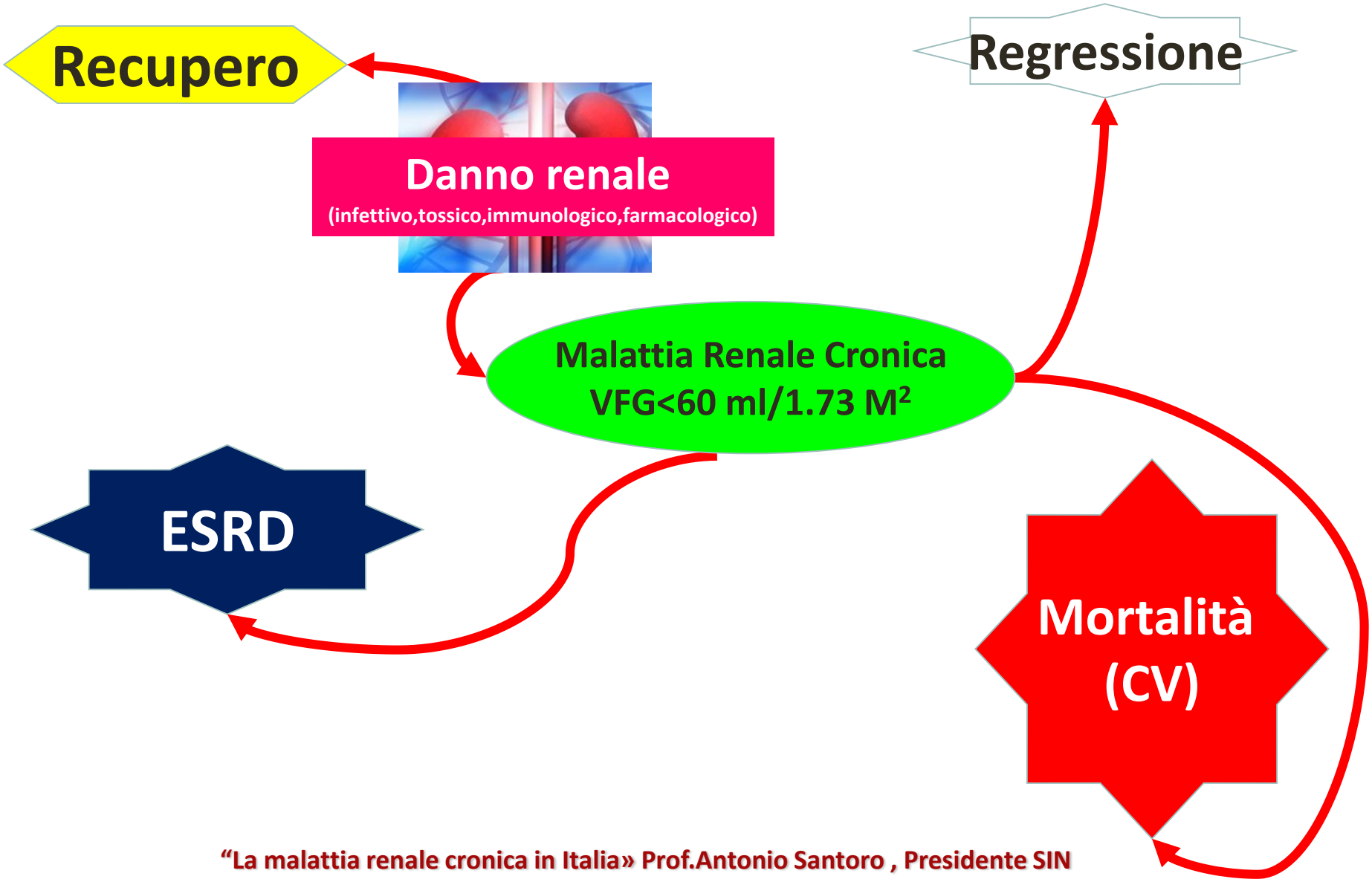
Fenomenologia nazionale dell'uremia terminale il peso delle comorbidità

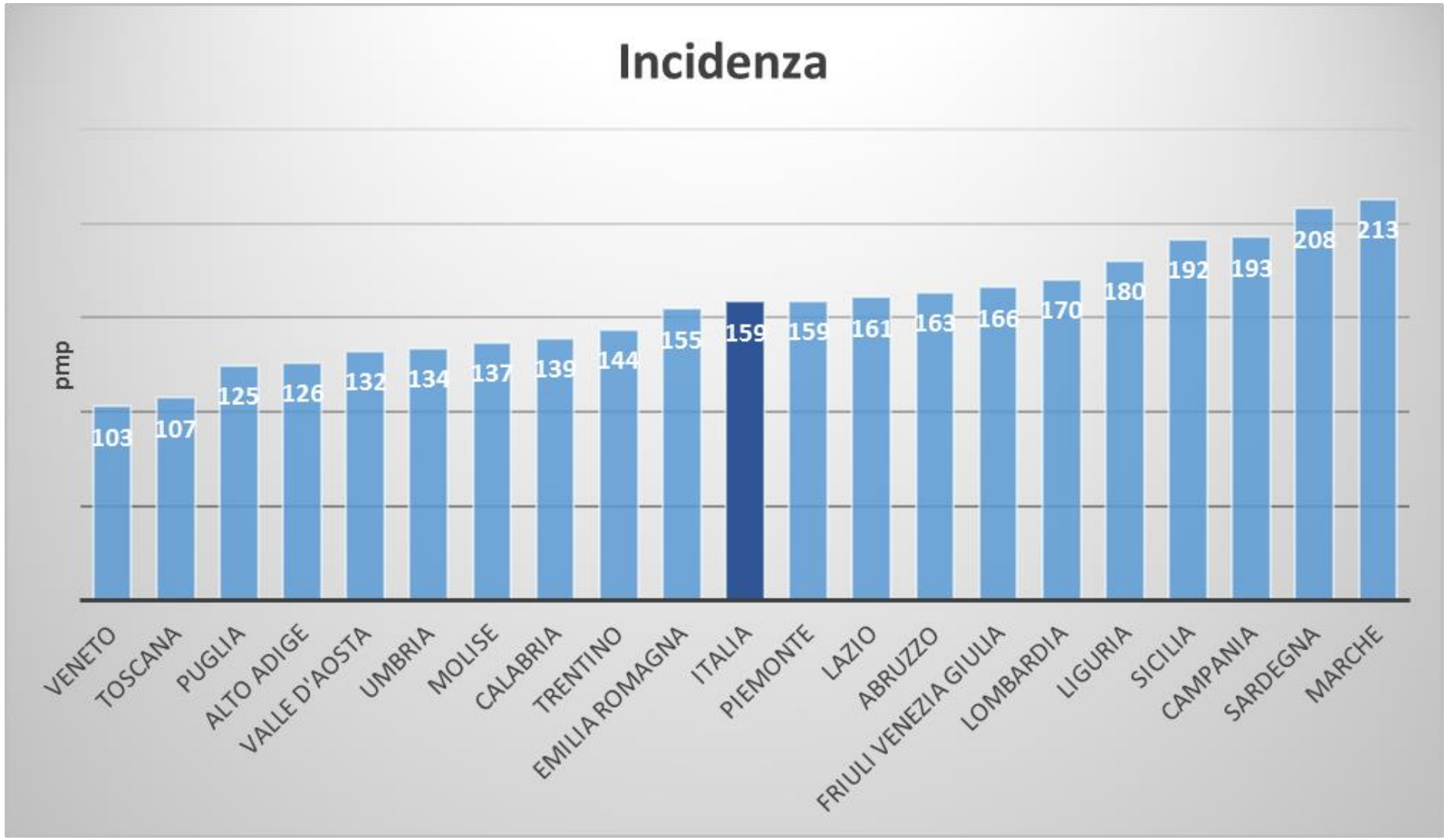
Antonio Santoro, MD, FERA

Past President della Società Italiana di Nefrologia

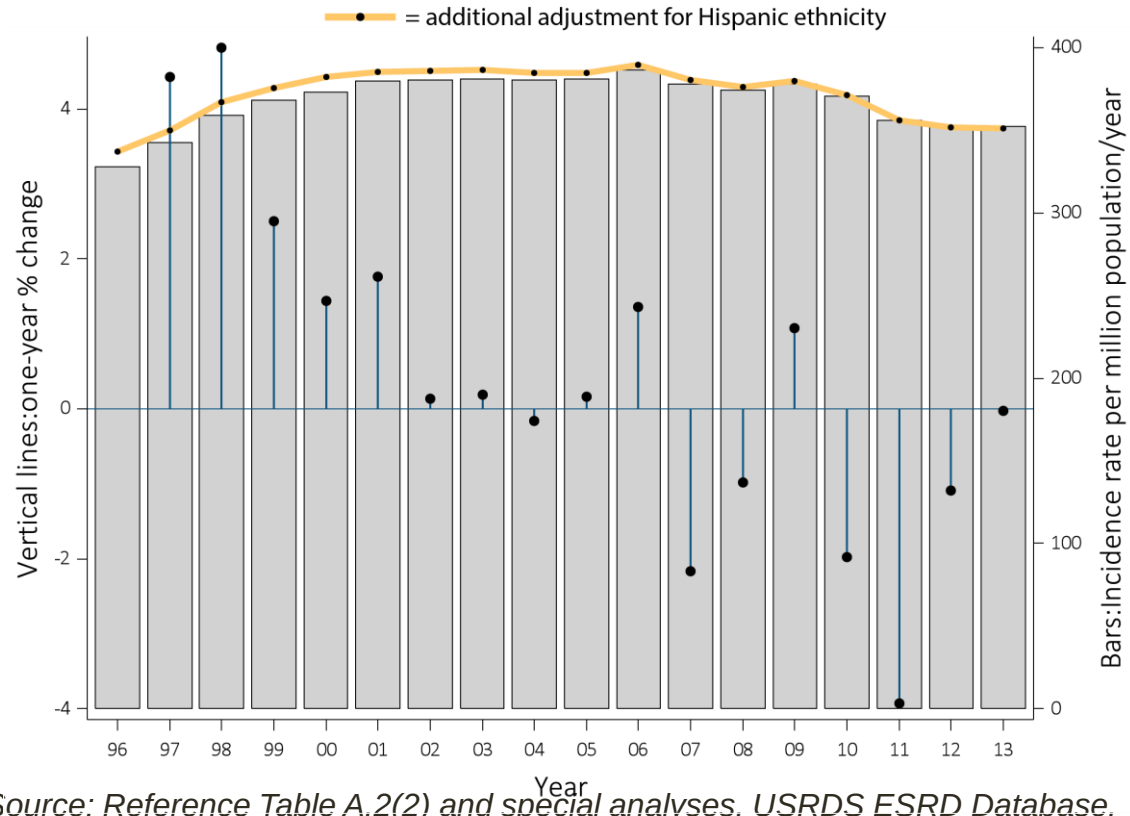


"La malattia renale cronica in Italia» Prof.Antonio Santoro , Presidente SIN


Incidenza
130
135
138
140
146
160
158
145
155
152
168
162
168
166
160
159
1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014


Incidenza
pmp
103
107
125
126
132
134
137
139
144
155
159
159
161
163
166
170
180
192
193
208
213
VENETO
TOSCANA
PUGLIA
ALTO ADIGE
VALLE D'AOSTA
UMBRIA
MOLISE
CALABRIA
TRENTINO
EMILIA ROMAGNA
ITALIA
PIEMONTE
LAZIO
ABRUZZO
FRIULI VENEZIA GIULIA
LOMBARDIA
LIGURIA
SICILIA
CAMPANIA
SARDEGNA
MARCHE

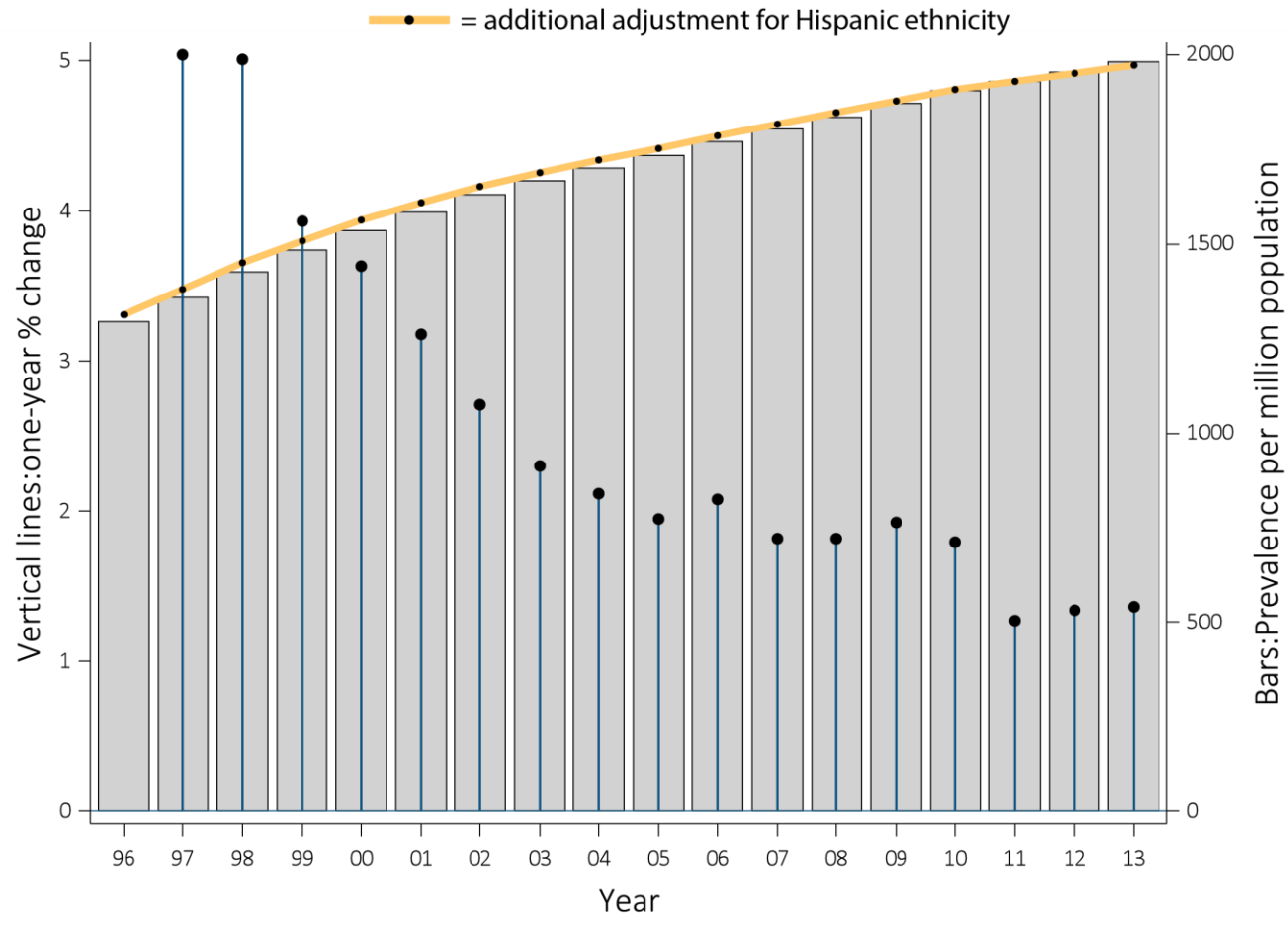
Trends in the adjusted* incidence rate (per million/year) of ESRD (bars; scale on right), and annual change (%) in the adjusted* incidence rate of ESRD in the U.S. population, 1996-2013



Data Source: Reference Table A.2(2) and special analyses, USRDS ESRD Database.
**Adjusted for age, sex, and race.*
The standard population was the U.S. population in 2011. Abbreviation: ESRD, end-stage renal disease.

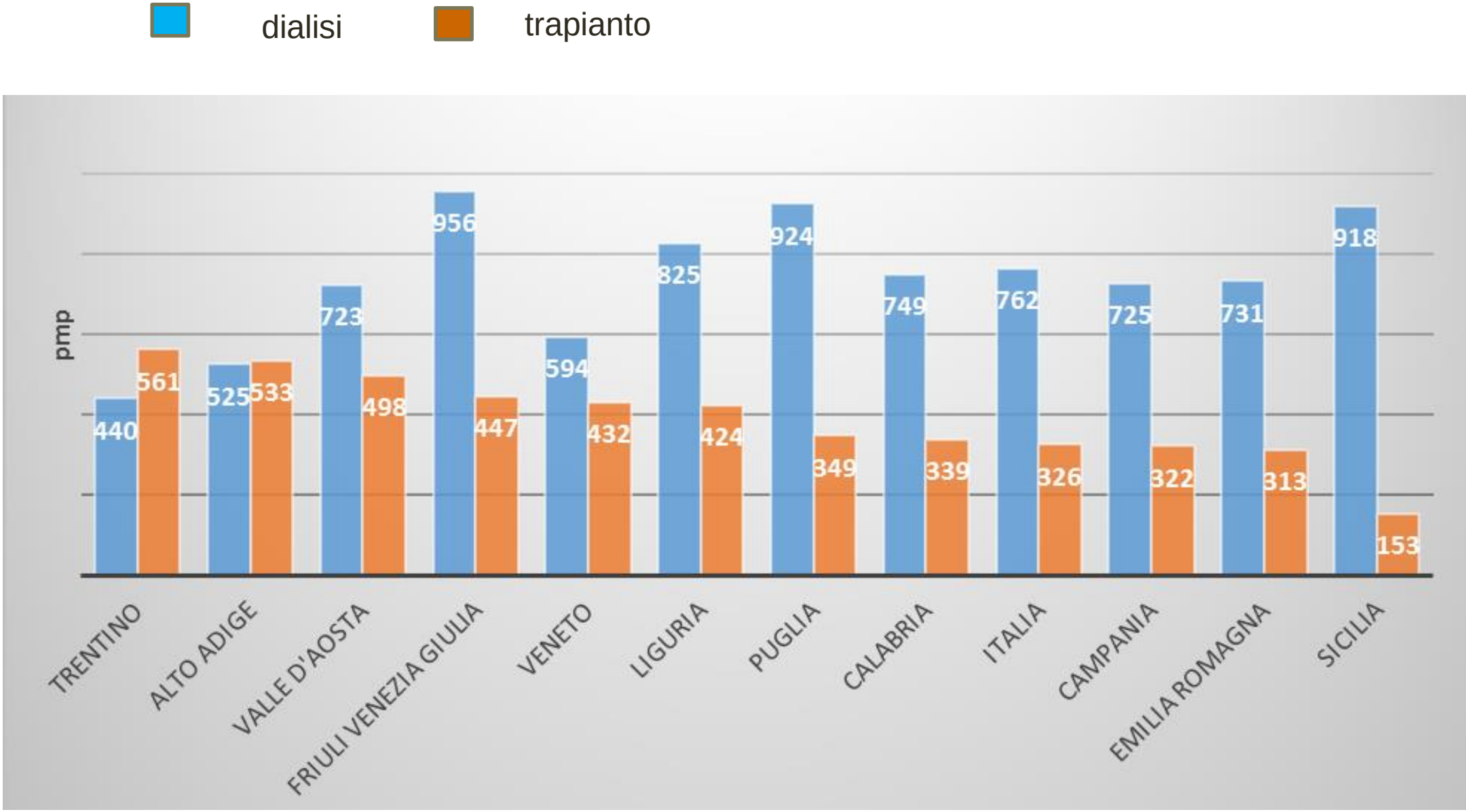

Prevalenza dializzati in Italia
720
748
740
750
770
790
788
759
760
762
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
circa 45.000 pazienti in Italia
Spesa per i pazienti in dialisi : oltre 2 miliardi di euro

Trends in the adjusted* ESRD prevalence (per million) (bars; scale on left), and annual change (%) in adjusted* prevalence of ESRD (lines; scale on right), in the U.S. population, 1996-2013



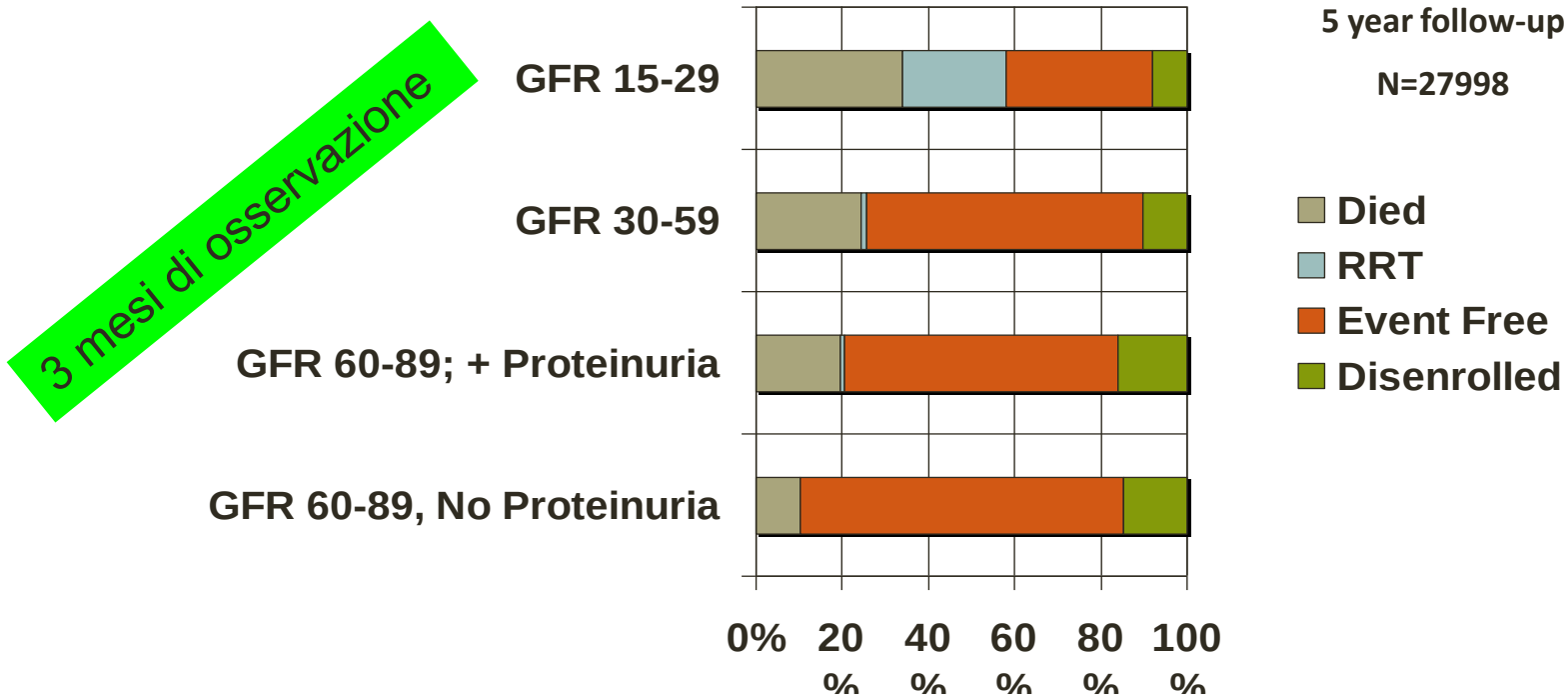
*Data Source: Reference Table B.2(2) and special analyses, USRDS ESRD Database. *Adjusted for age, sex, and race.*

The standard population was the U.S. population in 2011. Abbreviation: ESRD, end-stage renal disease.

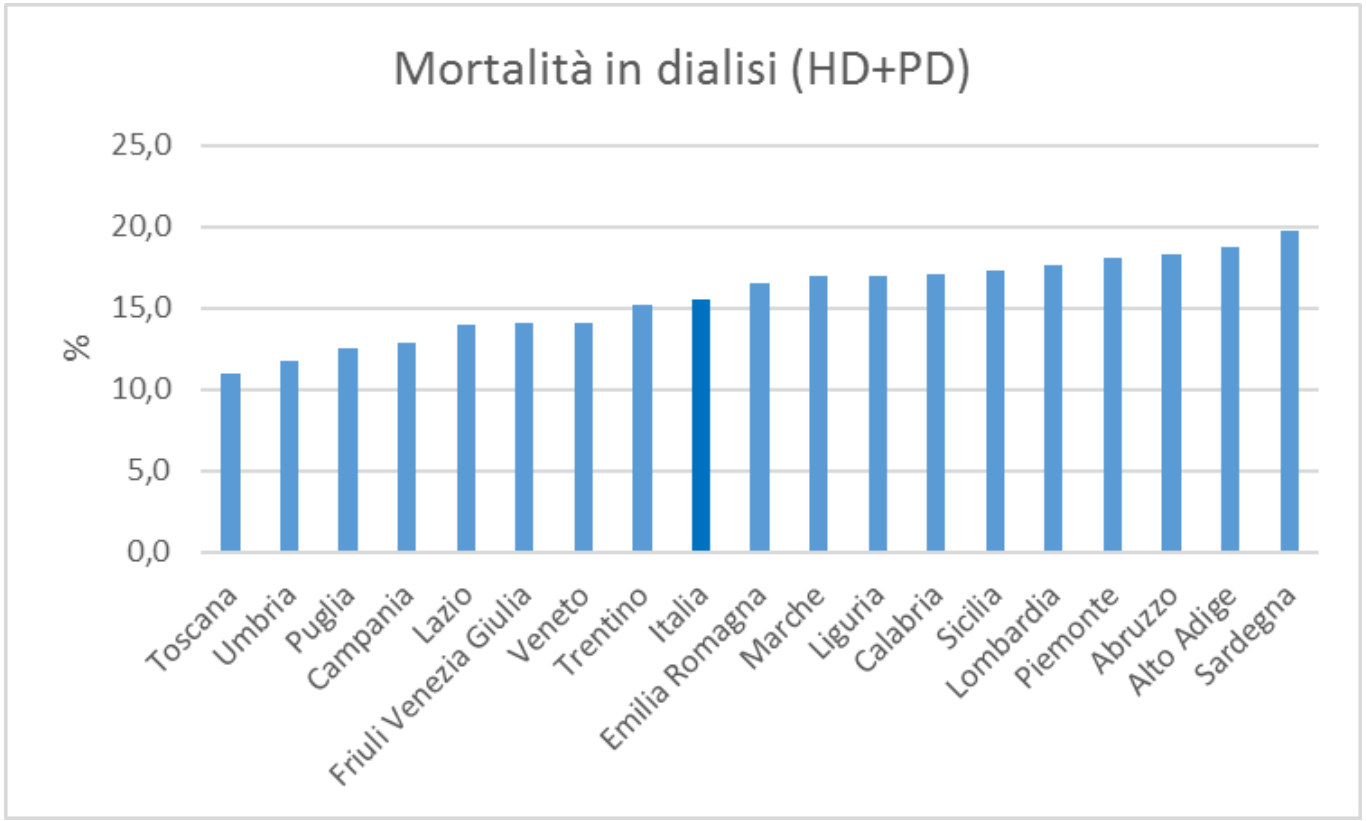

dialisi
trapianto
pmp
440
561
525
533
723
498
956
447
594
432
825
424
924
349
749
339
762
326
725
322
731
313
918
153
TRENTINO
ALTO ADIGE
VALLE D'AOSTA
FRIULI VENEZIA GIULIA
VENETO
LIGURIA
PUGLIA
CALABRIA
ITALIA
CAMPANIA
EMILIA ROMAGNA
SICILIA

CKD Patients Are More Likely to Die than to Progress to ESRD

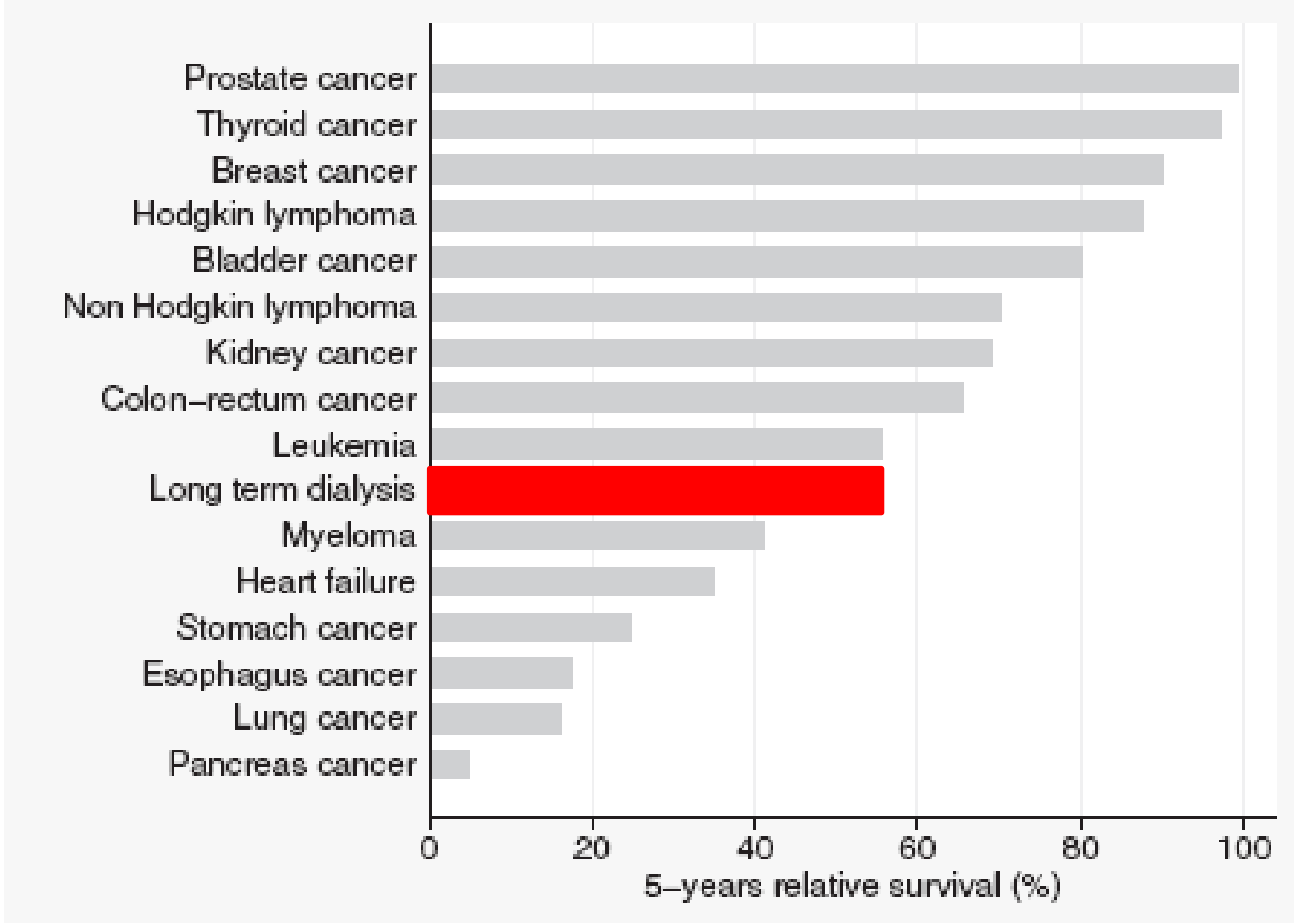
In 1996 Keith et al. identified 27 998 patients in their health plan who had estimated glomerular filtration rates of less than 90 mL/min per 1.73 m(2) on 2 separate measurements at least 90 days apart. They followed up patients from the index date of the first GFR of less than 90 mL/min per 1.73 m(2) until renal replacement therapy, death, disenrollment from the health plan, or June 30, 2001.



Keith, et al, Arch Int Med; 2004; 164:659-663


Mortalità in dialisi (HD+PD)
%
25,0
20,0
15,0
10,0
5,0
0,0
Toscana
Umbria
Puglia
Campania
Lazio
Friuli Venezia Giulia
Veneto
Trentino
Italia
Emilia Romagna
Marche
Liguria
Calabria
Sicilia
Lombardia
Piemonte
Abruzzo
Alto Adige
Sardegna

Comparison of 5-year relative survival



Comparison between General Mortality and Dialysis Mortality

Country	Death rates per 100 patient years		
	General population age 55-69 y	HD population age 55-69 y	Ratio of HD to general population
Australia	0.83	16.1	19.4
Belgium	1.10	21.3	19.4
Canada	0.97	16.1	16.6
France	1.01	13.7	13.6
Germany	1.13	15.6	13.8
Italy	0.97	11.4	11.8
Japan	0.82	5.2	6.3
New Zealand	1.02	16.2	15.9
Spain	0.98	15.7	16.0
Sweden	0.85	18.7	22.0
United Kingdom	1.16	16.5	14.2
United States	1.22	19.0	15.6

Ref: Dor et al, Int J Health Care Finance Econ. 2007

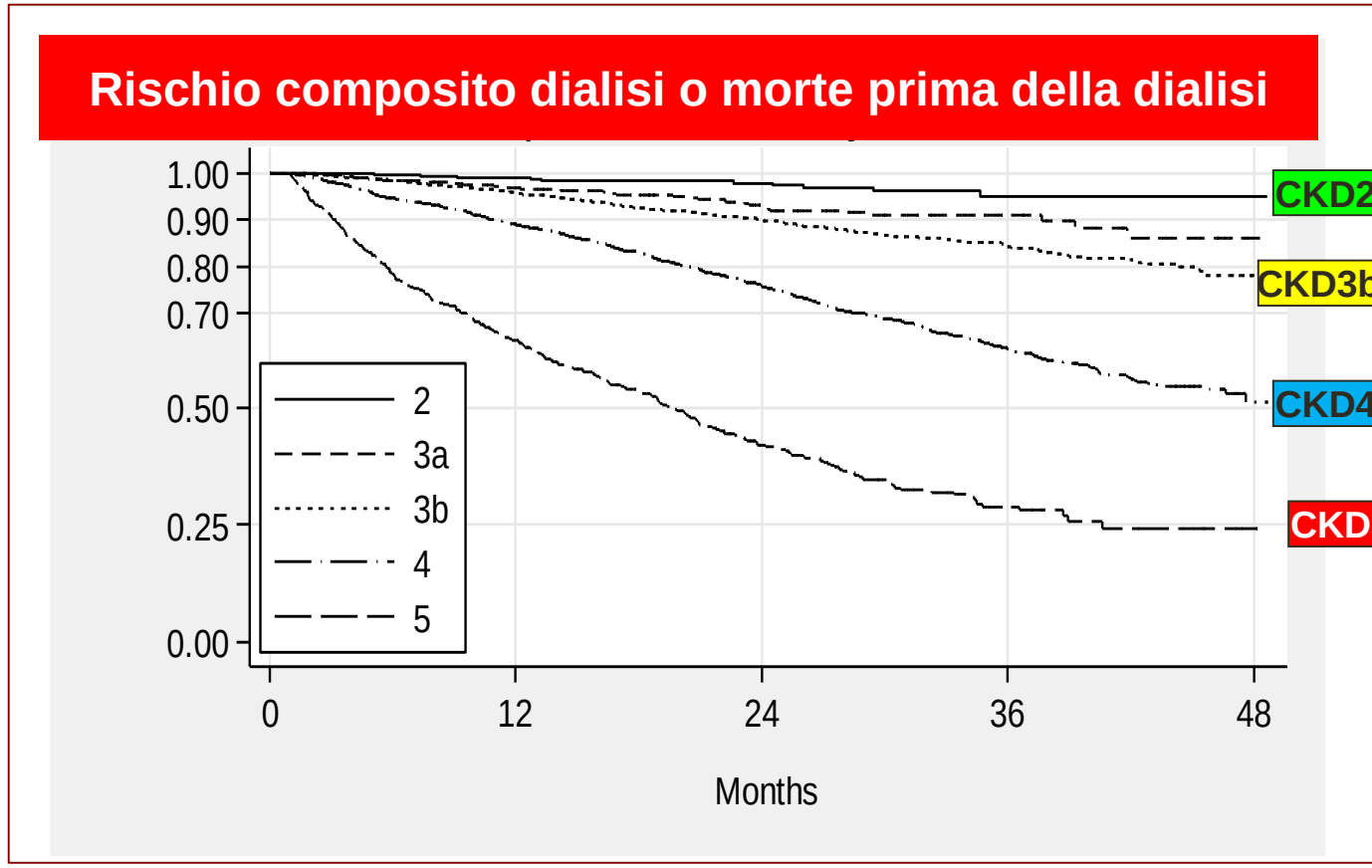
J Nephrol. 2016 Oct;29(5):663-71. doi: 10.1007/s40620-015-0239-4. Epub 2015 Oct 26.

Excess mortality attributable to chronic kidney disease. Results from the PIRP project.

Gibertoni D[1], Mandreoli M[2], Rucci P[3], Fantini MP[3], Rigotti A[4], Scarpioni R[5], Santoro A[6].

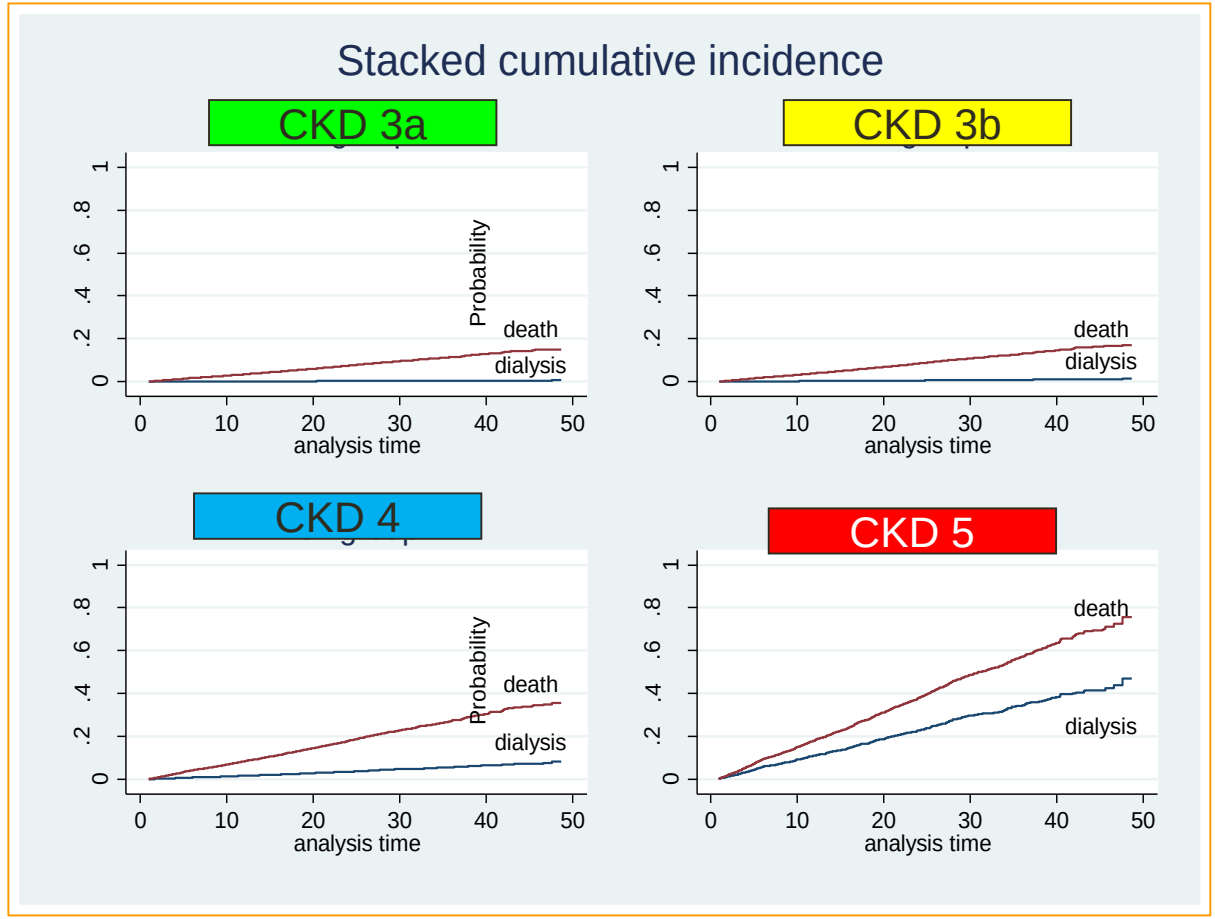
Relative survival was the ratio of survival observed in CKD patients to the expected survival of the general population. Multivariate parametric survival analysis was used to identify factors predicting excess mortality. ***The relative survival of CKD patients at 9 years was 0.708.*** *Survival was significantly lower in CKD patients with cardiovascular comorbidities, proteinuria, diabetes, anemia and high phosphate levels and in advanced CKD stages, males, older patients and those who underwent dialysis.*

Curve di Kaplan – Meier negli stadi CKD



22.000 patients , PIRP Project Emilia-Romagna

Analisi comparativa dei due competing risk



22.000 patients , PIRP Project Emilia-Romagna

Propensity-Matched Mortality Comparison of Incident Hemodialysis and Peritoneal Dialysis Patients

Eric D. Weinhandl,* Robert N. Foley,*† David T. Gilbertson,* Thomas J. Arneson,* Jon J. Snyder,* and Allan J. Collins*†

J Am Soc Nephrol 21: 499–506, 2010.

6337 patient pairs who initiated dialysis in 2003in the US

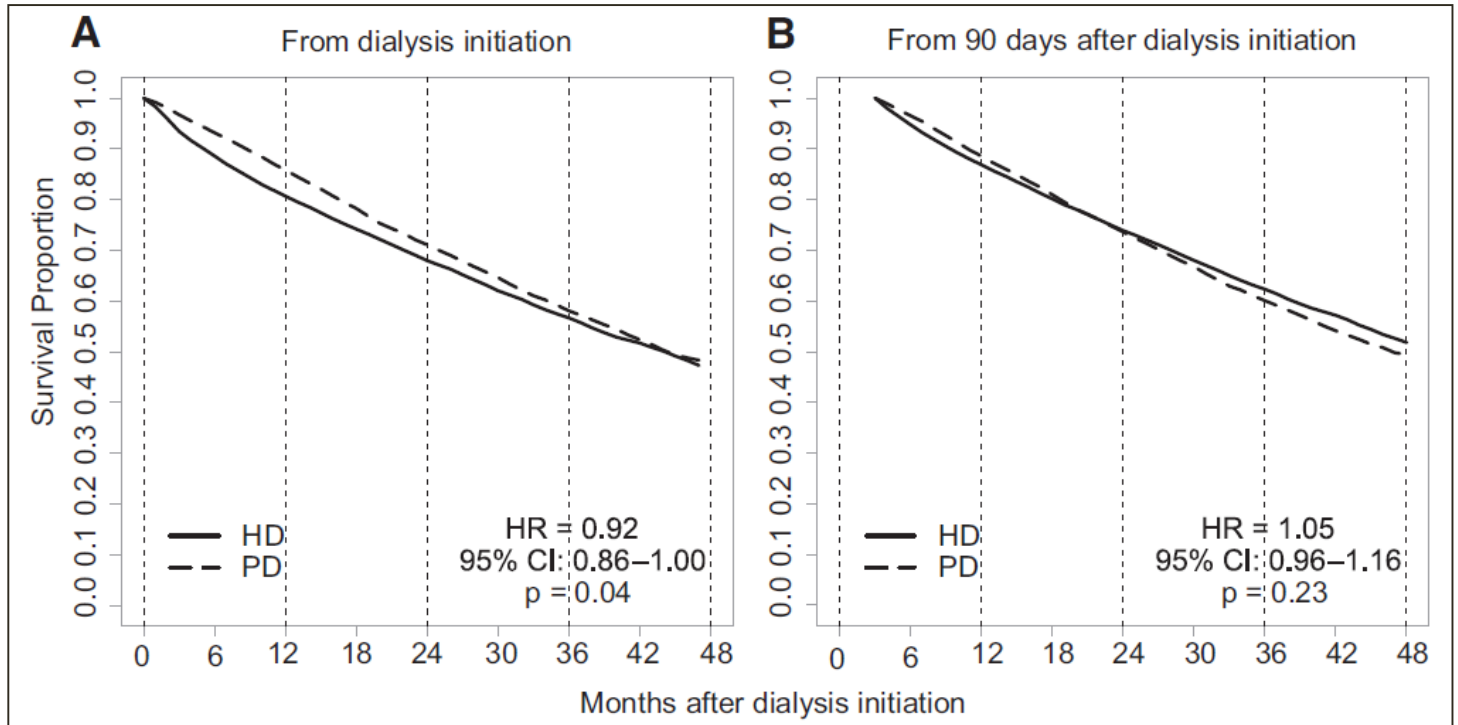
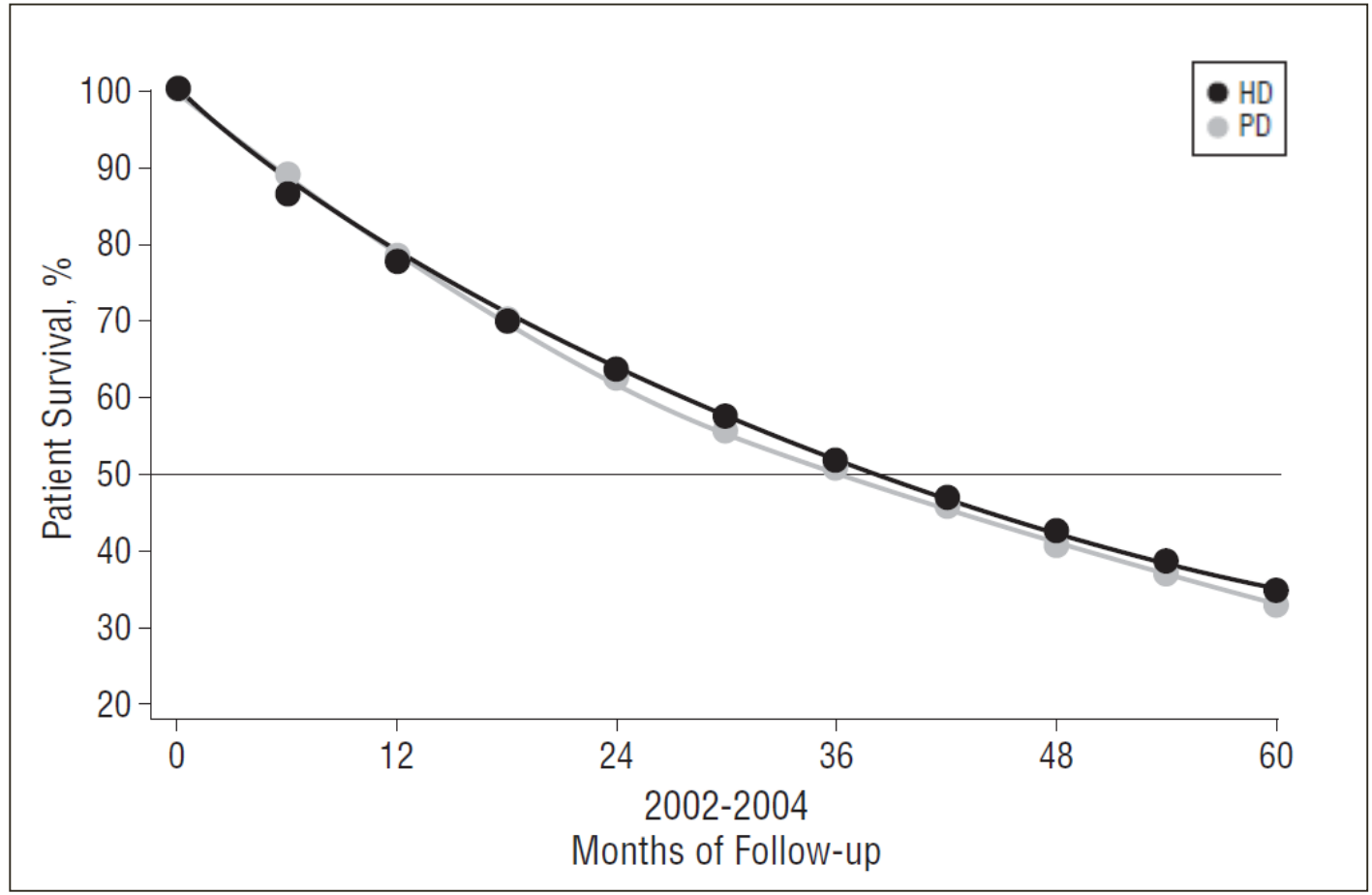


Figure 1. Intention-to-treat in the matched cohort showed lower death risk in PD when follow up began at initiation of dialysis. Risks were similar when follow-up began at day 90. HD, hemodialysis; PD, peritoneal dialysis.

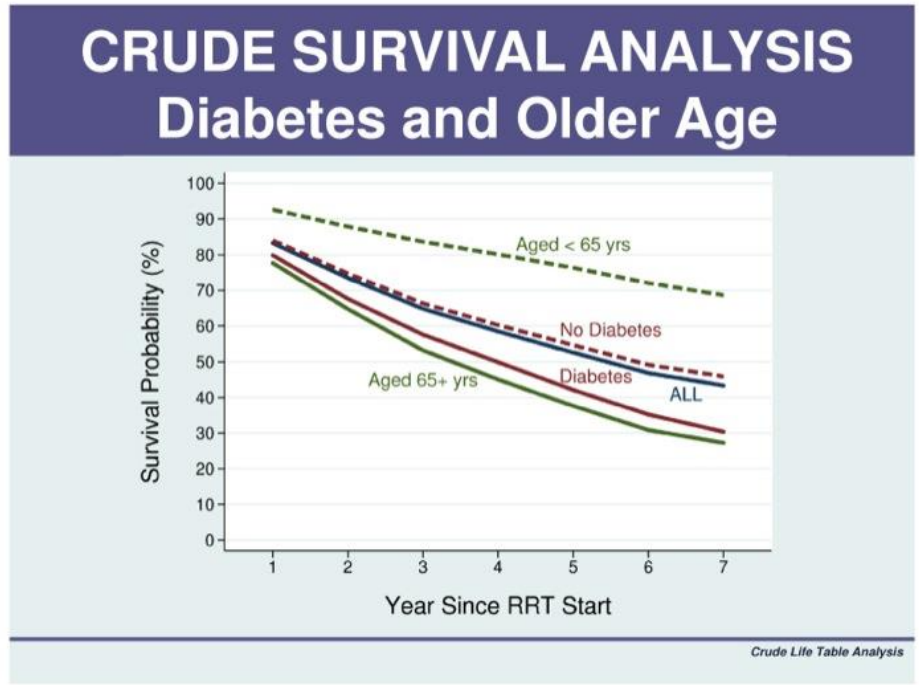
Similar Outcomes With Hemodialysis and Peritoneal Dialysis in Patients With End-Stage Renal Disease

Rajnish Mehrotra, MD; Yi-Wen Chiu, MD; Kamyar Kalantar-Zadeh, MD; Joanne Bargman, MD; Edward Vonesh, PhD

Arch Intern Med. 2011;171(2):110-118.



Mortality on chronic dialysis in Italy



Italian Dialysis &Transplant Registry

Nordio M et al, Am J Kidney Dis 2012

Survival of elderly patients with stage 5 CKD: comparison of conservative management and renal replacement therapy

Chandna SM, et al. Nephrol Dial Transplant 2011;26:1608-1614

Conservative management programme

Patients opting for conservative management were offered ongoing support by the multidisciplinary team in liaison with community, primary care and hospice services. Full medical treatment was continued, which included the use of erythropoietin as appropriate to treat or prevent anaemia.

Table 1. Demographic and clinical details of patients treated by dialysis and conservative kidney management

	Conservative	Dialysis	P-value
Number	155 (18%)	689 (82%)	
Age at stage 5 (years)	77.5 ± 7.6	58.5 ± 15.0	<0.001
% >75 years	68.4	11.2	<0.001
% Male	59.4	66.6	NS
% Non-white	14.2	15.7	NS
% Diabetes	35.5	34.3	NS
% High comorbidity	49.7	17.3	<0.001
eGFR at stage 5 (mL/min/1.73 m^2)	13.2 ± 1.4	13.2 ± 1.4	NS

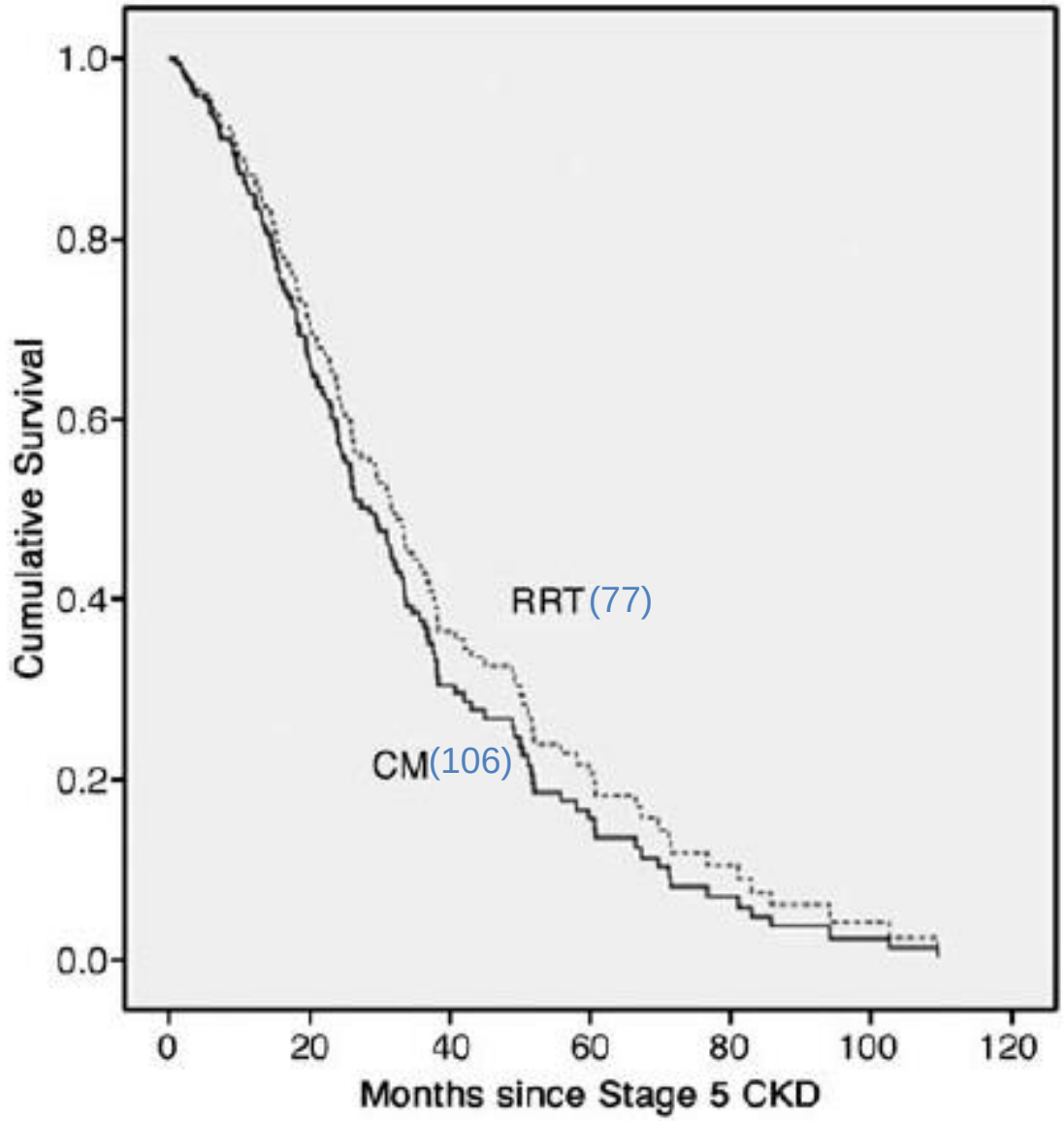


Fig. 3. Cox proportional model survival curve of patients aged >75 years—CM vs RRT—adjusted for age, gender, ethnicity, the presence of diabetes and the presence of high comorbidity. Median survival in RRT patients is better by <4 months, which is not statistically significant (P = 0.43).

Chandna SM, et al. Nephrol Dial Transplant 2011;26:1608-1614

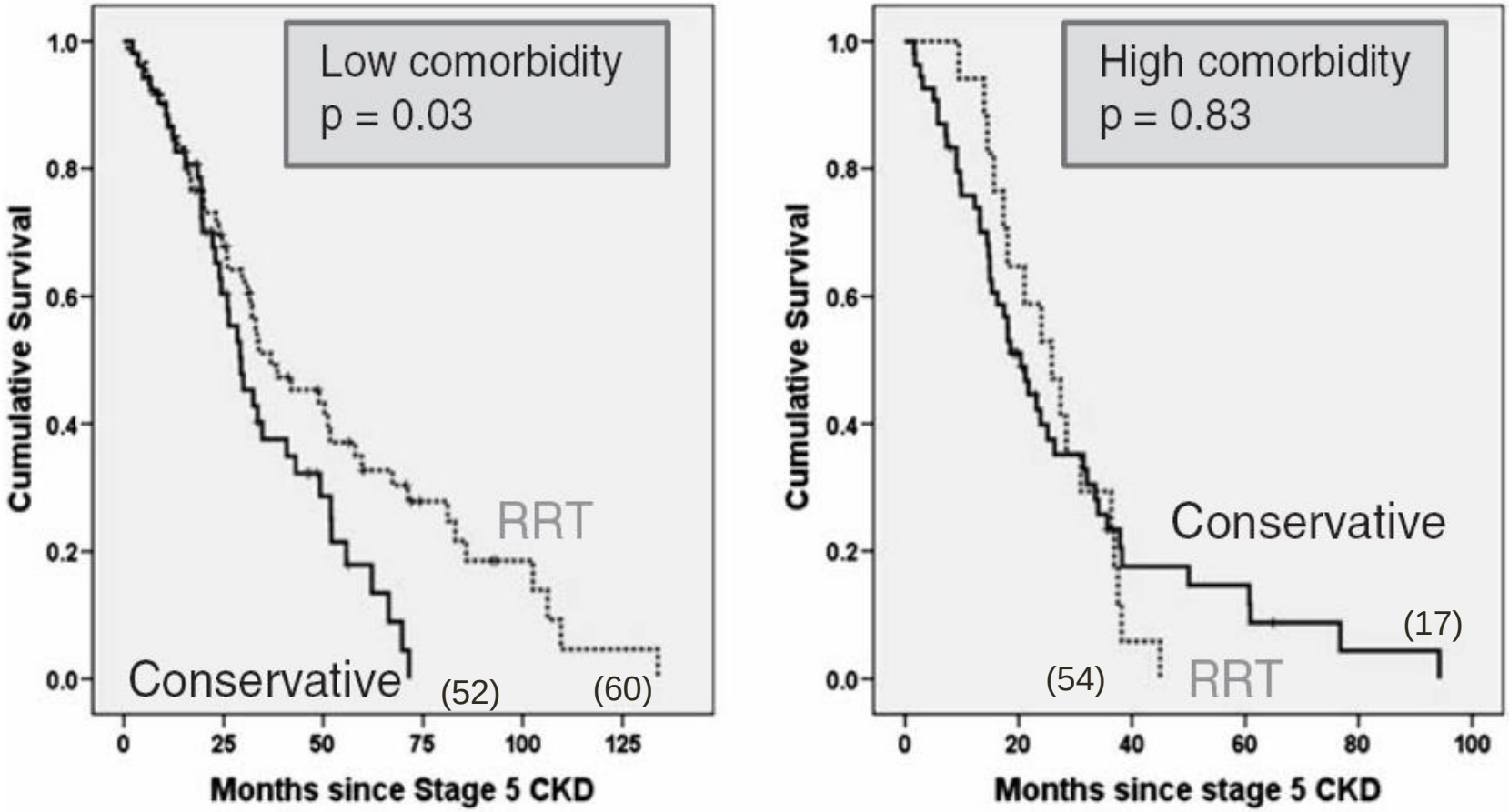
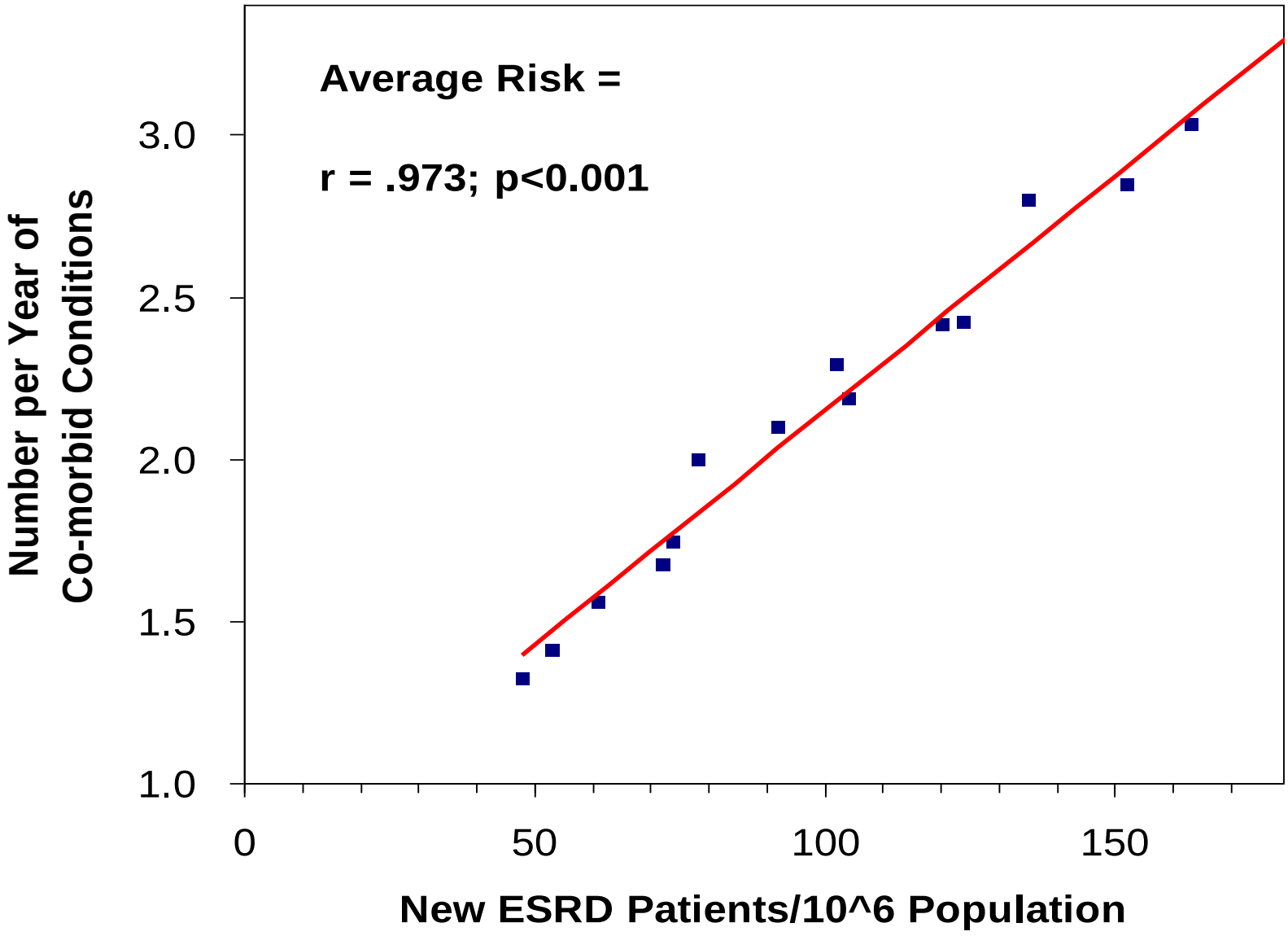


Fig. 2. Comparison of Kaplan–Meier survival curves by modality (RRT vs conservative kidney management) in patients >75 years. The panel on the left depicts the relationships in those with low comorbidity and that on the right in those with high comorbidity.

Chandna SM, et al. Nephrol Dial Transplant 2011;26:1608-1614


Average Risk =
r = .973; p<0.001
Number per Year of Co-morbid Conditions
3.0
2.5
2.0
1.5
1.0
0
50
100
150
New ESRD Patients/10^6 Population

Charlson Comorbidity Scoring System

Charlson ME, J Chron Dis, 1987

Score	Condition
1	Myocardial infarction (history, not ECG changes only) Congestive heart failure Peripheral vascular disease (including aoritc aneurysm $\geq$ 6 cm) Cerebrovascular disease: CVA with mild or no residua or TIA Dementia Chronic pulmonary disease Connective tissue disease Peptic ulcer disease Mild liver disease (without portal hypertension, includes chronic hepatitis) Diabetes without end-organ damage (excludes diet-controlled alone)
2	Hemiplegia Moderate or severe renal disease Diabetes with end-organ damage (retinopathy, neuropathy, nephropathy, or brittle diabetes) Tumor without metastases (exclude if > 5 y from diagnoses) Leukemia (acute or chronic) Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumor AIDS (not just HIV positive)

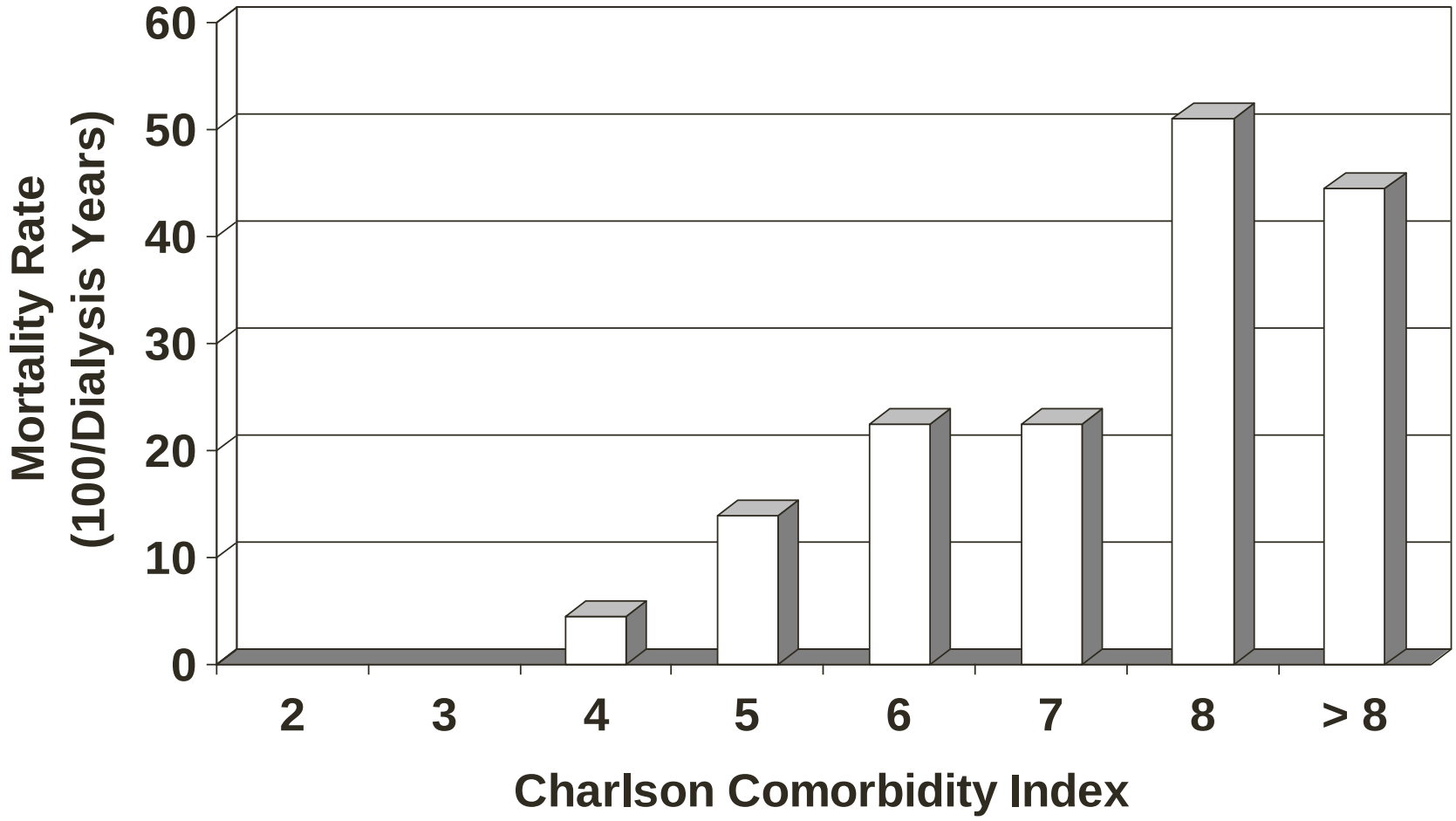
Note: *for each decade > 40 years of age, a score of 1 is added to the above score*

Modified Charlson Comorbidity Index

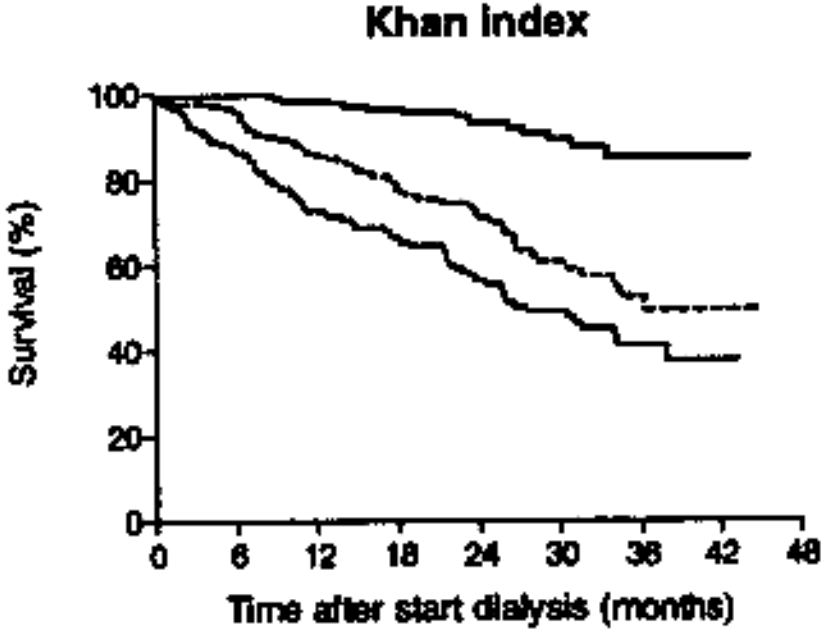
Beddhu S, Am J Med, 2000

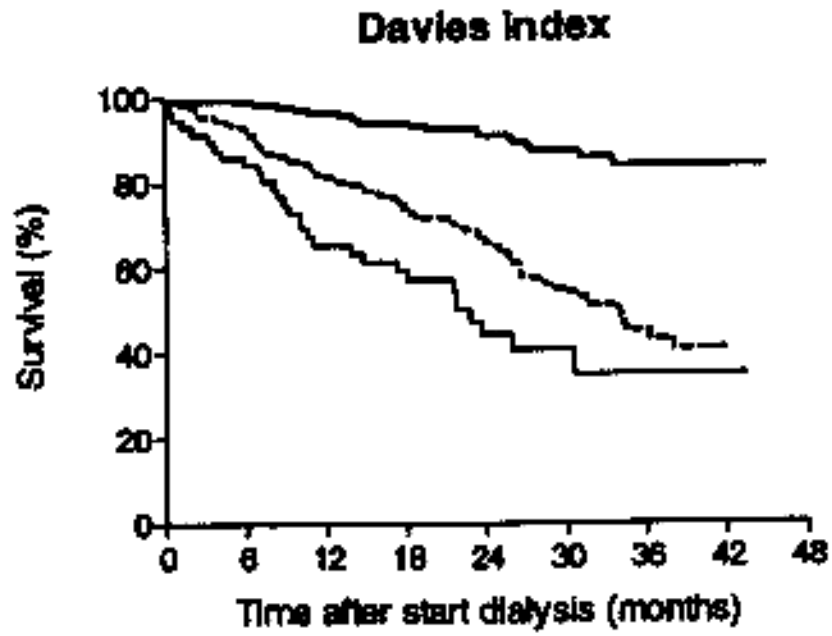
Score	Condition
1	**Coronary artery disease** Congestive heart failure Peripheral vascular disease (including aoritc aneurysm ≥ 6 cm) Cerebrovascular disease: CVA with mild or no residua or TIA Dementia Chronic pulmonary disease Connective tissue disease Peptic ulcer disease Mild liver disease (without portal hypertension, includes chronic hepatitis) Diabetes without end-organ damage (excludes diet-controlled alone)
2	Hemiplegia Moderate or severe renal disease Diabetes with end-organ damage **Any tumor, leukemia, lymphoma**
3	Moderate or severe liver disease
6	Metastatic solid tumor AIDS (not just HIV positive)

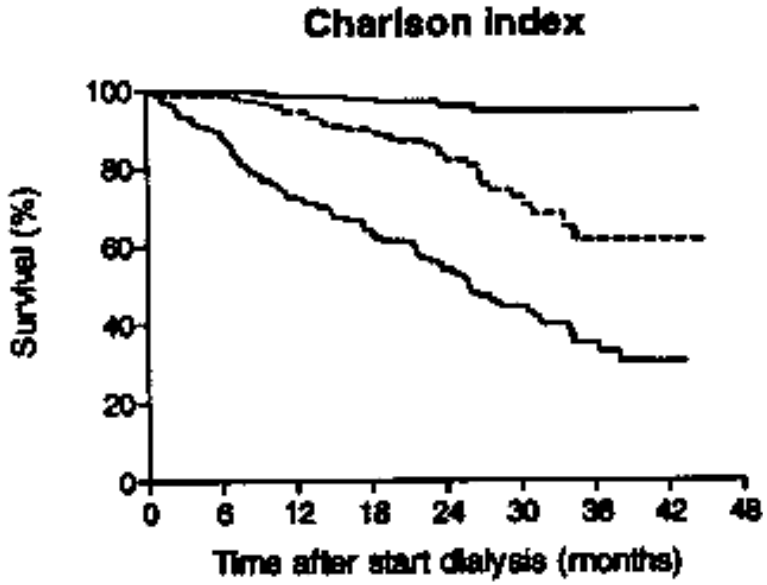
Note: *for each decade > 40 years of age, a score of 1 is added to the above score*



Fried L, et al. Am J Kidney Dis, 2001







	Concordance c Statistics (indices combined with age in 6 classes)*
Khan index	0.72
Davies index	0.73
Charlson index	0.74

NOTE. Testing population, n = 589.
*Concordance c statistic for age alone is 0.66.

V Manen JG, Am J Kidney Dis, 2002

BMC Nephrology

RESEARCH ARTICLE Open Access

Analysis of factors predicting mortality of new patients commencing renal replacement therapy 10 years of follow-up

Oliver T Browne[1], Victoria Allgar[3] and Sunil Bhandari[1,2*]

Table 3 Kaplan-Meier survival analysis of factors affecting mortality

Factor	Mean survival (Months)	95% CI	P-value (Log rank test –Mantel Cox)
Age <65 years	85.4	(69.2-101.7)	
Age >65 years	51.7	(40.1-63.3)	0.001
Vascular disease	52.3	(38.6-66.0)	
No vascular disease	77.4	(63.891.0)	0.014
Highest quartile of the calcium phosphate product	60.4	(38.3-82.5)	
Lowest quartile of the calcium phosphate product	65.0	(54.8-77.2)	0.700
Diabetes mellitus	49.6	(33.6-66.6)	
No diabetes m ellitus	74.0	(61.9-86.0)	0.032

Registrazione dati di Comorbidità

SI'

- **Abruzzi**
- **Basilicata**
- **Calabria**
- **Campania**
- **Emilia-Romagna**
- **Lazio**
- **Liguria**
- **Lombardia**
- **Piemonte**
- **Puglia**
- **Sardegna**
- **Sicilia**
- **Toscana**
- **Umbria**

NO

- **Val d'Aosta**
- **Marche**
- **Veneto**
- **Friuli**
- **Trentino**
- **Molise**

Usano **“schemi di codifica”**:

- Calabria
- Lombardia
- Piemonte
- Puglia

Usano **definizioni di riferimento**:

- Campania
- Piemonte
- Puglia
- Sardegna
- Emilia
- Basilicata

Usano un “**grading**” di severità:

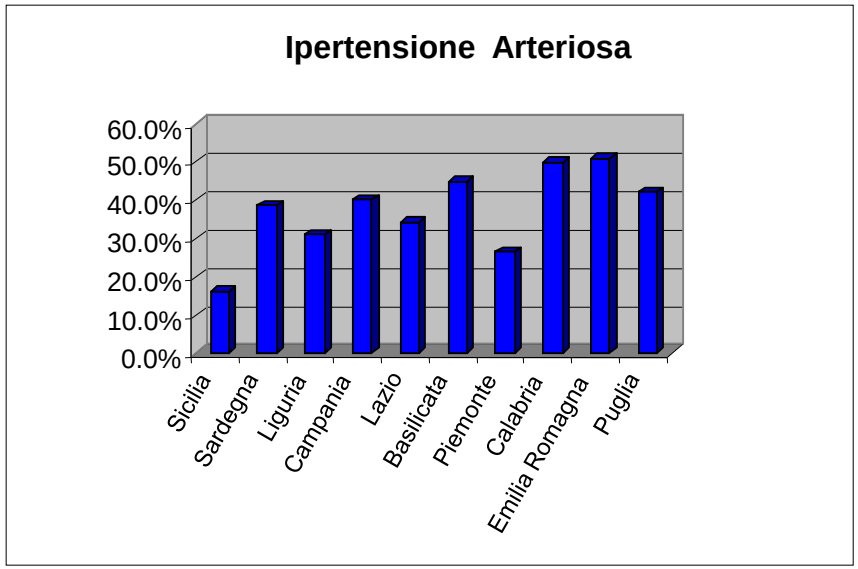
- Puglia

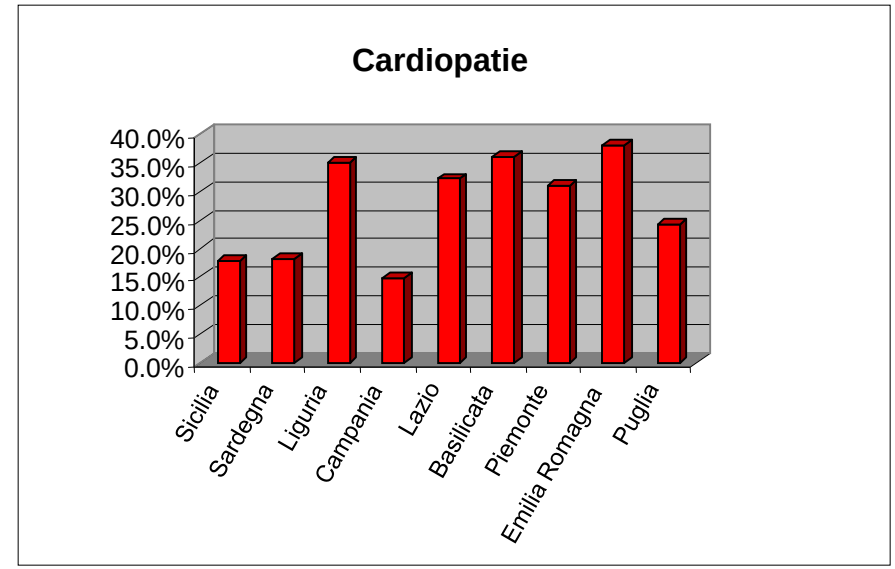
Usano uno **“score”**
come indice globale di severità:

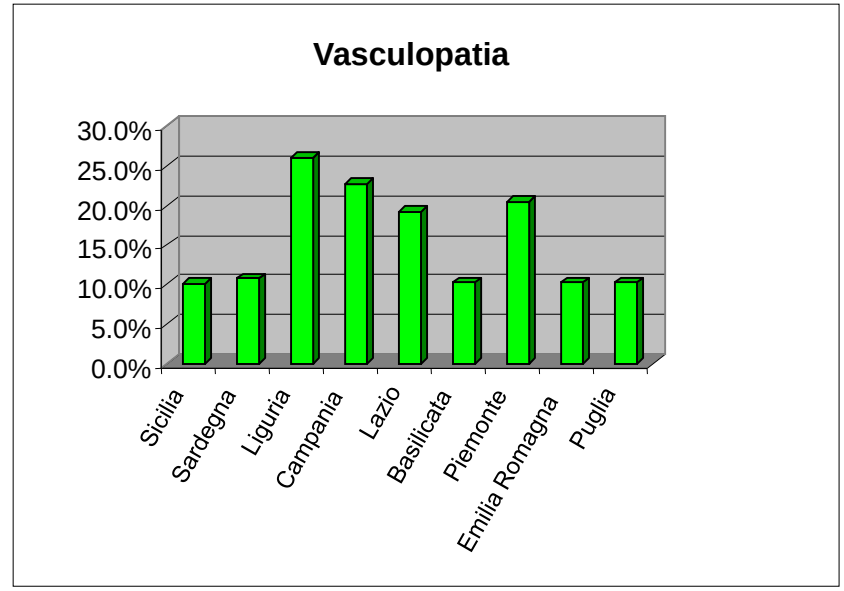
- Campania
- Puglia

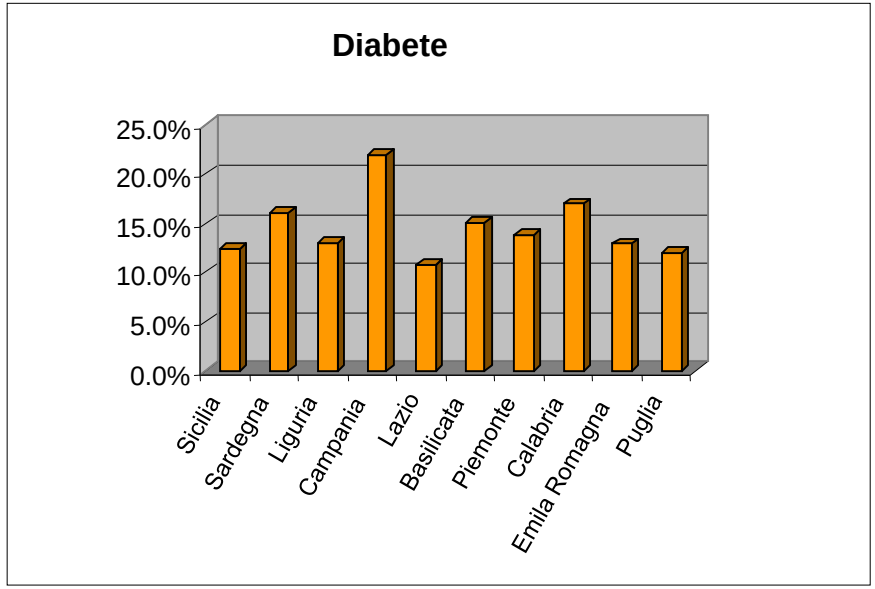
Registrazione dati di Comorbidità

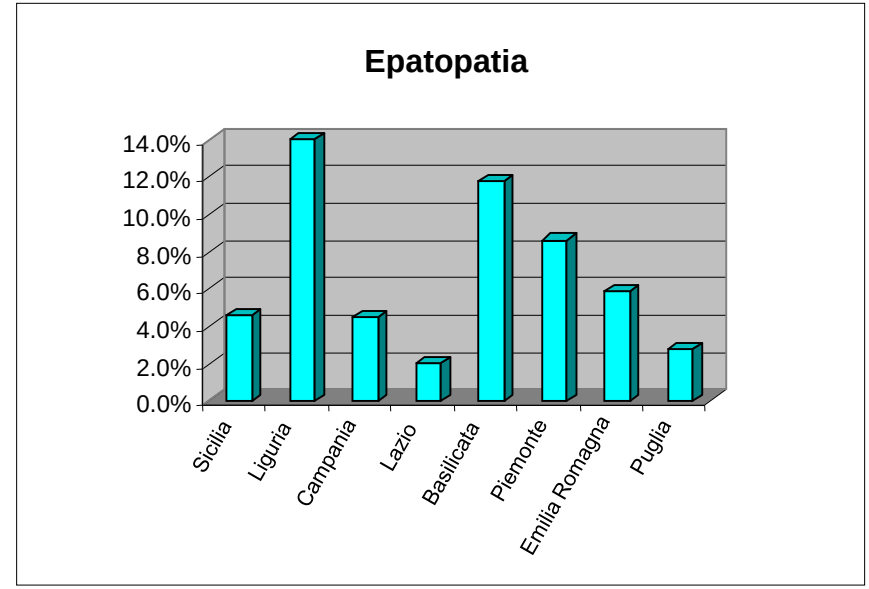
70%

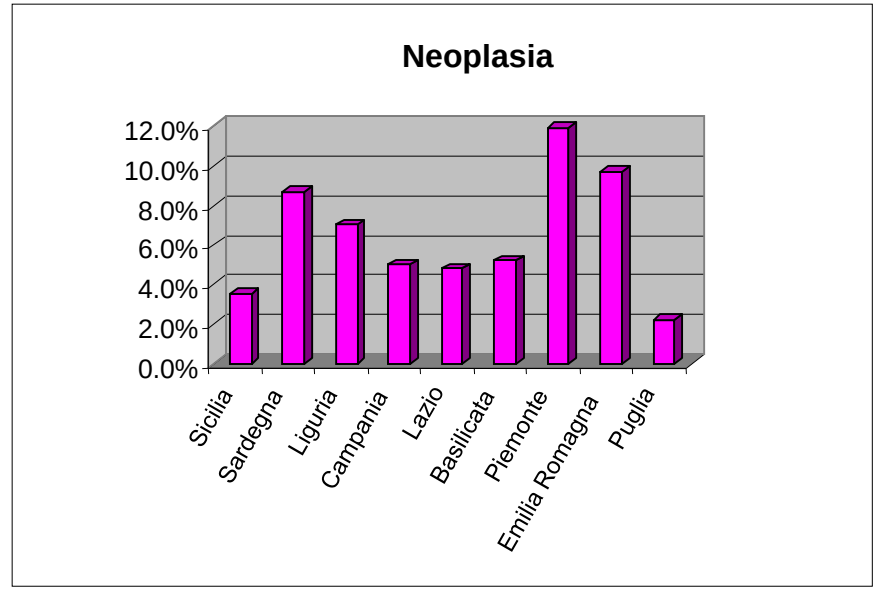

Ipertensione Arteriosa
60.0%
50.0%
40.0%
30.0%
20.0%
10.0%
0.0%
Sicilia
Sardegna
Liguria
Campania
Lazio
Basilicata
Piemonte
Calabria
Emilia Romagna
Puglia


Cardiopatie
40.0%
35.0%
30.0%
25.0%
20.0%
15.0%
10.0%
5.0%
0.0%
Sicilia
Sardegna
Liguria
Campania
Lazio
Basilicata
Piemonte
Emilia Romagna
Puglia

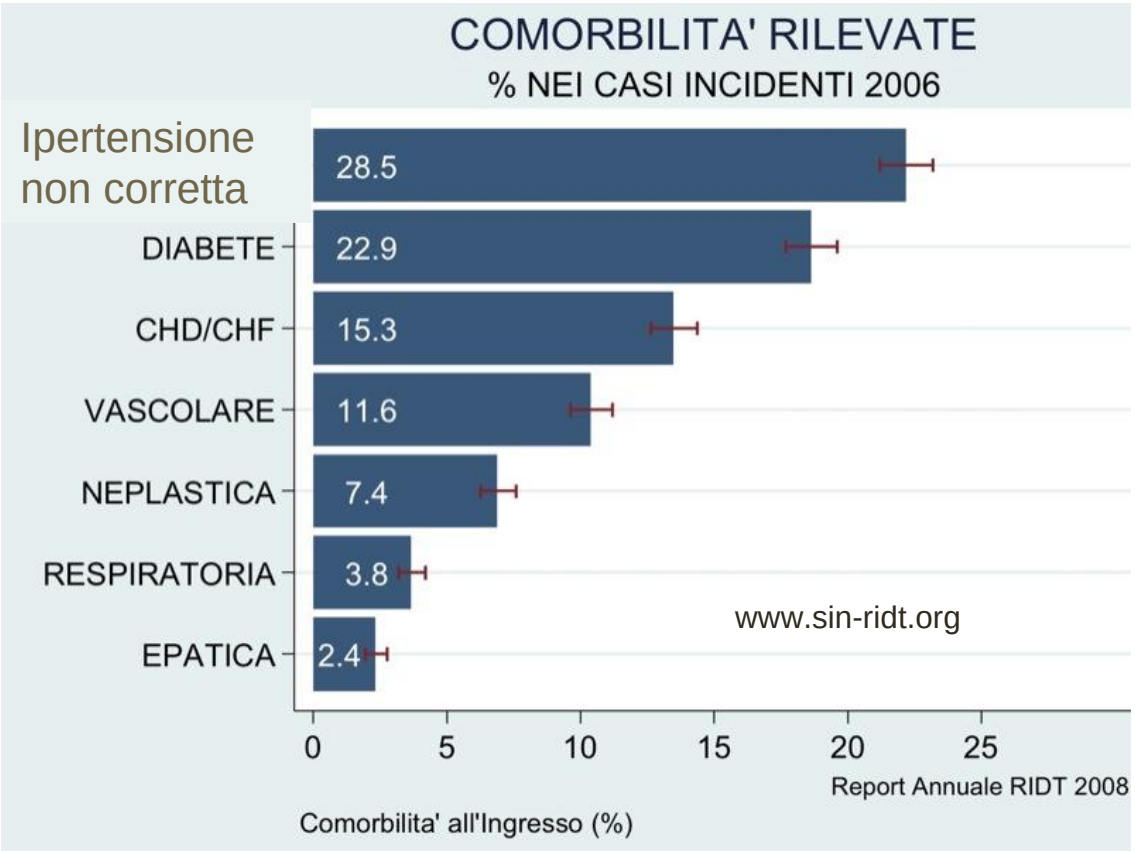

Vasculopatia
30.0%
25.0%
20.0%
15.0%
10.0%
5.0%
0.0%
Sicilia
Sardegna
Liguria
Campania
Lazio
Basilicata
Piemonte
Emilia Romagna
Puglia


Diabete
25.0%
20.0%
15.0%
10.0%
5.0%
0.0%
Sicilia
Sardegna
Liguria
Campania
Lazio
Basilicata
Piemonte
Calabria
Emila Romagna
Puglia


Epatopatia
14.0%
12.0%
10.0%
8.0%
6.0%
4.0%
2.0%
0.0%
Sicilia
Liguria
Campania
Lazio
Basilicata
Piemonte
Emilia Romagna
Puglia

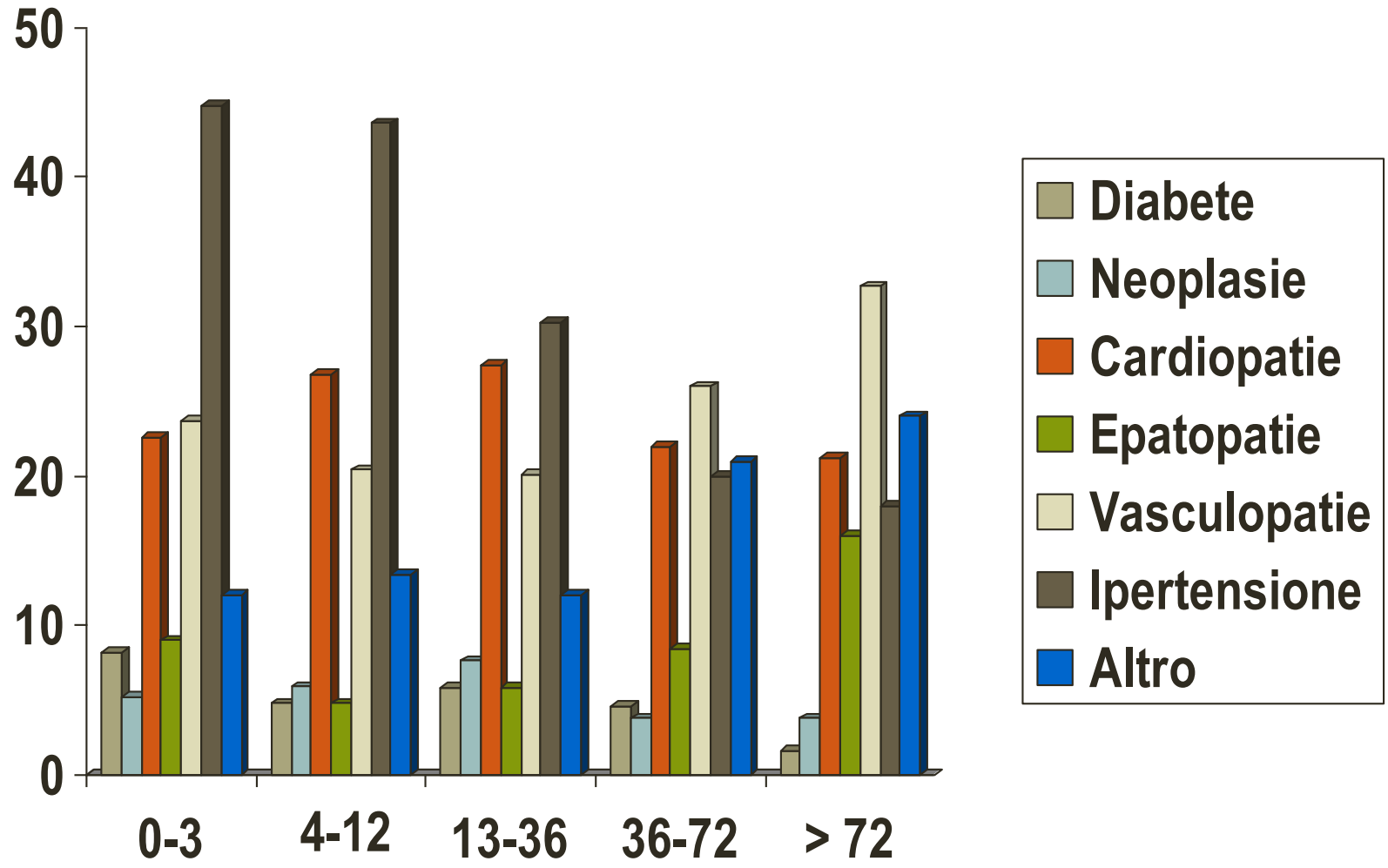

Neoplasia
12.0%
10.0%
8.0%
6.0%
4.0%
2.0%
0.0%
Sicilia
Sardegna
Liguria
Campania
Lazio
Basilicata
Piemonte
Emilia Romagna
Puglia

Prevalence of comorbid conditions at baseline

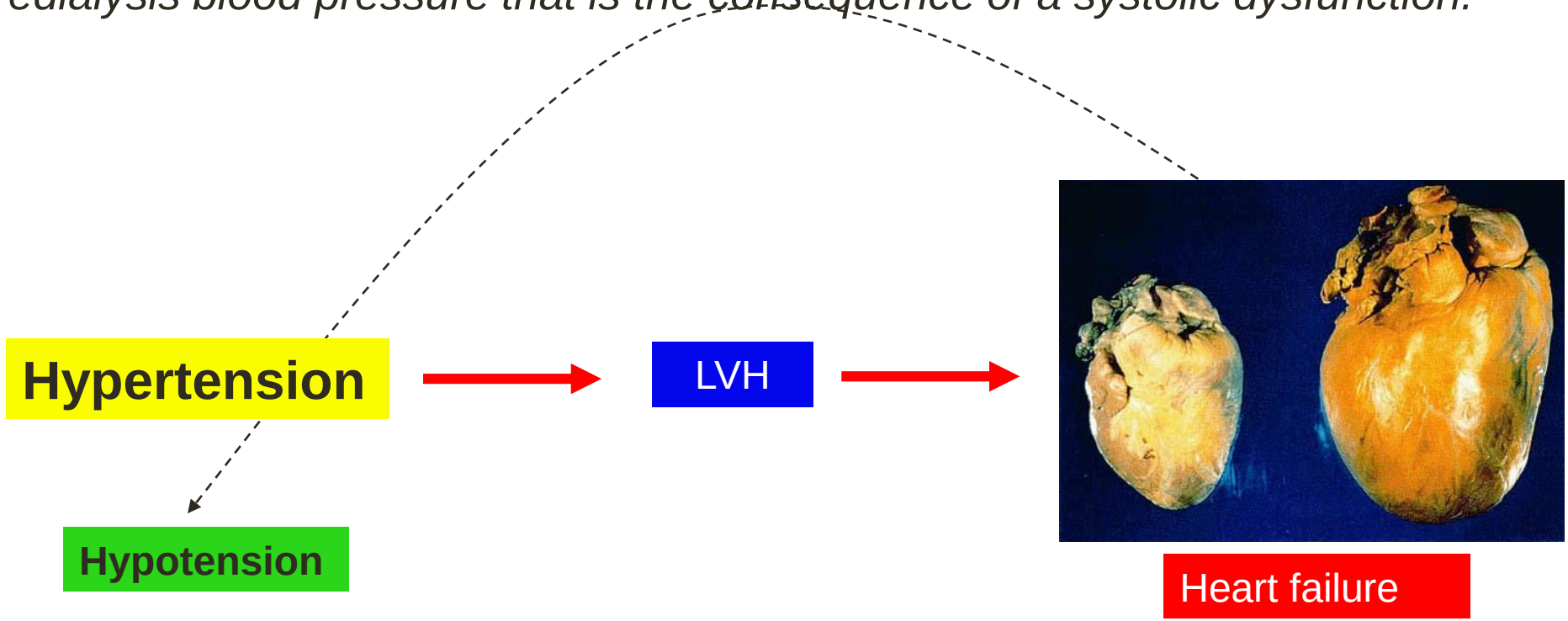


Registro Italiano di Dialisi e Trapianto (RIDT)

ETA' DIALITICA (mesi) E FATTORI DI RISCHIO (%)



The "safety margin" for blood pressure to decline during ultrafiltration is further reduced among older patients since the elderly may have a lower average predialysis blood pressure that is the consequence of a systolic dysfunction.

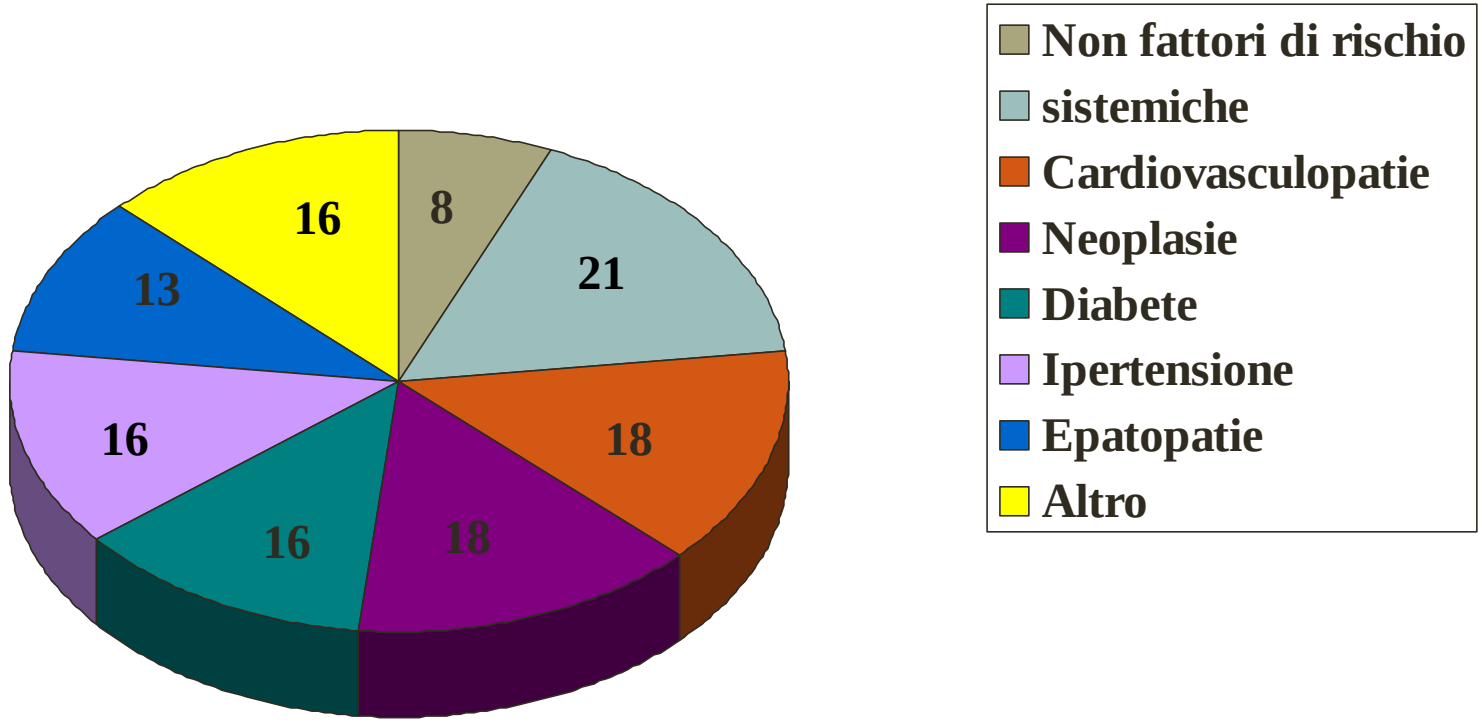


"*reverse causality*"

Heart failure modifies the risk factor because it lowers BP

GIORNATE DI OSPEDALIZZAZIONE/ANNO:

FATTORI DI RISCHIO



The Emilia-Romagna Dialysis Registry

1994

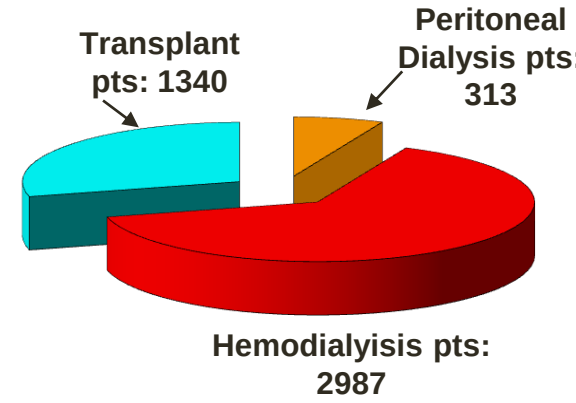
2014

Regional Dialysis Centres

- ***Nephrology Departments: 13***
- ***Limited Care Centres: 52***

Intention-to-Treat approach

Any patient starting chronic dialysis is recorded from his/her first dialysis as Incident Patient



Dialysis (PD+HD): 3300

Registry Consistency dec 31.2013
14.479 records

1994 – 2004: 20 years observation

	1994	2013	Difference
Inhabitants (No)	3,922,702	**4,452,782**	+13.5%
On RRT (No)	2343	**4640**	+98%
On dialysis (HD+PD) (No)	1933	**3300**	+71%
Prevalence on dialysis (pmp)	492.8	**741.1**	+50.4%
Incidence on dialysis (pmp)	94,8	**134**	+41.3%
Incident patients: mean age (years±SD)	60.9±16.2	**67.4±15.5**	+6.5
Incident patients: Karnofsky score *(performance status)*	KS 80-100: 49.2% KS 40-70: 47.3% KS 10-30: 3.5%	**KS 80-100: 38.7%** **KS 40-70: 52.6%** **KS 10-30: 8.7%**	↓↓ ↑ ↑↑
Gross Mortality (%)	12.3	**16.1**	↑

Rationale, Study aim, Design

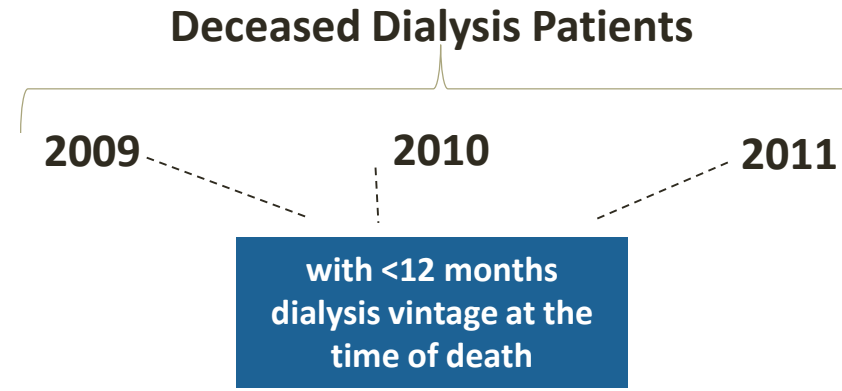
Rationale: a Registry based on the ITT permits an effective analyis of mortality, avoiding the possibility of an underestmation.

Study aim: evaluating the phenomenon of **early mortality** as a part of the overall mortality

Early Mortality: death occurring during the first 12 months of dialysis treatment (HD, DP)

Study design: retrospective analysis of the Registry data.

Study coohort:



Results: overall mortality and Early Mortality

2009, 2010, 2011:

Overall number of deaths:

1714

40.3% F, 59.7% M
504 HD; 20 PD

N=1190

Dialysis vintage

>12 months

(69.4%)

N=524

Dialysis vintage

≤12 months

(30.6%)

Early mortality

Overall number of incident patients: 2228

Early mortality : 14.2%

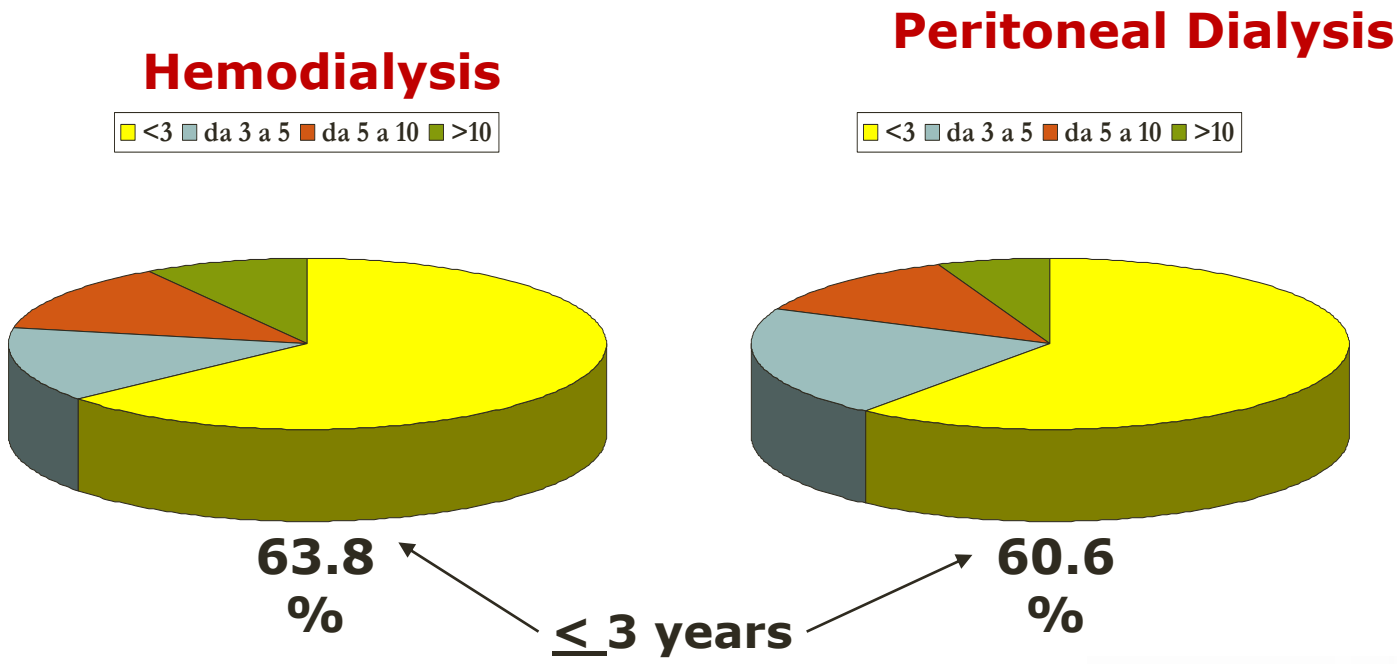
Age at death

Age (years)	%
<15	0
15-25	0
45-65	14.2 %
65-75	22.16%
>75	63.63%

Early death : classification on the basis of the dialysis modality and dialysis vintage (months)

	Hemodialysis (Number and %) Overall early deaths : 504	Peritoneal Dialysis (Number and %) Overall early deaths : 20
<3 months	**260 (51.6%)**	**3 (15%)**
3-6 months	107 (21.2%)	5 (25%)
6-12 months	137 (27.2%)	12 (60%)

Mortality on dialysis (%) on the basis of the dialysis vintage : Hemodialysis *versus* Peritoneal Dialysis – *focus at 3 years*



Registro Regionale Emiliano-Romagnolo di Dialisi e Trapianto *(RER-DT)*

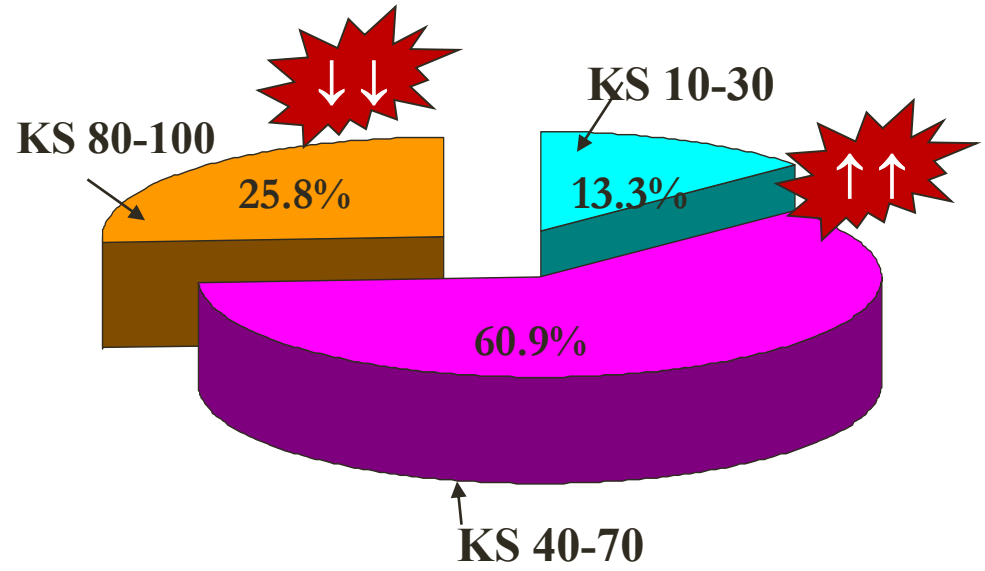
Causes of death in "Early Mortality" - *(12 and 3 months)*

	Death in the first year *(% of the group)*	Death in the first three months *(% of the group)*
Absolute number	**524**	**270**
Cachexia	11.1%	11.9%
Cardiovascular	**49.3%**	**54.2%**
Infection	15.3%	10.1%
Malignancy	5.6%	3.4%
Unknown	8.3%	8.5%
Other causes	10.4%	11.8%

Registro Regionale Emiliano-Romagnolo di Dialisi e Trapianto *(RER-DT)*

Karnofsky score at dialysis entry in patients dying before 12 months dialysis vintage

KARNOFSKY SCORE	
Score	**Condition**
100	Normal, no evidence of disease
90	Able to carry on normal activities, minor signs or symptoms of disease
80	Normal activity with effort, some signs or symptoms of disease
70	Cares for self, unable to carry on normal activity or to do active work
60	Requires occasional assistance, but is able to care of most of his/her needs
50	Requires considerable assistance and frequent medical care
40	Disabled, requires special care and assitance
30	Severely disabled
20	Hospitalisation necessary, very sick, active supportive treatment necessary
10	Moribund, fatal process processing rapidly



Sub-analysis: Hemodynamic stability during HD

(350/504 HD patients):

hypotension-prone: 218 (62%)

clinically stable: 132

Registro Regionale Emiliano-Romagnolo di Dialisi e Trapianto *(RER-DT)*

Type of vascular access at dialysis entry in patients who died in the first year of dialysis treatment

AV Fistula

19.1%

Tunnelled CVC

26.4%

A «permanent» access

45.5%

Temporary CVC

54.5%

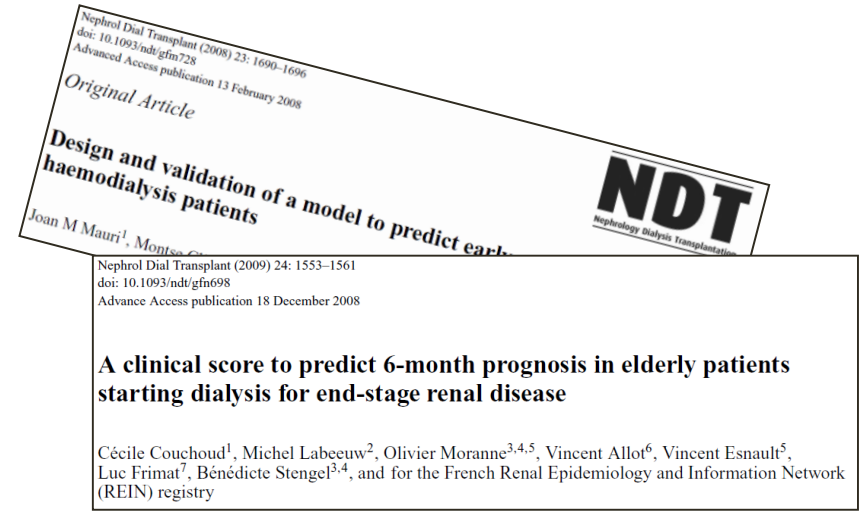
Registro Regionale Emiliano-Romagnolo di Dialisi e Trapianto *(RER-DT)*

Early mortality is a dramatic phenomenon that can be captured only by those Dialysis Registries recording all the patients incident to dialysis, independent of the survival period.

The possibility of an early death should be discussed with the families of the older and more comorbid patients before starting up a chronic dialysis program.

Issues to be considered

Predictive mortality scores: to be implemented in the clinical practice?


Nephrol Dial Transplant (2008) 23: 1690–1696
doi: 10.1093/ndt/gfm728
Advanced Access publication 13 February 2008

Original Article

Design and validation of a model to predict early haemodialysis patients

Joan M Mauri[1], Monse

NDT
Nephrology Dialysis Transplantation

Nephrol Dial Transplant (2009) 24: 1553–1561
doi: 10.1093/ndt/gfn698
Advance Access publication 18 December 2008

A clinical score to predict 6-month prognosis in elderly patients starting dialysis for end-stage renal disease

Cécile Couchoud[1], Michel Labeeuw[2], Olivier Moranne[3,4,5], Vincent Allot[6], Vincent Esnault[5], Luc Frimat[7], Bénédicte Stengel[3,4], and for the French Renal Epidemiology and Information Network (REIN) registry

Palliative care: should be considered as an alternative valid option

Clinical judgement: remains a valid parameter in a multivariate model to predict 1-year mortality

"SurSurprise Question"

Would I be surprised if this patient died within the next 6 months?

Cohen LM, CJASN 2010

nephroMEET

Documento condiviso SICP-SIN
Le Cure Palliative nelle persone con malattia renale cronica avanzata

Gruppo di Lavoro SIN-SICP

Le cure palliative, nel paziente con elevato grado di comorbidità e ridotta spettativa di vita possono portare a :

- miglior qualità di vita

- risparmio di risorse

Health outcomes on dialysis

Time-varying comorbidity → Morbidity, hospitalisation

Time-varying comorbidity → Mortality

- Demographic factors
- Socio-economical factors
- Physiological parameters
- Genetic factors
- Compliance
- **Treatment-related factors**

……

……

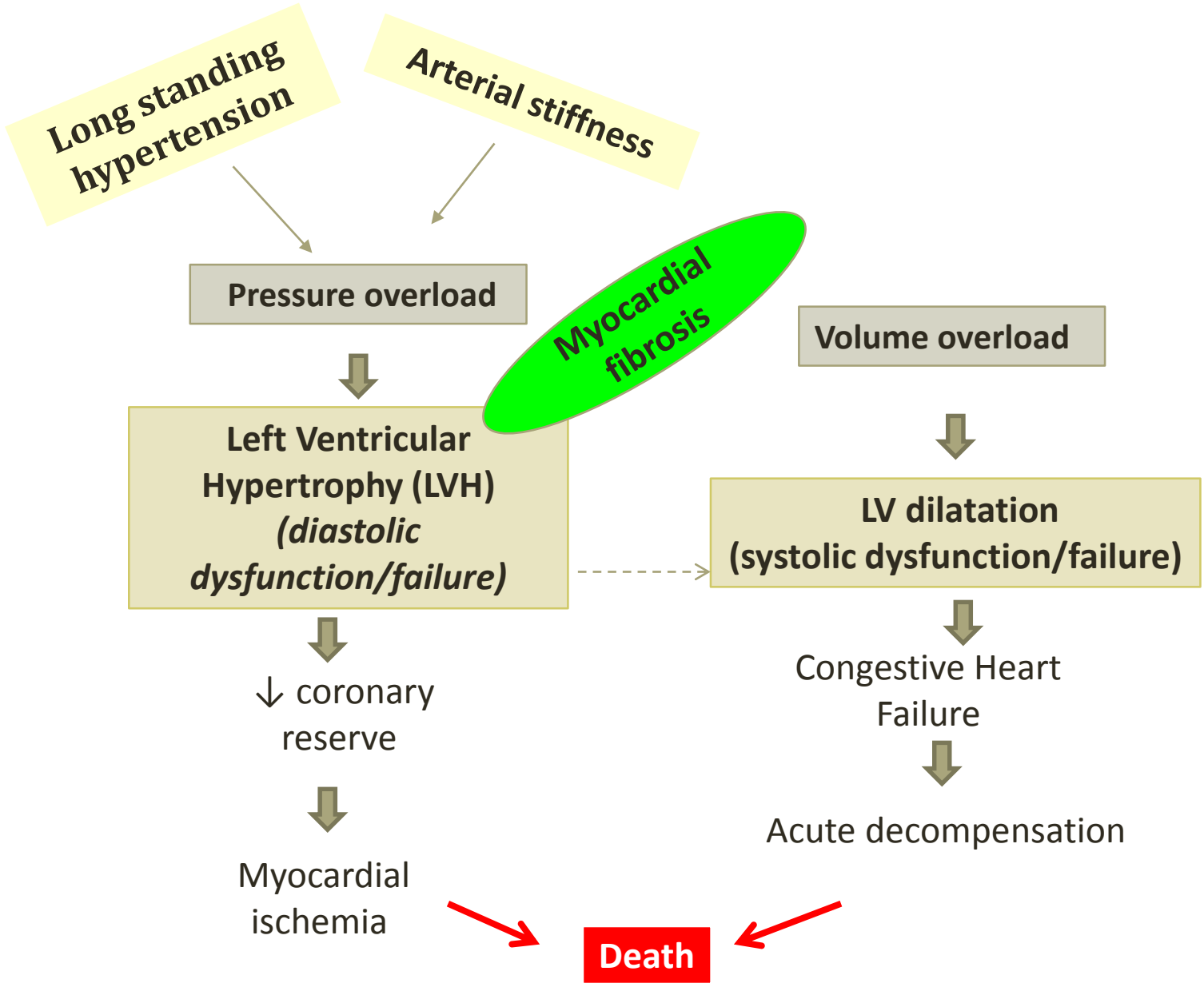
HR for mortality of Time-varying comorbidity >>>

- HR basal comorbidity
- Age
- Albumin
- Diabetes
- Dialysis vintage

Miskulin DC, AJKD 2003
Plantinga LC, AJKD 2007
Chang TI, Hemodial Int 2010

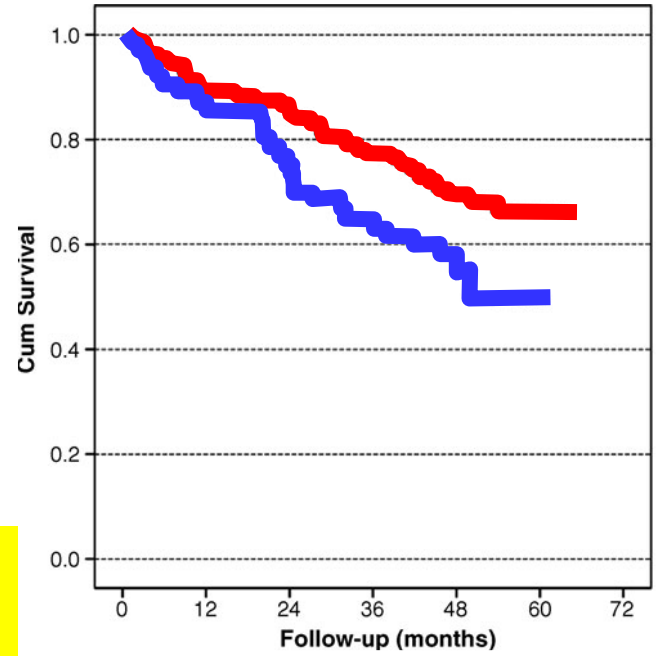
Preventable (or Potentially Preventable) & Non Preventable comorbitity

The dramatic chain leading to death



Hyperhydration, higher mortality

- 269 HD pts
- 3 European Centres
- Pre-HD BCM



Relative Hydration Status

- ECW <15%
- ECW >15%

Cox adj HR

Age	1.047
BP*sys*	0.986
Diabetes	2.766
PVD	1.683
ΔHS*pre* >15%	2.102

Wizeman V et al, Nephrol Dial Transplant 2009

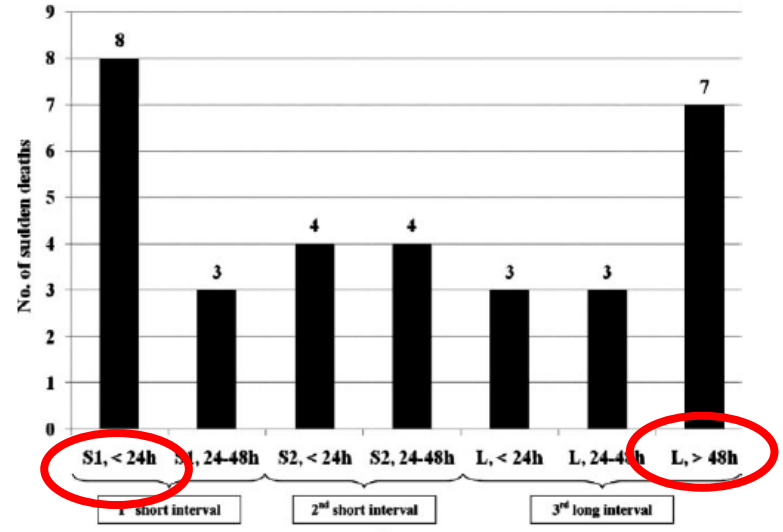
Sudden death

Unexpected death within 1 hour of symptom onset, or unexpected death witout obvious non-cardiac cause in patients known to be well within the past 24 h - EF < 35% main predictor in the general population

Incidence in dialysis pts:
(20-30%) higher than myocardial infarction (USRDS)

Precipitating factors:

- Electrolyte (K+) / volume status acute changes
- Acute coronary ischemia
- Autonomic acute changes
- Sleep-apnoea hypoxemia



Genovesi S, NDT 2009

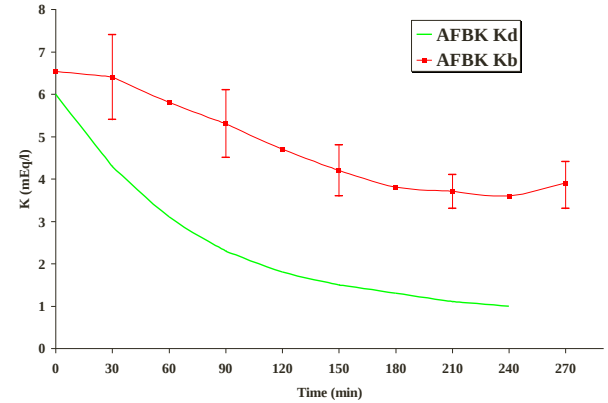
Major independent predictors in HD pts:
Left Ventr Hypertrophy.
Diabetes , AF

Sudden death prevention : during HD / out of HD

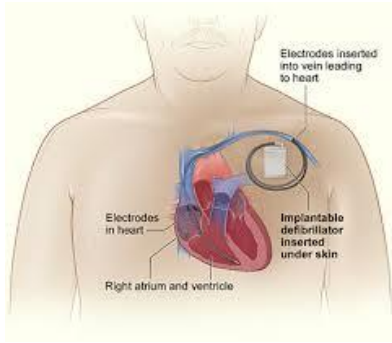
Avoiding sudden K removal during HD

- Frequent dialysis
- Avoid low K_{dial}
- Intradialysis K supplementation
- K profiling
- Pay attention also to Ca^{++}/Mg^{++}

Santoro A, Mancini E, Blood Purif



Implantable Cardioverter Defibrillator



General population: In primary or secondary prevention if sever LVSystolic Dysfunction (**EF <35%;** NYHA Class II/III)

ClassI, level A; AHA, ACC

Dialysis patients, USRDS

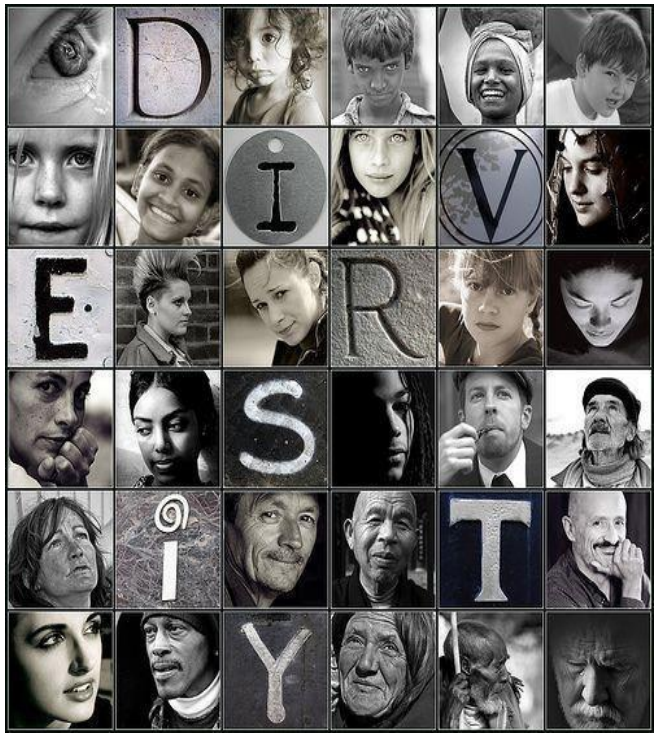
Median survival after ICD :

Primary Prev: Di…pts (18 mths) <<…pts

Secondary Prev…alysis pts <<< non-Dialysis pts

NO RCTs, No EBM

...dal paziente giusto



Comorbidità

- Diabete mellito
- Ipertensione
- Malattie cardiache
- Malattie vascolari periferiche
- Malattie cerebrovascolari
- Malattie respiratorie
- Malattie epatiche
- Malattie neoplastiche
- Malnutrizione

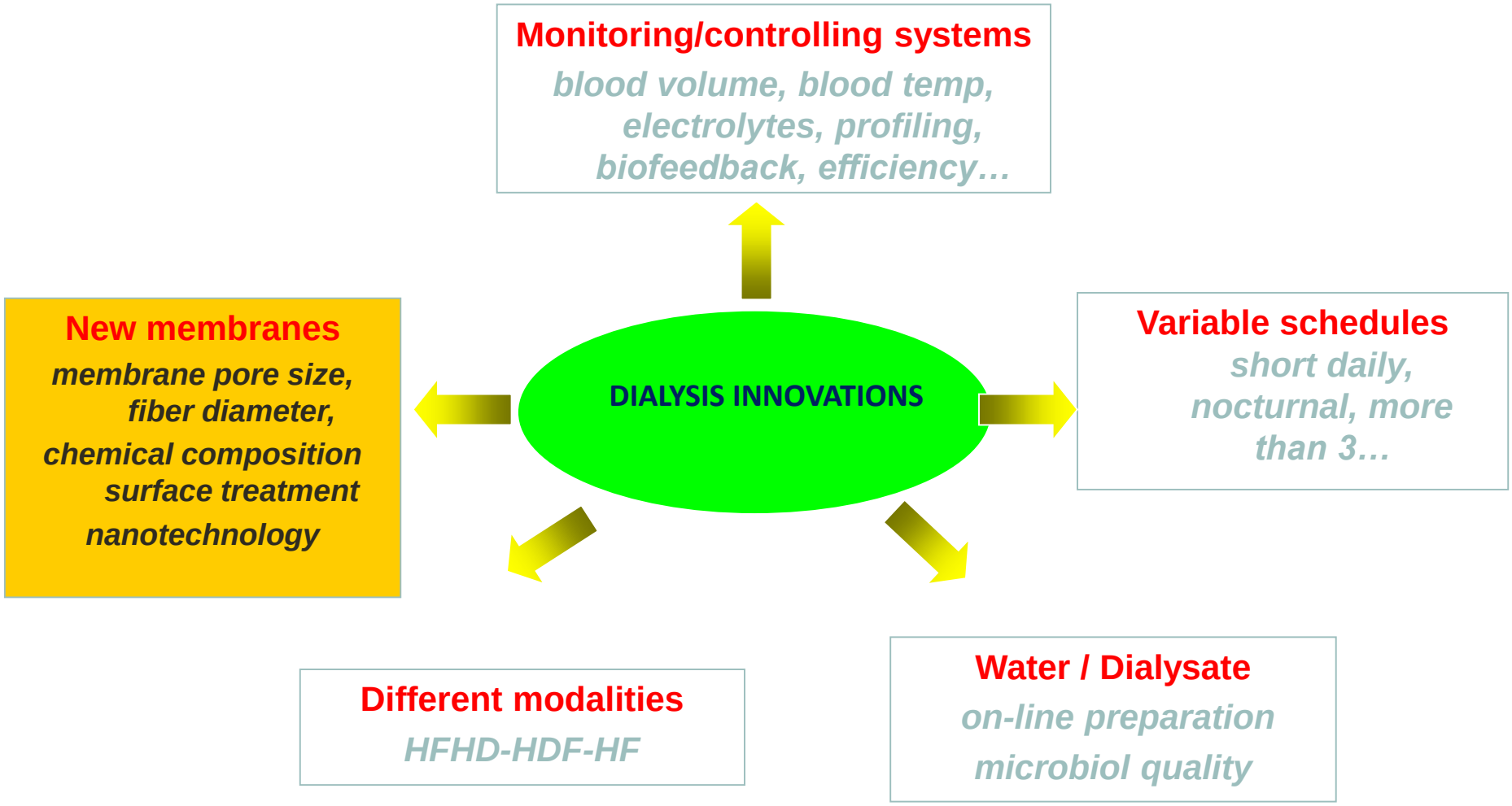
Profilo del paziente

- Funzione renale residua
- Bisogni metabolici
- Compliance dietetica
- Tolleranza generale
- Tolleranza cardiovascolare

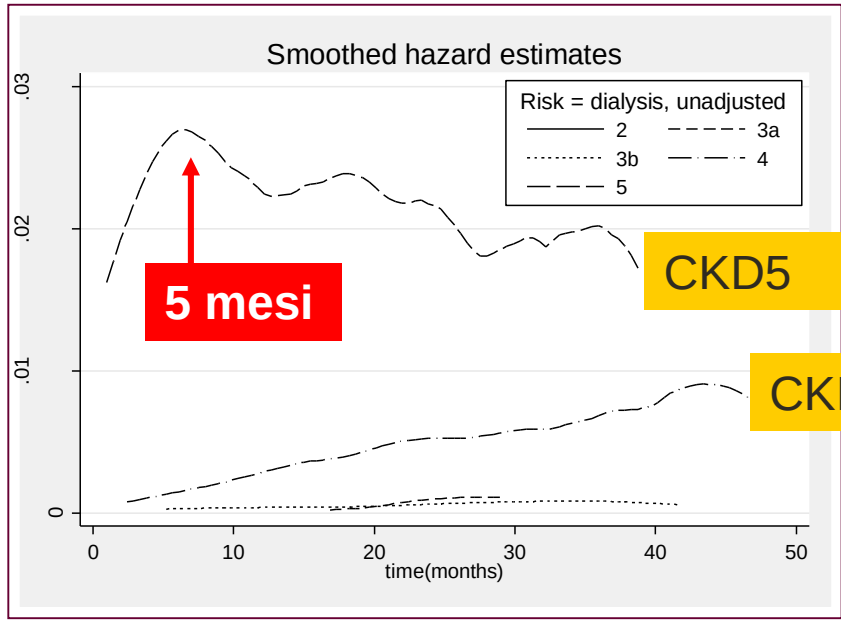
Dialisi personalizzata

- Modalità di trattamento
- Tipo di membrana
- Ultrafiltrazione oraria
- Farmaci prescritti
- Flusso sangue
- Definizione del ‘peso secco’
- Frequenza e durata

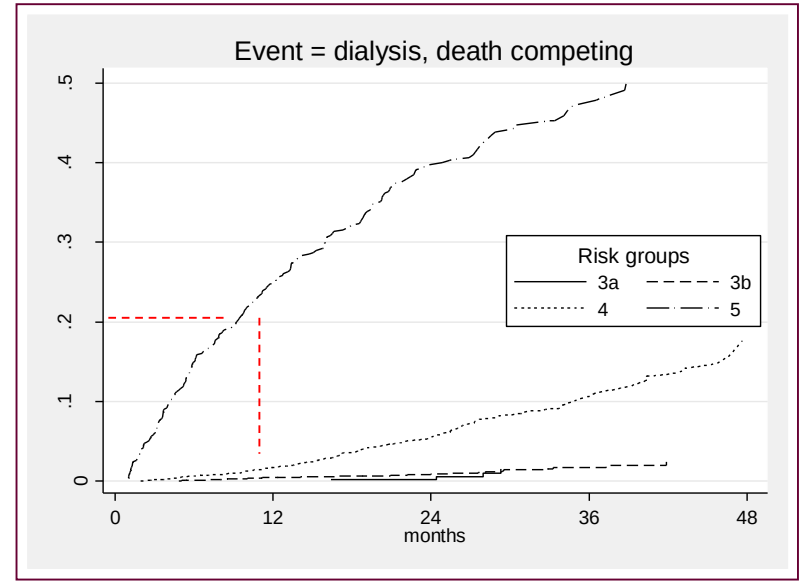
Personalization of dialysis treatment



Rischio = dialisi, morte come rischio concorrente



Probabilità di entrare in dialisi accumulata nel tempo



Rischio = morte prima della dialisi, dialisi come rischio concorrente