Metabolic Response to Surgery

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Ersta diakoni

Disclosures

- None

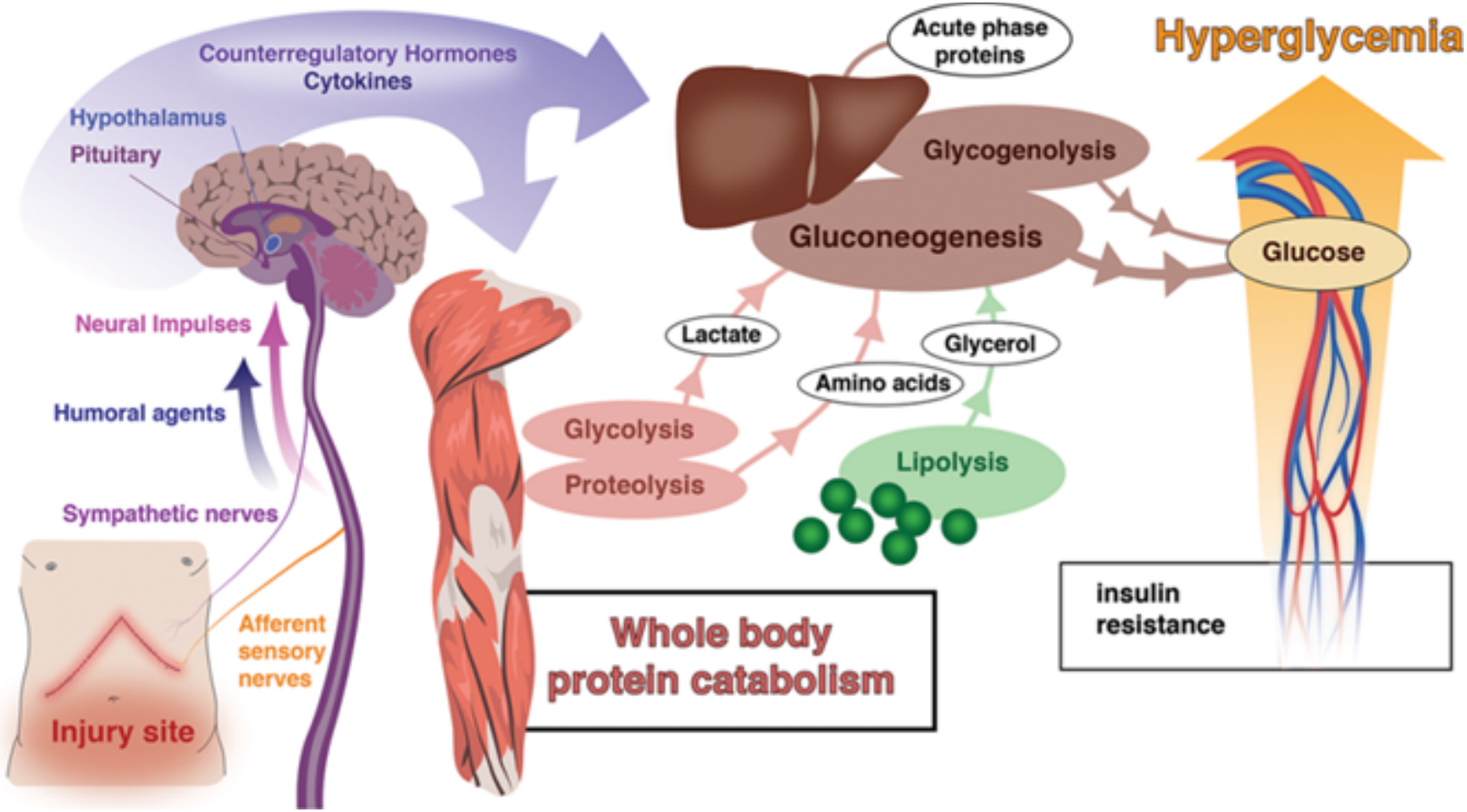
The response to major surgery leads to morbidity

- **Metabolic homeostasis**
  - Inflammation, insulin resistance, catabolism
- **Fluid balance**
  - Hypoperfusion, overhydration, oedemia
- **Pain**
  - Somatic, visceral, neuropathic
- **Gut dysfunction**
  - Nausea, vomiting, paralysis
- **Cognitive dysfunction**
  - Delirium, confusion, sleep disruption
- **Post-operative deconditioning**
  - Immobilisation, fatigue, anemia, starvation

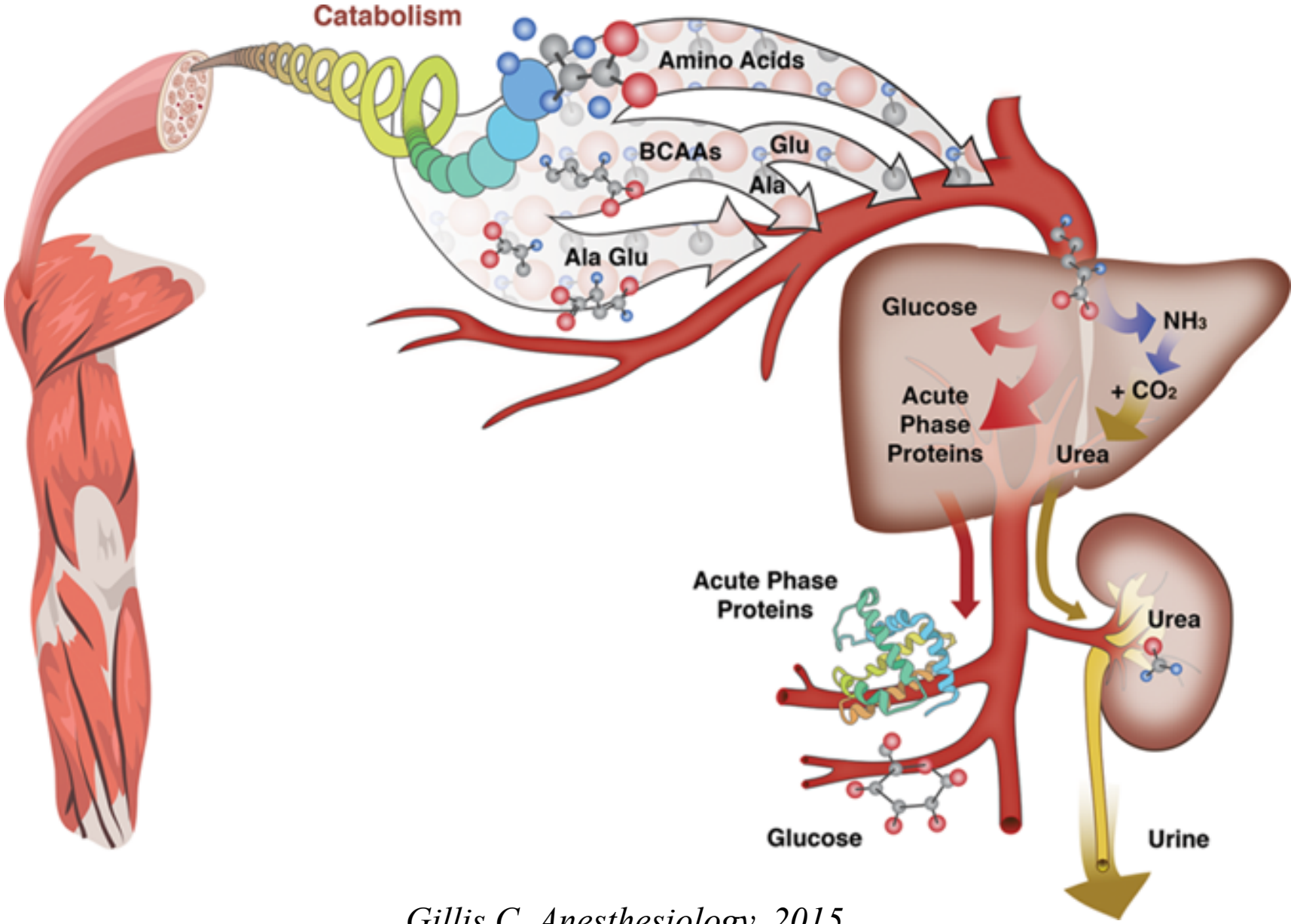
It´s more to it than a perfect operation

Metabolic response to trauma

- **Neuroendocrine response**
  - Cortisol, catecholamines, glucagon, GH
- **Insulin resistance**
  - Catabolism
  - Lipolysis
  - Protein breakdown
  - Hyperglycemia
- **Inflammation**
  - Cytokines

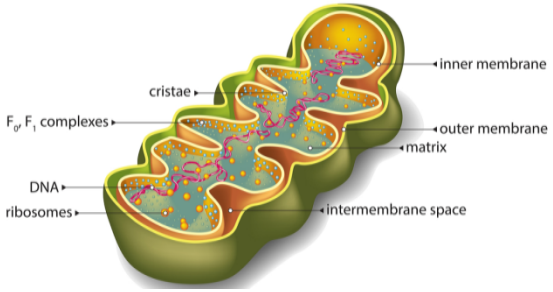


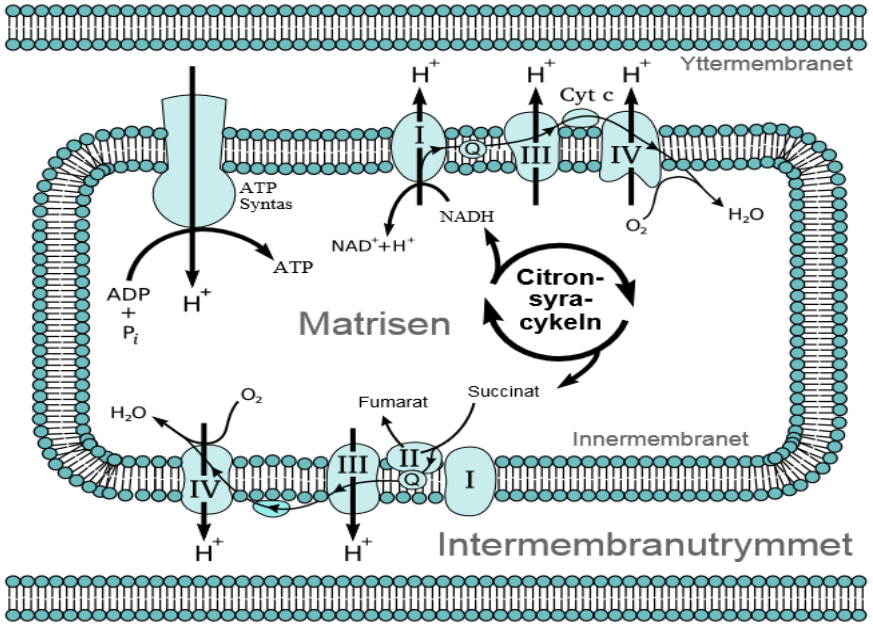
Gillis C, Anesthesiology, 2015



Gillis C, Anesthesiology, 2015

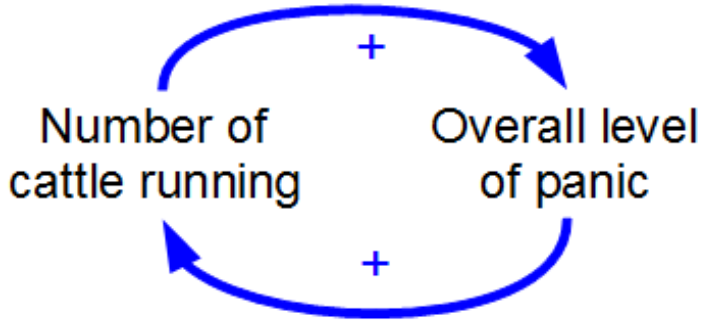
Mitochondrial dysfunction





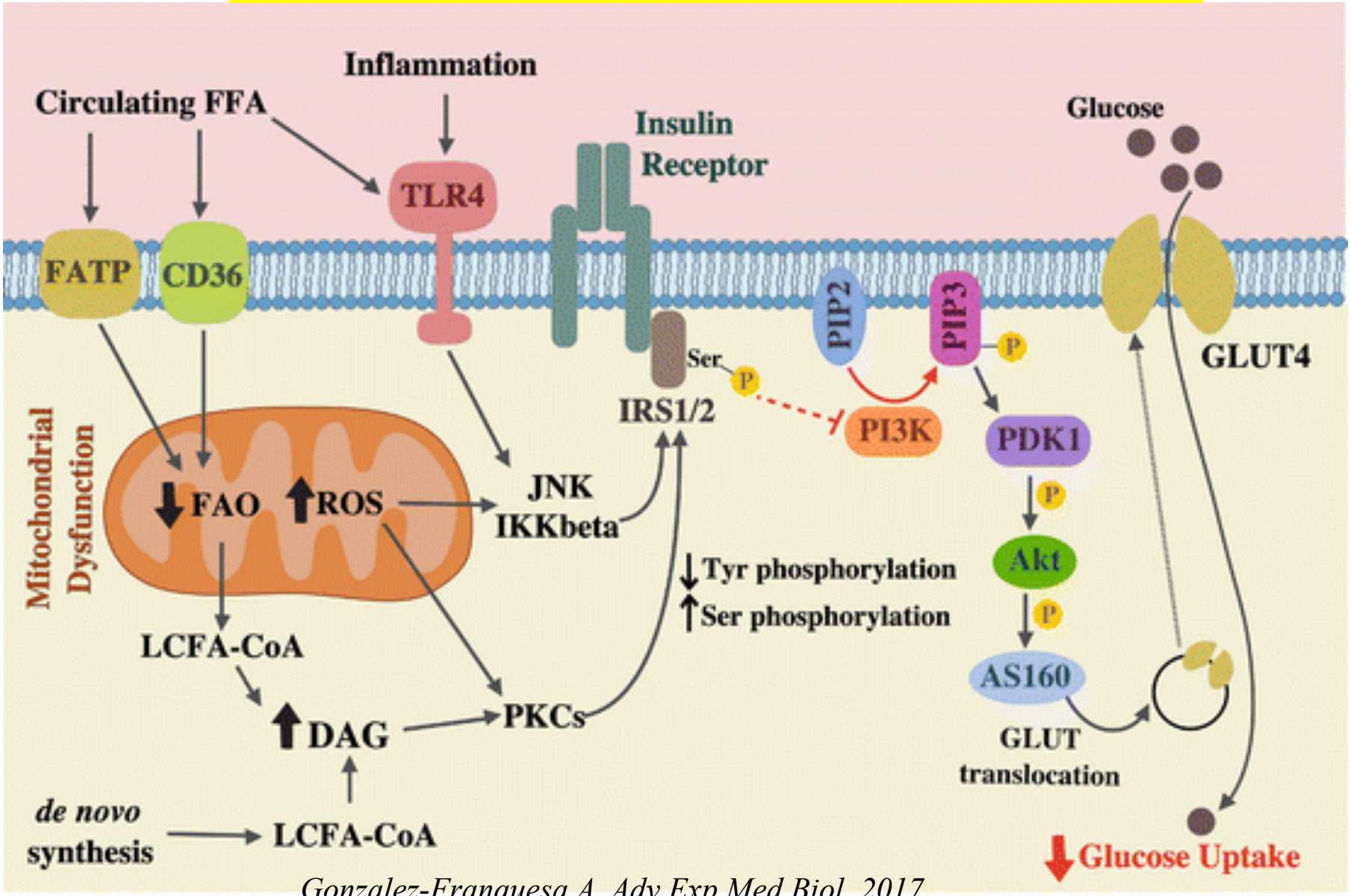
- Energy production / oxidative phosphorylation / ATP
- Decrerased fatty acid oxidation
- Inhibiting insulin action / Insulin resistance
- Toxic lipid metabolite accumulation
- ROS production / oxidative stress
- Uncoupling

Harmful positive feedback loop



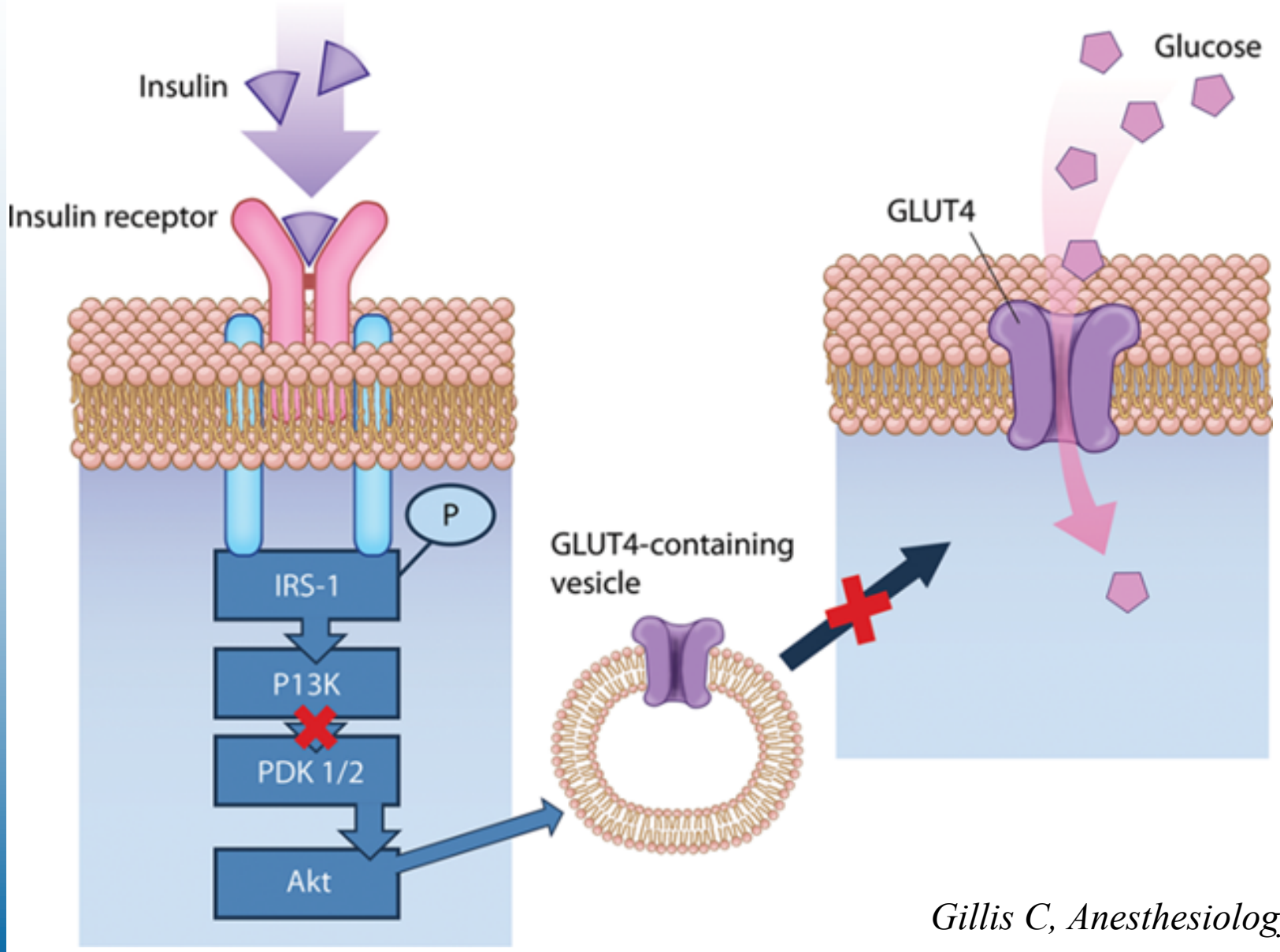
Gonzalez-Franquesa A, Adv Exp Med Biol, 2017

Mitochondrial dysfunction and insulin resistance



Gonzalez-Franquesa A, Adv Exp Med Biol, 2017

Effect of Insulin on Glucose Uptake



Gillis C, Anesthesiology, 2015

Preoperative insulin resistance increased risk for complications

273 patients open cardiac surgery, insulin sensitivity determined at the end of op

Complication	OR for every decrease by 1 mg/kg/min (Insulin sensitivity)	P value
Death	2.33 (0.94-5.78)	0.067
Major complication	2.23 (1.30-3.85)	0.004
Severe infection	4.98 (1.48-16.8)	0.010
Minor infection	1.97 (1.27-3.06)	0.003

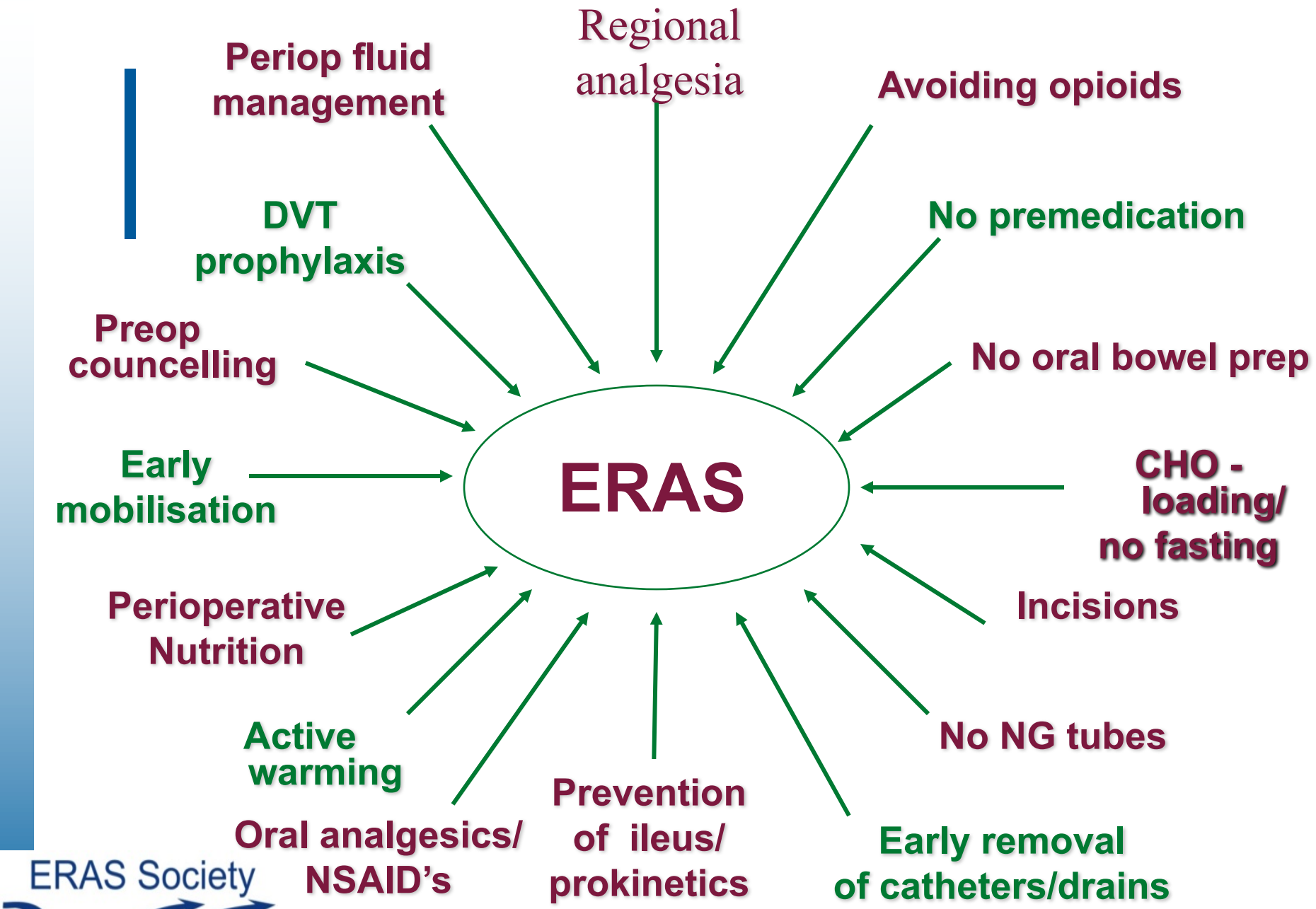
The ORs were adjusted for potential confounders

Sato et al, JCEM 2010; 95: 4338-44

Controlling perioperative physiology
Many small pieces of the puzzle

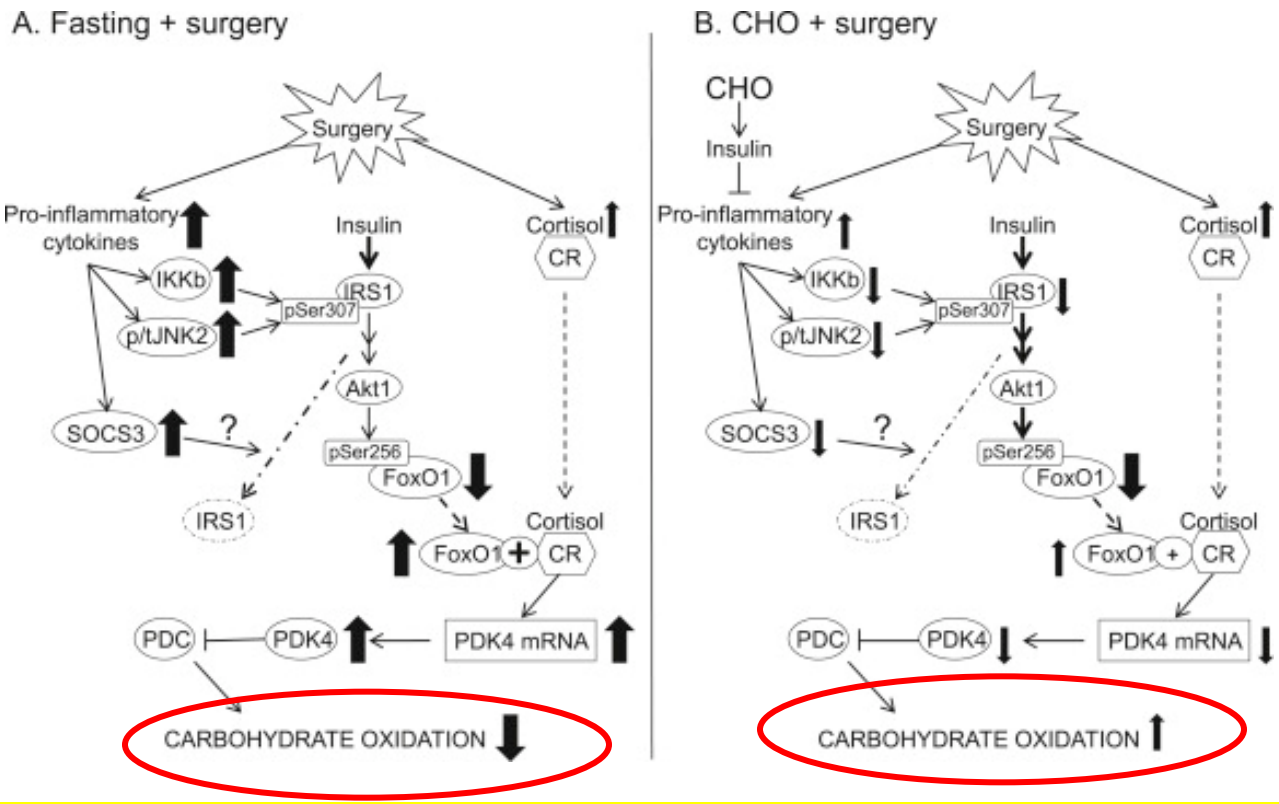
	Hormonal	Metabolic	Inflammatory
Minimally invasive surgery	✓	✓	✓
Neural blockade	✓	✓	✓
Opioid-sparing pain control	✓		
Prevention of hypothermia	✓	✓	
Perioperative fluid management	✓		
Anabolic agents (*e.g.*, growth hormone)	✓	✓	
Glucocorticoids	✓	✓	✓
β-blockade	✓	✓	
α2-agonists	✓		✓
Exercise	✓	✓	✓
Carbohydrate loading	✓	✓	✓
Immunonutrition		✓	✓
Early oral nutrition	✓	✓	✓
Adequate dietary protein		✓	
Insulin (glycemic control)	✓	✓	✓

Gillis C, Anesthesiology, 2015



ERAS Society

Postoperative muscle mitochondrial dysfunction improves by carbohydrate loading



Preoperative carbohydrate loading

- Reduced muscle inflammatory response
- Improved inhibition of FOX01 mediated PDK4
- Supported by clinical studies
  - (Awad S, Ann Surg, 2010, Wang ZG, BJS, 2010, Yu Y, ChJS, 2013)

Hagve M, Am J Physiol Endocrinol Metab, 2015, Gjessing, P, Clin Nutr, 2015

ERAS and clinical outcome ?

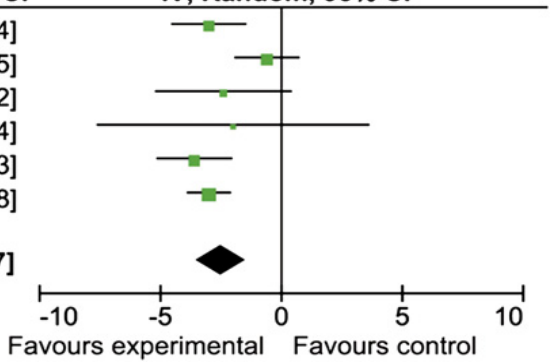
Review of 6 RCTs (n=452)

Hospital stay

Study or Subgroup	ERAS Mean	ERAS SD	ERAS Total	TC Mean	TC SD	TC Total	Weight	Mean Difference IV, Random, 95% CI
Anderson 2003[19]	4	1.8	14	7	2.1	11	19.3%	-3.00 [-4.56, -1.44]
Delaney 2003[20]	5.2	2.5	31	5.8	3	33	21.7%	-0.60 [-1.95, 0.75]
Gatt 2005[21]	6.6	4.4	19	9	4.6	20	9.6%	-2.40 [-5.22, 0.42]
Khoo 2007[22]	5	8.5	35	7	14.75	35	3.1%	-2.00 [-7.64, 3.64]
Muller 2009[3]	6.7	4.84	76	10.3	4.97	75	19.2%	-3.60 [-5.17, -2.03]
Serclova 2009[4]	7.4	1.3	51	10.4	3.1	52	27.1%	-3.00 [-3.92, -2.08]
Total (95% CI)			**226**			**226**	**100.0%**	**-2.51 [-3.54, -1.47]**

Heterogeneity: Tau² = 0.80; Chi² = 11.04, df = 5 (P = 0.05); I² = 55%

Test for overall effect: Z = 4.76 (P < 0.00001)

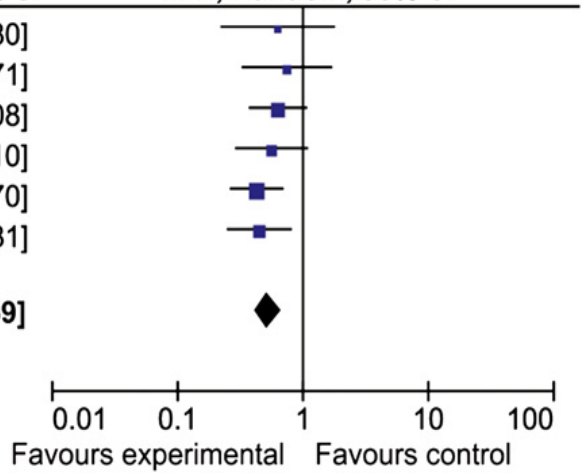


Complications

Study or Subgroup	ERAS Events	ERAS Total	TC Events	TC Total	Weight	Risk Ratio M-H, Random, 95% CI
Anderson 2003[19]	4	14	5	11	6.0%	0.63 [0.22, 1.80]
Delaney 2003[20]	7	31	10	33	9.6%	0.75 [0.32, 1.71]
Gatt 2005[21]	9	19	15	20	23.1%	0.63 [0.37, 1.08]
Khoo 2007[22]	9	35	16	35	14.9%	0.56 [0.29, 1.10]
Muller 2009[3]	16	76	37	75	27.5%	0.43 [0.26, 0.70]
Serclova 2009[4]	11	51	25	52	18.8%	0.45 [0.25, 0.81]
Total (95% CI)		**226**		**226**	**100.0%**	**0.53 [0.41, 0.69]**
Total events	56		108			

Heterogeneity: Tau² = 0.00; Chi² = 2.26, df = 5 (P = 0.81); I² = 0%

Test for overall effect: Z = 4.81 (P < 0.00001)



Vardhan, Clin Nutr, 2010

Lap CRC surgery

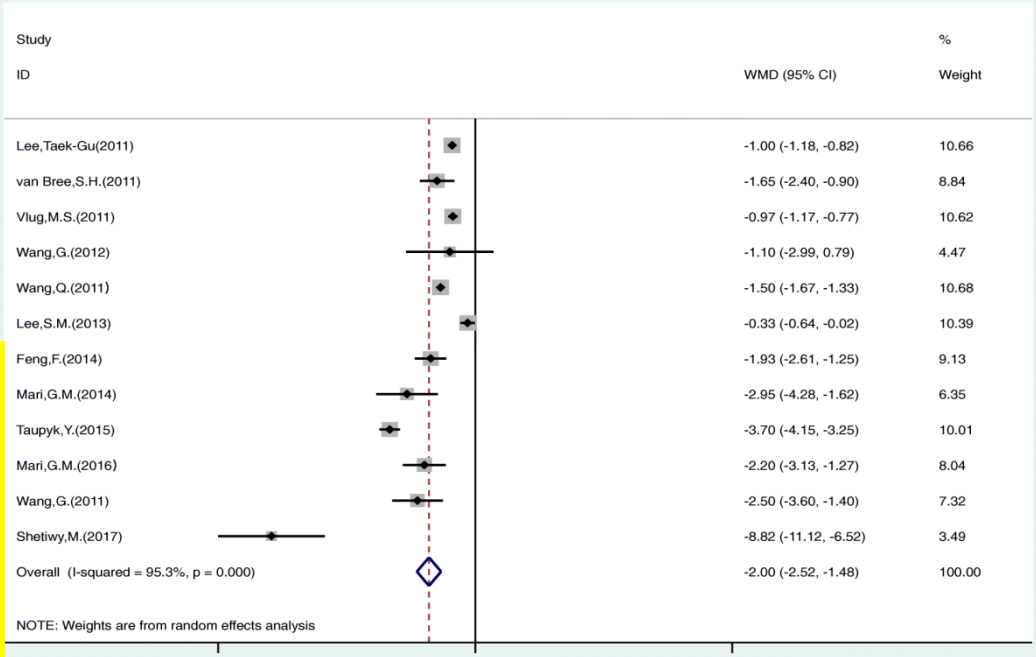
ERAS vs Trad

Meta-analysis
13 RCT, n=1298

- Shorter LOS
- Reduced complications
- Faster return
  - bowel function
- Less SIRS
  - CRP
  - IL6

Ni X, J Gastrointest Surg, 2019

LOS



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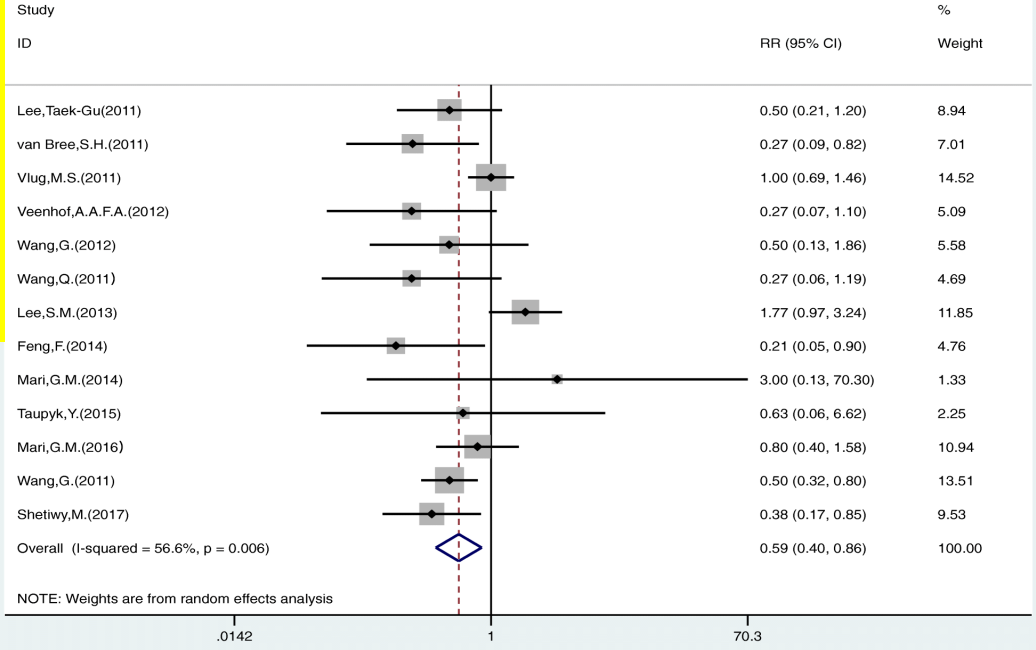
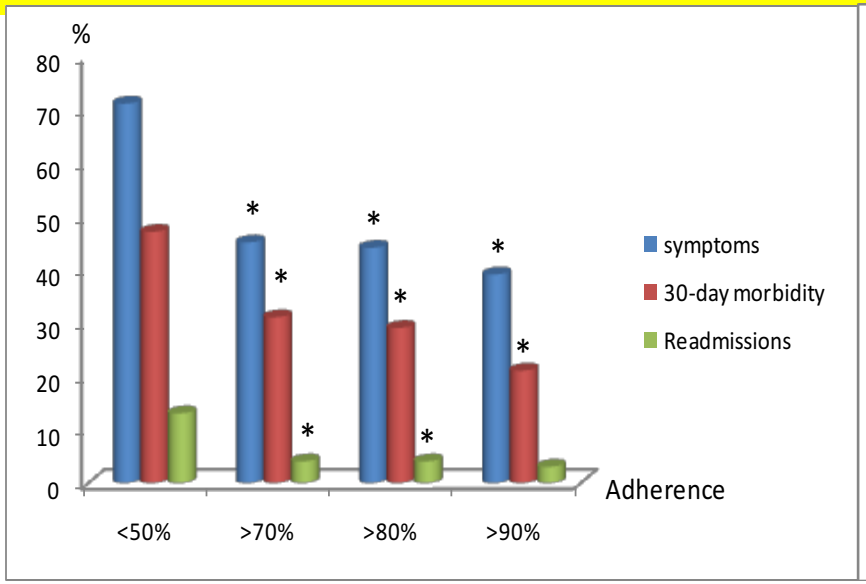
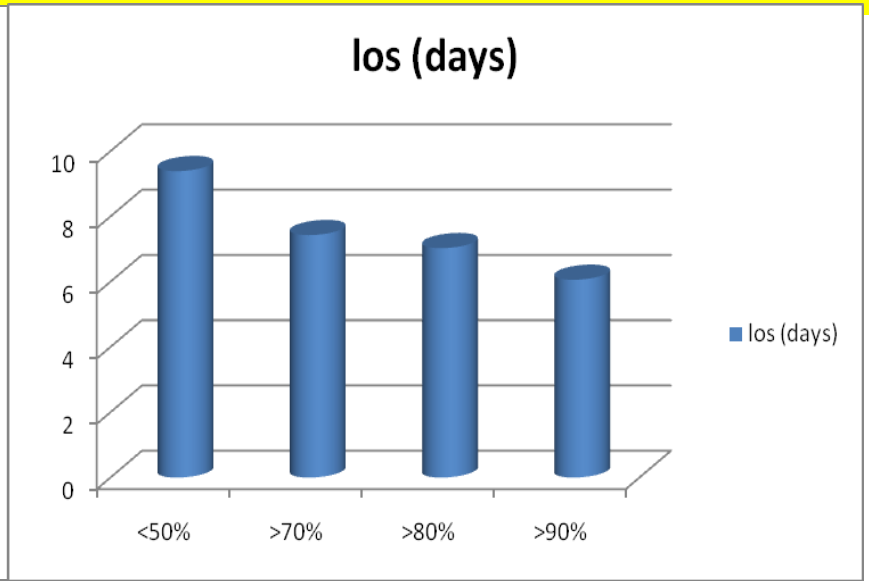


Compliance to ERAS predict outcomes after colorectal cancer surgery n=953





- Predictors for improved clinical outcome
  - Preoperative carbohydrate loading
  - Perioperative fluid volume

Gustafsson U, Arch Surg, 2011

Table 1 Modified fast-track care perioperative plan

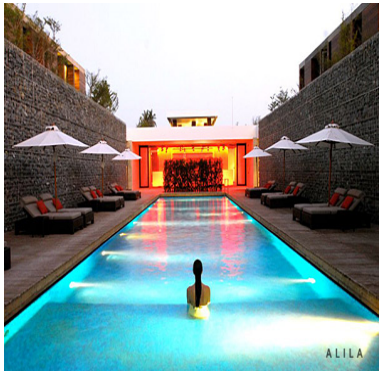
	Preoperative
	Detailed information of the nature of the surgery and perioperative care
	Emphasis on the plan for early discharge, specifically <2 days
*	Bowel preparation: mechanical and oral antibiotics
	IV antibiotics 30 min before initiation of the procedure
	Intraoperative
	8–10 mg dexamethasone at induction of anesthesia
	Laparoscopic approach
*	No use of drains and tubes
*	No use of epidural anesthesia
	No use of urinary catheter for right and transverse colon resections; immediate removal of catheter after low anterior colon resections
	Postoperative
	Admission to regular nursing floor
	Immediate postoperative general diet that was emphasized to the nursing staff
*	Ambulation same evening of surgery
*	No use of patient-controlled analgesia pumps; pain control achieved with routine IV ketorolac and supplemented as needed with IV and oral narcotics
	No use of laxatives or prokinetics
	Postoperative reinforcement of discharge plan by attending surgeon
	Neither flatus nor bowel movement a requirement for discharge
	Patient agreement of readiness and acceptance of discharge
	Follow-up evaluation at outpatient clinic within 1 wk after discharge

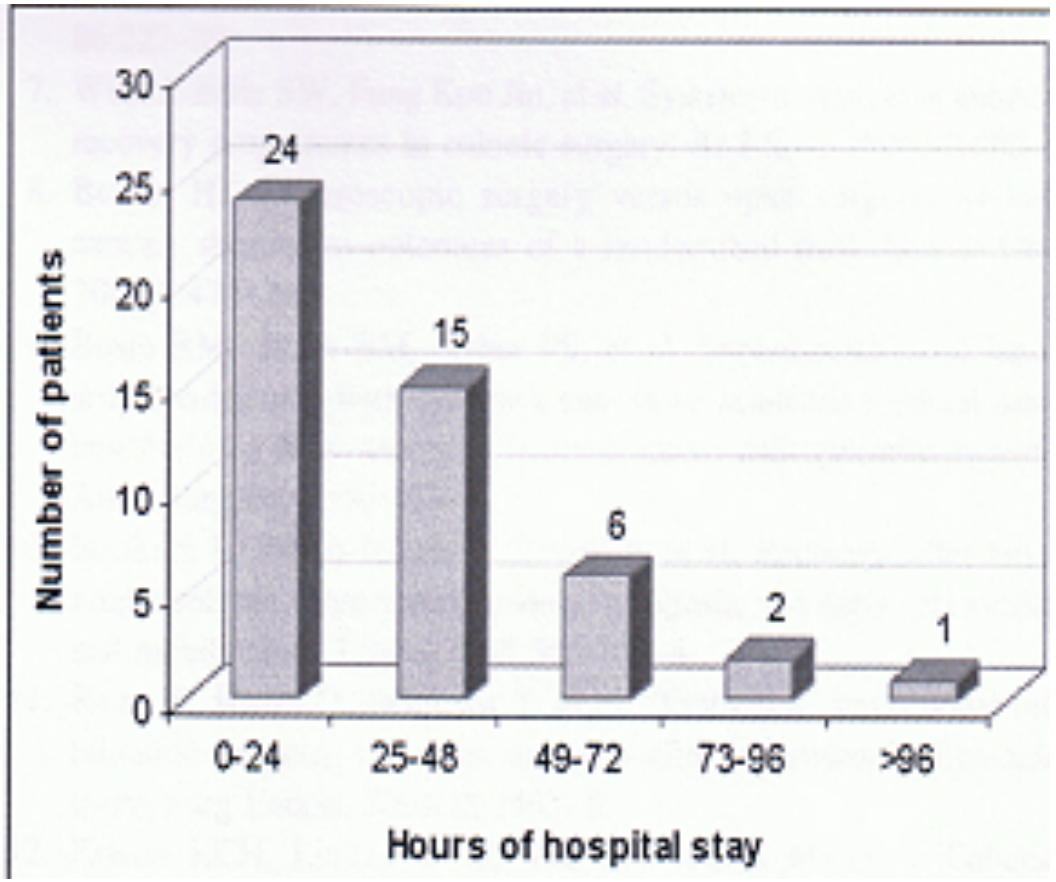
IV = intravenous.

ERAS

Lap Colonic resection

- n=48
- 2 Complications
- 1 Readmission





Patel G, Am J Surg, 2010, Levy BF, Dis Col Rect, 2009

*	Undernutrition: Nutritional repletion required
	NRS-2002[4]: >5*
	SGA[63]: C
	Weight loss[63]: >10–15% within 6 months
	BMI[63]: <18 kg/m^2
*	Poor functional capacity: Consider prehabilitation
	Six-minute walking test[161,169]: <60% of predicted*
*	Frailty: Consider prehabilitation
	Frailty index[164]: Increase in risk for each unit increase in this 11-point frailty index
	Fried[162]: Frailty is identified by the presence of three or more components
*	Poor glycemic control: Appropriate intervention before surgery
	HbA1c[157]: >6%*

Predicted six-minute walk test is a calculation based on gender and age.[169,172]

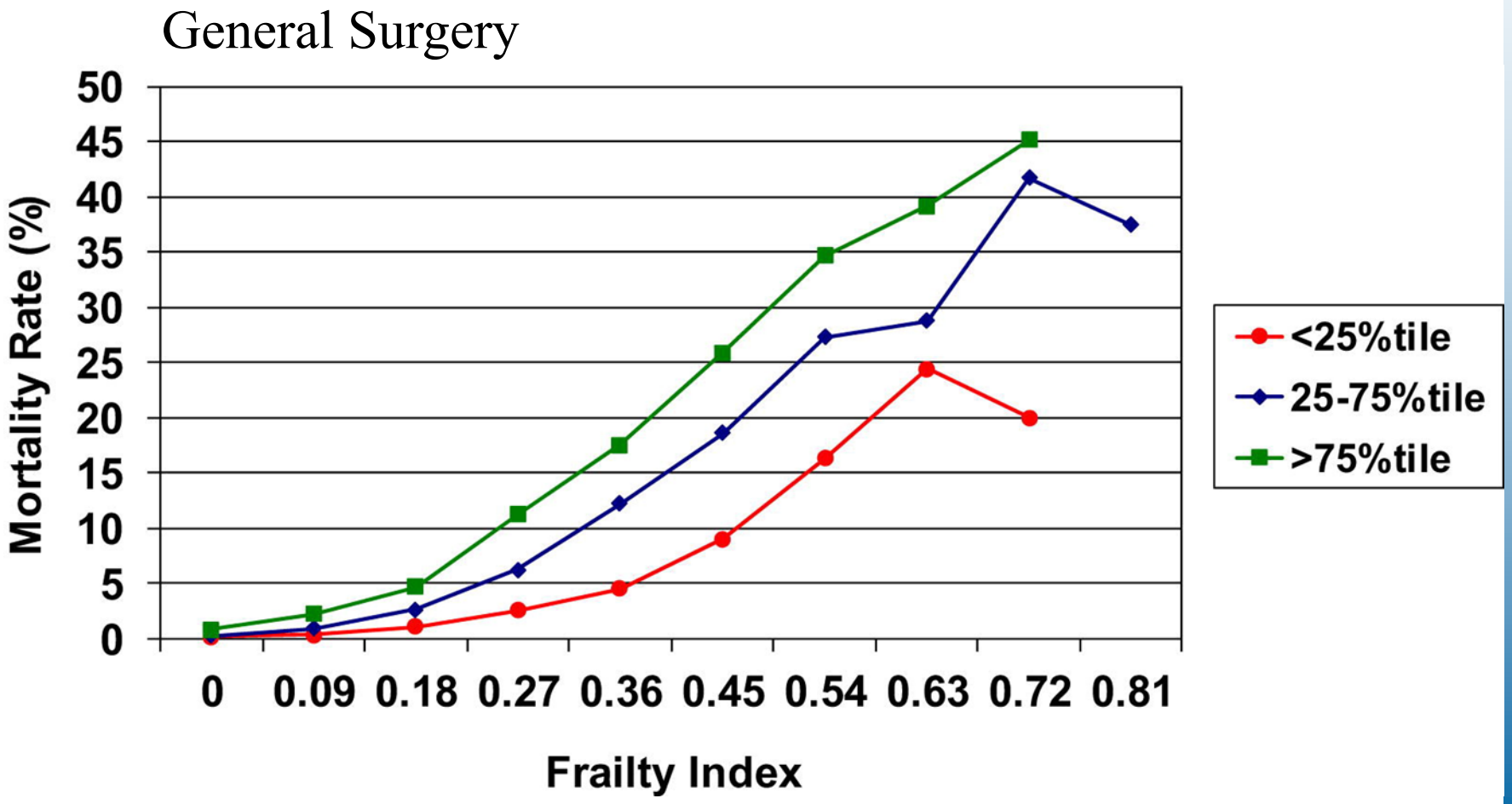
* Based on little available evidence to identify preoperative cutoff value for surgical patients.

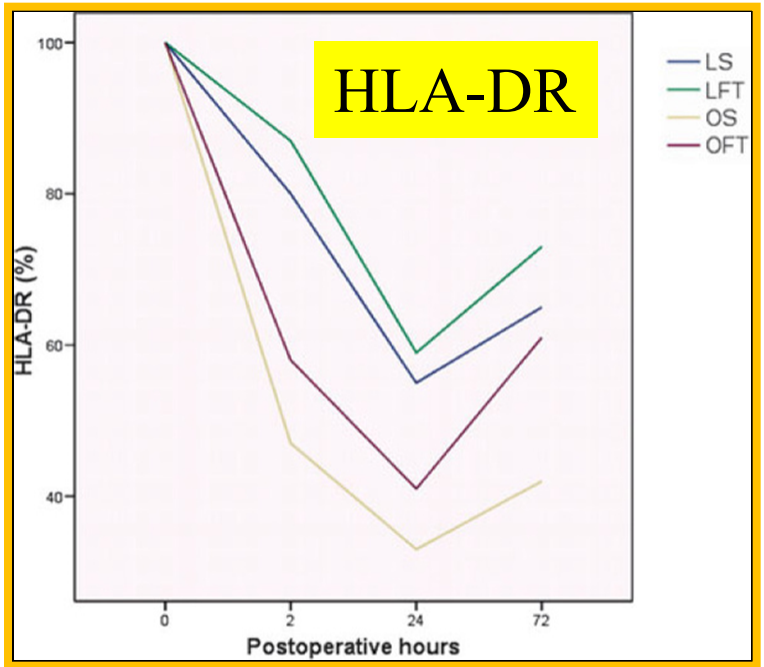
BMI = body mass index; HbA1c = glycated hemoglobin; NRS-2002 = nutritional risk screening tool-2002; SGA = subjective global assessment.

Gillis C, Anesthesiology, 2015

Frailty index as a predictor of postoperative morbidity and mortality

N= 971 434 (NSQIP)

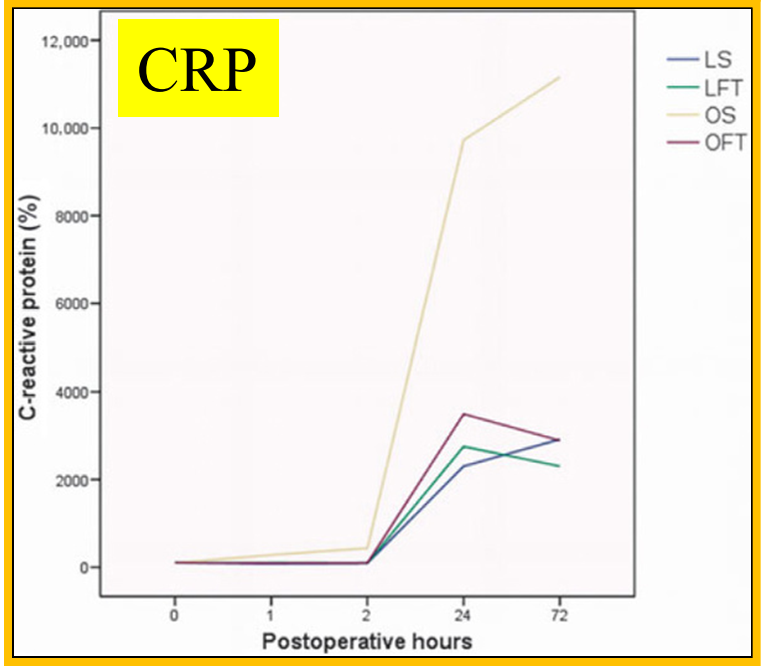


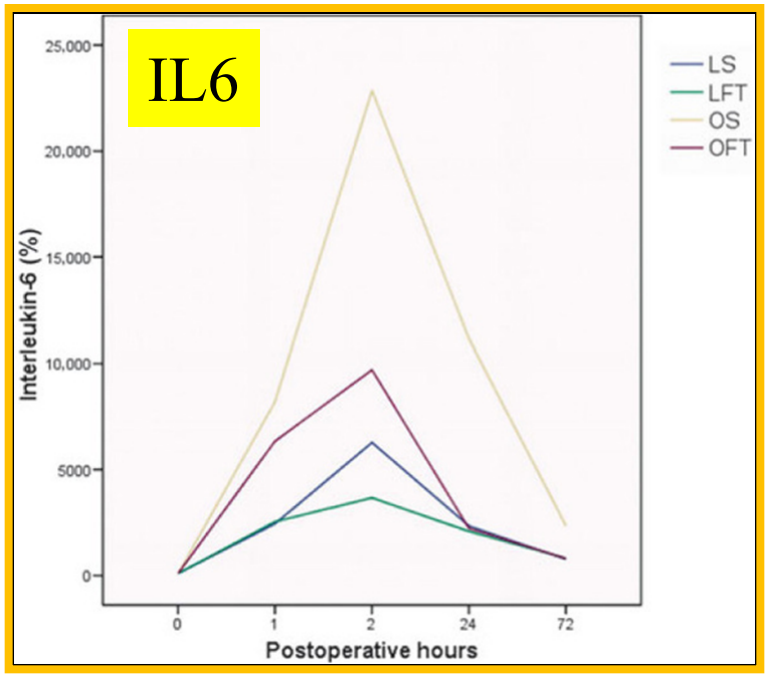


LAFA trial, n=79

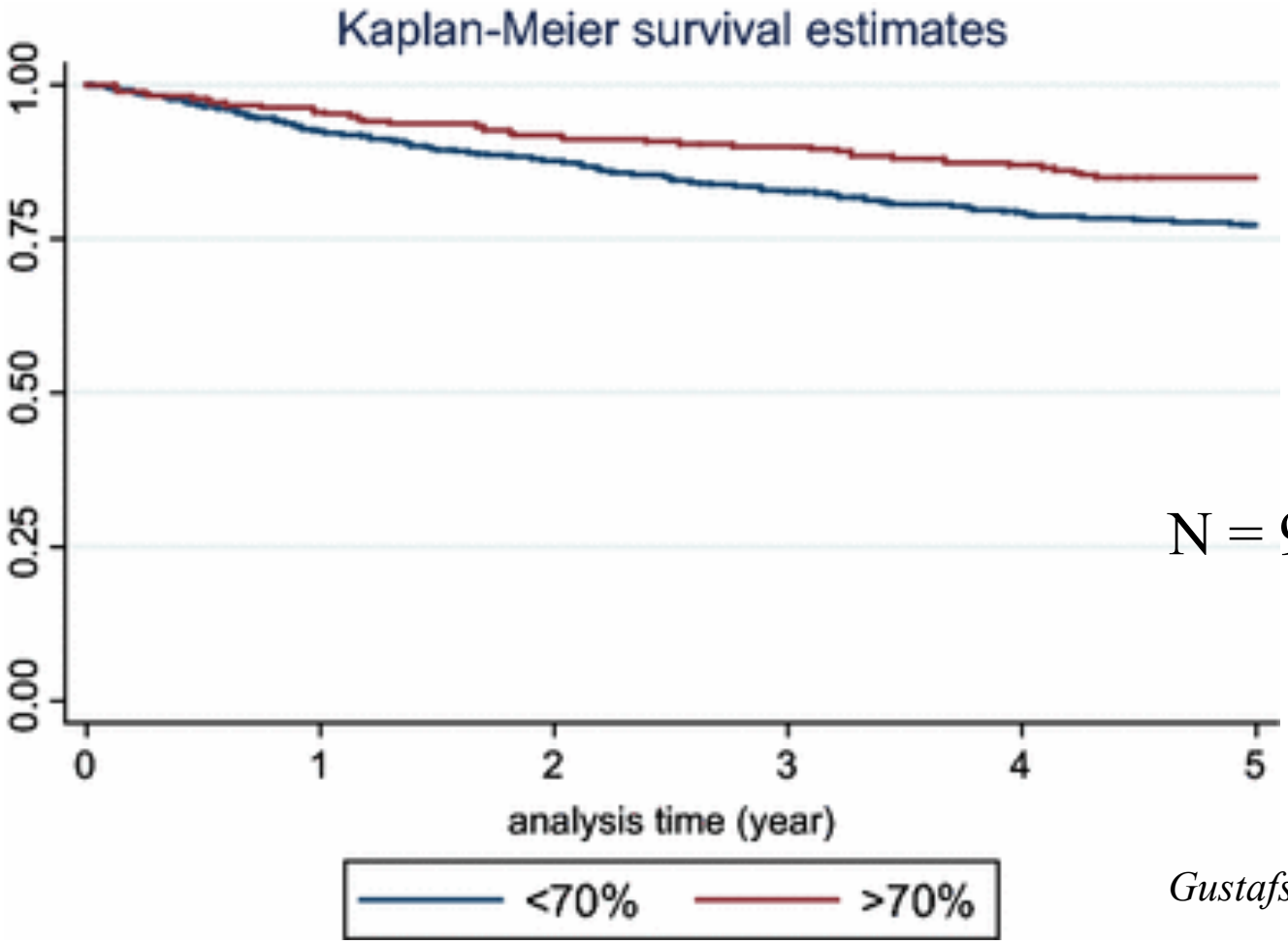
Veenhof A, Ann Surg, 2012

LS	Lap	Standard
LFT	Lap	FT
OS	Open	Standard
OFT	Open	FT



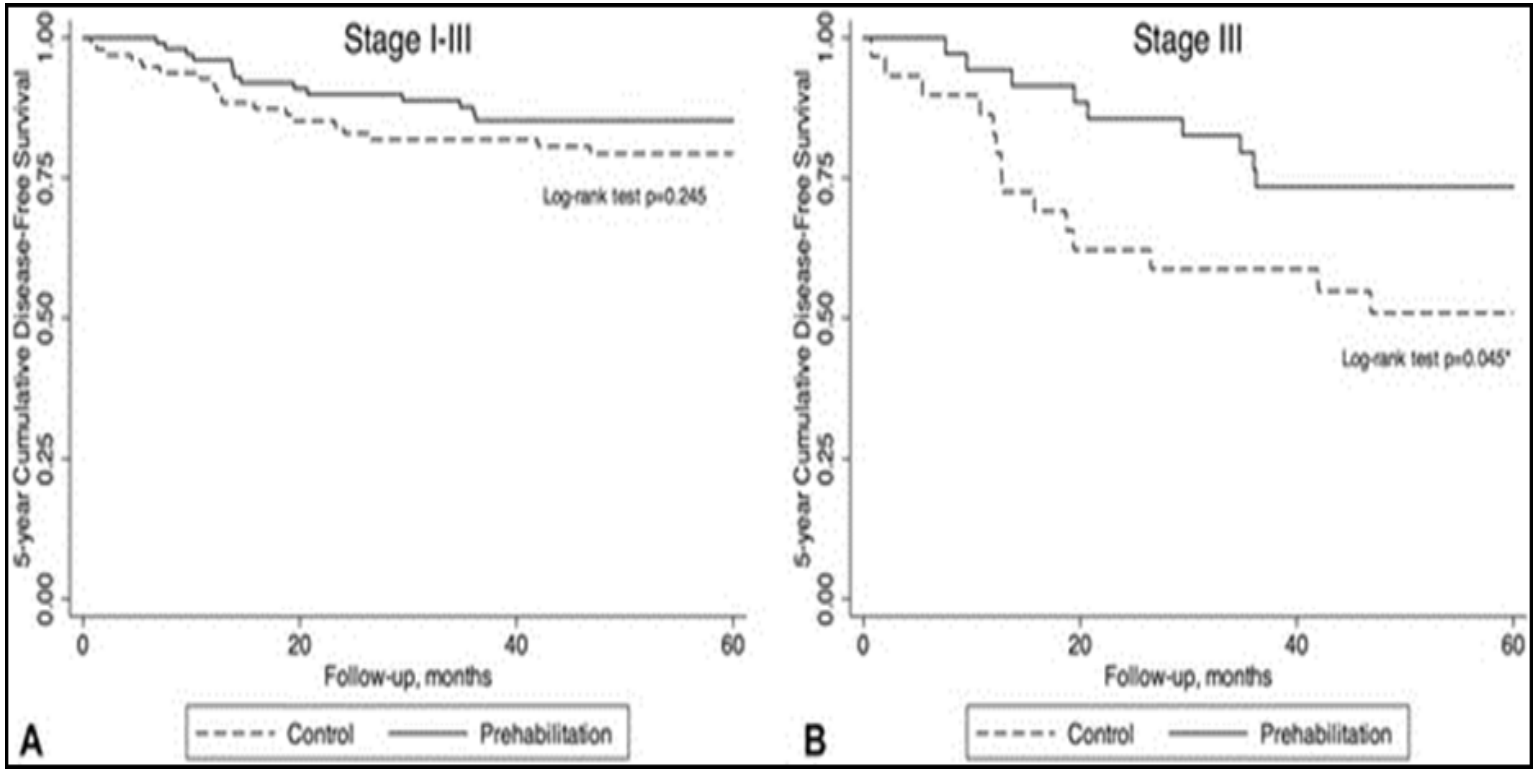


Increased ERAS compliance
42% less cancer specific death at 5 years



N = 911

Gustafsson UO, WJS, 2016



N=202

Improved Disease-free Survival After Prehabilitation for Colorectal Cancer Surgery.

Trepanier, Maude; Minnella, Enrico; Paradis, Tiffany; Awasthi, Rashami; Kaneva, Pepa; Schwartzman, Kevin; MD, MPH; Carli, Franco; MD, MPhil; Fried, Gerald; Feldman, Liane; Lee, Lawrence; MD, PhD

Annals of Surgery. 270(3):493-501, September 2019.
DOI: 10.1097/SLA.0000000000003465

FIGURE 2 . Kaplan-Meier survival curves of 5-year disease-free survival in patients undergoing prehabilitation vs control for (A) all stages and (B) stage III disease.

Summary

- Major surgery
  - significant morbidity and surgical stress
- ERAS are evidence based perioperative protocols
  - reduces surgical stress
  - improves postoperative outcome
- Stress reduction
  - associated to long term oncologic outcome


It´s more to it than a perfect operation

The million dollar question

- Postoperative insulin resistance – Good or bad ?

Beneficial when you were injured in ancient times ?

	Postop	NIDDM
Hyperglycemia	+	+
Insulin sensitivity	-	-
Glucose production	+	+
Glucose uptake	-	-
GLUT4 translocation	-	-
Glycogen formation	-	-