Ischemic and bleeding risk stratification in NSTE ACS

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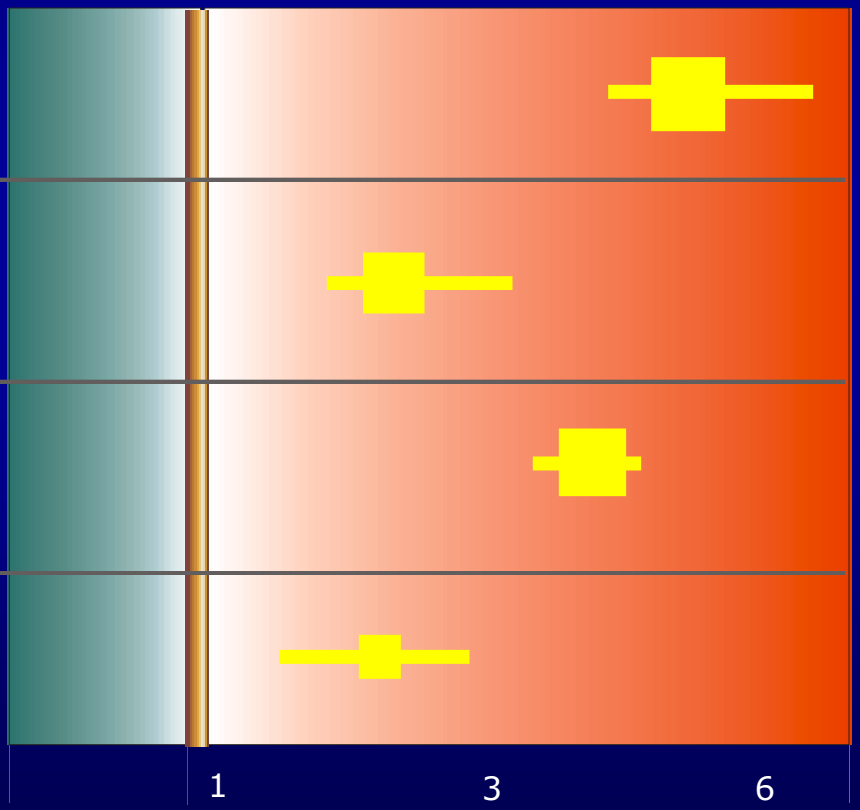
Disclosure

Andrzej Budaj, MD, PhD, reports the following potential conflicts of interest:

Company Name	Relationship
• Sanofi-Aventis	Research grant
• AstraZeneca	Speaker fees, research grant, consultant
• Boehringer Ingelheim	Research grant
• GlaxoSmithKline	Research grant
• Bristol Myers Squibb/PFIZER	Speaker fees, research grant, consultant
• Novartis	Consultant

Impact on mortality

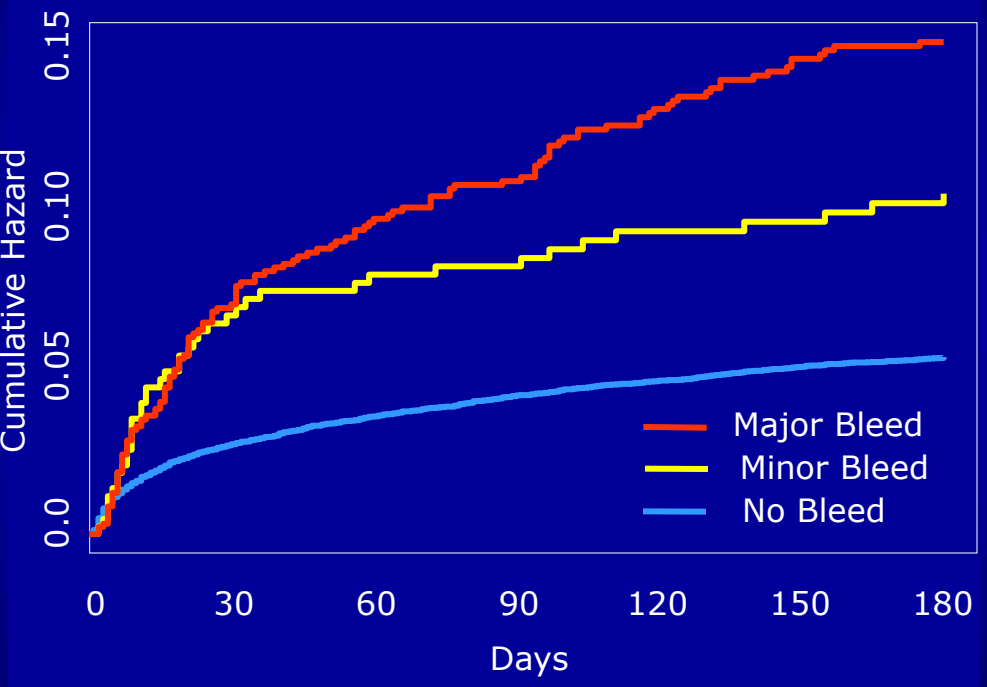
	HR (95% CI)
MI	HR 5.7 (4.7 - 6.9)
Refractory ischemia	HR 2.7 (2.0 - 3.6)
Major bleeding	HR 4.2 (3.5 - 5.1)
Minor bleeding	HR 2.2 (1.7 - 3.0)



OASIS 5 Investigators, NEJM 2006;354:1-13

Impact on DEATH

OASIS-5 bleeding



MAJOR BLEEDING

Death	OR (95%CI)	p <
30 days	3.46(2.60-4.60)	0.0001
180 days	3.11(2.55-3.79)	0.0001

MINOR BLEEDING

Death	OR (95%CI)	p <
30 days	2.01(1.32-3.06)	0.001
180 days	1.54(1.10-2.16)	0.01

Also significant impact on MI, stroke, stent thrombosis

Budaj A, Eikelboom J et al. Eur Heart J 2009;30:655-661

Ischemic and bleeding risk stratification NSTEACS

2007

European Heart Journal
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ESC Guidelines

Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes

The Task Force for the Diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes of the European Society of Cardiology

Authors/Task Force Members, Jean-Pierre Bassand* (Chair) (France), Christian W. Hamm* (Co-Chair) (Germany), Diego Ardissino (Italy), Eric Boersma (The Netherlands), Andrzej Budaj (Poland), Francisco Fernández-Avilés (Spain), Keith A.A. Fox (UK), David Hasdai (Israel), E. Magnus Ohman (USA), Lars Wallentin (Sweden), William Wijns (Belgium)

2011

European Heart Journal
doi:10.1093/eurheartj/ehr236

ESC GUIDELINES

ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC)

Authors/Task Force Members: Christian W. Hamm (Chairperson) (Germany)*, Jean-Pierre Bassand (Co-Chairperson)*, (France), Stefan Agewall (Norway), Jeroen Bax (The Netherlands), Eric Boersma (The Netherlands), Hector Bueno (Spain), Pio Caso (Italy), Dariusz Dudek (Poland), Stephan Gielen (Germany), Kurt Huber (Austria), Magnus Ohman (USA), Mark C. Petrie (UK), Frank Sonntag (Germany), Miguel Sousa Uva (Portugal), Robert F. Storey (UK), William Wijns (Belgium), Doron Zahger (Israel).

ESC GD NSTEACS 2011
Risk stratification

Recommendations	Class [a]	Level [b]
In patients with a suspected NSTE-ACS, diagnosis and short-term ischaemic/bleeding risk stratification should be based on a combination of clinical history, symptoms, physical findings, ECG (repeated or continuous ST monitoring), and biomarkers.	I	A
It is recommended to use established risk scores for prognosis and bleeding (e.g. GRACE, CRUSADE).	I	B

Prognostic risk assessment

- clinical assessment
  including physical examination
- electrocardiogram
- biochemical markers
- echocardiography
- imaging of coronary anatomy

Biomarkers

INDIVIDUAL BIOMARKERS
Tn, BNP(NT-proBNP), hsCRP, glycemia, CrCl(eGFR)
currently recommended

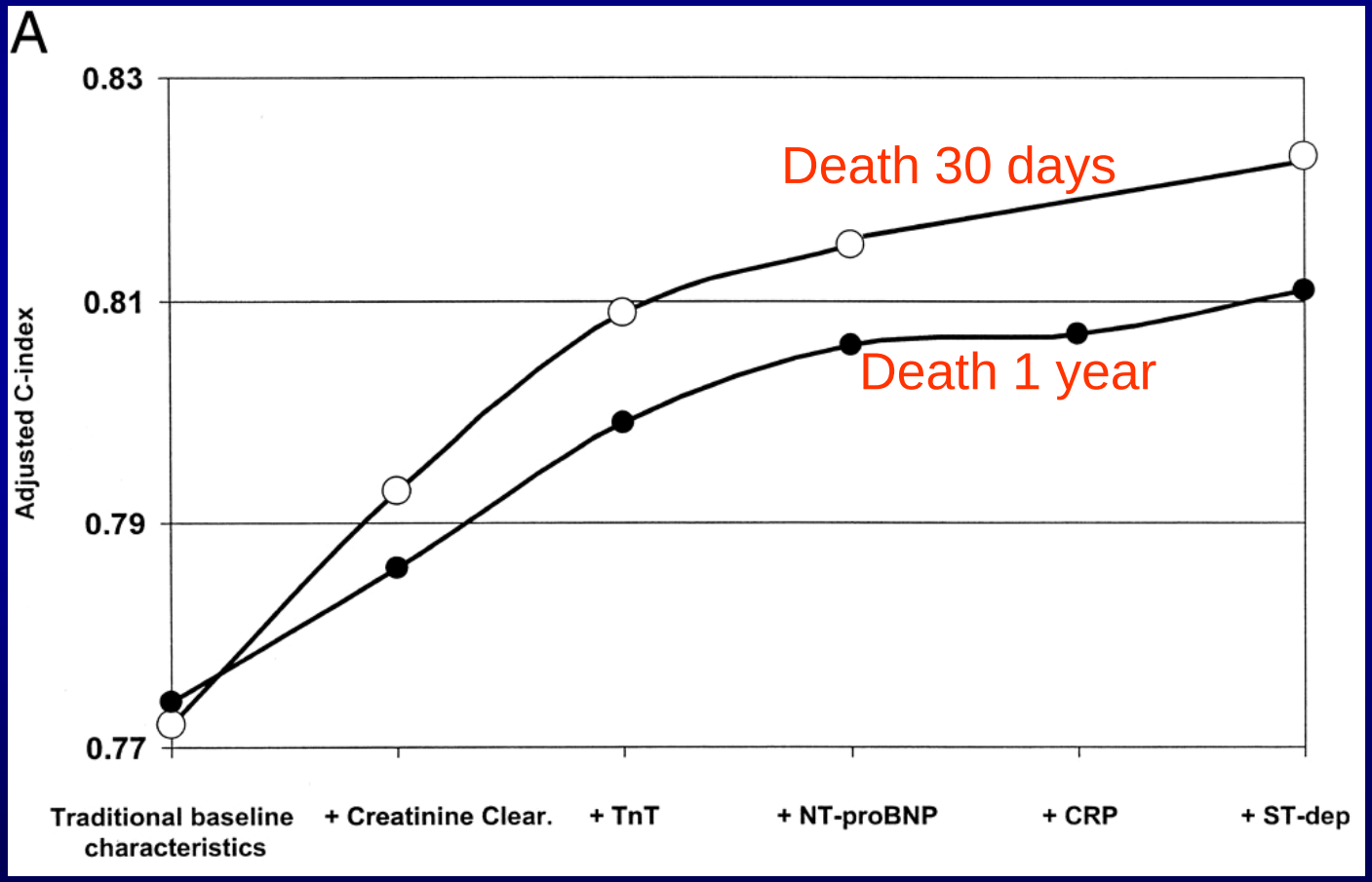
NOVEL BIOMARKERS
(myeloperoxidase, CD40 ligand, H-FABP, other)
still not recommended

MULTIMARKER APPROACH
Tn, CrCl (eGFR), BNP(NT-proBNP), hsCRP
improves risk stratification

Risk stratification – the added value of ST depression and multiple biomarkers

n = 7 800 NSTE ACS GUSTO - IV

Increase in adjusted c-statistics



Westerhout CM et al. JACC 2006;48:939-47

Imaging of the coronary anatomy

GOLD STANDARD
conventional invasive coronary angiography

HIGH RISK

- **LM, multivessel disease**
- **complex, long, calcified, angulated with tortuisity, intracoronary thrombosis**

angio CT – recommended in very low risk pts

ESC NSTEMI/UA Guidelines 2011

Adding angiographic data to risk scores

n=237 NSTEACS PCI

	Odds ratio	95% confidence interval	P
30-day mortality			
Extent score > median	12.7	1.6–99.0	0.02
180-day mortality			
Extent score > median	8.8	2.3–33.7	0.002
Distal culprit lesion	3.1	1.0–9.4	0.04
3-year mortality			
Extent score > median	3.5	1.6–8.0	0.003

Angiographic extent score significantlty improved lower predictive value of TIMI Risk Score c=0.61-0.77, but not higher predictive value of GRACE RS c=0.79-0.89

Maciejewski P, Budaj A. Kardiol Pol 2013;71:1-7

Risk stratification/Risk scores

Practical applications

- selection of the site of care
- selection of therapy
- information for pts and relatives
- use in clinical research
- comparisons across institutions

GRACE Risk Model

Derived in 21 688 patients
Deaths:1046 in-hospital, 711 post discharge
Validated in 22 122 patients and in GUSTO IIb 12 142 patients

Variables predicting > 90% of the risk

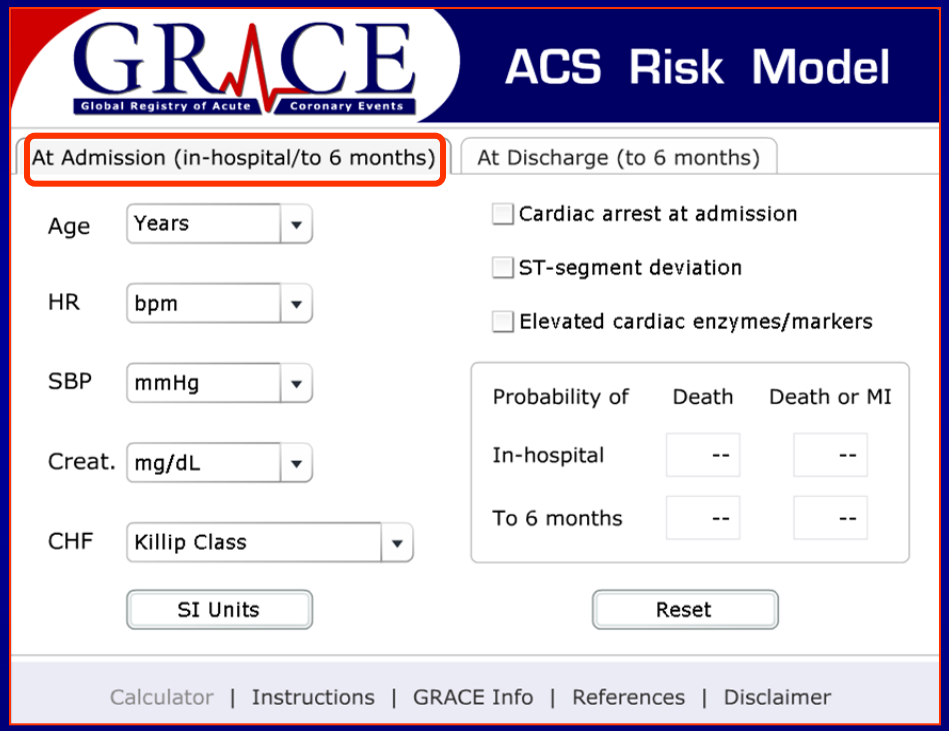
- Age (continuous)
- Killip class
- Low blood pressure
- ST deviation
- Cardiac arrest
- Elevated creatinine
- Elevated CK-MB or Tn
- Increased heart rate

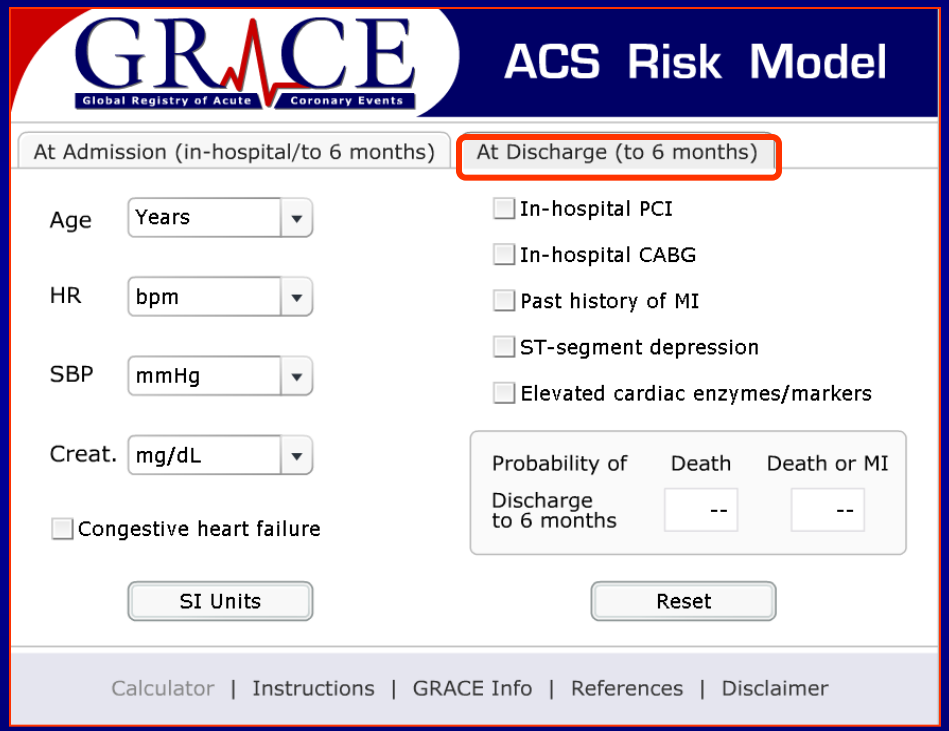
C-index = 0.84 death (in-hosp)

C-index = 0.82 death (6 months)

Granger Ch. Archives Int Med 2003;163;2345, Eagle K. JAMA 2004; 291: 2727
Fox KAA BMJ 2006;333:1091

GRACE Risk Score Calculator





www.outcomes.org/grace

Risk of death according to GRACE Risk Score

Risk category (tertile)	GRACE risk score	In-hospital death (%)
Low	≤108	<1
Intermediate	109–140	1–3
High	>140	>3
Risk category (tertile)	**GRACE risk score**	**Post-discharge to 6-month death (%)**
Low	≤88	<3
Intermediate	89–118	3-8
High	>118	>8

www.outcomes.org/GRACE

Selection of therapies according to ischemic risk in NSTEACS

Beneficial in high and intermediate risk groups

- early invasive strategy
- GP IIb/IIIa inhibitors
- ticagrelor, prasugrel vs clopidogrel

Beneficial in all risk groups

- clopidogrel

modifiable risk

CRUSADE Bleeding Risk Score

NSTEMI, 89 134 pts 80% derivation and 20% validation, in-hospital major bleeding

Predictor	score 0-100
• Baseline Ht	0-9
• Creatinine clearance	0-39
• Heart rate	0-11
• Female sex	8
• CHF	7
• Prior vascular disease	6
• Diabetes mellitus	6
• Systolic blood pressure	1-10

C-statistics 0.72

Risk	score	bleeding (%)
• Very low	<20	3.1
• Low	21-30	5.5
• Moderate	31-40	8.6
• High	41-50	11.9
• Very high	>50	19.5

Limitations

- Age and weight nonsignificant
- Lack of Hb, prior bleeding
- Only NSTEMI pts
- Pts excluded: UA, CABG, died within 48 h, transferred, on warfarin, early outpatient bleeding not captured

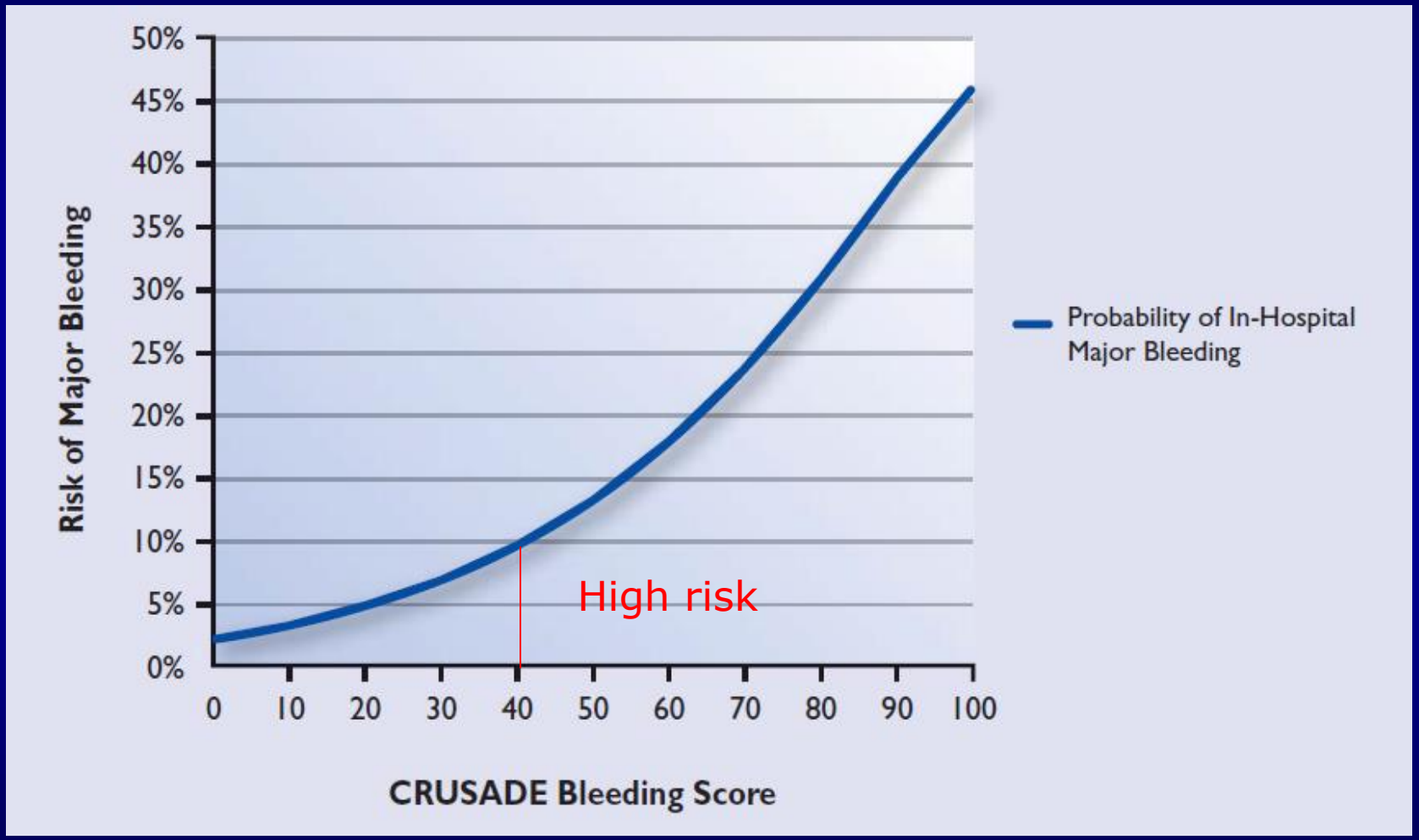
Subherbal S et al. Circulation 2009;119;1873

CRUSADE Bleeding Risk Score

Predictor	Score
Baseline haematocrit, %	
<31	9
31–33.9	7
34–36.9	3
37–39.9	2
≥40	0
Creatinine clearance,[a] mL/min	
≤15	39
>15–30	35
>30–60	28
>60–90	17
>90–120	7
>120	0
Heart rate (b.p.m.)	
≤70	0
71–80	1
81–90	3
91–100	6
101–110	8
111–120	10
≥121	11
Sex	
Male	0
Female	8
Signs of CHF at presentation	
No	0
Yes	7
Prior vascular disease[b]	
No	0
Yes	6
Diabetes mellitus	
No	0
Yes	6
Systolic blood pressure, mmHg	
≤90	10
91–100	8
101–120	5
121–180	1
181–200	3
≥201	5

ESC Guidelines NSTEACS Eur Heart J 2011

CRUSADE Bleeding Risk Score



ESC Guidelines NSTEACS Eur Heart J 2011

CRUSADE Bleeding Risk score

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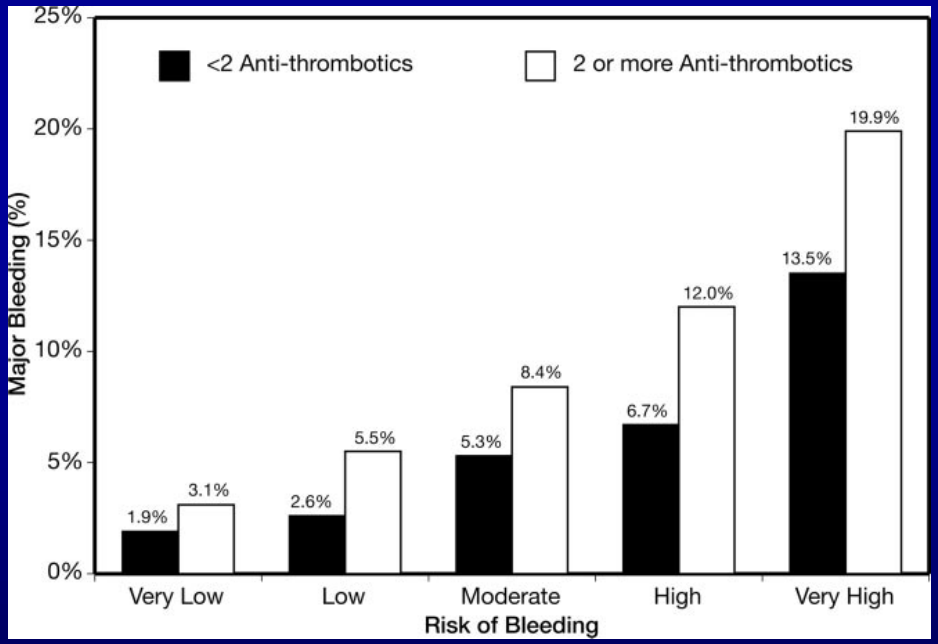
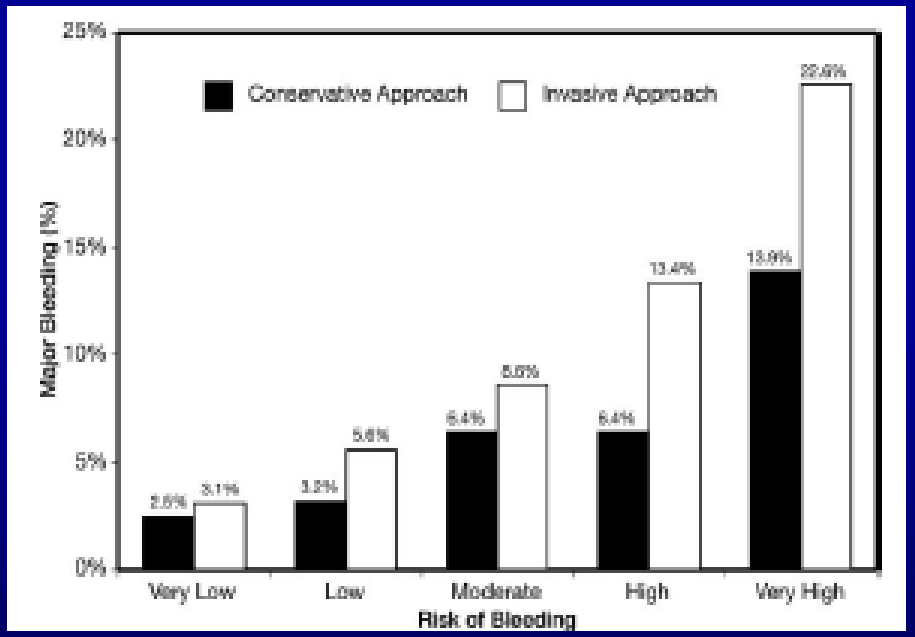
Major bleeding according to the category of risk of bleeding by treatment (<2 vs >=2 antithrombotics and conservative vs invasive approach)





Subherbal S et al. Circulation 2009;119;1873

Selection of therapies according to bleeding risk

High risk pts require the use of safer therapies

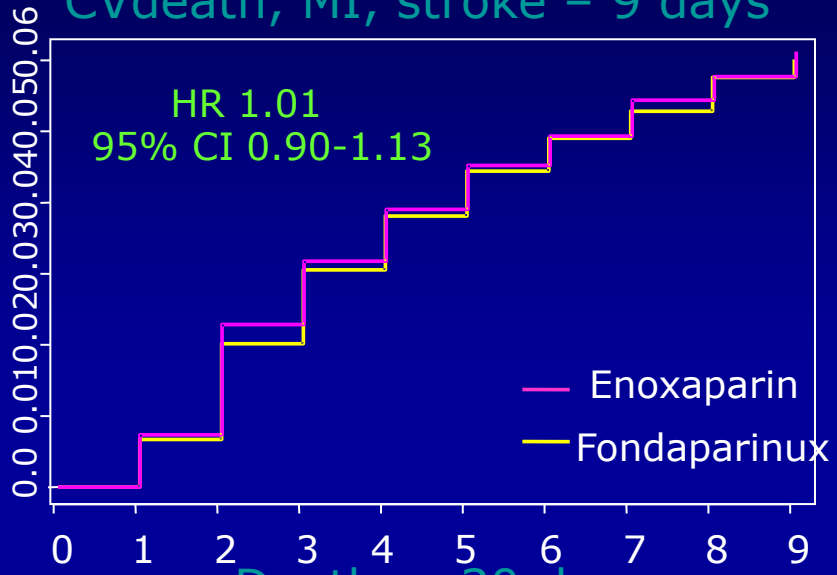
- fondaparinux,
- bivalirudin
- clopidogrel vs new antiplatelets
- lower doses of antithrombotic and antiplatelet drugs
- avoidance of GPIIb/IIIa inhibitors
- radial approach

modifiable risk

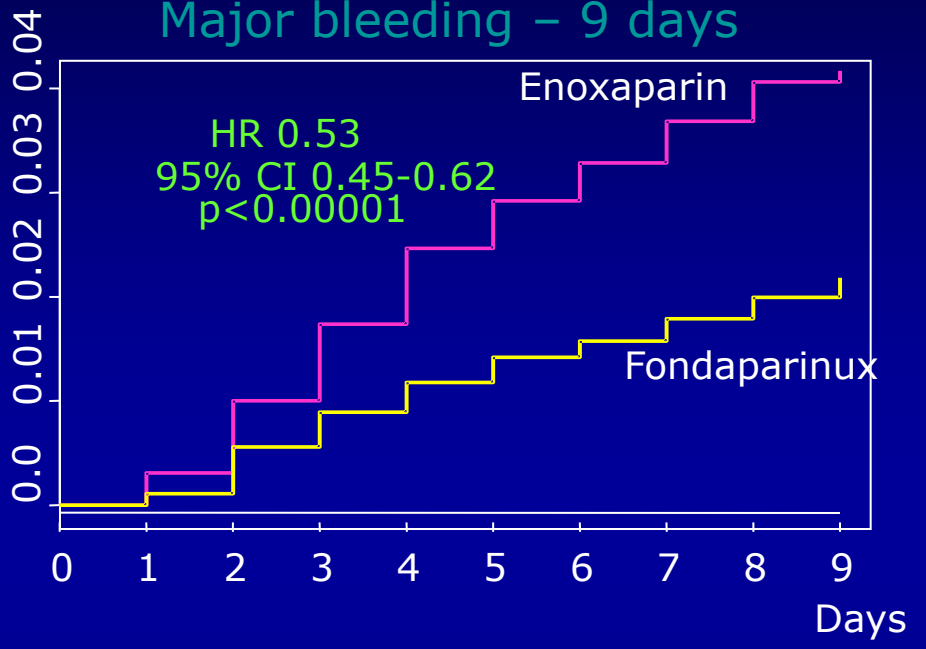
Fondaparinux in NSTEMI

n=20 000, NSTE ACS, fondaparinux vs enoxaparin

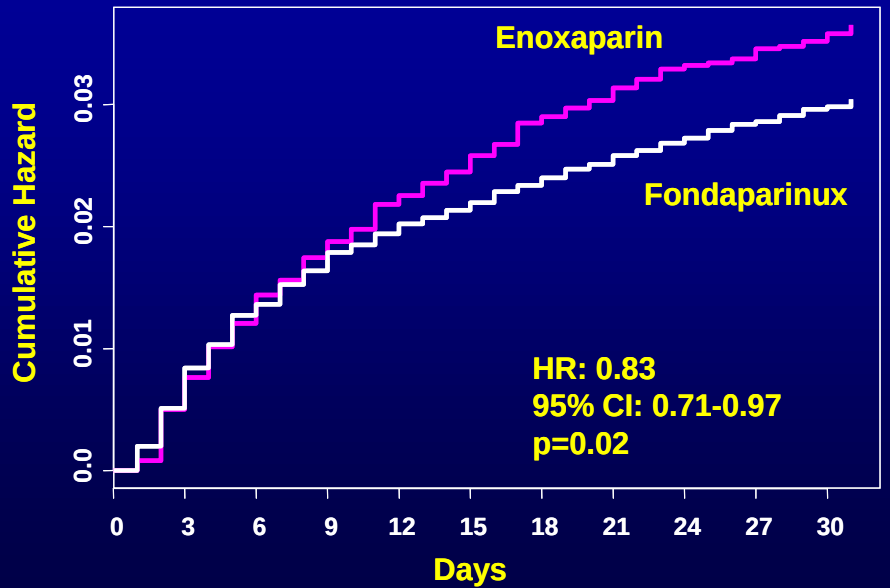
CVdeath, MI, stroke – 9 days



Major bleeding – 9 days



Death – 30 days



Fondaparinux

–

Reduction
bleeding 9 days 47%
deaths 30 days 17%

Yusuf S et al. OASIS 5 Invest, NEJM 2006;354:1-13

Common predictors of death and bleeding

- age
- female sex
- renal insufficiency
- baseline anemia
- heart rate
- blood presure
- heart failure
- DM

Integrated ischemic and bleeding risk score needed

RISK SCORES – potential advances

Specific additional outcomes

stroke, renal failure, stent thrombosis, vascular complications

Long term prognosis

GRS validated up to 7 years

Alternative approaches

Simple risk scores
3-5 factors, eg.: SRI age, HR, systolic pressure

Complex risk scores including biomarkers, angiographic data, echo data, arrhythmias, results of PCI or CABG, co-morbidities

Dynamic risk stratification

Continuous risk stratification including in-hospital events, eg: bleeding, transfusion, stroke, renal failure, heart failure, re-MI,

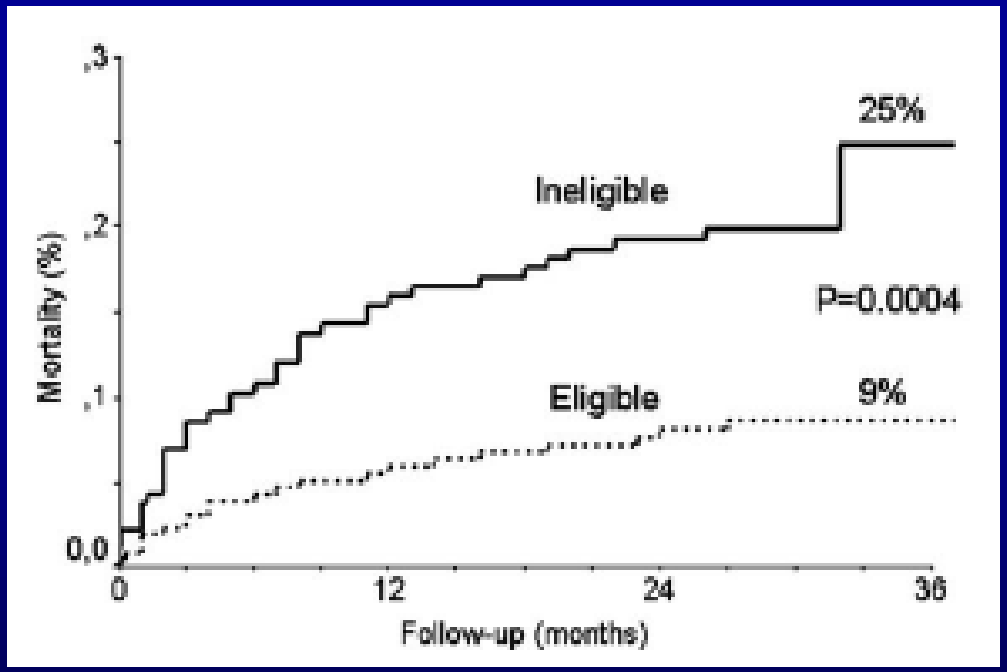
Practical application

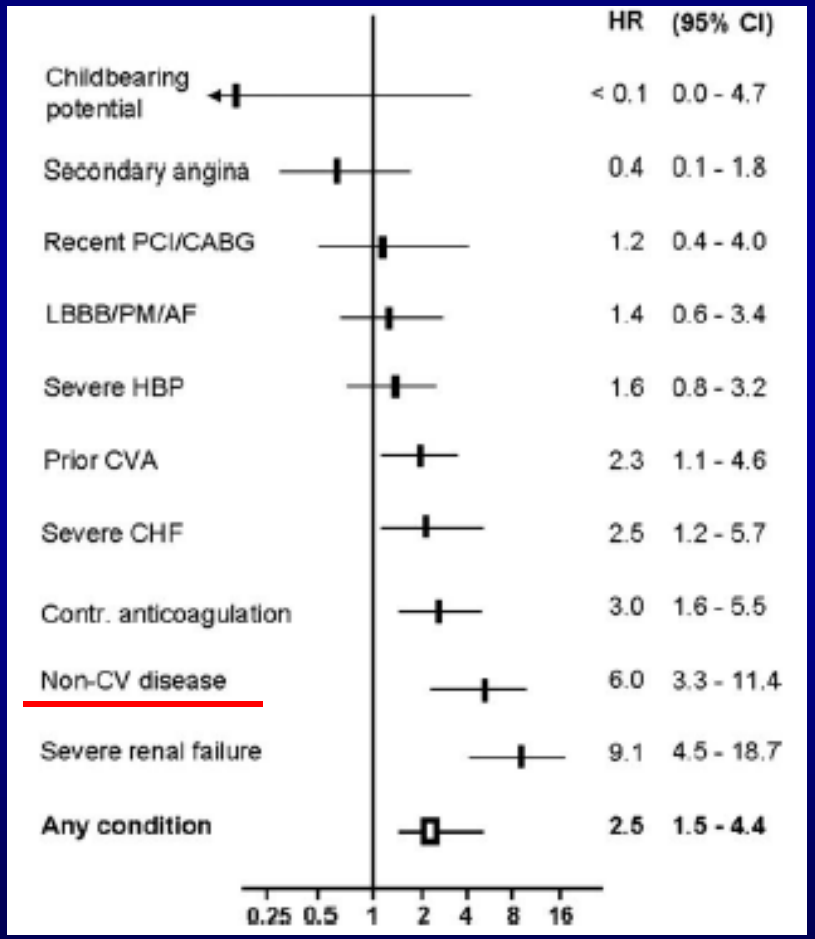
Handhold devices, phones, computers

Ineligibility in randomized controlled trials and prognosis

n=452 pts NSTE ACS with typical exclusion criteria in RCT

Mortality





Bosch X et al. Int J Cardiol 2008;124:86-91

Conclusions

- Bleeding carries as high risk of death as ischemic complications in ACS.
- Integration of ischemic and bleeding risk estimates as well as indices of co-morbidities and frailty into overall risk assessment warrants further studies.
- Ischemic and bleeding risk stratification, including risk scores, should be wider applied in clinical practise according to the guidelines.
- Dynamic and practical approach to risk stratification may improve its clinical relevance.

better use risk score, not only clinical judgement