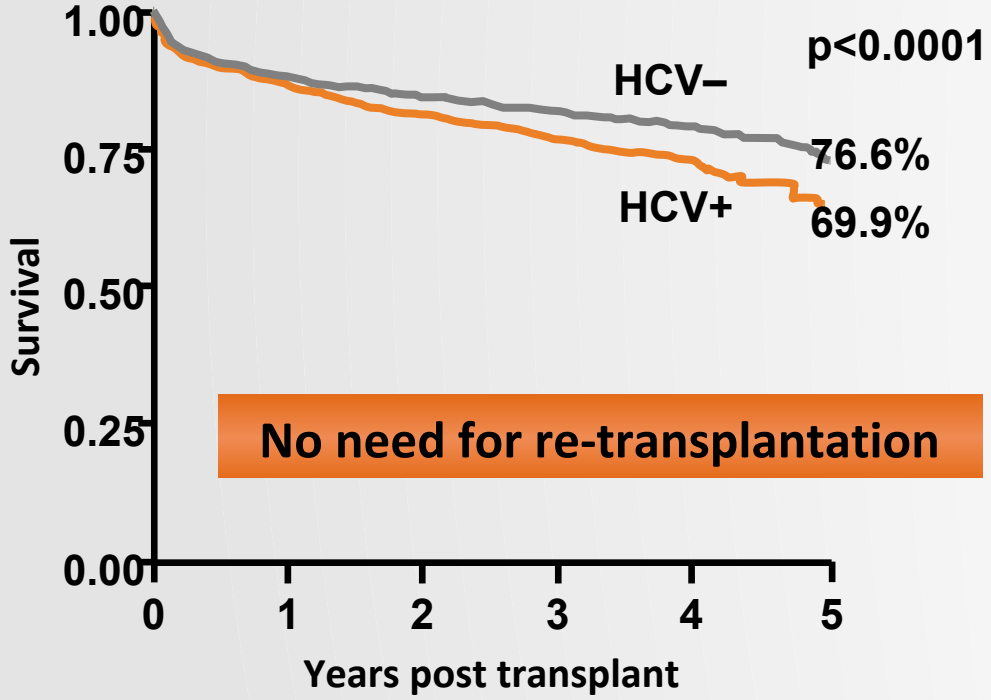


Nair S et al. Hepatology 2002; 35: 1179.

Improve the results of LT: target #1

Prevent/treat disease recurrence

Prevention/eradication of HCV ≈ 100%

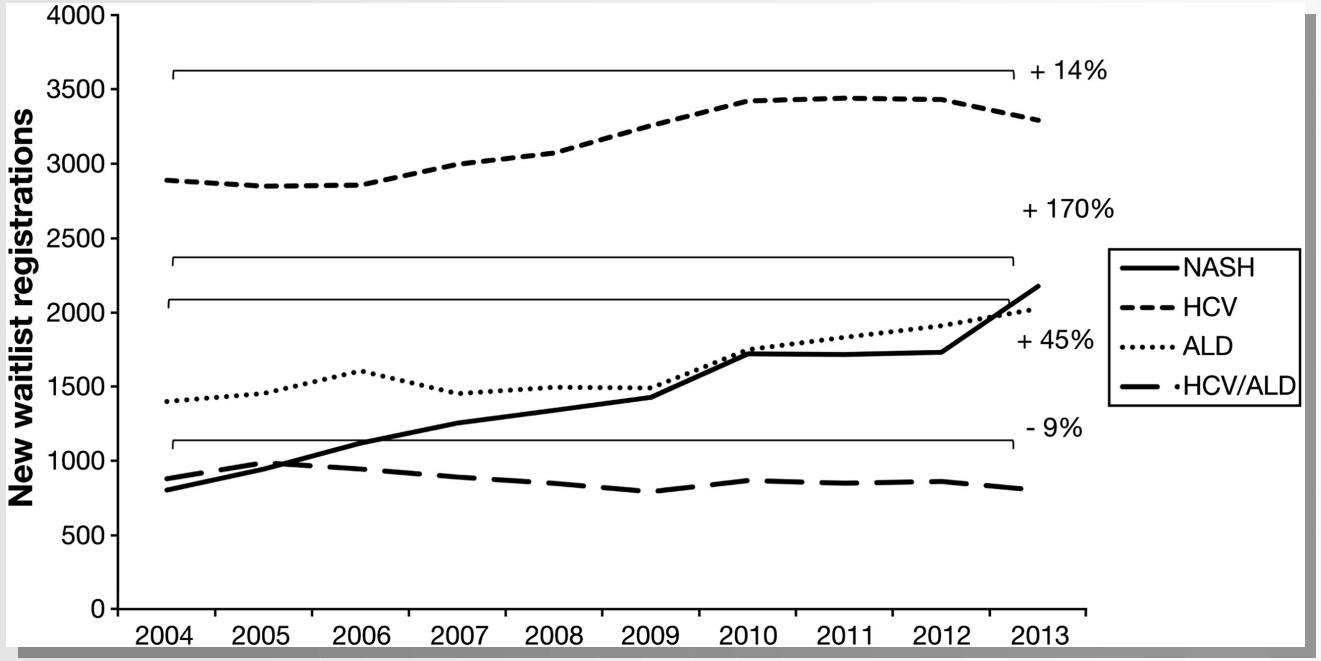


- **Recurrence of HCC**
  - **10-15%**
- **Primary sclerosing cholangitis**
  - **10-30%**
  - **no treatment**
- **Primary biliary cholangitis**
  - **10%**
- **Auto-immune hepatitis**
  - **Not uncommon**

Forman LM et al. Gastroenterology 2002;122:889–96

Improve the results of LT: target # 2

Management of dysmetabolic syndrome



Post-transplant	
Diabetes	33%
Hypertension	60%
Dyslipidemia	50%
Obesity	30%

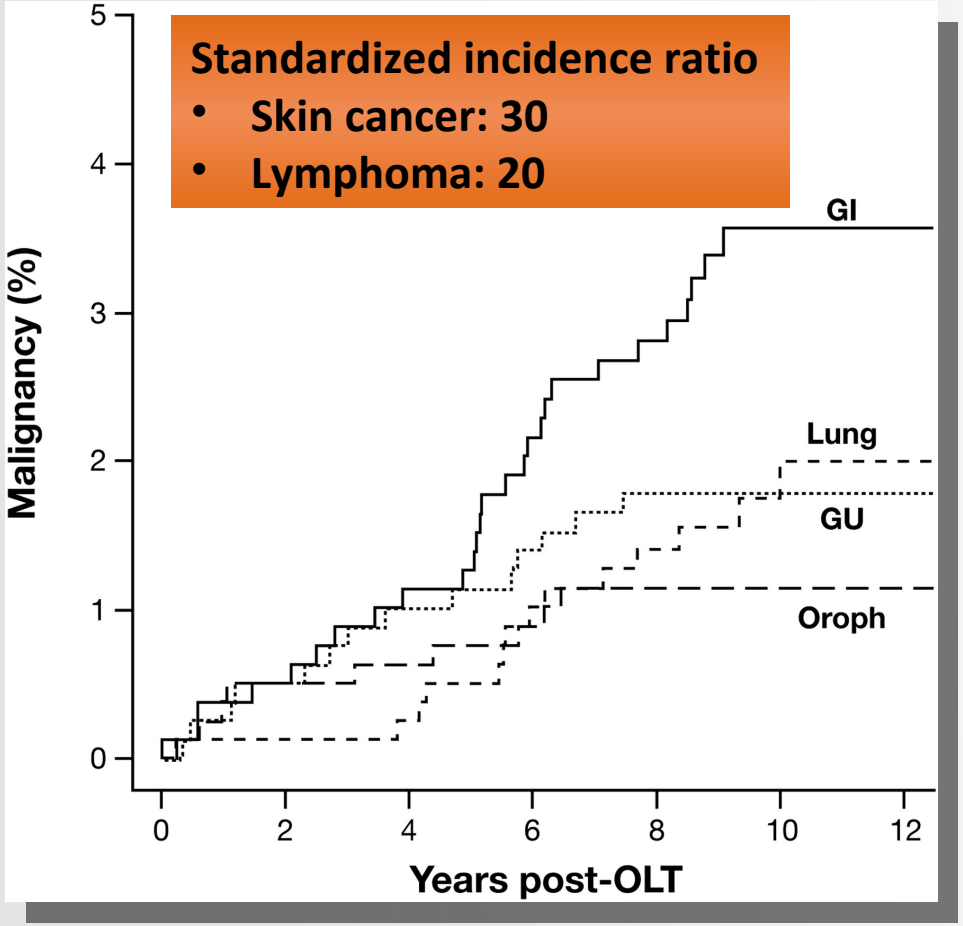
NASH: second leading cause of cirrhosis in candidates for LT

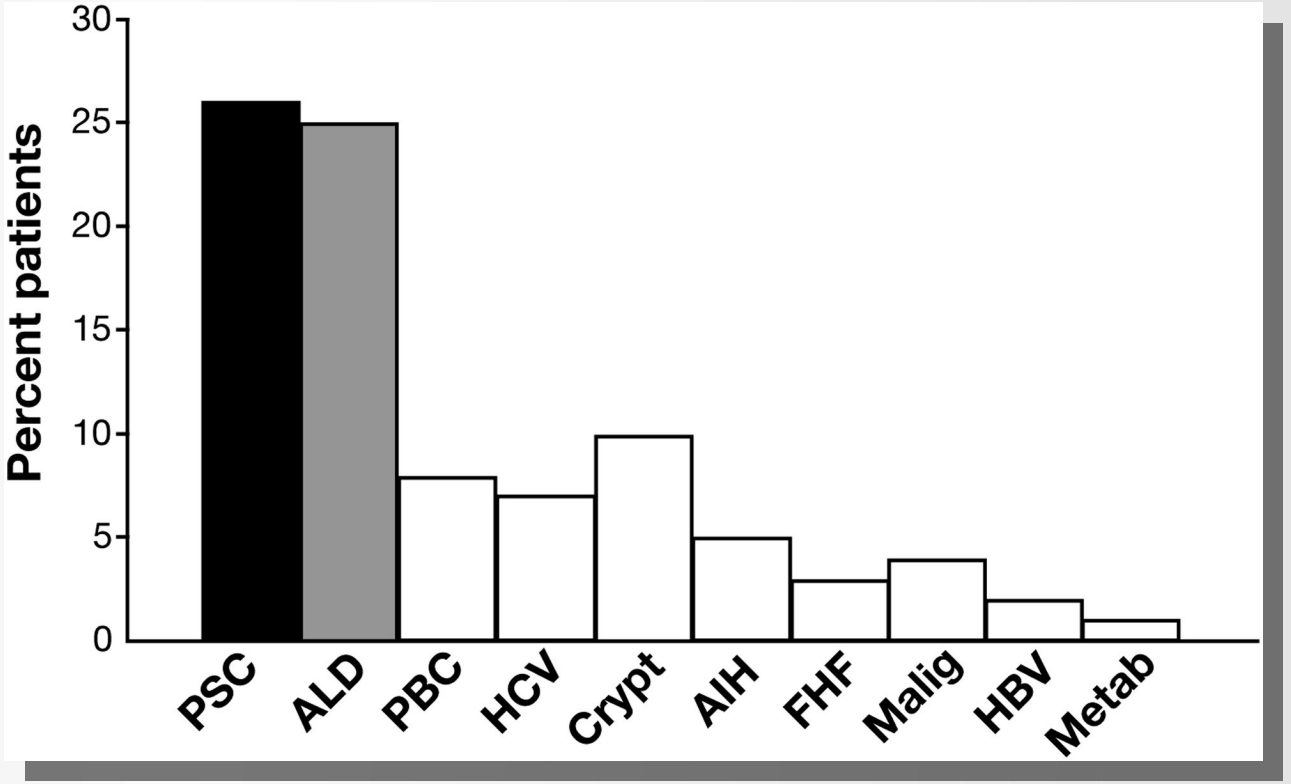
Statins ?

Wong RJ et al. Gastroenterology 2015; 148: 547.
Charlton MR. Liver Transplantation 2016; 22: S71.

Improve the results of LT: target # 3

Prevent/cure de novo malignancy



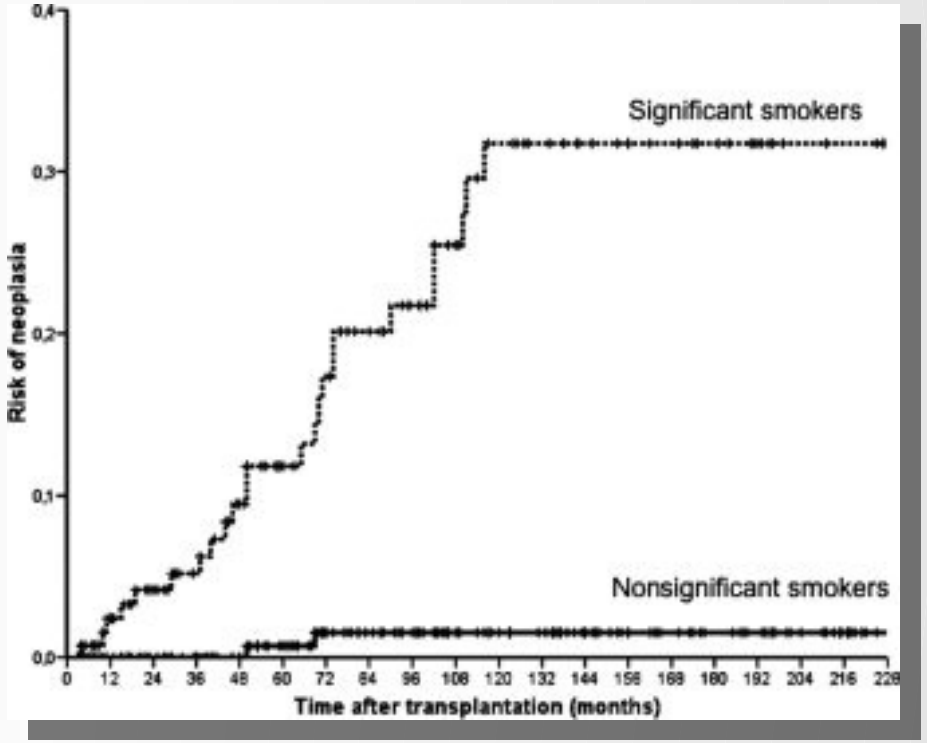


Malignancy by underlying liver disease

Watt KD et al. Gastroenterology 2009; 137: 2010.

Prevent/cure de novo malignancy

Modifiable risk factors



Risk of lung, head and neck, esophageal, kidney and urinary tract cancer according to smoking status

Herrero JI et al. Liver Transplantation 2011; 17: 402.

De novo malignancy: mTOR inhibitors

Controlled trials in kidney transplantation

Authors	Campistol JM				Alberu J		
Immunosuppression	SRL + CsA + St	SRL + St	p value		CNI	SRL	p value
Patients	215	215			275	555	
Follow up	5y	5y			2y	2y	
Skin cancer	7.4%	3.7%	0.09		4.3%	1.2%	<0.001
Non skin cancer	9.6%	4%	0.03		2.1%	1%	0.06

Campistol JM et al. J Am Soc Nephrol 2006; 17: 581.
Alberu J et al. Transplantation 2011; 92: 303.

Limitations of mTOR inhibitors

	Tacrolimus ± MMF 1 month			p
	TAC standard	EVR + TAC reduced	EVR +TAC discontinuation	
Patients	243	245	231	
Acute rejection	7%	3%	-*	0.03
Composite acute rejection, graft loss, death	9.7%	6.7%	-	ns
GFR 1 year (mL/min/1.732)	70	81	-	0.001
Wound healing problems	14%	18%	-	ns

* Enrollment prematurely discontinued: too high rate of rejection

Fung J et al. Liver Transplantation 2012; 18: S109

Target # 4: protect the kidney

- Treat pre-transplant episodes of AKI
  - Pre-transplant AKI impacts on post transplant outcome
- Delayed introduction of CNIs in patients with post-operative AKI
  - Basiliximab + steroids + MMF without CNIs during the first 7-14 days
- CNIs minimization
  - Low target trough levels
  - Adjunction of MMF
- Control of hypertension
- Control of diabetes
- Nephroprotective approaches

Target # 5: Humoral rejection and DSA

1270 patients

Multivariate analysis on the risk of death

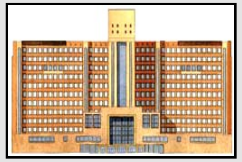
	HR	p value
Preformed DSA	1.6	<0.001
AA recipient	1.8	<0.001
HCV	1.7	<0.001
Donor age > 50	1.4	0.006

	HR	p value
Preformed iGg3 DSA	2.4	<0.001
AA recipient	1.9	<0.001
HCV	1.7	<0.001
Donor age > 50	1.4	0.01

	No DSA	Preformed iGg3 DSA	p
Liver-related death	6%	12%	0.004

Which therapy ?

O'Leary JG et al. Am J Transplant 2015; 15: 1003



Take home messages

- Significant improvements in early mortality have been achieved
- Improvements in late mortality still need to be achieved
- HCV cure will improve long term outcomes
- NASH as a growing indication will negatively impact on long term outcomes
- Late deaths are mainly unrelated to the liver
  - Comorbidities need a multidisciplinary approach
- The role of humoral rejection needs to be better understood
- The pool f donors is limited
  - Think about transplant benefit in the selection of candidates