Novel Risk Markers in ACS

(Hyperglycemia, Anemia, GFR)

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TIMI Risk Score

- Age ≥65 years
- ≥3 CAD Risk Factors
- Prior Coronary Stenosis >50 %
- ST deviation
- ≥2 Anginal events ≥24 hours
- ASA in last 7 days
- Elevated Cardiac Markers (CK-MB or troponin)

Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *JAMA*. 2000;284:835-842.

PURSUIT Risk Score

PURSUIT (0–18)	Age, separate points for enrolment diagnosis Decade [UA (MI)]	
	50	8 (11)
	60	9 (12)
	70	11 (13)
	80	12 (14)
	Sex	
	Male	1
	Female	0
	Worst CCS-class in previous 6 weeks	
	No angina or CCS I/II	0
	CCS III/IV	2
	Signs of heart failure	2
	ST-depression on presenting ECG	1

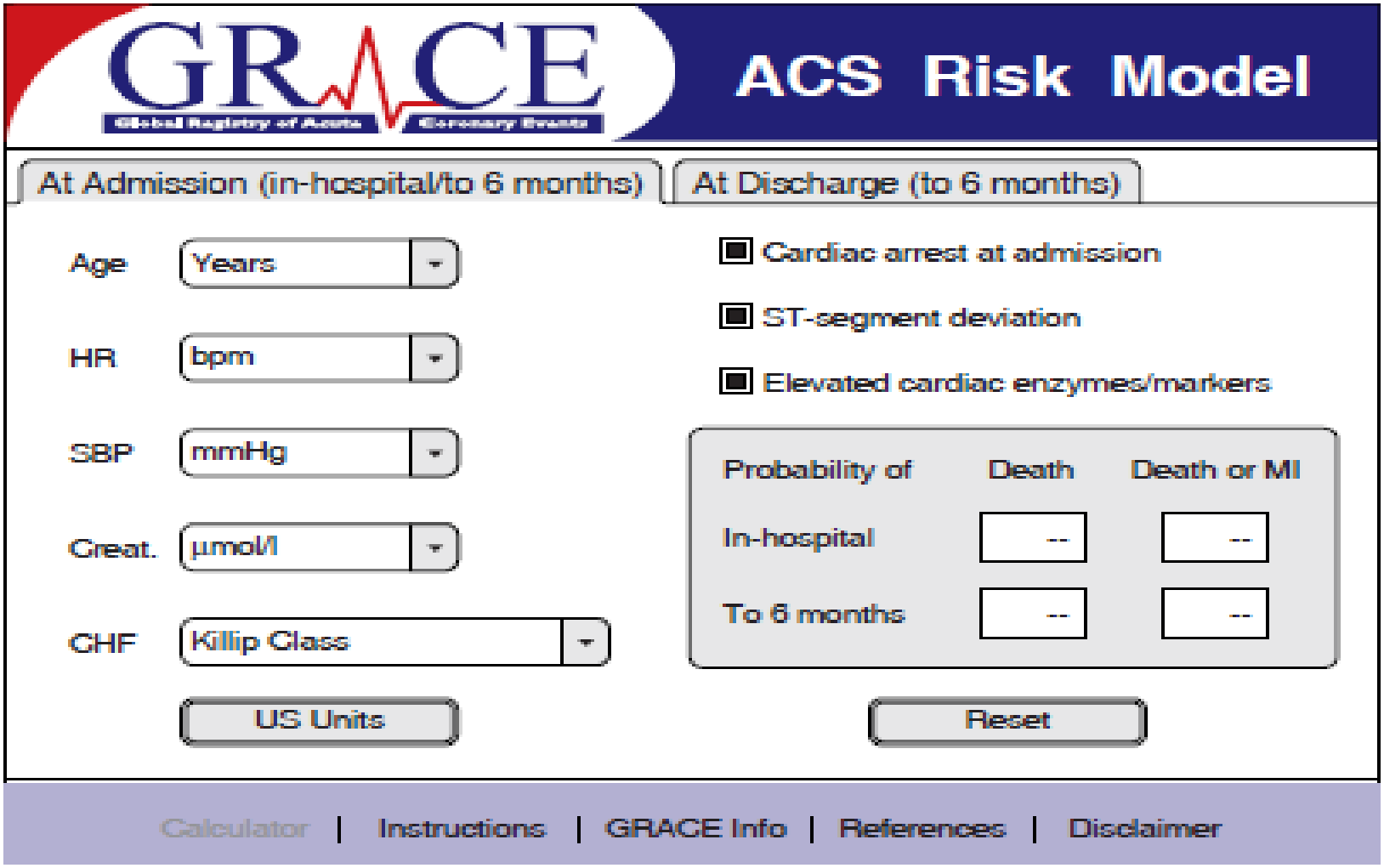
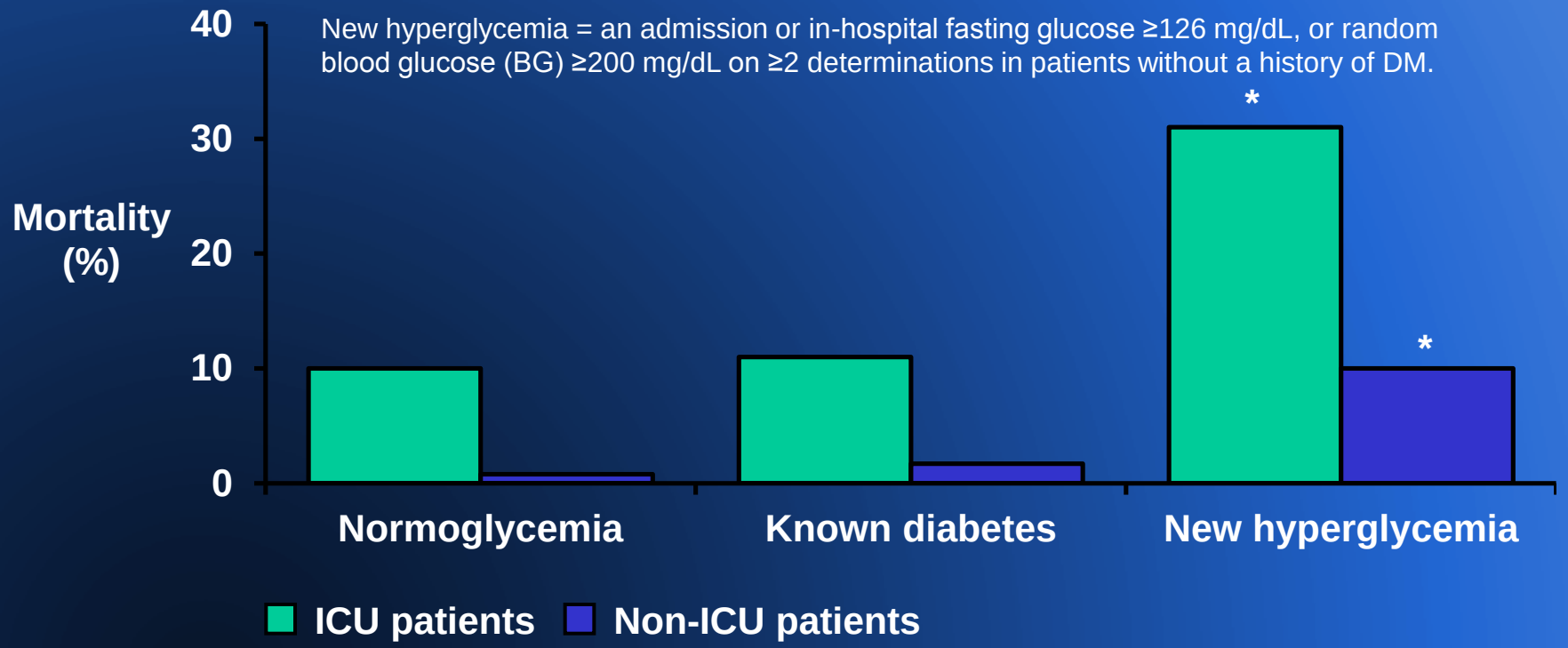


Fig 2 GRACE risk calculator for death or myocardial infarction from admission to hospital to six months after discharge with the simplified model (www.outcomes.org/grace)

New-onset hyperglycemia linked to highest rate of in-hospital mortality

N = 2030 hospital patients

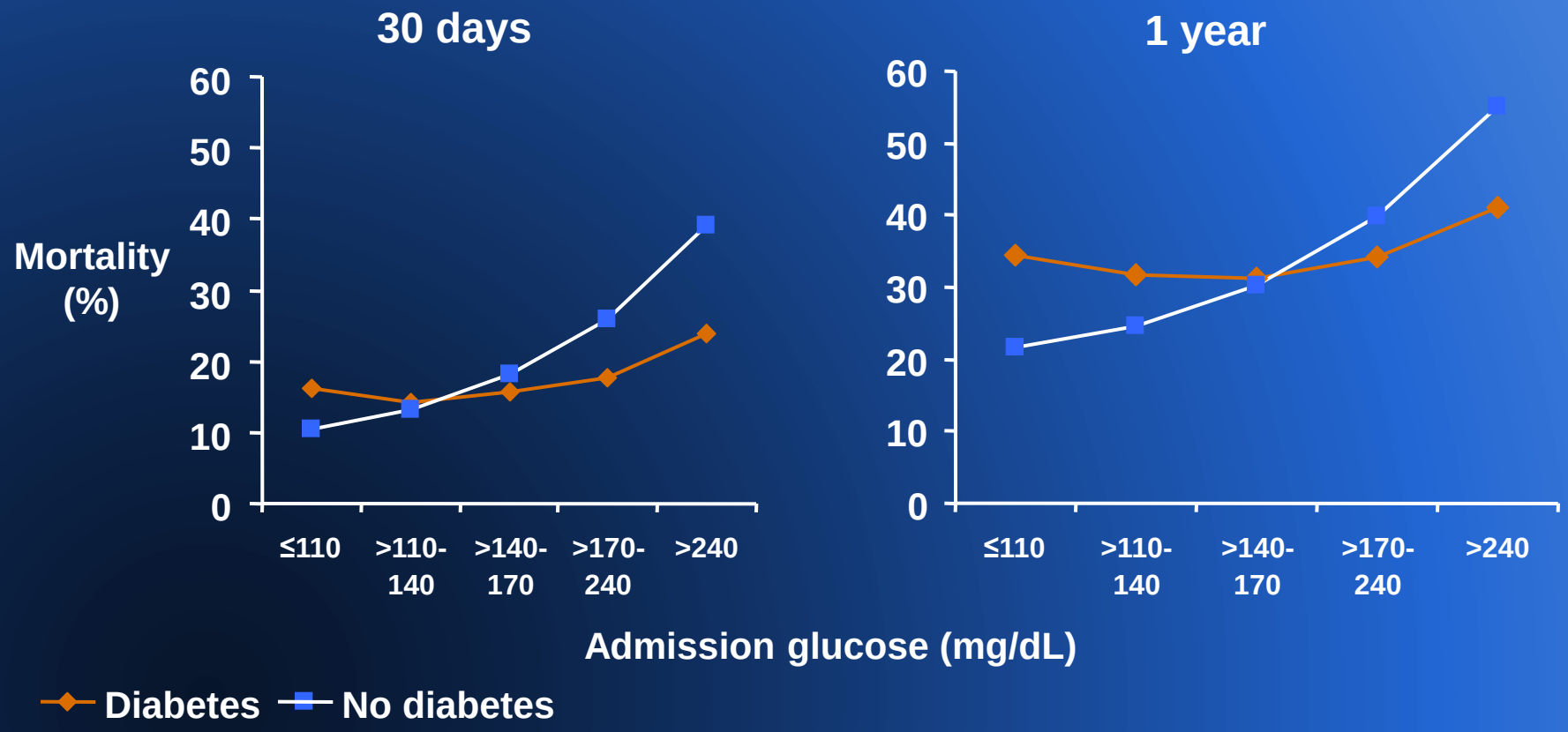


***P < 0.01 vs normoglycemia and known diabetes**

Umpierrez GE et al. *J Clin Endocrinol Metab*. 2002;87:978-82.

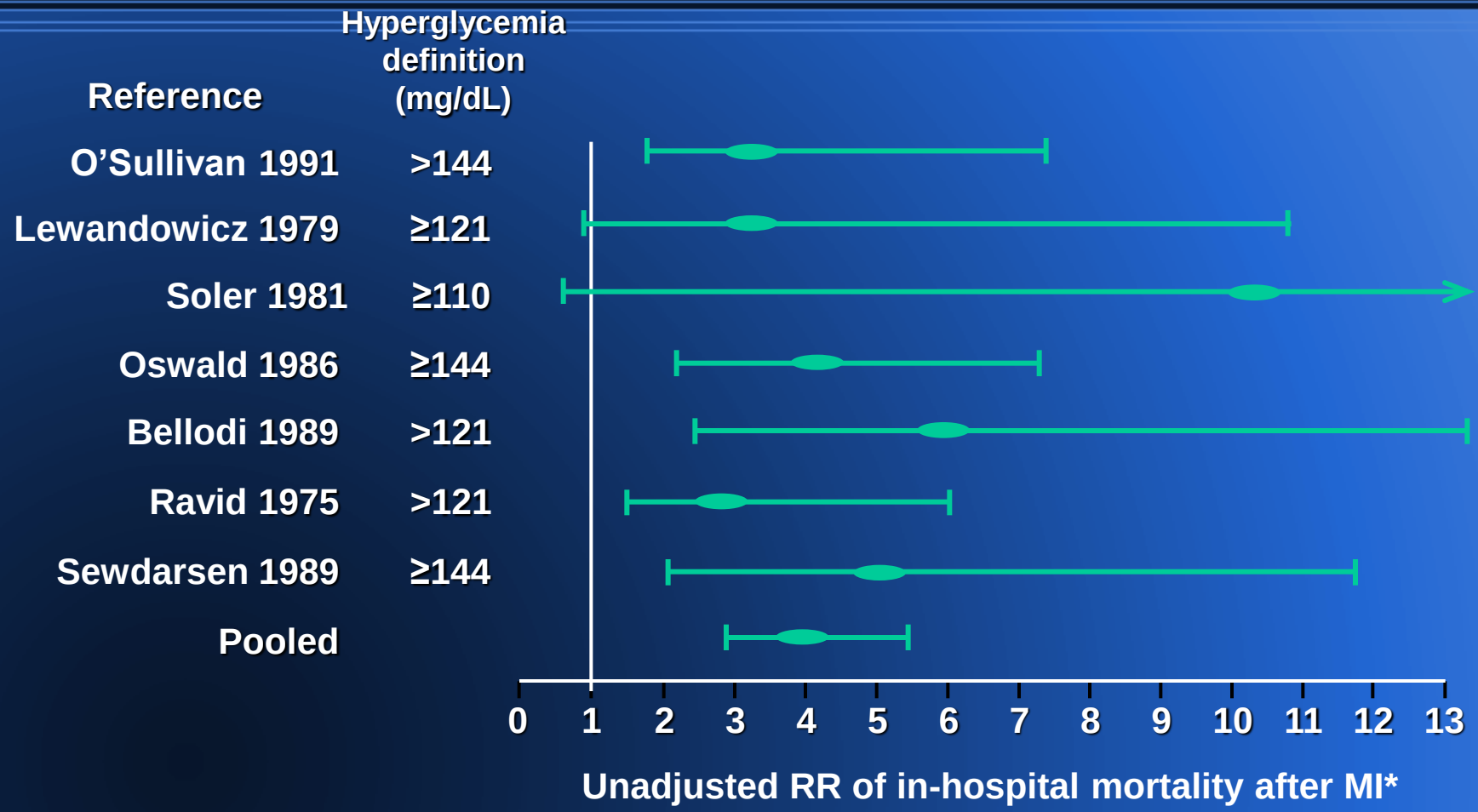
Admission glucose in AMI associated with mortality, independent of T2DM diagnosis

N = 141,680 hospitalized with AMI



Kosiborod M et al. *Circulation*. 2005;111:3078-86.

Stress hyperglycemia in AMI: Association with mortality risk in patients without known diabetes

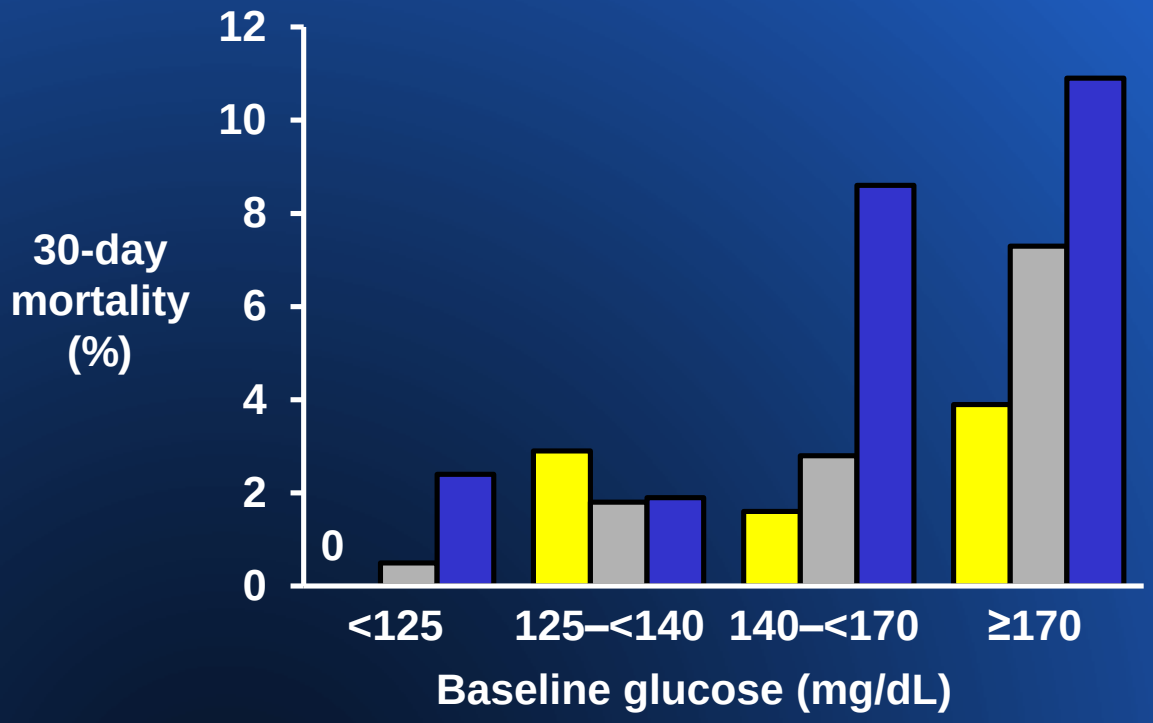


*vs patients with normoglycemia

Capes SE et al. *Lancet.* 2000;355:773-8.

Admission glucose and glucose change within 24 hours predict mortality risk

N = 1469 with AMI (n = 1219 without DM)



↓9% in 30-day mortality per ↓11 mg/dL glucose in first 24 hr (P = 0.002)*

ΔGlucose (24 hr vs baseline)

- ≥30 mg/dL decrease
- No change to <30 mg/dL decrease
- Increase

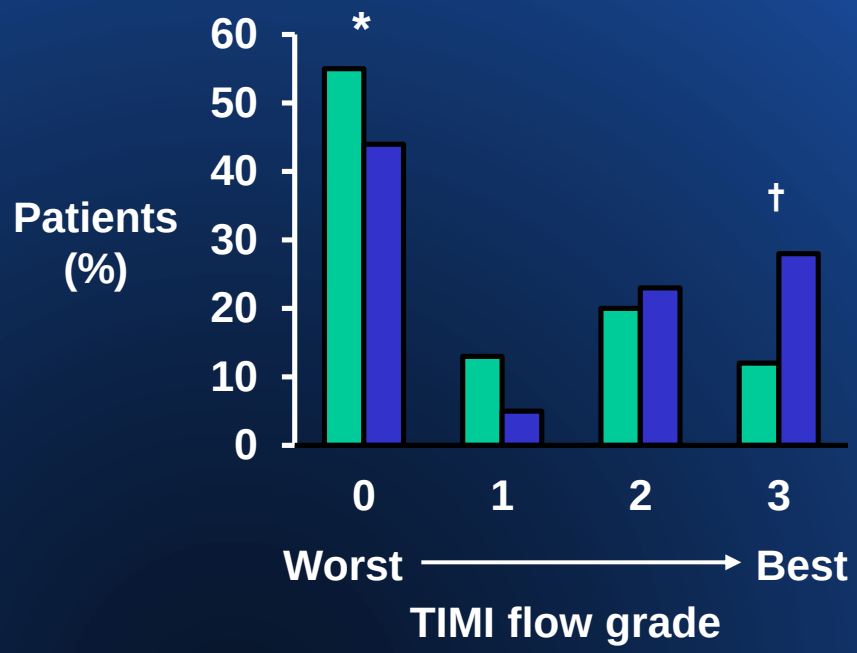
*Multivariate analysis

Goyal A et al. *Eur Heart J*. 2006;27:1289-97.

Hyperglycemia: Independent predictor of impaired myocardial blood flow in STEMI

N = 507

Initial TIMI flow grade vs admission glucose ≥140 vs <140 mg/dL



TIMI 0-2 predictors‡

	OR	P
Glucose ≥140 mg/dL	2.6	0.001
Nonsmoking	1.6	0.13
Male gender	1.1	0.96
Age (per year)	1.0	0.17
Diabetes history	0.5	0.15

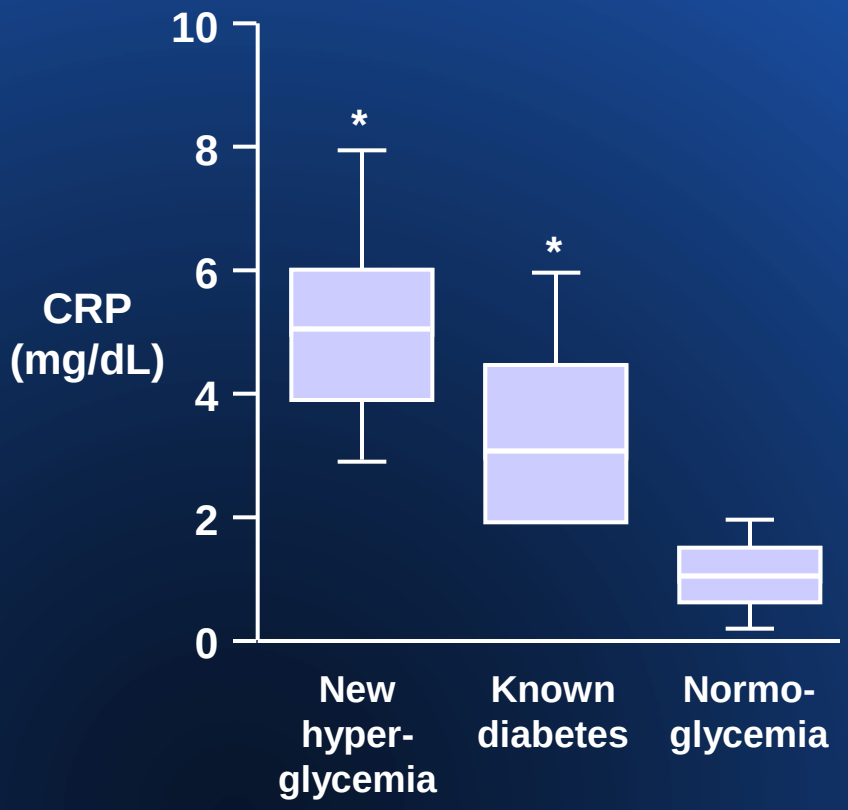
*P = 0.03 vs TIMI 1-3; †P < 0.001 vs TIMI 0-2

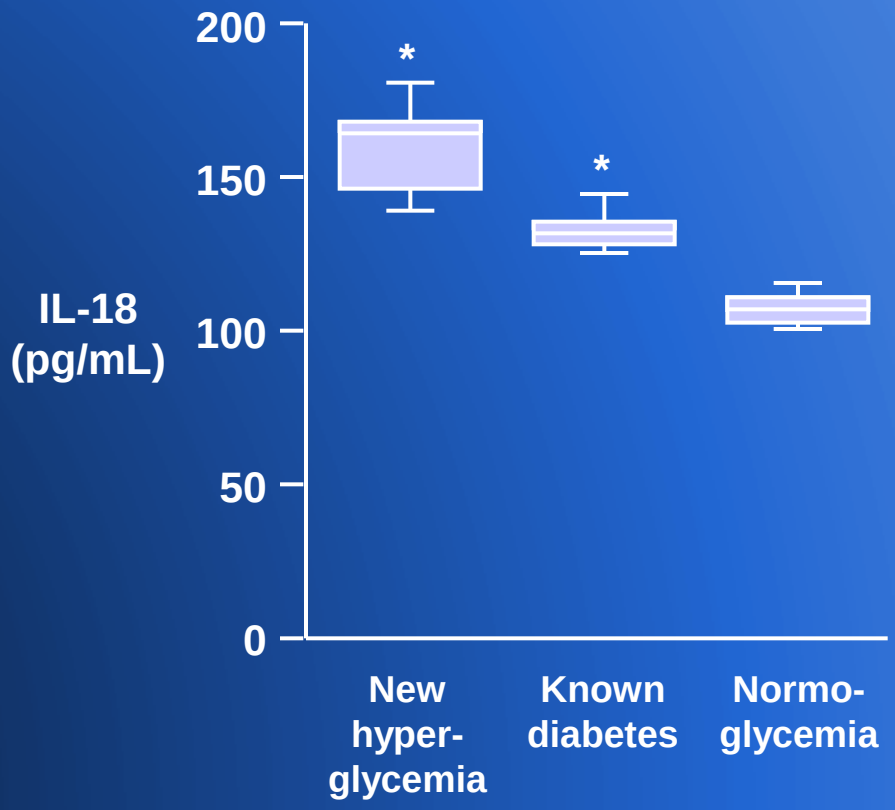
‡After multivariate analysis

Timmer JR et al. *J Am Coll Cardiol.* 2005;45:999-1002.

Hyperglycemia associated with increased inflammatory markers in AMI

N = 108





*P < 0.005 vs normoglycemia

CRP = C-reactive protein; IL = interleukin

Marfella R et al. *Diabetes Care*. 2003;26:3129-35.

ANEMIA

Definition

World Health Organization; 1968

Haematocrit	< 39% for men
	< 36% for women
Haemoglobin levels	< 13 g/dL for men
	< 12 g/dL for women

M.Sabatine et al.

Circulation 2005

Association of Hemoglobin Levels with Clinical Outcomes in ACS

….Anemia was observed

in 30,6% of cases of ACS

but only 5,4%

had hemoglobin < 10 g/dL…

M.Sabatine et al.

Circulation 2005

Association of Hemoglobin Levels with Clinical Outcomes in ACS

TABLE 3. Clinical Outcomes Through 30 Days in STEMI Patients Stratified by Baseline Hemoglobin

	Hemoglobin on Admission, g/dL									
End Point	<10 (n=191)	10–11 (n=288)	11–12 (n=962)	12–13 (n=2502)	13–14 (n=5077)	14–15 (n=6926)	15–16 (n=5702)	16–17 (n=2783)	>17 (n=968)	*P*
Cardiovascular death, % (1086 events)	14.7	11.9	10.1	7.1	4.8	3.3	2.8	2.8	4.2	<0.001
Congestive heart failure, % (2041 events)	12.7	12.5	12.5	10.8	8.8	6.8	7.1	6.8	8.9	<0.001
Composite, % (2744 events)	21.6	19.2	18.4	15.1	12.2	9.0	8.8	8.7	11.2	<0.001

TABLE 4. Clinical Outcomes Through 30 Days in NSTE ACS Patients Stratified by Baseline Hemoglobin

	Hemoglobin on Admission, g/dL										
End Point	<8 (n=137)	8–9 (n=306)	9–10 (n=342)	10–11 (n=343)	11–12 (n=976)	12–13 (n=2331)	13–14 (n=3520)	14–15 (n=3390)	15–16 (n=2130)	16–17 (n=812)	>17 (n=216)	*P*
Cardiovascular death, % (248 events)	3.7	2.3	2.3	3.8	2.4	1.8	1.7	1.5	1.3	1.5	0.9	<0.001
Myocardial (re)infarction, % (591 events)	5.1	2.9	5.3	5.8	4.7	4.0	3.9	4.4	3.2	4.5	3.7	0.191
Recurrent ischemia, % (1879 events)	37.2	25.8	27.1	15.6	12.8	12.8	11.7	11.7	12.0	13.6	16.7	<0.001
Composite, % (2347 events)	40.2	27.5	29.2	19.2	16.8	15.5	14.8	15.0	14.5	17.0	19.9	<0.001

Anemia for Risk Assessment of Patients With Acute Coronary Syndromes

Nicolas Meneveau, MD, PhD*, François Schiele, MD, PhD, Marie-France Seronde, MD, Vincent Descotes-Genon, MD, Joanna Oettinger, MD, Romain Chopard, MD, Fiona Ecarnot, MSc, and Jean-Pierre Bassand, MD, on behalf of the Reseau de Cardiologie de Franche Comte

added. Anemia was detected in 381 patients (27%). They were older, had more co-morbidities, had higher Global Registry of Acute Coronary Events (GRACE) risk scores, received fewer guideline-recommended treatments, and, as a result, had 4-fold higher mortality. When included in a prediction model based on the GRACE risk score, anemia remained an independent predictor of mortality. The addition of anemia improved both the discriminatory capacity and calibration of the models. According to the GRACE risk score, the population was divided into 4 groups of different risk levels of <1%, 1% to <5%, 5% to <10%, and ≥10%. The addition of anemia to the model made it possible to reclassify 9%, 43%, 47%, and 23% of patients into the different risk categories,

Am J Cardiol 2009; 103 :442-447

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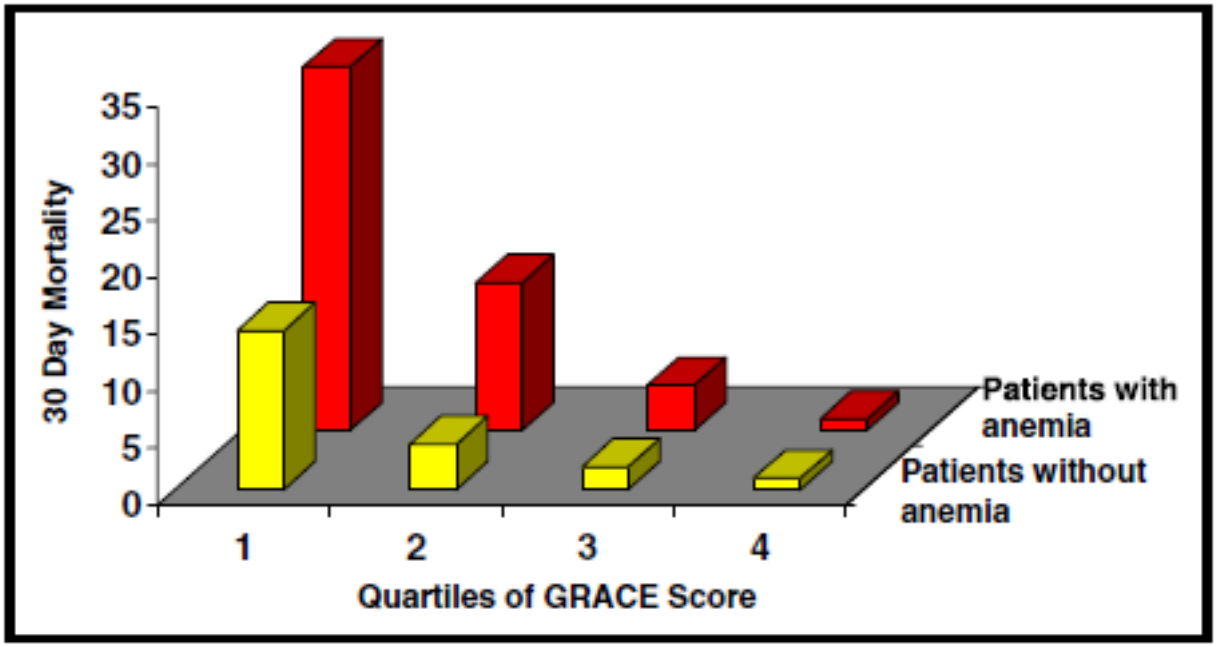
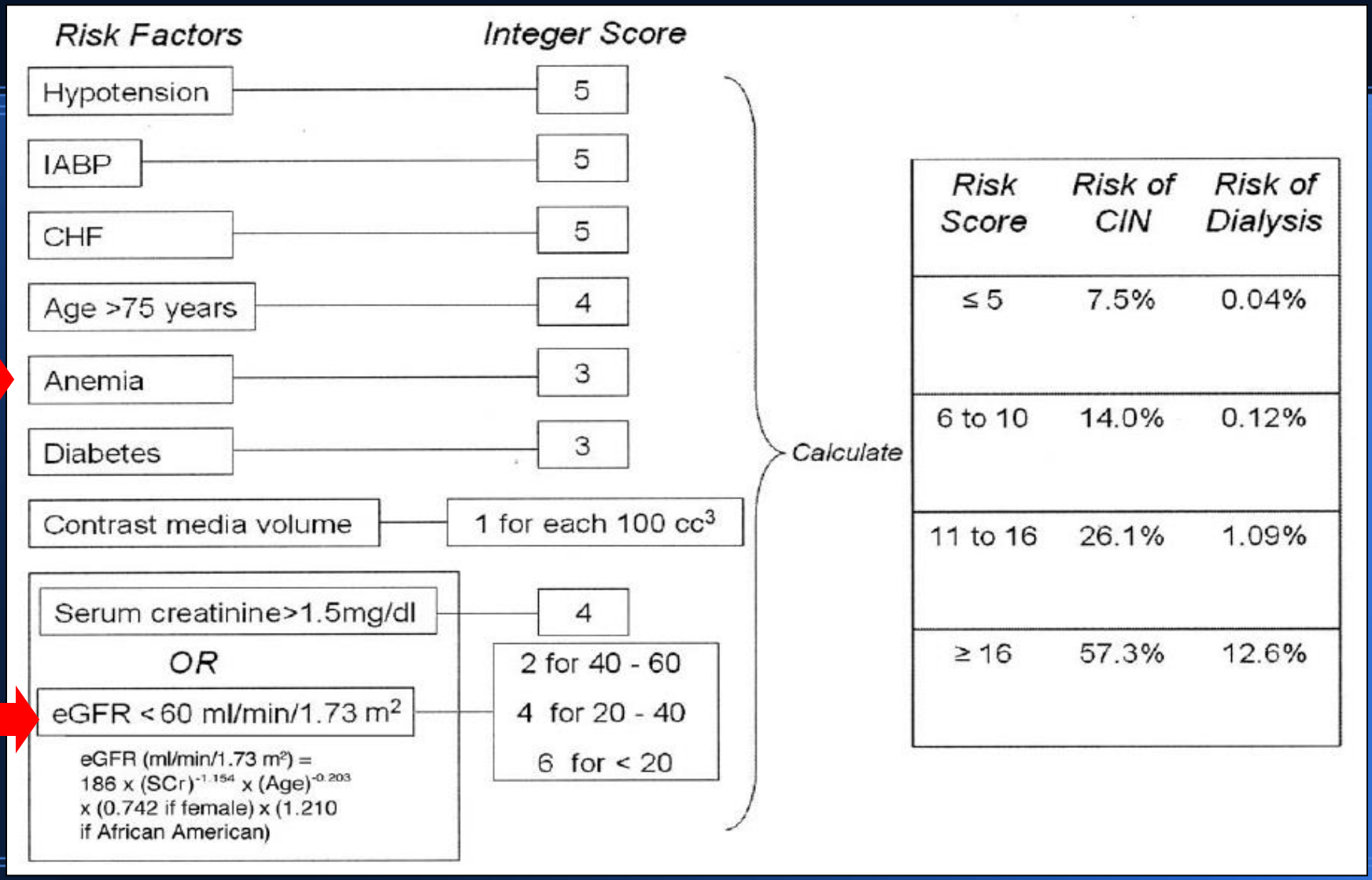


Figure 4. Thirty-day mortality rates according to quartiles of GRACE risk score and the presence of anemia.

Am J Cardiol 2009; 103 :442-447

Risk of renal failure



Mehran et al, JACC 2004

Increased bleeding risk

Development and validation of a prognostic risk score for major bleeding in patients undergoing percutaneous coronary intervention via the femoral approach

Eugenia Nikolsky[1], Roxana Mehran[1], George Dangas[1], Martin Fahy[1], Yingbo Na[1], Stuart J. Pocock[2], A. Michael Lincoff[3], and Gregg W. Stone[1]*

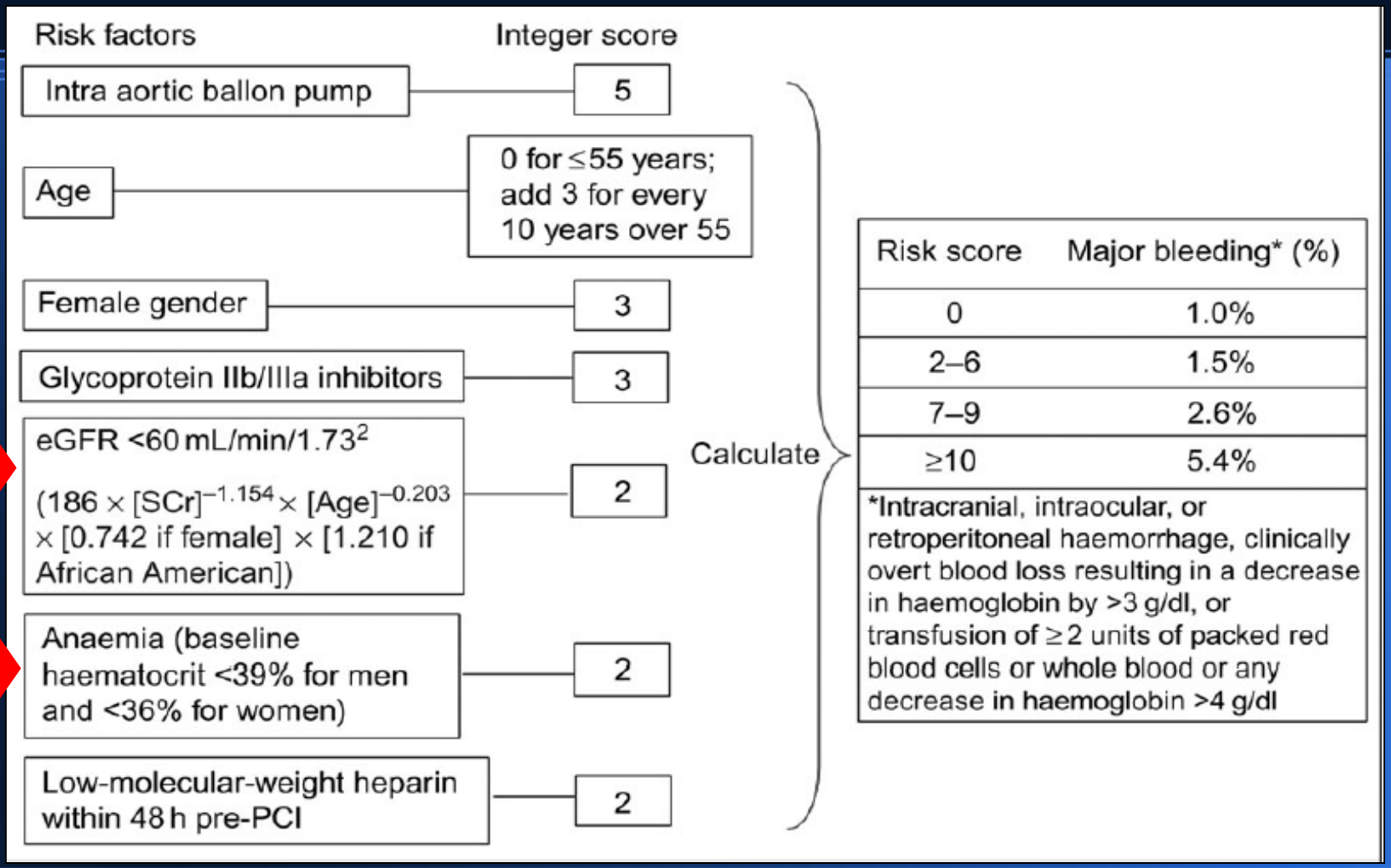
Aims Major bleeding after percutaneous coronary intervention (PCI) is an independent risk factor for early and late mortality. We developed and validated a risk score predictive of major bleeding after PCI using the femoral approach.

Methods and results Baseline clinical and procedural variables from two contemporary, multicentre, randomized PCI trials were used for risk score development (the REPLACE-2 trial, $n = 6002$) and validation (the REPLACE-1 trial, $n = 1056$). On the basis of the odds ratio, independent risk factors were assigned a weighted integer, the sum of which comprised a total risk score. Seven variables were identified as independent correlates of major bleeding (age >55 years, female gender, estimated glomerular filtration rate <60 mL/min/1.73 m^2, pre-existing anaemia, administration of low-molecular-weight heparin within 48 h pre-PCI, use of glycoprotein IIb/IIIa inhibitors, and intraaortic balloon pump use). In the development set, the risk of major bleeding varied from 1.0% in patients without risk factors to 5.4% in high-risk patients. The discriminatory power of this risk model was confirmed in the validation data set (area under the receiver operating curve = 0.62).

Conclusion A simple risk score of baseline clinical and procedural variables is useful to predict the incidence of major peri-procedural bleeding after contemporary PCI using the femoral approach.

Nikolsky et al, EHJ 2007

Development and validation of a prognostic risk score for major bleeding in patients undergoing PCI via the femoral approach

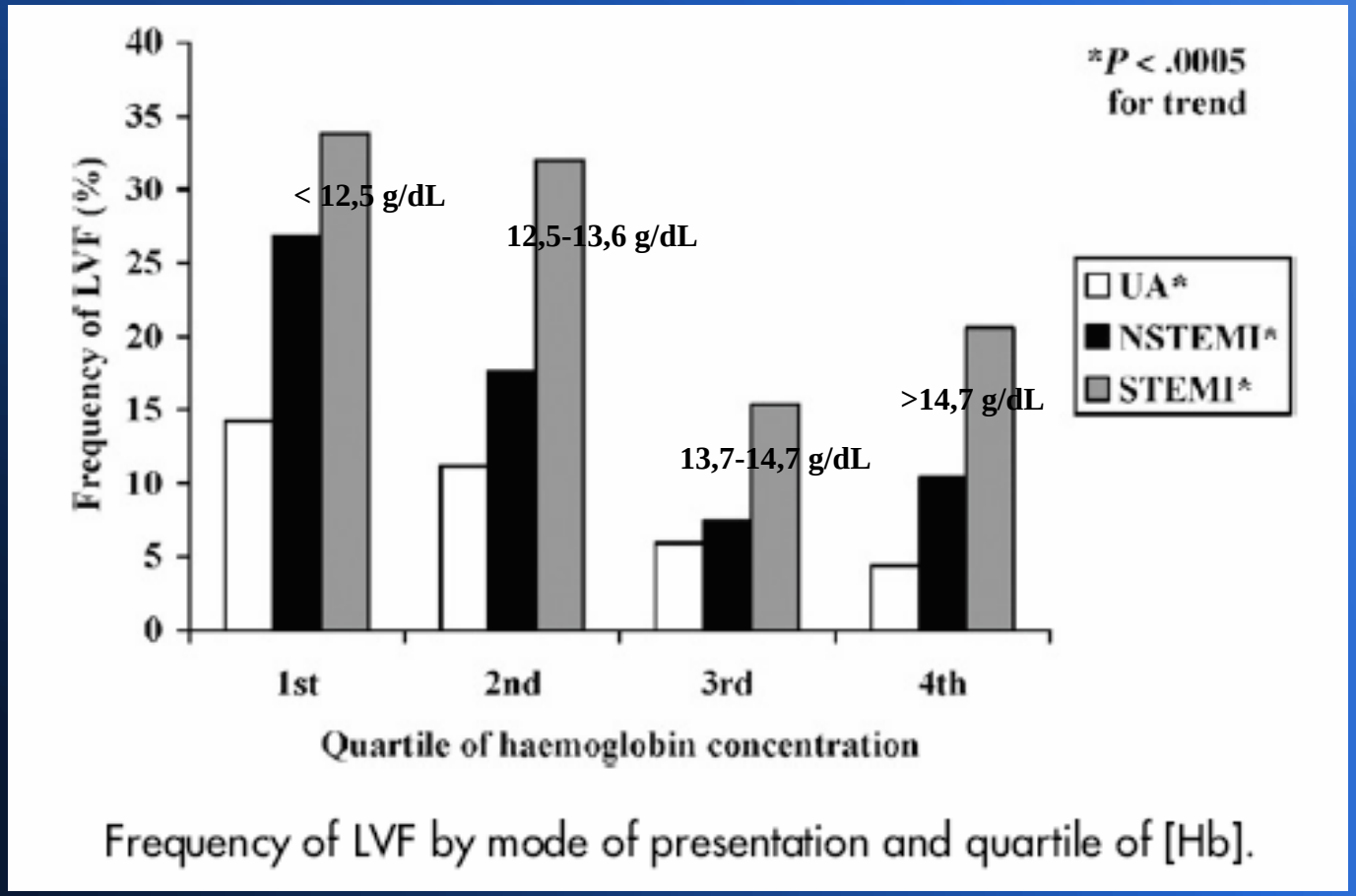


Nikolsky et al, EHJ 2007

R.A. Archibold et al.

American Heart Journal, 2006

Hemoglobin concentration is an independent determinant of heart failure in ACS: cohort analysis of 2310 patients



Frequency of LVF by mode of presentation and quartile of [Hb].

E. Cavusoglu et al.

The American Journal of Cardiology 2006

Usefulness of Anemia in Men as an Independent predictor of Two-Year vascular Outcome in Patients Presenting With ACS

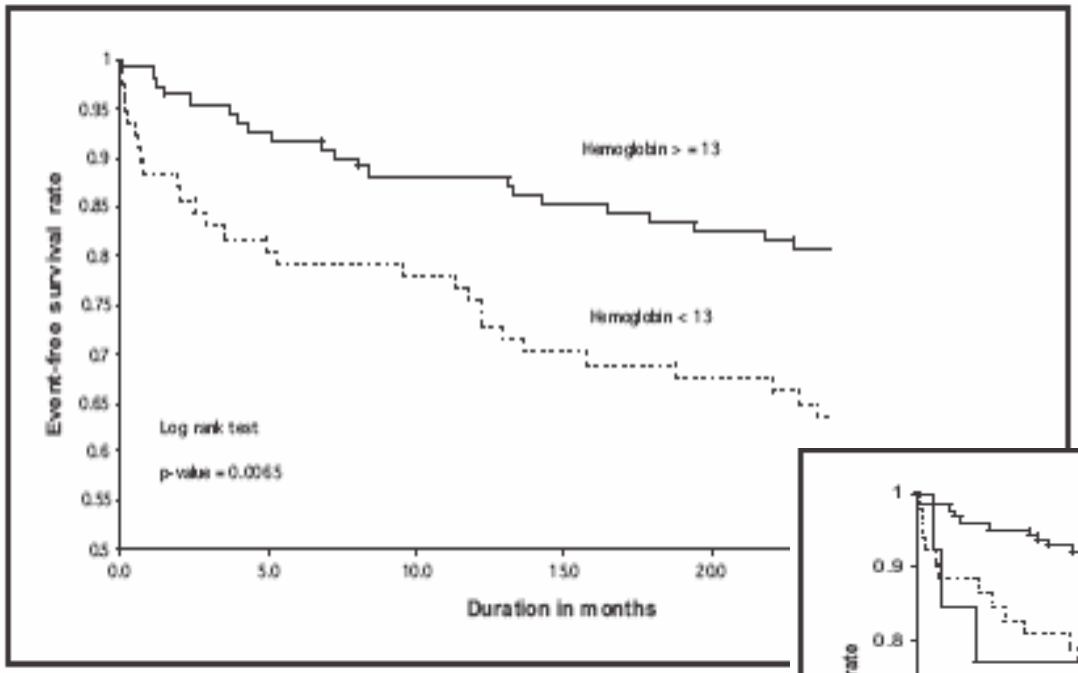
193 men with ACS who were referred for coronary angiography.

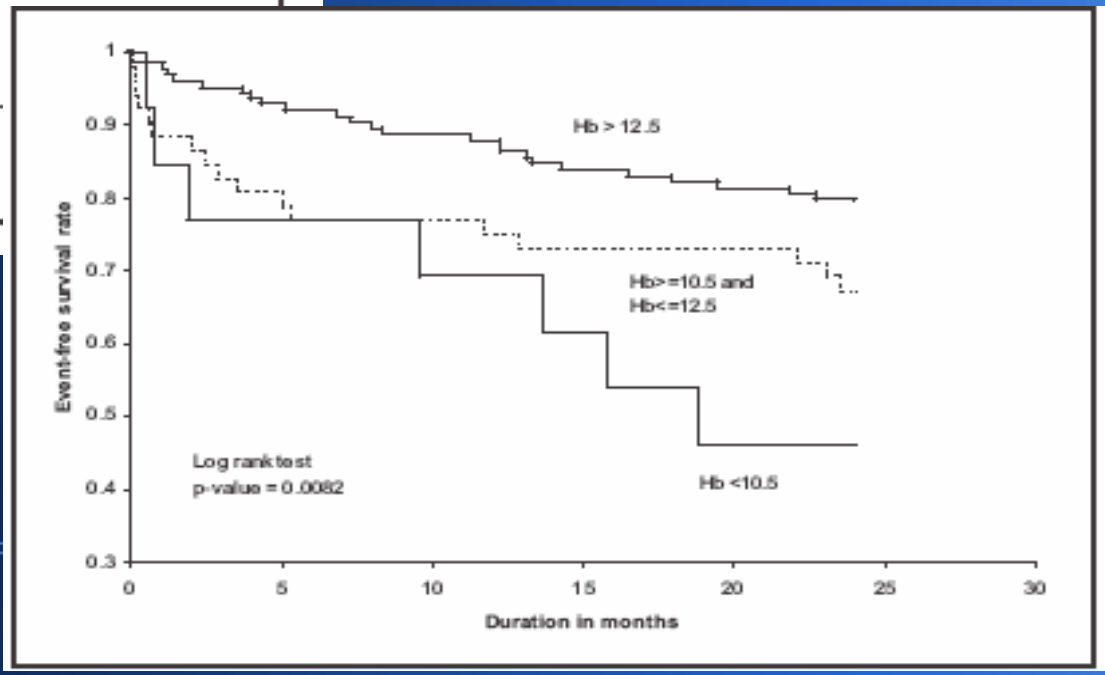
End point : death or AMI at 24 months

Follow-up : the event-free survival was 64% in the group with HB level <13 g/dl compared with 81% in the group with HB level >13 g/dl (p 0.0065 by log-rank test).

E. Cavusoglu et al.

Usefulness of Anemia in Men as an Independent predictor of Two-Year vascular Outcome in Patients Presenting With ACS





The American Journal of Cardiology 2006

D. Aronson et al.

European Heart Journal 2007

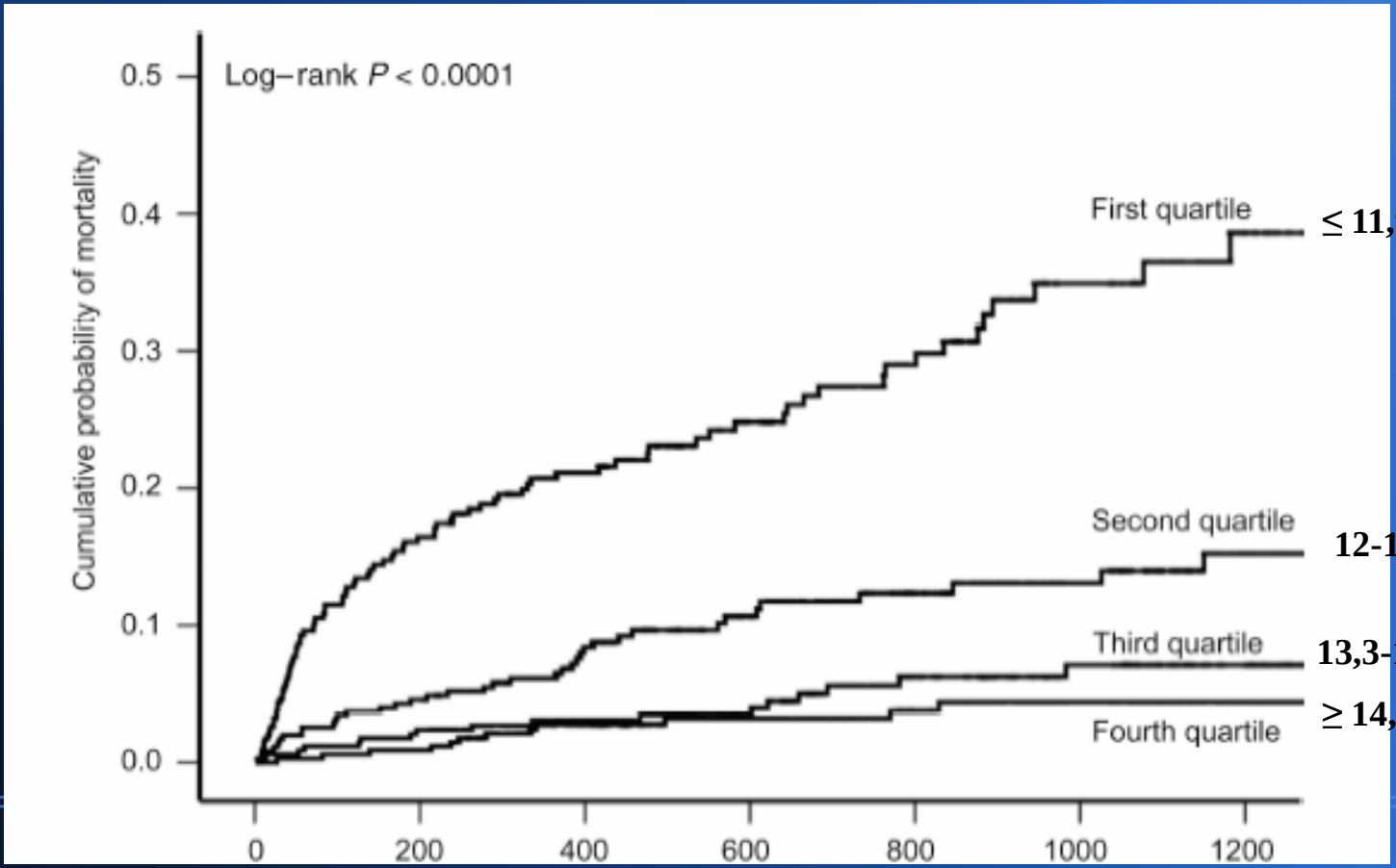
Changes in Hemoglobin Levels during hospital course and long-term outcome after acute myocardial infarction

- ***1390 pts***
- ***Anemia on admission 17,8%***
- ***Anemia on discharge 36,1%***
- ***Nadir heamoglobin was 1,3 g/dL lower when compared with baseline haemoglobin***

D. Aronson et al.

European Heart Journal 2007

Changes in Hemoglobin Levels during hospital course and long-term outcome after acute myocardial infarction



Journal of American College of Cardiology 2004

Impact of anemia in Patients With AMI Undergoing Primary PCI

Analysis From the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) Trial

Table 3. In-Hospital, 30-Day, and 1-Year Outcomes Stratified by Baseline Anemia

	Patients With Anemia n = 260	Patients Without Anemia n = 1,767	p Value
All-cause mortality			
In-hospital	4.6%	1.1%	0.0003
30-day	5.8%	1.5%	< 0.0001
1-year	10.2%	3.5%	< 0.0001
Cardiac mortality			
In-hospital	2.4%	1.0%	0.06
30-day	2.8%	1.4%	0.02
1-year	6.1%	2.5%	0.002
Noncardiac mortality			
In-hospital	2.3%	0.2%	0.001
30-day	3.2%	0.3%	< 0.0001
1-year	4.2%	1.1%	0.0002
Disabling stroke			
In-hospital	0.4%	0.0%	0.12
30-day	0.8%	0.1%	0.005
1-year	2.1%	0.4%	0.0007
Reinfarction			
In-hospital	0.8%	0.2%	0.12
30-day	1.6%	0.7%	0.16
1-year	2.9%	2.3%	0.58
Target vessel revascularization			
In-hospital	2.7%	2.4%	0.83
30-day	3.5%	3.8%	0.85
1-year	14.2%	16.7%	0.34
Composite adverse events			
In-hospital	7.7%	3.6%	0.004
30-day	10.4%	5.2%	0.0008
1-year	20.3%	17.3%	0.15

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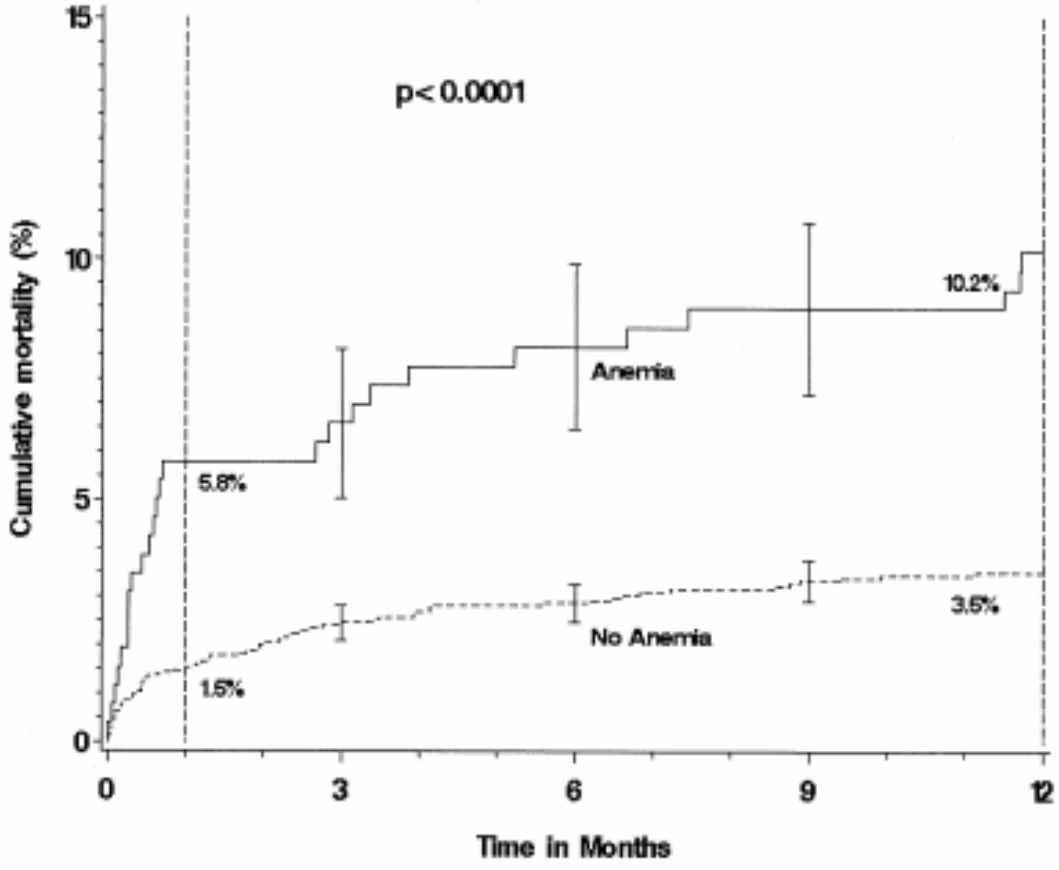

Figure 1. Cumulative risk of death in patients with versus without anemia.

Cumulative risk of death in patients with versus without anemia

Journal of American College of Cardiology 2004

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Table 4. Multivariate Predictors of Mortality

	Hazard Ratio (95% Confidence Interval)	p Value
In-hospital mortality		
Ejection fraction (lower)	1.10 (1.05, 1.15)	< 0.0001
Creatinine clearance (lower)	1.03 (1.01, 1.06)	0.02
Baseline anemia	3.26 (1.01, 10.52)	0.048
1-year mortality		
Ejection fraction (lower)	1.05 (1.03, 1.09)	< 0.0001
Age (older)	1.05 (1.02, 1.08)	0.0004
Left anterior descending infarct artery	2.60 (1.32, 5.09)	0.006
Triple-vessel disease	2.27 (1.20, 4.30)	0.01
Baseline anemia	2.38 (1.18, 4.81)	0.016
Female gender	1.89 (1.02, 3.50)	0.04

Predictors of mortality in patients with versus without anemia

Renal Function & Risk Prediction in ACS

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 23, 2004 VOL. 351 NO. 13

Relation between Renal Dysfunction and Cardiovascular Outcomes after Myocardial Infarction

Nagesh S. Anavekar, M.D., John J.V. McMurray, M.D., Eric J. Velazquez, M.D., Scott D. Solomon, M.D., Lars Kober, M.D., D.Sc., Jean-Lucien Rouleau, M.D., Harvey D. White, D.Sc., Rolf Nordlander, M.D., Aldo Maggioni, M.D., Kenneth Dickstein, M.D., Steven Zelenkofske, D.O., Jeffrey D. Leimberger, Ph.D., Robert M. Califf, M.D., and Marc A. Pfeffer, M.D., Ph.D.

Valsartan in Acute Myocardial Infarction Trial (VALIANT)

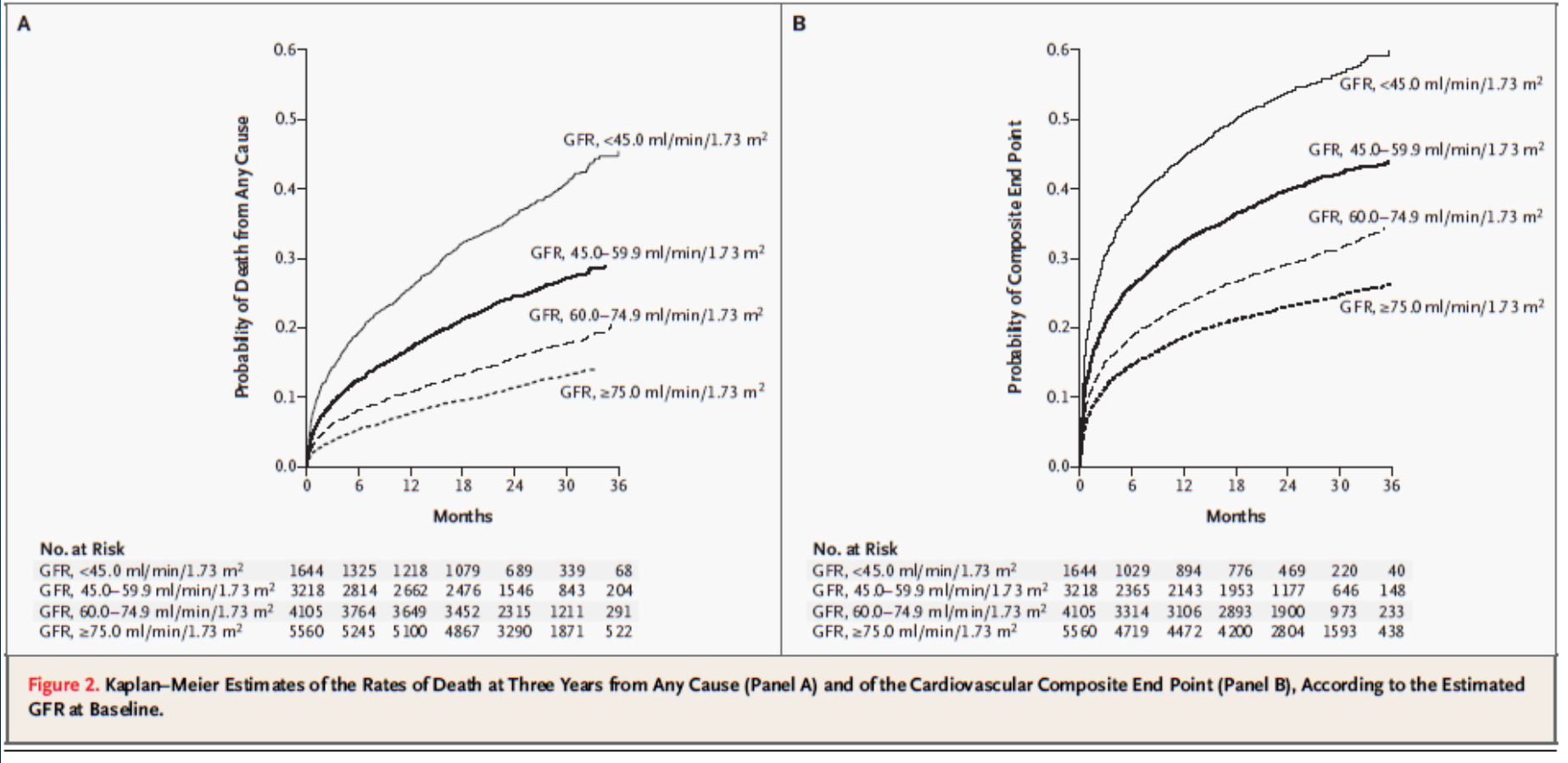

Figure 2. Kaplan–Meier Estimates of the Rates of Death at Three Years from Any Cause (Panel A) and of the Cardiovascular Composite End Point (Panel B), According to the Estimated GFR at Baseline.

N=14,527

Valsartan in Acute Myocardial Infarction Trial (VALIANT)

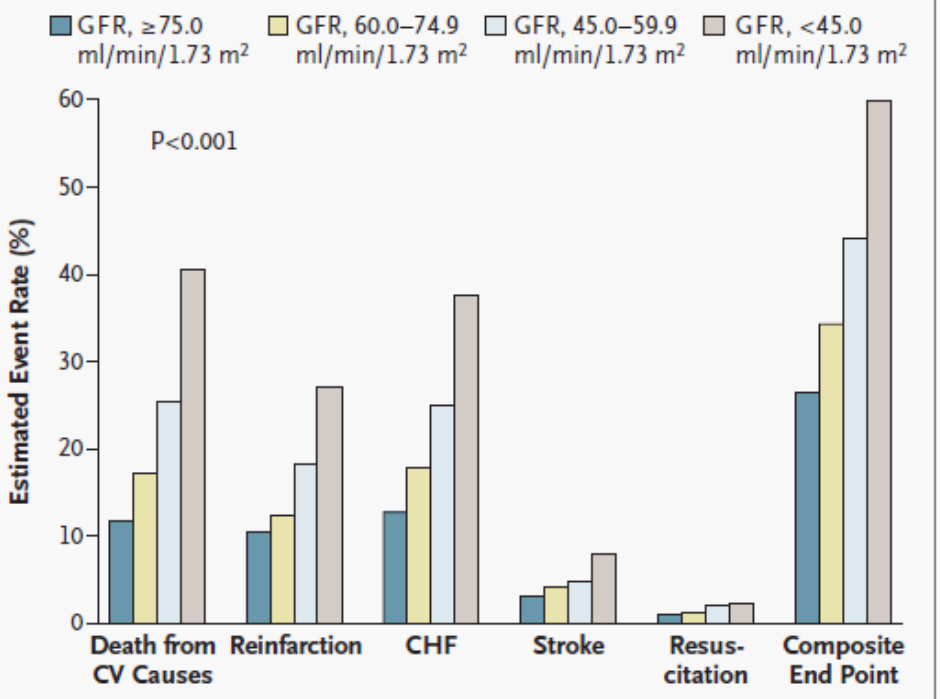

Figure 3. Kaplan–Meier Estimates of the Rates of Death at Three Years from Cardiovascular (CV) Causes, Reinfarction, Congestive Heart Failure (CHF), Stroke, Resuscitation after Cardiac Arrest, and the Composite End Point, According to the Estimated GFR at Baseline.

Data on patients with noncardiovascular events were censored. The P value is from the Cox model.

Valsartan in Acute Myocardial Infarction Trial (VALIANT)

Table 2. Hazard Ratios for Death and Composite Outcomes According to the Estimated GFR and Creatinine Levels at Baseline.*

Outcome	GFR, <45.0 ml/min/1.73 m²; Creatinine, 1.7±0.4 mg/dl (N=1644)	GFR, 45.0–59.9 ml/min/1.73 m²; Creatinine, 1.3±0.2 mg/dl (N=3218)	GFR, 60.0–74.9 ml/min/1.73 m²; Creatinine, 1.1±0.1 mg/dl (N=4105)	GFR, >75.0 ml/min/1.73 m²; Creatinine 0.9±0.1 mg/dl (N=5560)
Death (%)	45.5	28.9	20.5	14.1
Unadjusted hazard ratio (95% CI)	3.78 (3.39–4.21)	2.29 (2.07–2.53)	1.42 (1.28–1.58)	1.0†
Adjusted hazard ratio (95% CI)‡	1.70 (1.50–1.93)	1.38 (1.24–1.54)	1.14 (1.02–1.27)	
Composite end point (%)§	59.9	44.1	34.3	26.5
Unadjusted hazard ratio (95% CI)	2.94 (2.7–3.2)	1.92 (1.78–2.08)	1.33 (1.23–1.44)	1.0†
Adjusted hazard ratio (95% CI)‡	1.49 (1.35–1.65)	1.26 (1.16–1.37)	1.10 (1.02–1.19)	

Valsartan in Acute Myocardial Infarction Trial (VALIANT)

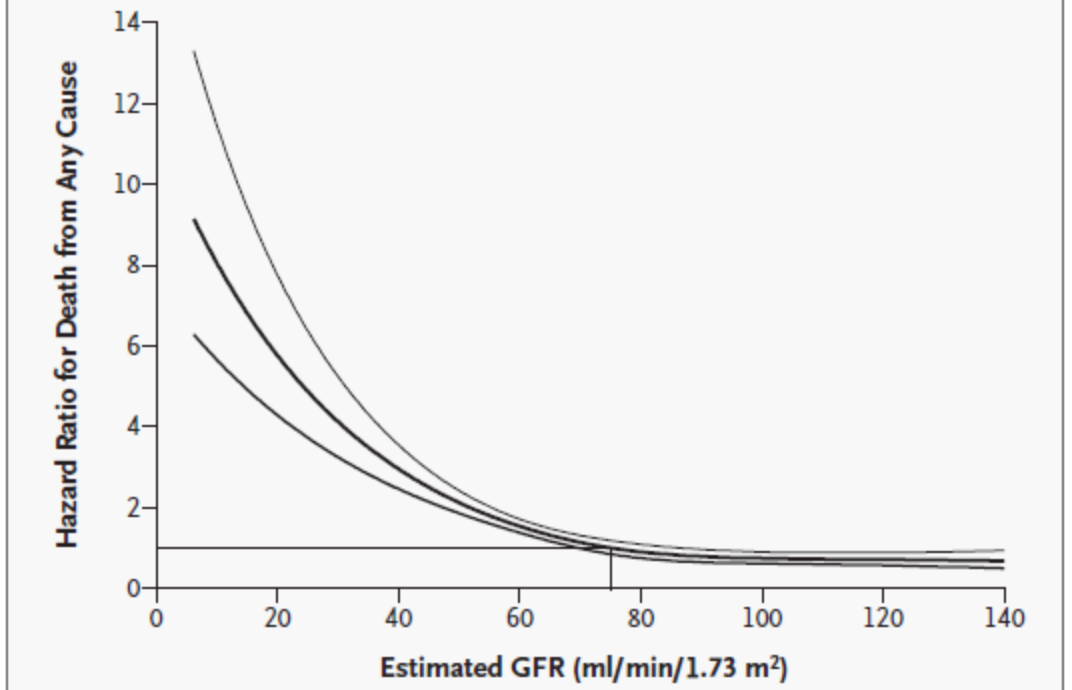

Figure 4. Unadjusted Hazard Ratio for Death from Any Cause, According to the Estimated GFR at Baseline.

The estimated hazard ratio (middle curve) is shown with the 95 percent confidence limits (upper and lower curves).

Renal Impairment Predicts Long-Term Mortality Risk after Acute Myocardial Infarction

Grace L. Smith,* Frederick A. Masoudi,† Michael G. Shlipak,‡ Harlan M. Krumholz,*§ and Chirag R. Parikh‖

The Cooperative Cardiovascular Project

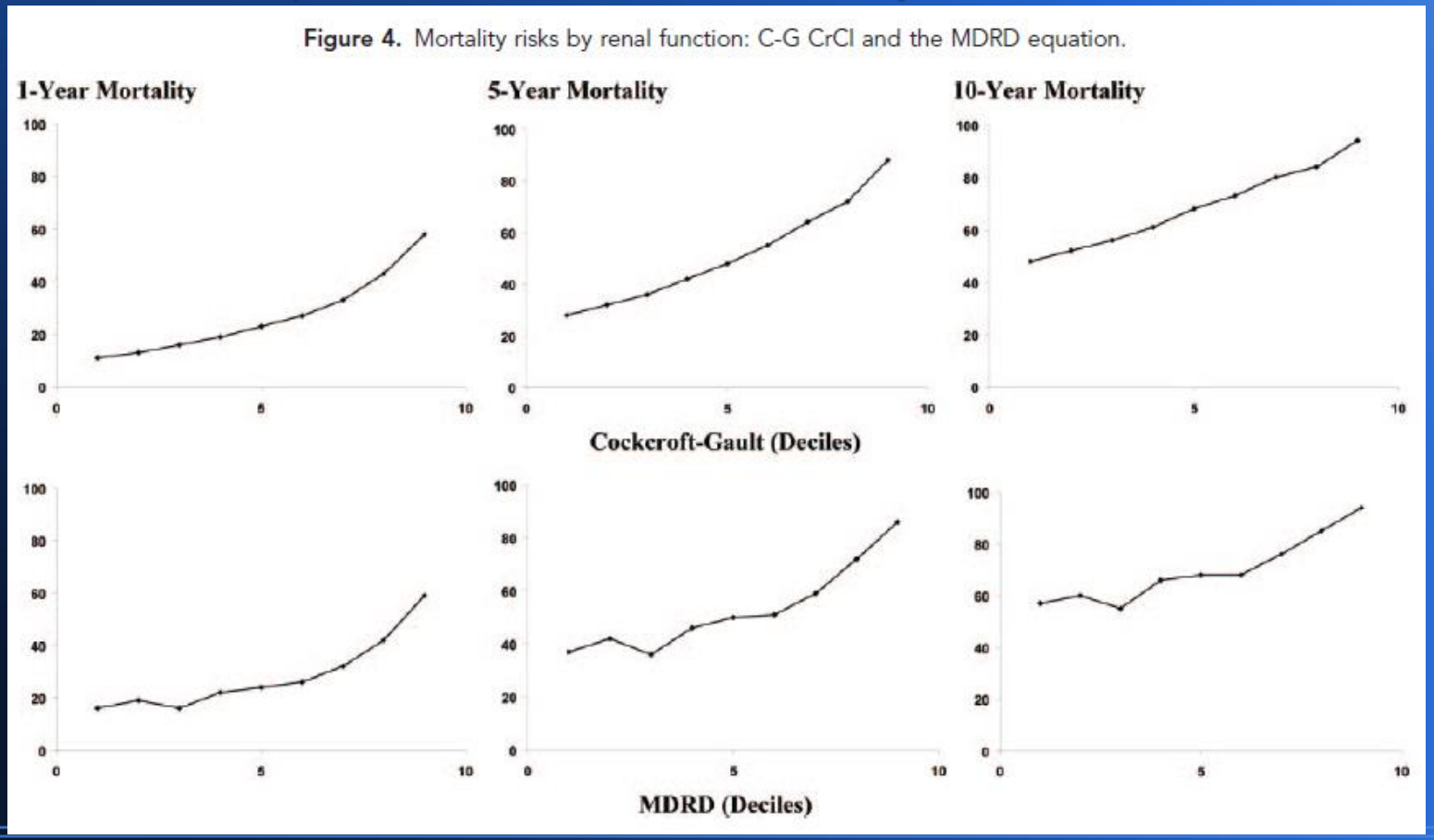

Figure 4. Mortality risks by renal function: C-G CrCl and the MDRD equation.

N = 118,753 Age ≥ 65

J Am Soc Nephrol 19: 141–150, 2008

Renal Impairment Predicts Long-Term Mortality Risk after Acute Myocardial Infarction

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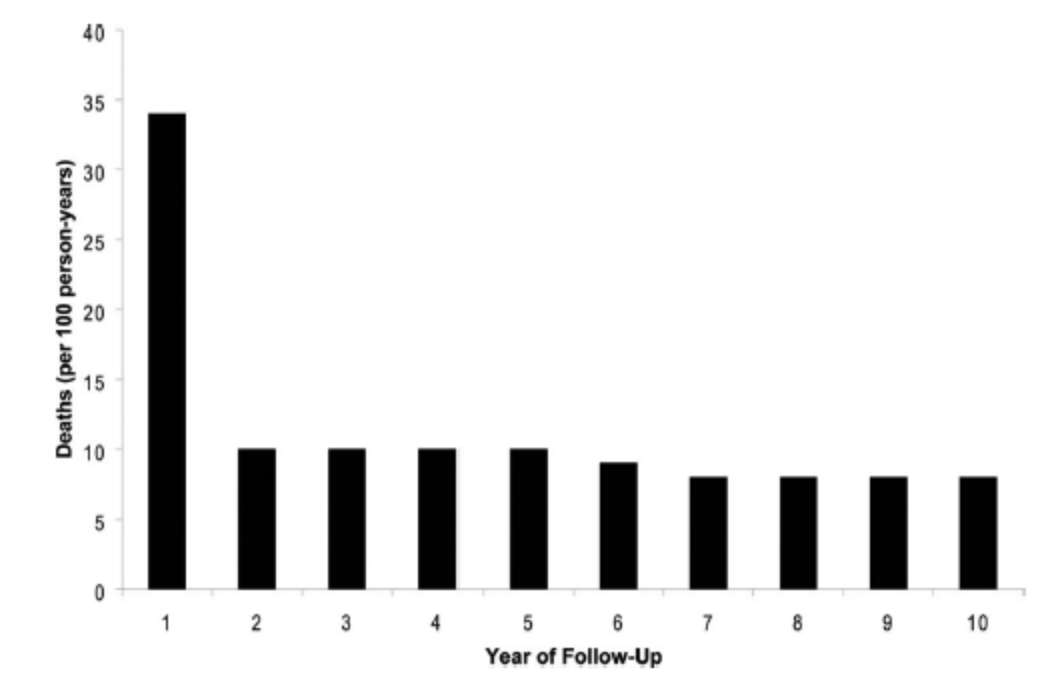

J Am Soc Nephrol **19:** 141–150, 2008

Even a minimal increase in creatinine level is a bad predictor of short and long-term mortality

Table 3. Adjusted risks of 1-, 5-, and 10-yr mortality by creatinine level[a]

Parameter	Creatinine									
	≤0.7	0.8	0.9	1.0	1.1	1.2	1.3	1.4 to 1.5	1.6 to 1.8	≥1.9
1-yr										
HR	1.00	0.98	1.03	1.06	1.14	1.17	1.26	1.37	1.57	1.95
95% CI	–	0.91 to 1.06	0.96 to 1.10	0.99 to 1.13	1.06 to 1.22	1.09 to 1.26	1.17 to 1.35	1.28 to 1.46	1.46 to 1.67	1.82 to 2.08
5-yr										
HR	1.00	0.98	1.03	1.04	1.08	1.12	1.22	1.31	1.50	1.86
95% CI	–	0.93 to 1.03	0.98 to 1.08	0.99 to 1.08	1.03 to 1.13	1.07 to 1.17	1.16 to 1.28	1.26 to 1.37	1.44 to 1.57	1.78 to 1.94
10-yr										
HR	1.00	0.98	1.00	1.01	1.06	1.10	1.17	1.26	1.44	1.80
95% CI	–	0.94 to 1.02	0.97 to 1.04	0.98 to 1.05	1.02 to 1.10	1.06 to 1.14	1.13 to 1.22	1.21 to 1.31	1.38 to 1.50	1.73 to 1.87
Subset HR	1.00	0.97	0.99	0.98	1.01	1.05	1.13	1.21	1.37	1.68

[a]Adjusted models include age, gender, race, comorbidities, laboratory values, hospital events, and hospital/physician characteristics. Subset refers to the adjusted 10-yr HR after exclusion of patients who died within 30 d of hospitalization (n = 102,174 patients included).

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Table 4. Relative importance of renal function for predicting mortality compared with other risk factors[a]

Parameter	χ^2 for Each Variable[b]		
	1-Yr	5-Yr	10-Yr
Renal function			
CrCl	1606	2325	2296
MDRD eGFR[c]	1261	2031	2310
Other predictors			
LVSF	1687	1498	1350
Age	121	1090	2232
Systolic BP	1440	923	660
Hematocrit	63	242	283
Previous HF	18	304	407
Previous MI	9	63	150

J Am Soc Nephrol **19:** 141–150, 2008

CLINICAL STUDIES **Acute Coronary Syndromes**

Influence of Concurrent Renal Dysfunction on Outcomes of Patients With Acute Coronary Syndromes and Implications of the Use of Glycoprotein IIb/IIIa Inhibitors

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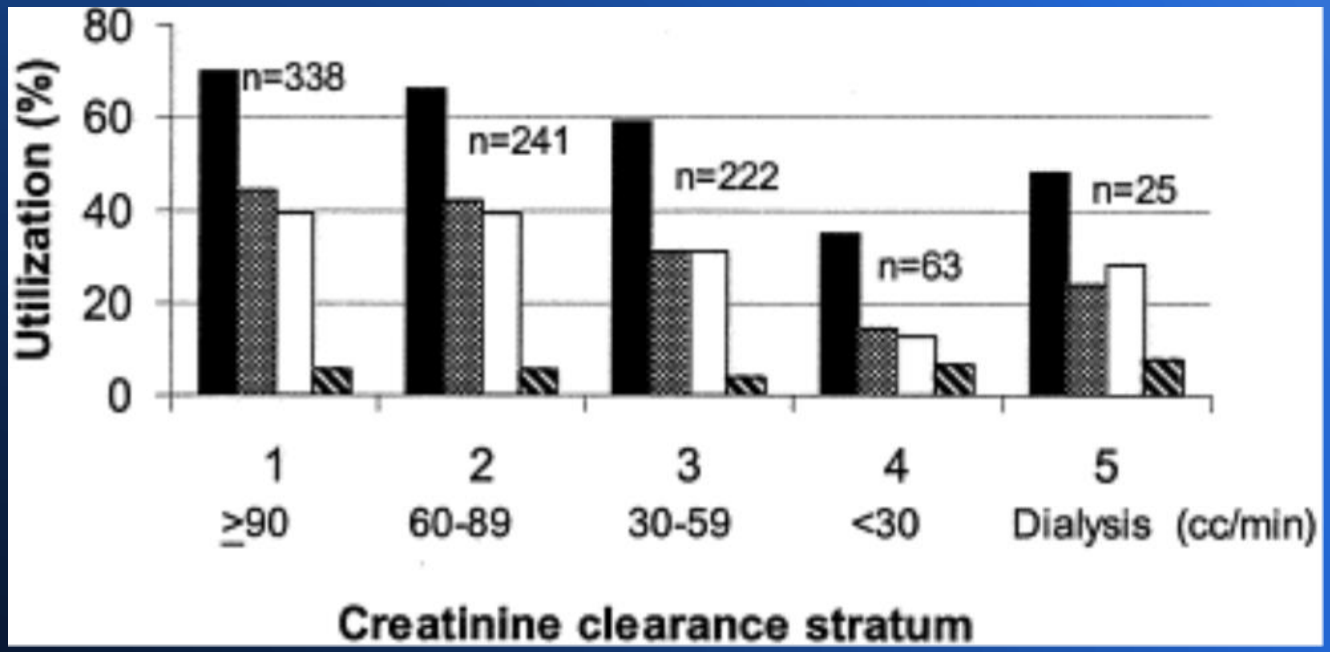
J Am Coll Cardiol. 2003;41(5):718-724.

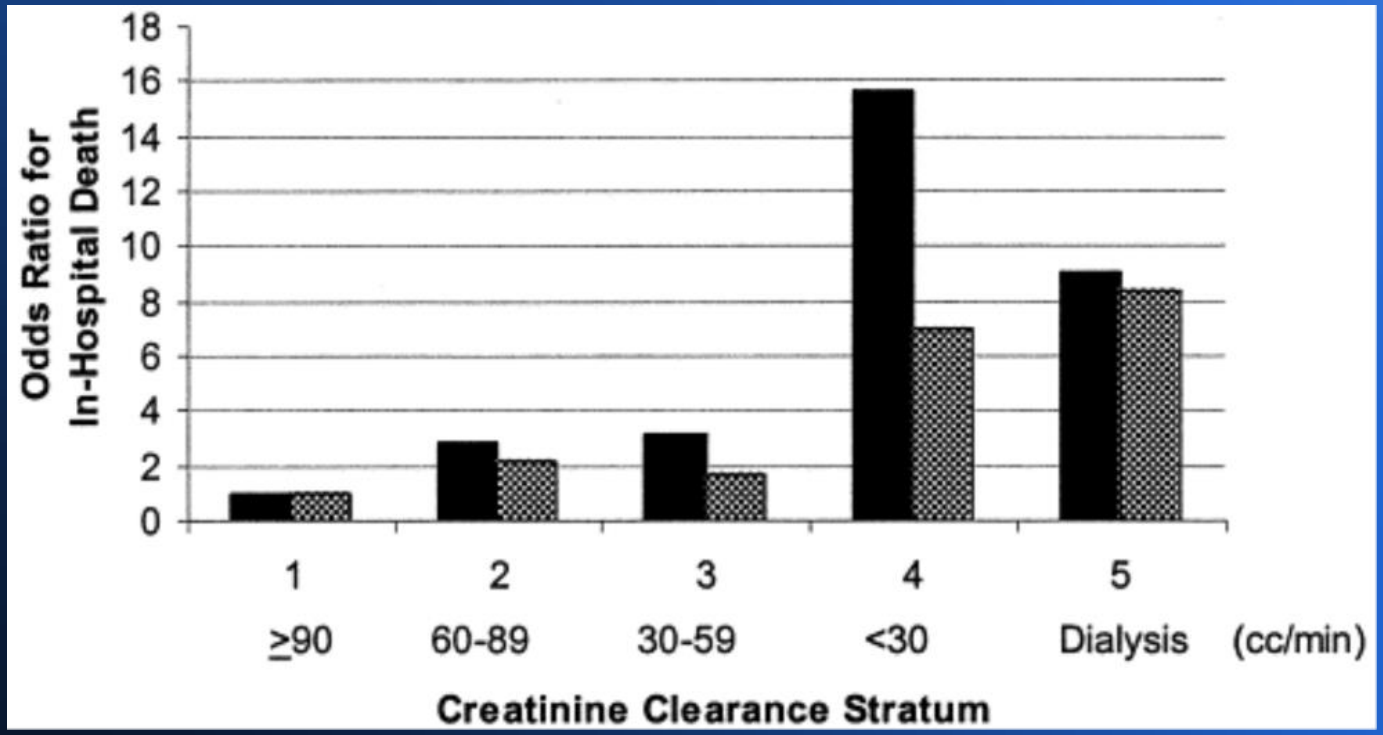
Utilization of cardiovascular diagnostic tests and therapeutics across creatinine clearance stratum



Black bars = catheterization; white bars = glycoprotein IIb/IIIa antagonist; hatched bars = percutaneous coronary intervention; striped bars = coronary artery bypass graft surgery.

J Am Coll Cardiol. 2003;41(5):718-724.

Unadjusted and adjusted odds ratios for mortality stratified by creatinine clearance.

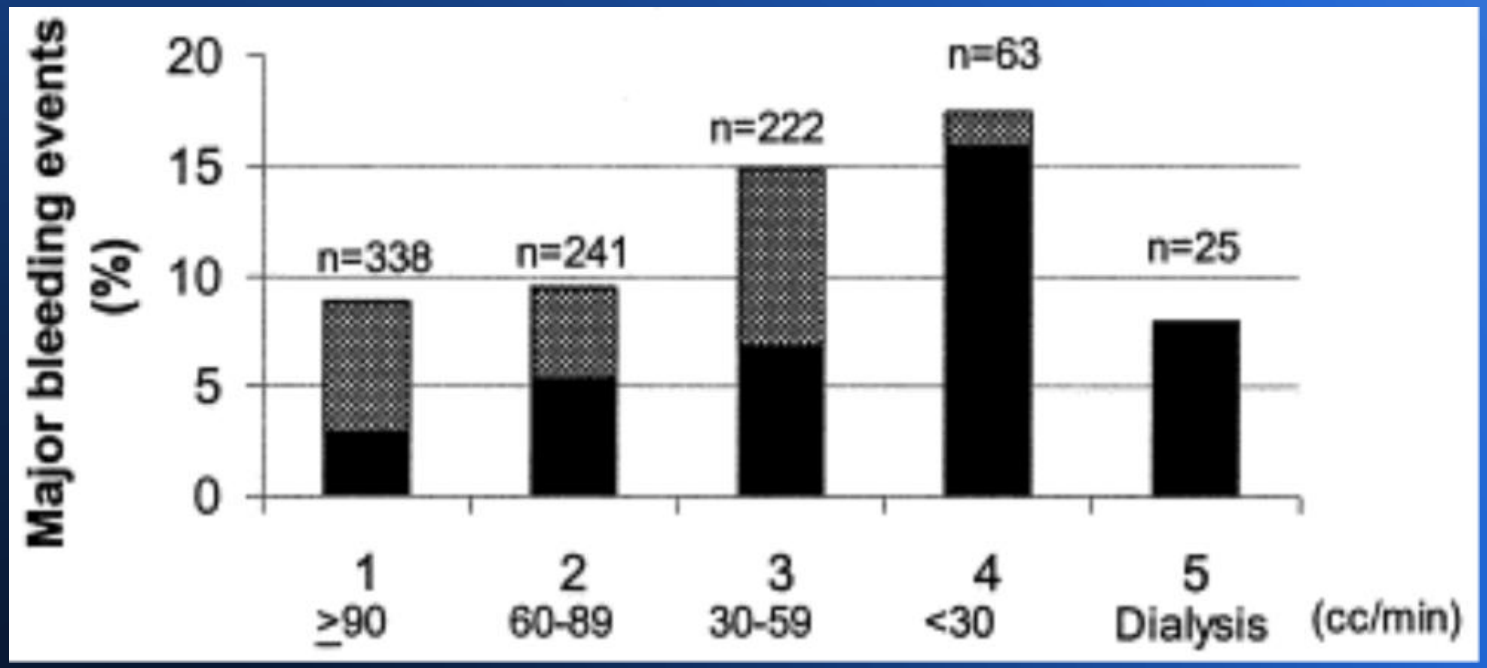


Black bars = unadjusted; hatched bars = adjusted.

J Am Coll Cardiol. 2003;41(5):718-724.

JACC Journals

Absolute major bleeding event rate and creatinine clearance stratum



The lighter portion of each bar represents the relative proportion that received glycoprotein IIb/IIIa antagonists during hospitalization. Numbers at the top of each bar are the total number of patients within each creatinine clearance stratum, and the percentages represented by each bar are the respective portion of that total number. Hatched bars = did not receive glycoprotein IIb/IIIa antagonists; black bars = received glycoprotein IIb/IIIa antagonists.

J Am Coll Cardiol. 2003;41(5):718-724.

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Multiple Biomarkers at Admission Significantly Improve the Prediction of Mortality in Patients Undergoing Primary Percutaneous Coronary Intervention for Acute ST-Segment Elevation Myocardial Infarction

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Table 2 Hazard Ratios for Mortality for the Individual Biomarkers in Univariate Cox Regression

	Mortality (n = 1,034)		
Biomarker	**% (n/N)**	**Hazard Ratio (95% CI)**	**p Value**
Troponin T (μg/l)			
<0.05	8.8 (38/510)	Reference	
0.05–0.23	16.4 (33/253)	1.73 (1.09–2.76)	0.02
≥0.24	20.2 (49/261)	2.78 (1.82–4.24)	<0.001
Glucose (mmol/l)			
<8	7.6 (33/509)	Reference	
8–9	14.7 (36/289)	2.00 (1.25–3.21)	<0.01
≥10	27.3 (51/236)	3.68 (2.38–5.71)	<0.001
NT-proBNP (ng/l)			
<150	6.9 (25/521)	Reference	
150–599	16.1 (32/254)	2.73 (1.62–4.61)	<0.001
≥600	27.0 (63/259)	5.93 (3.73–9.43)	<0.001
eGFR (ml/min)			
≥90	6.4 (36/640)	Reference	
60–89	18.5 (36/263)	2.59 (1.63–4.11)	<0.001
<60	43.4 (48/131)	8.11 (5.26–12.50)	<0.001
CRP (mg/l)			
<7	11.2 (68/756)	Reference	
≥7	22.5 (52/278)	2.23 (1.55–3.19)	<0.001

CI = confidence interval; other abbreviations as in Table 1.

Multiple Biomarkers at Admission Significantly Improve the Prediction of Mortality in Patients Undergoing Primary Percutaneous Coronary Intervention for Acute ST-Segment Elevation Myocardial Infarction

Table 4 Multimarker Risk Score for Mortality

Biomarker	Add to Score
Glucose (mmol/l)	
<8	0
8–9	+2
≥10	+3
NT-proBNP (ng/l)	
<150	0
150–599	+2
≥600	+3
eGFR (ml/min)	
≥90	0
60–89	+2
<60	+4
	Total score
Total score	
≤4	Low risk
5–6	Intermediate risk
>6	High risk

Abbreviations as in Table 1.

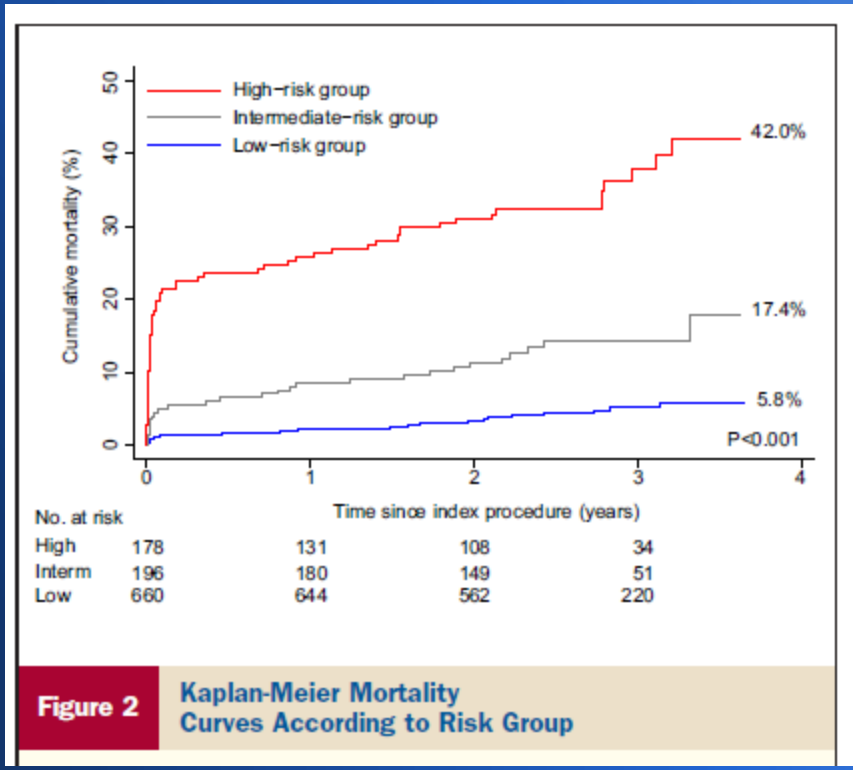

Figure 2 Kaplan-Meier Mortality Curves According to Risk Group

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Conclusions

- Hyperglycemia on admission, low HB level and low GFR – are strong predictors of early, late and very late adverse outcomes and mortality post ACS.

- However, the most widely used risk scores in ACS (GRACE & TIMI) do not incorporate anemia and glucose level on admission.

Conclusions

- In clinical practice, the addition of admission levels of glucose and HB to the GRACE score may further improve risk stratification and prediction of mortality in patients with ACS.