POLYPATHOLOGY and POLYPHARMACY: NEW CHALLENGES

ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI IRCCS

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Milano, 26th September 2013

POLYPATHOLOGY and POLYPHARMACY

- CHANGING THE TRESHOLD OF NORMALITY INCREASES THE NUMBER OF PRESCRIPTIONS

TRESHOLD OF NORMALITY	’70	‘80-’90	TODAY
BLOOD GLUCOSE mg/dl	160	140	126
BLOOD CHOLESTEROL mg/dl	240	220	< 200
BLOOD PRESSURE mm Hg	160/90	140/90	120/80

The optimal approach to the reduction of cardiovascular risk in diabetes should focus on aggressive management of the standard cardiovascular risk factors rather than on intensive glycaemic control."

Hiatt et al., FDA

Statins for all?

An epidemiologist's call for all healthy adults over 50 to take statins was uncritically reinforced by the media without proper discussion of risks and side effects, writes **Margaret McCartney**

For example, a consumer panel of over 10 000 current and former statin users found that muscular side effects were reported in 60% of former and 25% of current users. A French study reported that 104 (10%) of 1074 patients taking statins had muscular symptoms, which in turn led to 30% of these symptomatic patients stopping the treatment.

BMJ 2012;345:e6044 doi: 10.1136/bmj.e6044 (Published 12 September 2012)

Statins for the primary prevention of cardiovascular disease (Review)

Taylor F, Ward K, Moore THM, Burke M, Davey Smith G, Casas JP, Ebrahim S

18 January 2011

THE COCHRANE COLLABORATION®

A Cochrane review questions the evidence for prescribing statins for primary prevention in people at low cardiovascular risk, after finding selective reporting of outcomes, failure to report adverse events, and inclusion of people with cardiovascular disease in published studies.

Treatment blood pressure targets for hypertension.
***Cochrane Database Syst Rev* 2009; 3:CD004349.**

A new review has found that lowering blood pressure below the "standard" target of 140/90 mm Hg is not beneficial in terms of reducing mortality or morbidity, prolong survival or reduce stroke, heart attack, heart failure, or kidney failure.

8 July 2009

THE COCHRANE COLLABORATION®

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Who benefits from treating prehypertension?

With a drug company funded conference on prehypertension set to take place next year, **Ray Moynihan** examines the emergence of this controversial new classification

Global goldmine or useful classification?

Yet in the wake of the classification—and estimates that up to one in three adults has prehypertension (more than 50 million people in the United States alone)—the new entity is looming large as a possible goldmine for the drug industry.

BMJ 2010;341:c4442

Implications Of Expanding Disease Definitions: The Case Of Osteoporosis

When disease definitions are expanded, without evidence, patients might experience "net harm."

by M. Brooke Herndon, Lisa M. Schwartz, Steven Woloshin, and H. Gilbert Welch

ABSTRACT: The National Osteoporosis Foundation and American College of Obstetrics-Gynecology have expanded osteoporosis therapy recommendations by changing the treatment threshold. We determined the impact of this recommendation using nationally representative U.S. data. The new threshold changes the number of women for whom treatment is recommended from 6.4 million to 10.8 million among women age sixty-five and older (at a net cost of at least $28 billion) and from 1.6 million to 4.0 million among women ages 50–64 (at a net cost of at least $18 billion). Whether or not offering treatment to these additional women will reduce the number of hip fractures is unknown. [*Health Affairs* 26, no. 6 (2007): 1702–1711; 10.1377/hlthaff.26.6.1702]

POLYPATHOLOGY and POLYPHARMACY

- ARE DRUGS ONE OF THE CAUSES OF POLYPATHOLOGY?

Inappropriate prescribing for the elderly—a modern epidemic?

Gunhild Nyborg · Jørund Straand · Mette Brekke

Eur J Clin Pharmacol (2012) 68:1085–1094

Conclusions About one-third of the elderly Norwegian population is exposed to potentially inappropriate medications, and elderly females are at particular risk.

CONTRIBUTION OF DRUGS TO POLYPATHOLOGY

PROTON PUMP INHIBITORS (PPI)	30 %	↑	HIP FRACTURES
SULFONYLUREAS	20 %	↑	AMI, STROKES
BENZODIAZEPINES	46 %	↑	DEMENTIA
SSRIs		↑	SEX DISFUNCTIONS
ANTIPSYCHOTICS		↓	BRAIN WEIGHT
HORMONAL REPLACING THERAPY	26 %	↑	BREAST CANCER
ANTIDEPRESSANTS	55 %	↑	DIABETES
GLIPTINES		↑	PANCREATITIS
ASPIRIN and NSAIDs		↑	BLEEDING

POLYPATHOLOGY and POLYPHARMACY

- POLYPHARMACY INCREASES DRUG-DRUG INTERACTIONS

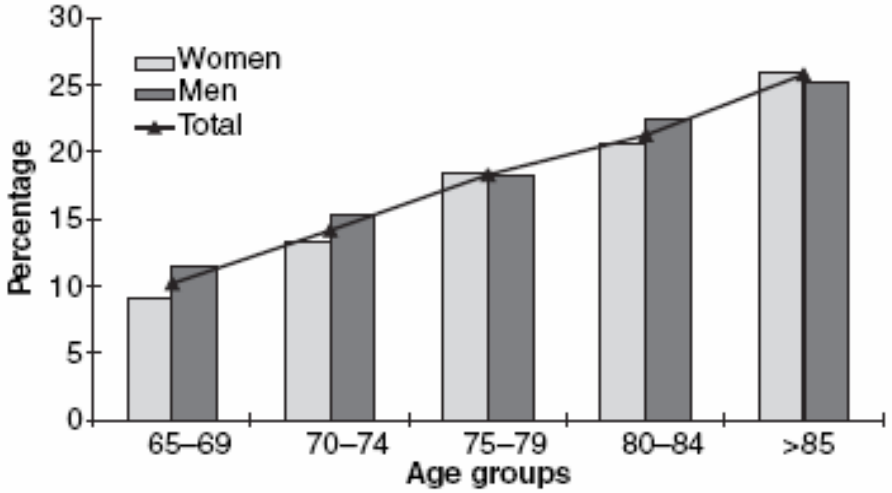


Fig. 3. Distribution of the elderly resident under Lecco Local Health Authorithy with at least one potentially severe drug interaction in relation to sex and age.

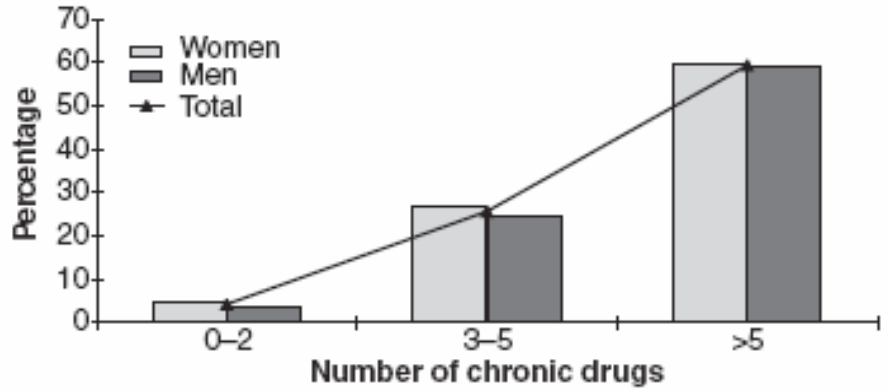


Fig. 4. Distribution of the elderly resident under Lecco Local Health Authorithy with at least one potentially severe drug interaction in relation to sex and number of chronic drugs taken.

doi:10.1111/j.1365-2710.2009.01021.x

Increasing Exposure to Drug-Drug Interactions Between 1992 and 2005 in People Aged ≥55 Years

Matthijs L. Becker,[1,2] *Loes E. Visser,*[1,2] *Teun van Gelder,*[2] *Albert Hofman*[1] and *Bruno H.Ch Stricker*[1,3]

Background: Drug-drug interactions (DDIs) are responsible for a variety of adverse reactions, particularly in an elderly population.

Objective: To assess the frequency and potential clinical relevance of DDIs in a population aged ≥55 years.

Methods: Exposure to DDIs was assessed in 7842 people participating in the Rotterdam Study, a population-based cohort study. These people were followed between 1 January 1992 and 1 July 2005. The DDI list of the Royal Dutch Association for the Advancement of Pharmacy, in which DDIs are categorized by potential clinical relevance and quality of evidence, was used. Simultaneous use of interacting drug combinations was calculated on the basis of drug dispensing data from community pharmacies.

Results: The incidence of a first dispensing of DDIs in the study period was 10.5 per 100 person-years and 2.7 per 100 person-years for potentially life-threatening DDIs. The prevalence of DDIs in people aged ≥70 years increased from 10.5% in 1992 to 19.2% in 2005. Ten DDIs comprised two-thirds of the total exposure time to DDIs. The prevalence of potentially life-threatening DDIs in people aged ≥70 years increased from 1.5% to 2.9%. This increase was most likely caused by an increase in use of spironolactone combined with renin-angiotensin-aldosterone system inhibitors.

Conclusion: A large number of people in the Netherlands aged ≥55 years are exposed to DDIs and this number has increased sharply between 1992 and 2005. Healthcare professionals should pay special attention to the potential risks of DDIs in these people, particularly if spironolactone is involved.

Drug Aging 2008;25:145-152

Non-degenerative mild cognitive impairment in elderly people and use of anticholinergic drugs: longitudinal cohort study

Marie L Ancelin, Sylvaine Artero, Florence Portet, Anne-Marie Dupuy, Jacques Touchon, Karen Ritchie

Longitudinal cohort study (1 year, n=370) found that elderly people taking anticholinergic drugs had significant deficits in cognitive functioning and were highly likely to be classified as mildly cognitively impaired.

Continuous use of anticholinergic drugs was a strong predictor of mild cognitive impairment (OR = 5.12, p=0.001)

Anticholinergic drugs: tricyclic antidepressants, antispasmodics, antihistamines, anxyolitics, cardiovascular (warfarin, digoxin), neuroleptics

Ancelin, BMJ 2006

Drugs With Anticholinergic Properties, Cognitive Decline, and Dementia in an Elderly General Population

A large study population (4 years, n=6.912) found a higher risk of incident dementia and cognitive impairment for continuous users (at least 2 years) of anticholinergic drugs but not in those who discontinued or never used anticholinergic drugs

Anticholinergic drugs: tricyclic antidepressants, antispasmodics, antihistamines, anxyolitics, cardiovascular (warfarin, digoxin), neuroleptics

Carriere, Arch Int Med 2009

The study suggests a potential reversibility of the association between anticholinergic use and dementia or MCI

Table 4. Patterns of Anticholinergic Use (Continuing or Discontinuing) During Follow-up and Incident Dementia (Cox Model With Delayed Entry)[a]

Group	HR (95% CI)	*P* Value
All participants with dementia (n=177)	n=6463	
Discontinuing	1.28 (0.59-2.76)	.53
Continuing	1.65 (1.00-2.73)	.05
Participants with Alzheimer dementia (n=113)	n=6399	
Discontinuing	1.72 (0.74-3.99)	.21
Continuing	1.94 (1.01-3.72)	.05

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a]The participants who used anticholinergics intermittently during follow-up were not considered in this analysis. The model was adjusted for center; age; sex; education; body mass index; alcohol, tobacco, and caffeine intake; mobility; hypercholesterolemia; *APOE*E4* (allele producing the ε4 type of apolipoprotein E); diabetes mellitus; asthma; depression; ischemic diseases; Parkinson disease; and hypertension.

POLYPATHOLOGY and POLYPHARMACY

- THE NUMBER OF DRUGS CAN BE REDUCED?

Box 2 Summary points

The piecemeal rise of diagnostic labels and biomarkers for illness has led to diagnosis that is often detached from symptoms

Current single disease approaches to research and guidelines encourages siloing of care that can be harmful, complex, and time consuming for patients with chronic comorbidity, and burdensome for health systems

Research rarely investigates, and guidelines rarely support, complex and difficult decisions about when to stop or not give treatments

Care for patients with chronic comorbid illness must be more closely driven by patients' individual experience of illness and treatment effects, and their priorities for care

Shifts in the frameworks of research, guidance, and funding, in addition to changes in the values and technologies underpinning healthcare systems, are needed to ensure care that focuses on the person rather than management that focuses on diseases

D.Mangin et al., 2012

Withdrawal of diuretics was maintained in 51-100% of subjects and was unsuccessful primarily when heart failure was present. Adverse effects from medication withdrawal were infrequently encountered. After withdrawal of antihypertensive therapy, many subjects (20-85%) remained normotensive or did not require reinstatement of therapy for between 6 months and 5 years, and there was no increase in mortality. Withdrawal of psychotropic medications was associated with a reduction in falls and improved cognition. In conclusion, there is some clinical trial evidence for the short-term effectiveness and/or lack of significant harm when medication withdrawal is undertaken for antihypertensive, benzodiazepine and psychotropic agents in older people.

S.Iyer et al., 2008

POLYPATHOLOGY and POLYPHARMACY

- CURE OR PALLIATIVE TREATMENTS?

How to move to a palliative approach to care for people with multimorbidity

Doctors must actively guide patients in decisions to scale back treatment when appropriate

Fred Burge professor of family medicine[1], Beverly Lawson senior research associate[1], Geoffrey Mitchell professor of general practice and palliative care[2]

[1]Dalhousie University, Family Medicine, NS, Halifax, Canada, B3H 2E2; [2]University of Queensland, Ipswich, QLD 4305, Australia

BMJ 2012;345:e6324 doi:

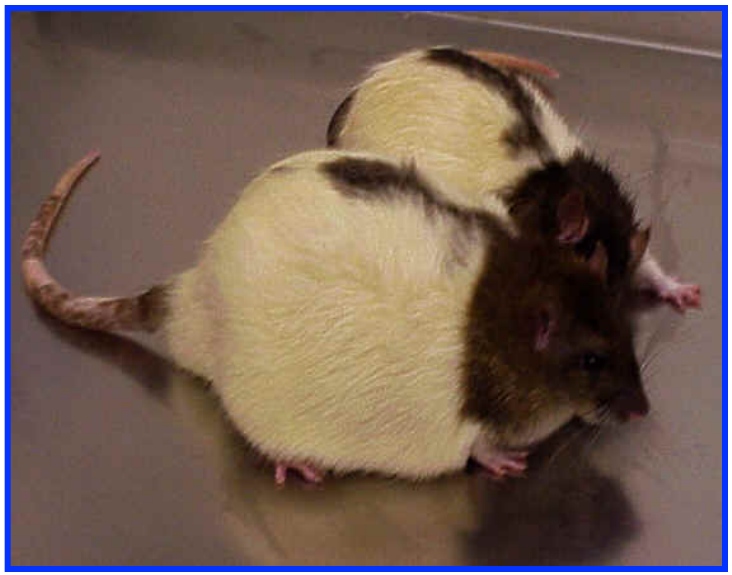
The transition to a palliative approach to care is not a "transition" from one form of care to another.
Just as the early symptom experience, the diagnosis, patient education, and chronic disease self management are all phases through which we progress, the palliative approach is the last phase in the continuum of good care for patients with multimorbidity in whom multiple active treatments are no longer appropriate.

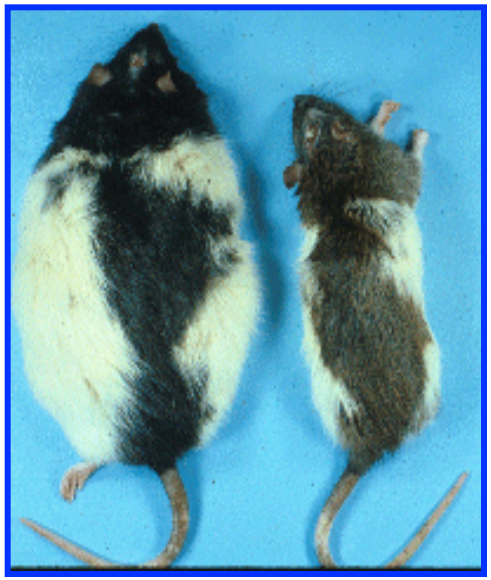
F.Burge et al., 2012

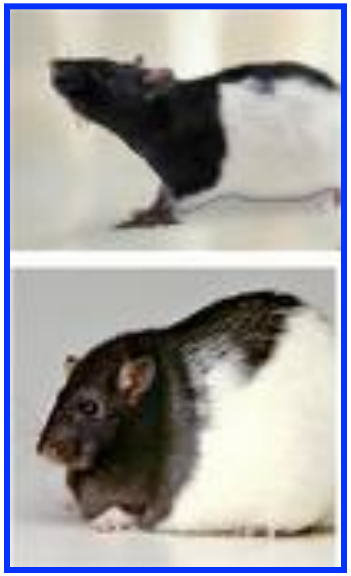
POLYPATHOLOGY and POLYPHARMACY

- NEED OF LABORATORY MODELS OF POLYPATHOLOGY

Zucker Fat Rats

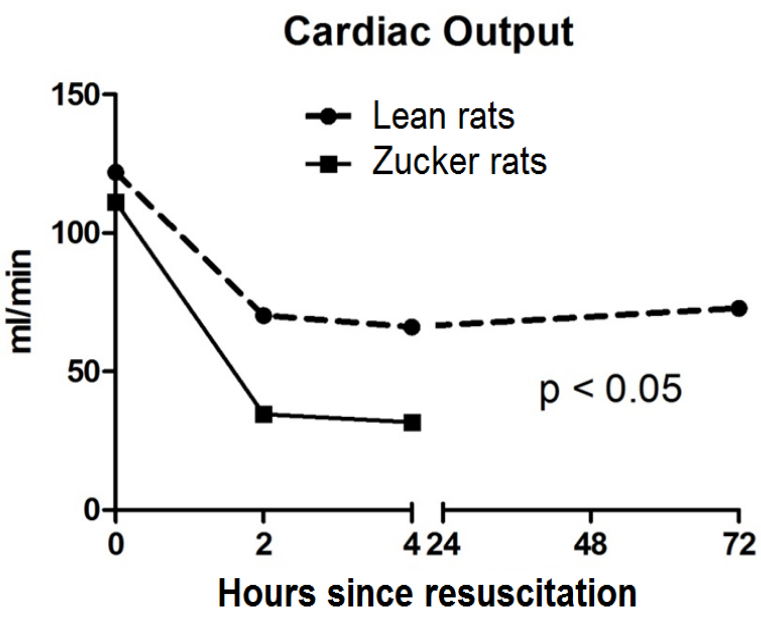


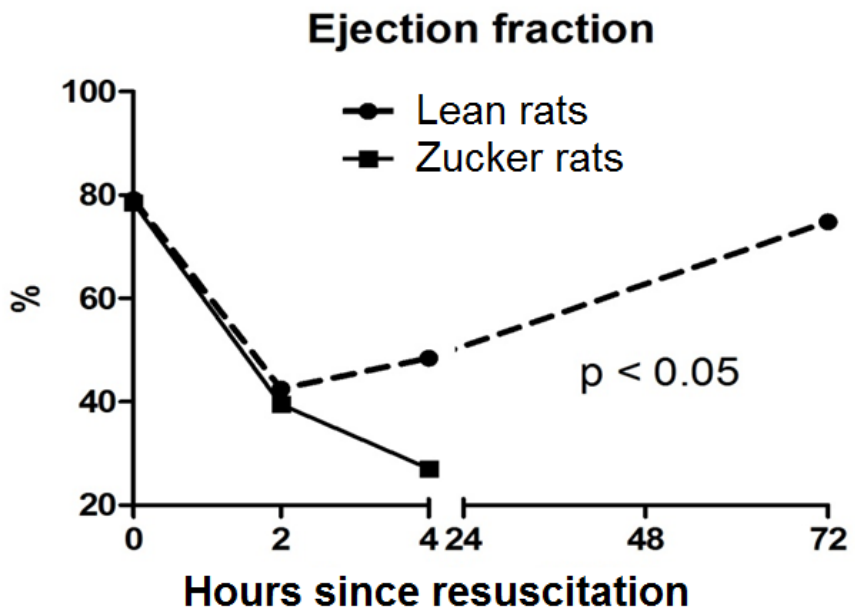


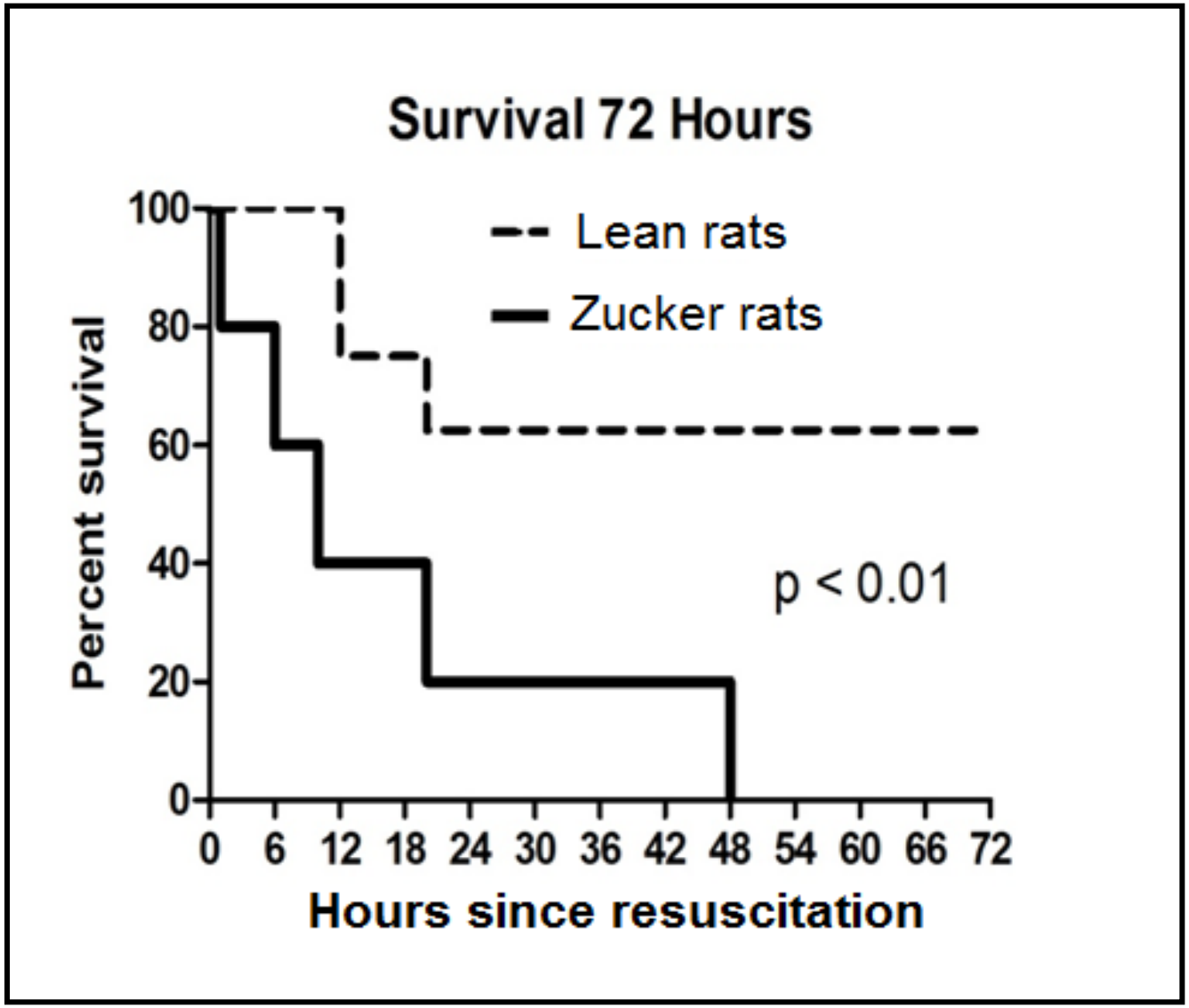


Characteristics:

obesity, insulin resistance, hyperinsulinemia, hypertriglyceridemia, hypercolesterolemia, metabolic syndrome


Cardiac Output
Lean rats
Zucker rats
150
100
50
0
ml/min
p < 0.05
0
2
4
24
48
72
Hours since resuscitation


Ejection fraction
Lean rats
Zucker rats
100
80
60
40
20
%
p < 0.05
0
2
4
24
48
72
Hours since resuscitation


Survival 72 Hours
Lean rats
Zucker rats
p < 0.01
Percent survival
100
80
60
40
20
0
0 6 12 18 24 30 36 42 48 54 60 66 72
Hours since resuscitation

Am J Physiol Heart Circ Physiol 302: H845–H854, 2012.
First published December 2, 2011; doi:10.1152/ajpheart.00261.2011.

Subtotal nephrectomy plus coronary ligation leads to more pronounced damage in both organs than either nephrectomy or coronary ligation

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Departments of [1]Cardiology, [2]Nephrology, and [3]Pathology, University Medical Center Utrecht, Utrecht; [4]Department of Nephrology, Meander Medical Center, Amersfoort, Netherlands; and [5]Department of Nephrology & Immunology, University of Alberta, Edmonton, Alberta, Canada

The increased risk for cardiac disease in advancing stages of chronic kidney disease (CKD) is now widely recognized. When CKD is complicated by myocardial infarction or left ventricular systolic dysfunction, prognosis is dismal.