

Cardiovascular risk assessment: Developing versus developed world

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Government**

Health

Disclosures

- **Research funding received**
 - Medical Research Council (MRC) South Africa
 - University of KwaZulu-Natal
 - South African Society of Anaesthesiologists
 - National Research Foundation
 - University of Cape Town
- **VISION (Vascular Events In Noncardiac Surgery) study**
 - Troponin kits- Roche Diagnostics
 - Over 50 grants internationally
- **MANAGE (Management of Myocardial Injury After NonCardiac SurGEry)**
 - Boehringer Ingelheim Trial funding, but importantly investigator independent trial
- **Meetings**
 - Teleflex, Smiths Aluta, Fresenius, GlobalSurg, RCS



Principles

- In the developing world
 - Perioperative cardiovascular events are important
 - Cardiovascular risk stratification guidelines are needed
 - Treatment of perioperative cardiovascular events must be prioritized

Myocardial injury after noncardiac surgery (MINS)

Clinical scenario

- Postop patient has mildly elevated troponins
- Clinical assessment is non-contributory
- Cardiologist 'clears' patient
- Patient is later discharged from hospital

Myocardial injury after noncardiac surgery (MINS)

- Develop diagnostic criteria based upon
 - assumption of shared pathophysiologyand
 - prognostic relevance (impact on 30-day mortality)



Botto et al. *Anesthesiology* 2014;120(3):564-78.



MINS diagnostic criteria

- Dependent variable – 30-day mortality
- Independent variables
 - Pre-op and surgical variables
 - Post op variables i.e. stroke, PE, DVT, pneumonia, sepsis, infection
 - Proposed MINS variables



Botto et al. *Anesthesiology* 2014;120(3):564-78.



MINS diagnostic criteria

Proposed MINS variables

post-op peak TnT ≥ 0.04 with clinical features

post-op peak TnT ≥ 0.04 without clinical features

post-op peak TnT ≥ 0.03

post-op peak TnT ≥ 0.02

MINS prognosis: 30 day mortality

	Incidence (%)	Adjusted HR (95% CI)	PAR (95% CI)
MINS (TnT \geq 0.03)	1200 (8.0)	3.9 (3.0-5.1)	34.0% (26.6-41.5)
Sepsis	812 (5.4)	7.2 (5.2-10)	30.5% (23.7-37.2)
Stroke	81 (0.5)	3.5 (2.1-6.0)	4.5% (1.3-7.8)
PE	95 (0.6)	6.1 (3.2-11.7)	3.5% (0.9-6.2)

PAR population attributable risk



MINS prognosis: 30 days

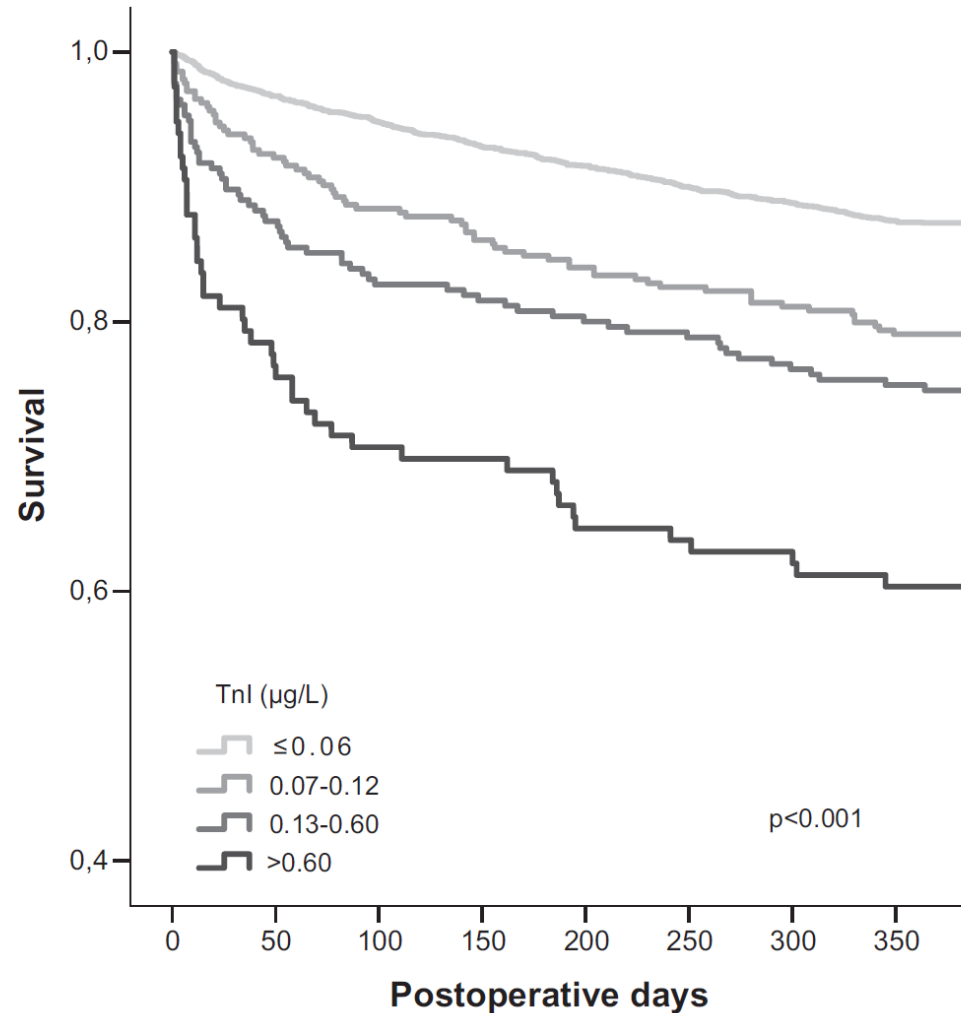
Outcome	No MINS n=13823	MINS patients n=1189	OR (95% CI)
Mortality	1.1%	9.8%	10.1 (7.8-12.9)
Cardiac arrest	0.06%	0.8%	14.6 (5.8-37)
CHF	1.0%	9.4%	10.3 (8.0-13.4)
Stroke	0.4%	1.9%	4.7 (2.9-7.6)
Composite	2.4%	18.8%	9.6 (8.0-11.5)

Postoperative troponins & prognosis

Peak troponin release	Vascular mortality (HR, 95% CI)	Nonvascular mortality (HR, 95% CI)
0.02ng/ml	1.7, 95% CI 0.7-3.7	2.6, 95% CI 1.5-4.4
0.03-0.29ng/ml	4.8, 95% CI 3.2-7.3	4.7, 95% CI 3.6-6.1
0.3ng/ml	10.1, 95% CI 5.3-18.9	7.7, 95% CI 4.4-13.3



MINS prognosis: 1 year



26% 1 year mortality



MINS is relevant in the developing world

- No subgroup effect in VISION
- Groote Schuur Hospital elective surgery MINS: 4.9%, 95% CI 2.8-8.5



1. The VISION Study Investigators. JAMA 2012; 307: 2295-2304
2. Coetzee et al. S Afr Med J 2018; 108: 408-12

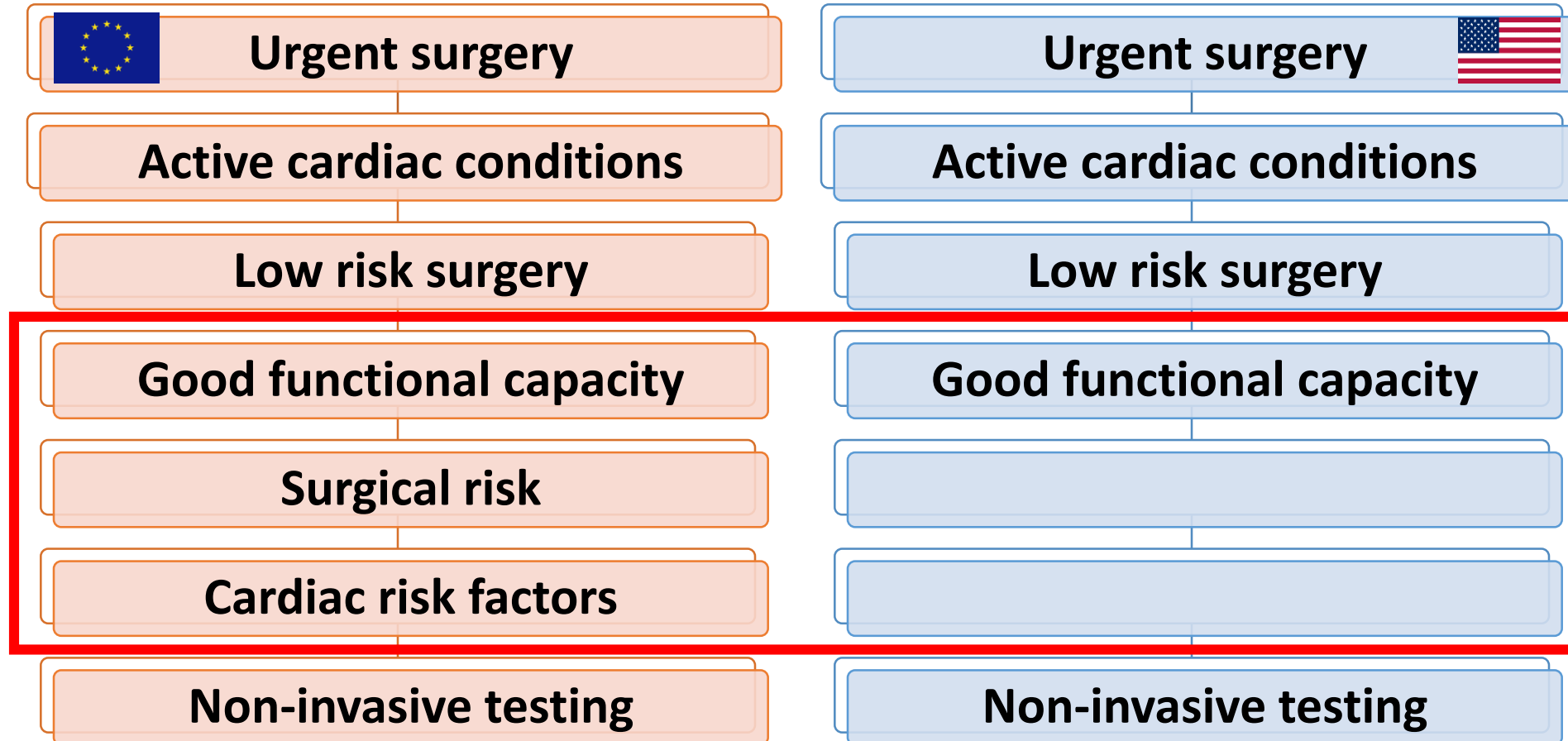


Diagnostic criteria for MINS: 5th gen hsTnT

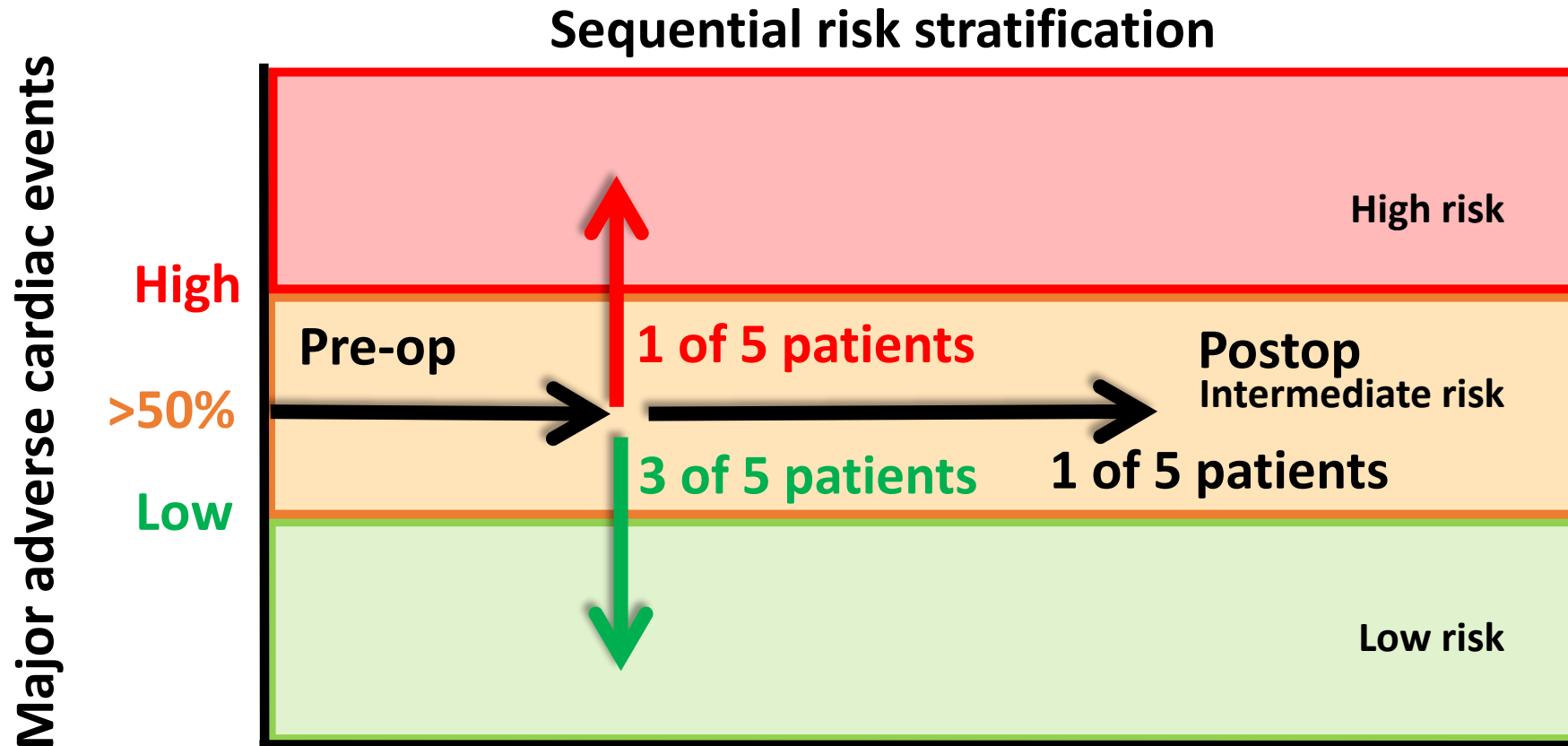
	hsTnT Thresholds, ng/L					
	<5	5 to <14	14 to <20	20 to <65	65 to <1000	≥1000
Patients, No. (%)	5318 (24.4)	8750 (40.1)	2530 (11.6)	4049 (18.6)	1118 (5.1)	54 (0.2)
Deaths, No. (%)	6 (0.1)	40 (0.5)	29 (1.1)	123 (3.0)	102 (9.1)	16 (29.6)
Adjusted hazard ratio (95% CI)	1 [Reference]	3.73 (1.58-8.82)	9.11 (3.76-22.09)	23.63 (10.32-54.09)	70.34 (30.60-161.71)	227.01 (87.35-589.92)
P Value		.003	<.001	<.001	<.001	<.001

Identifying patients at risk of MINS needs to be a priority

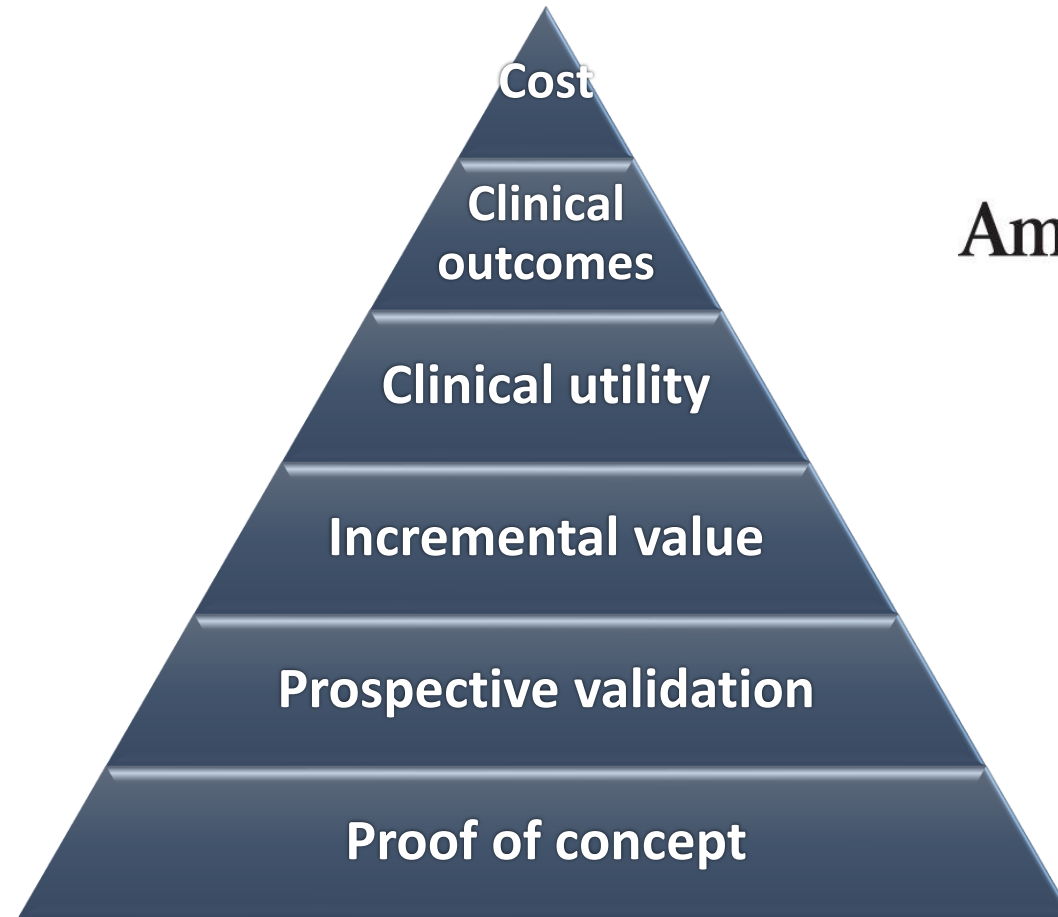
ESC vs AHA algorithms



Current state of perioperative risk stratification



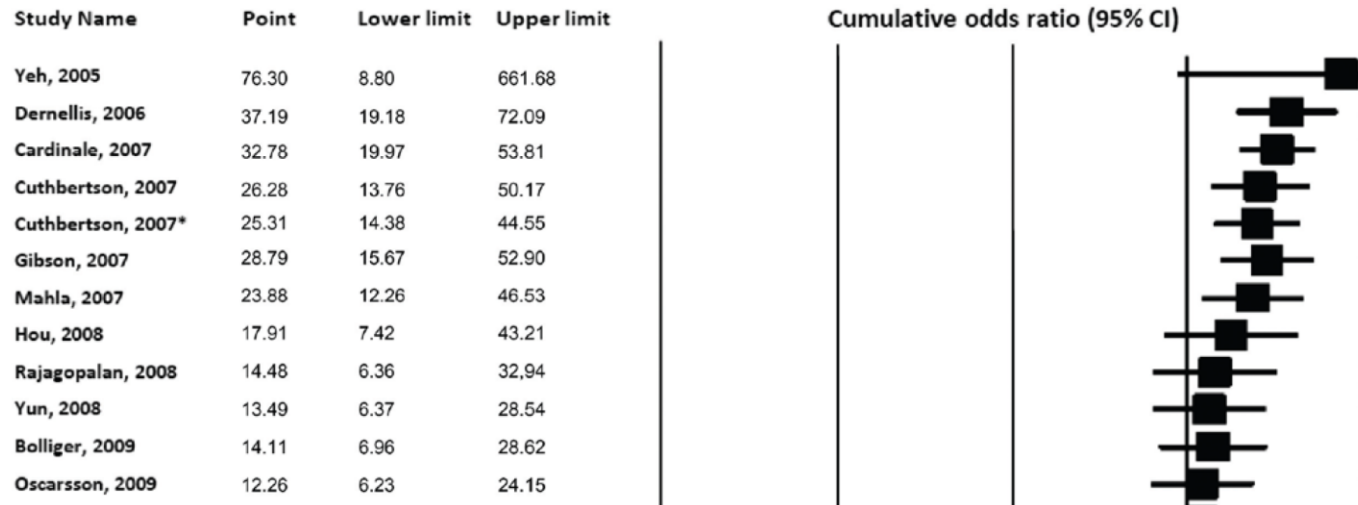
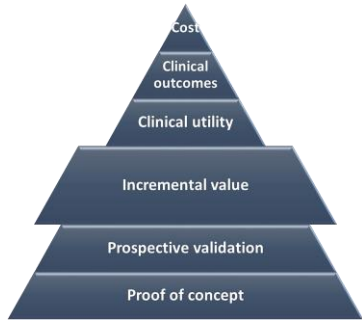
Integrating biomarkers into clinical practice



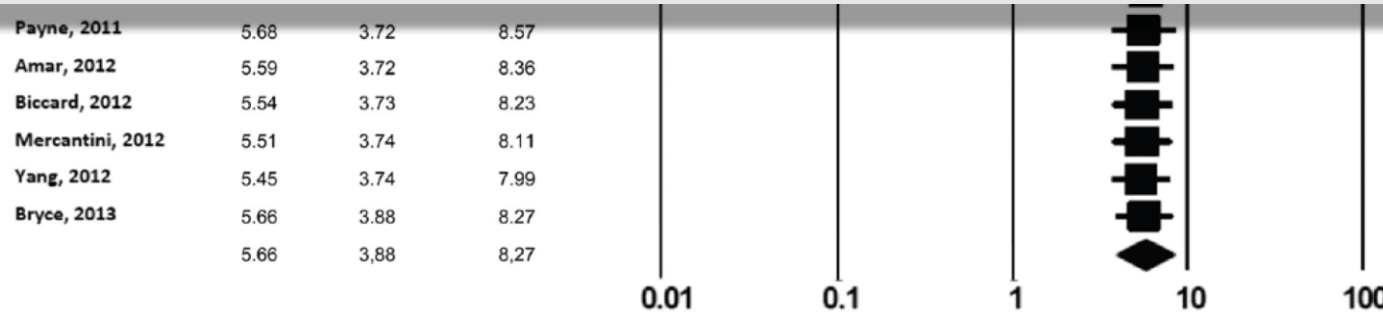
Hlatky et al. *Circulation* 2009; 119: 2408-16



Preoperative B-type NPs & incremental value



Conclusions: Further studies aiming only to demonstrate an association between a preoperative natriuretic peptide threshold and the risk of postoperative adverse cardiac events are not justified. Future investigation should focus on the clinical implications of these data and the application of these findings with regard to further investigation, optimisation and appropriate adaptation of perioperative management.

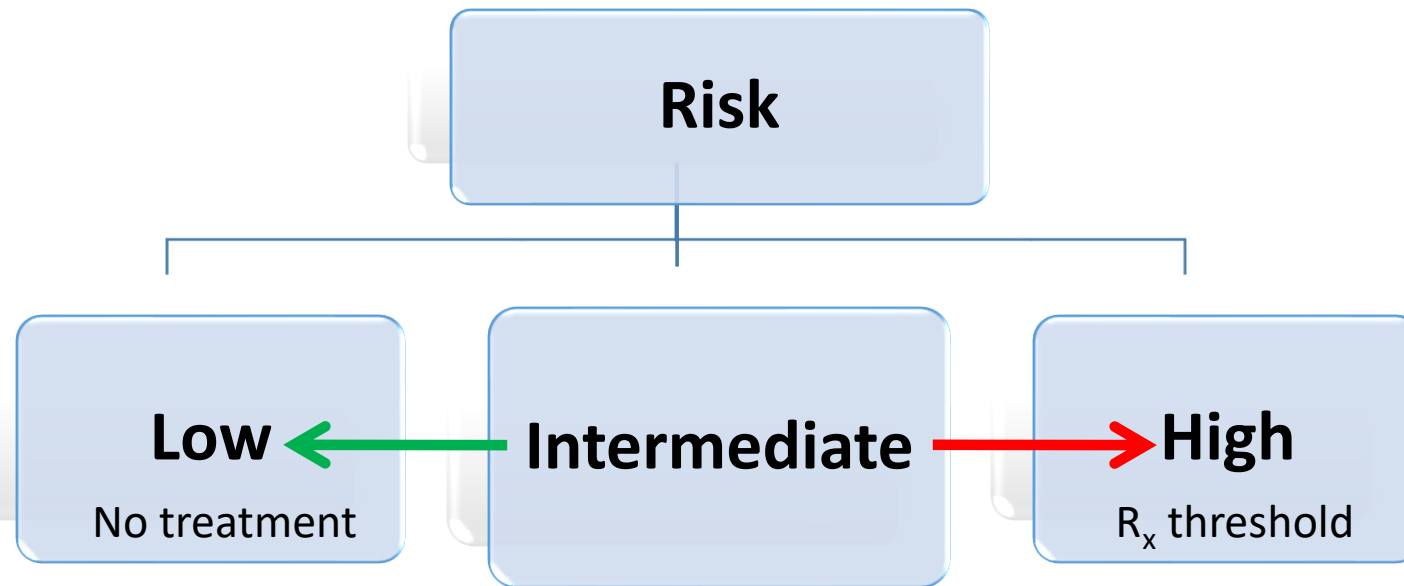
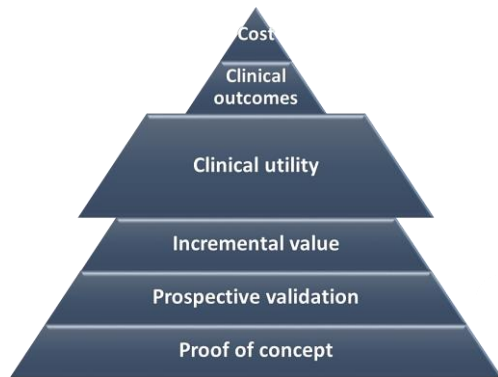


Ryan et al. South Afr J Anaesth Analg 2015; 21 (4): 12-22



Preoperative B-type NPs & clinical utility

- **Clinical utility and net reclassification improvement (NRI)**
- NRI= proportion of patients with and without events correctly reclassified



Preoperative B-type NPs & clinical utility

RCRI risk category	RCRI stratification	
	MACE	Total (n)
Low	5.9%	320
Intermediate	9.5%	476
High	20.4%	54

NRI 84%, p<0.001

MACE major adverse cardiac events

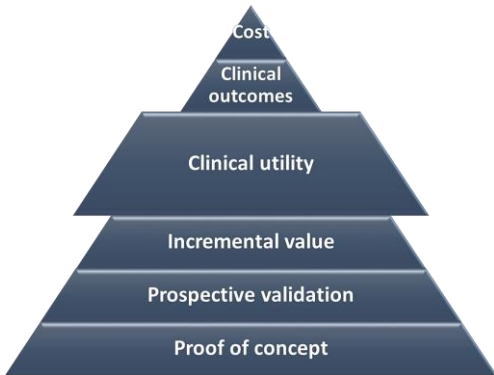


Preoperative B-type NPs & clinical utility

**B-type natriuretic
risk stratification**

**Net reclassification
improvement (NRI)
in
*vascular surgery***

**NRI
in
*all noncardiac
surgery***



Overall

58%

32%

Intermediate risk

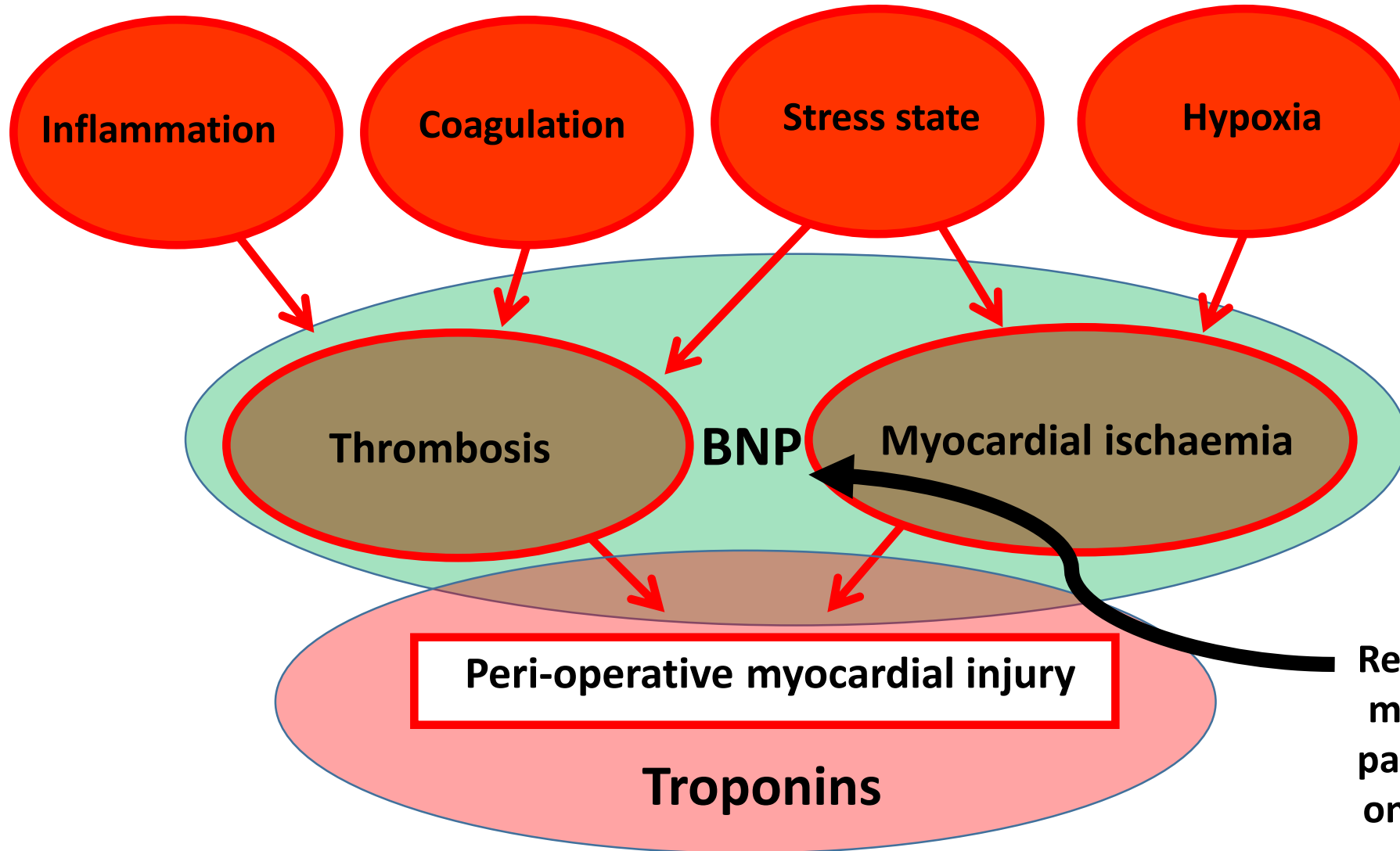
84%

59%

MACE major adverse cardiac events

Rodseth et al J Am Coll Cardiol 2011; 58: 522-9
Rodseth et al. J Am Coll Cardiol 2014; 63(2): 170-80





Reflects numerous myocardial injury pathways (and not only heart failure)

Risk stratification with B-type natriuretic peptides

Preoperative

BNP	92ng/ml	
NT-proBNP	300ng/ml	

Below these thresholds MACE is approximately 5% in major noncardiac surgery



Rodseth et al. *Anesthesiology* 2013;119(2):270-83
Rodseth et al. *J Am Coll Cardiol* 2014;63(2):170-80



Reservations concerning functional capacity

Table 1. Overall Net Reclassification Improvement for Myocardial Infarction and Cardiac Arrest When Totally Independent Functional Status Is Used, Based on the Model by Gupta et al.⁶

Risk reclassification using functional capacity			Percentage reclassified as:		Net correctly reclassified (%)	Net reclassification improvement (%)
Lower risk	Baseline	Higher risk	Lower risk	Higher risk		
Patients with myocardial infarction and cardiac arrest						
788 ^b	1371	583 ^a	57.5%	42.5%	-15%	
Patients without myocardial infarction and cardiac arrest						71.6%
195,924 ^a	210,039 ^b	14,115 ^b	93.3%	6.7%	86.6%	

^aImproved classification.

^bWorse classification.

Functional capacity reclassification Per 1000 patients

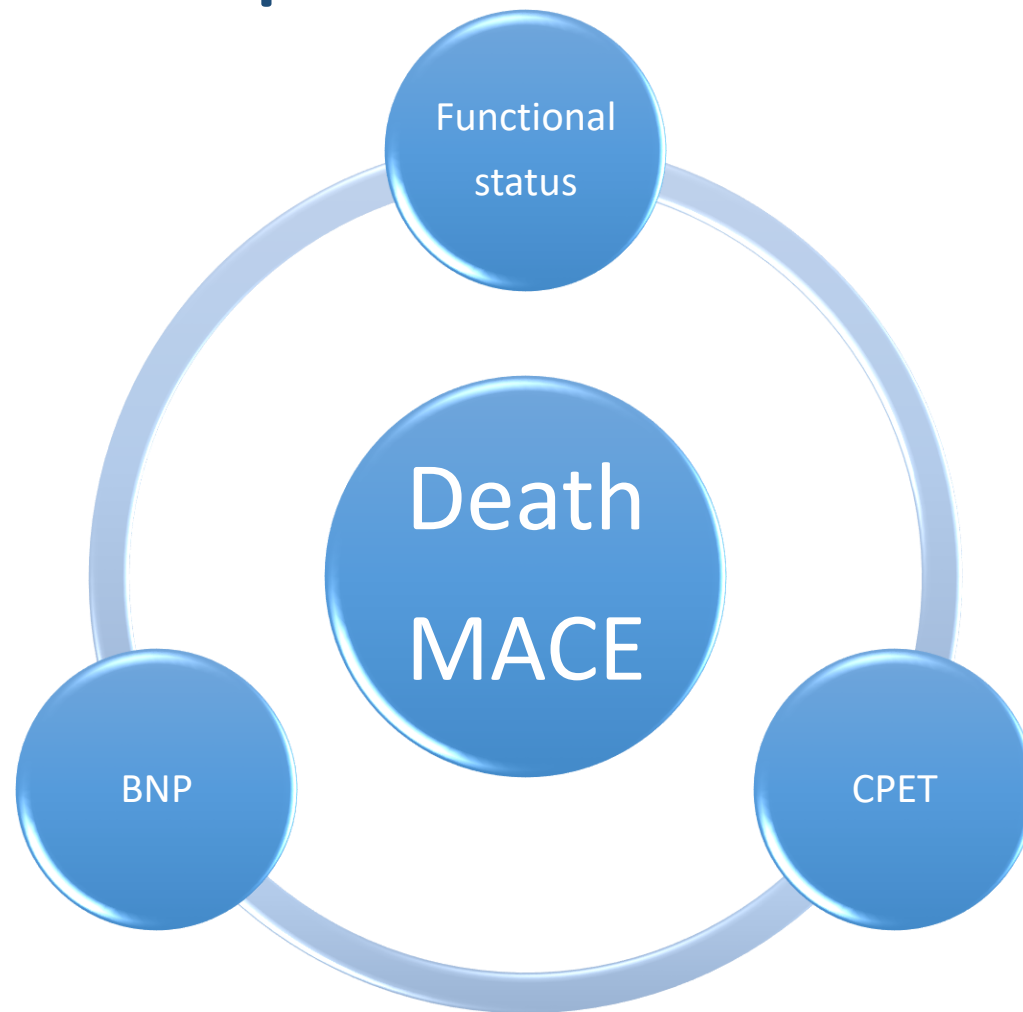
Adverse events avoided -1 per 1000

Extra investigation 64 per 1000

Biccard BM. Anes Analg 2015; 120: 543-553



METS: Relationship between function, BNP, CPET



METS results

Adjusted odds ratio (95% CI)

30-day death or myocardial infarction

Baseline model‡

Plus peak oxygen consumption	0.90 (0.71–1.16; p=0.45)§
Plus AT	0.96 (0.66–1.41; p=0.84)§
Plus DASI	0.91 (0.83–0.99; p=0.03)§
Plus NT PRO-BNP	1.88 (0.89–3.96; p=0.09)¶

30-day death or myocardial injury

Baseline model||

Plus peak oxygen consumption	1.03 (0.92–1.14; p=0.62)§
Plus AT	1.12 (0.96–1.31; p=0.16)§
Plus DASI	0.96 (0.92–0.99; p=0.05)§
Plus NT PRO-BNP	1.78 (1.21–2.62; p=0.003)¶



Current state of perioperative risk stratification

- **ACC/AHA Guidelines;**

*“These studies and... meta-analyses suggest that biomarkers may provide **incremental predictive value**...”*



Fleisher LA et al. J Am Coll Cardiol 2014;64(22):e77-137.
doi: 10.1016/j.jacc.2014.07.944.



Current state of perioperative risk stratification

- **Canadian Cardiovascular Society Guidelines;**

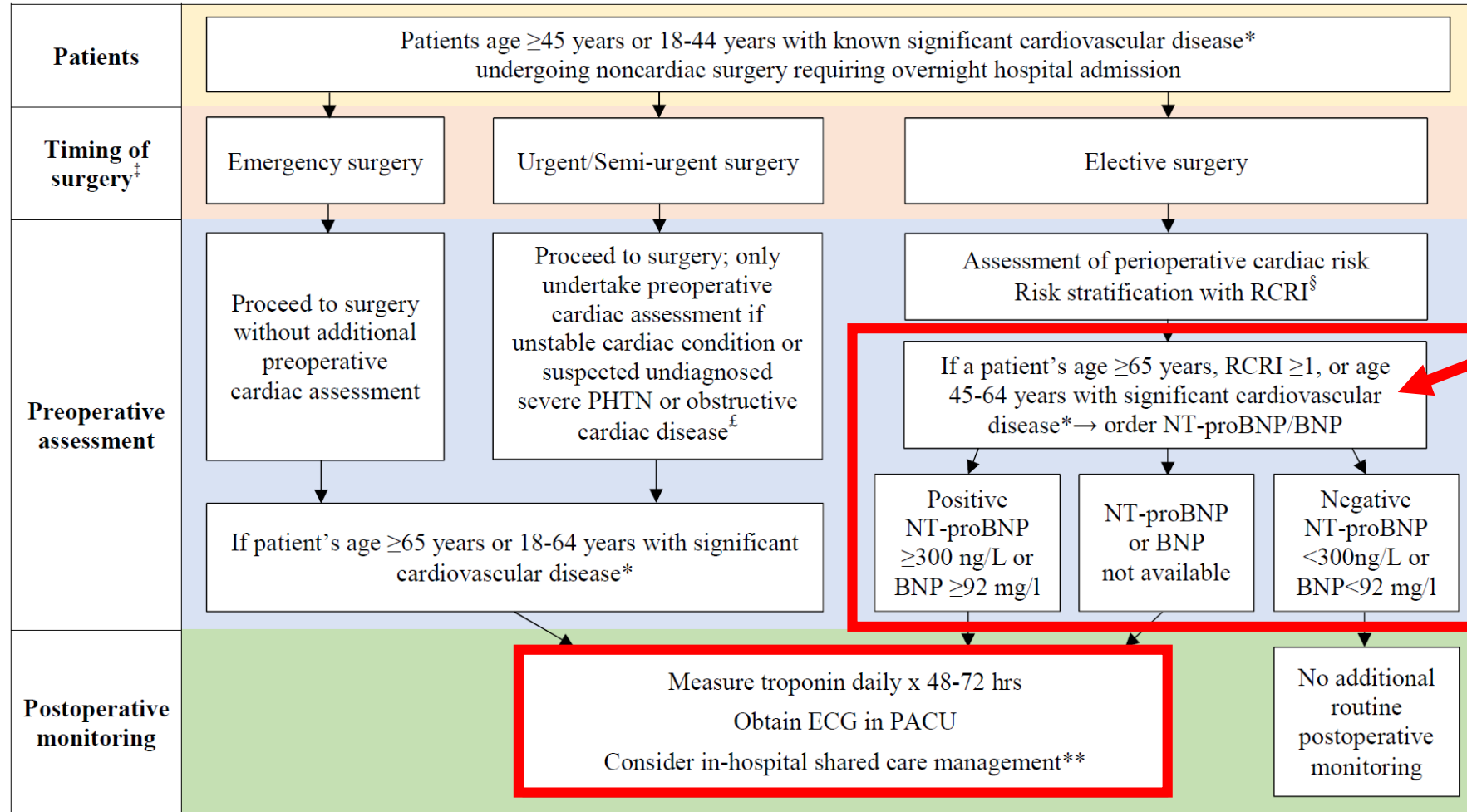
*“These studies and... meta-analyses suggest that biomarkers **do** provide **clinical utility**...”*

Current state of perioperative risk stratification

- **Canadian Cardiovascular Society Guidelines;**

*“These studies and... meta-analyses suggest that biomarkers **do provide clinical utility above subjective functional assessment**”*

Canadian Cardiovascular Society Guidelines



>5% risk of MACE



What does this mean for the developing world?

- **Guidelines**

- International disagreement
- We need our own guidelines
- Must be built on feasibility

Treating MINS needs to become a priority



Obstacles to treating MINS: troponin screening

- ESC/ESA algorithm

Assessment of cardiac troponins in high-risk patients, both before and 48–72 hours after major surgery, may be considered.	IIb	B	3,48,49
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Would you accept a 10% 30 day and 26% 1 year mortality where the predictors are asymptomatic in 85% of patients?

Obstacles to treating MINS: medical intervention

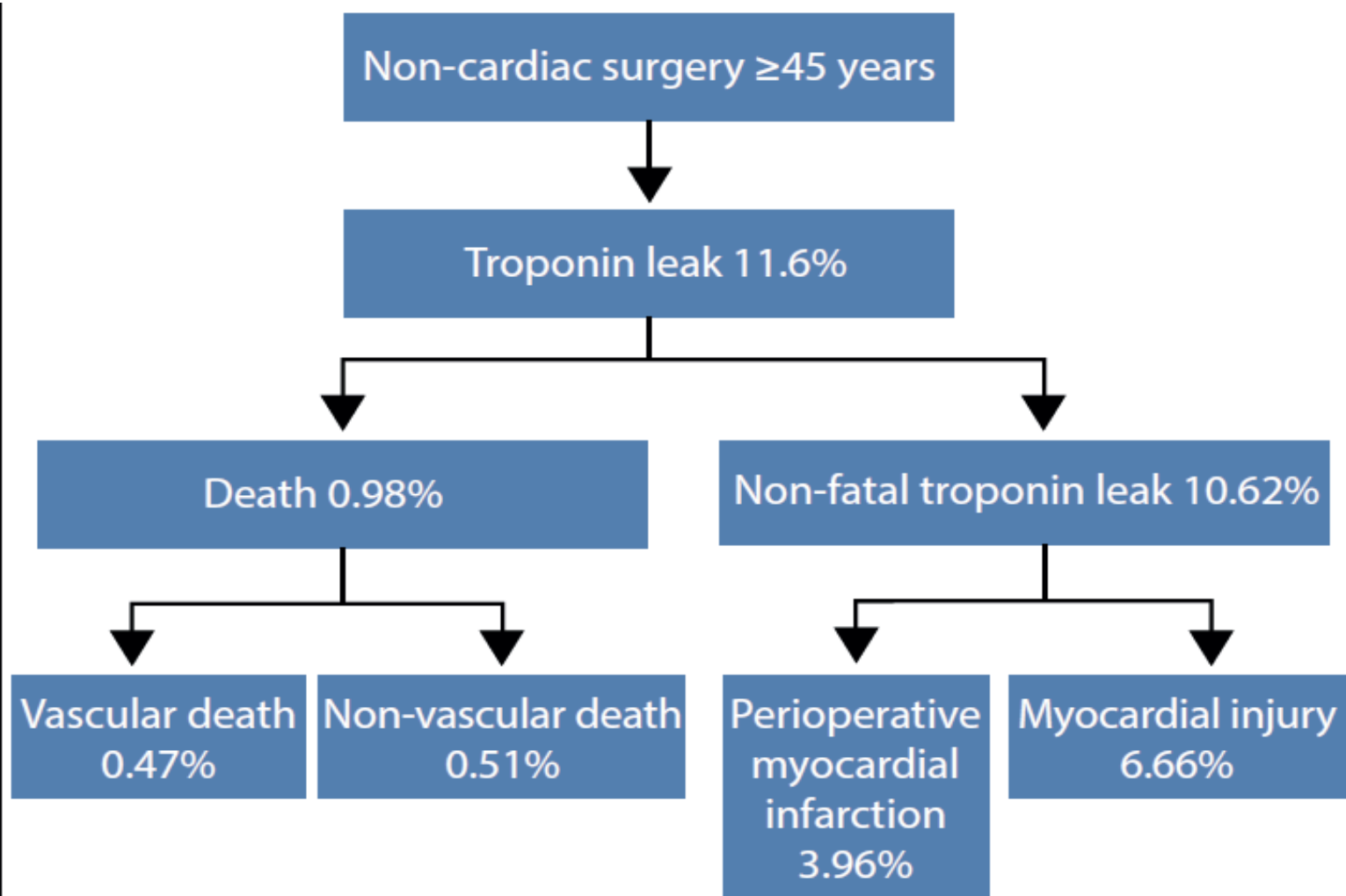
Suspected aetiology of MINS	Diagnosis of PMI	Intervention
All patients (100%)	7.9%	38.3%
Predisposing cardiac conditions (41%)	100%	65%
Perioperative triggers (28%)	39%	41%
Not specified (43%)	0%	18%

Treating MINS: simple interventions

Aspirin 0.54 (95% CI 0.29-0.99)

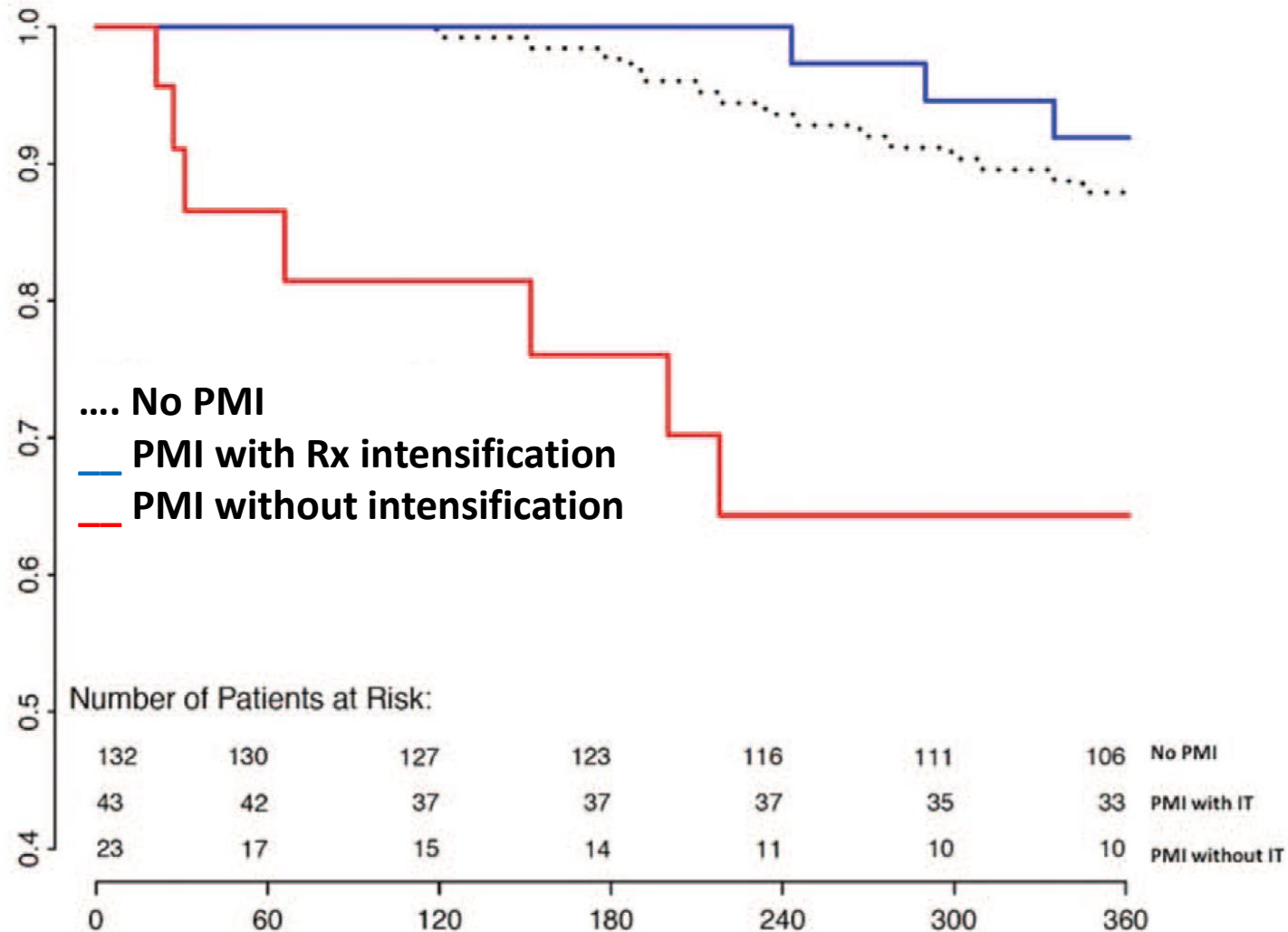
Statin 0.26 (95% CI 0.13-0.54)

Treating MINS: potentially cost-effective



Torborg et al. S Afr Med J 2014; 104 (9): 619-23

Treating MINS: optimisation of medical therapy



Foucrier A et al. Anesth Analg 2014;119(5):1053-63.



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Treating MINS: the way forward

- Difficult clinical environment
 - Silent
 - Financial concerns regarding troponin screening
 - There are reservations about the diagnosis of MINS and its implications
 - Therapy is difficult in the postoperative patient
- Positives
 - Simple therapies which are potentially cost-effective
- Requires urgent research

Treating MINS: Dabigatran

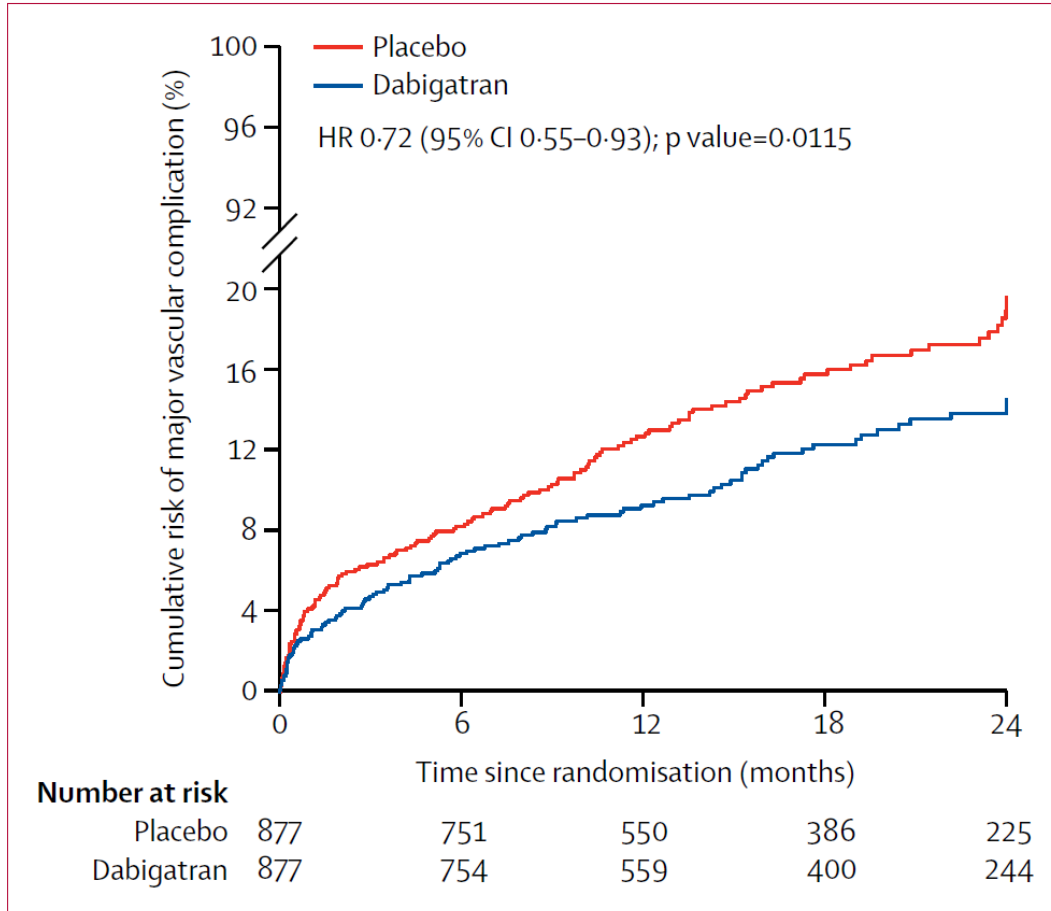


Figure 2: Kaplan-Meier estimates of the primary efficacy outcome
HR=hazard ratio.

Devereaux PJ, et al Lancet 2018;391(10137): 2325-2334.



Bruce Biccard @BruceBiccard · Jun 9

1. MINS is certainly not only an intra-coronary disease. For my views see; The pathophysiology of peri-operative myocardial infarction - Biccard - 2010 - Anaesthesia - Wiley Online Library onlinelibrary.wiley.com/doi/abs/10.1111... #flow #platelets #coagulation #demand #microvascular

1 2 1



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2. Dabigatran drove done both arterial and venous components of the MANAGE primary outcome (Table 2 (NB) and supplementary material). The pathophysiology in point 1 above, is likely systemic, hence anticoagulation may have broader benefits than 'just the heart', (Table 2)

1 1 1



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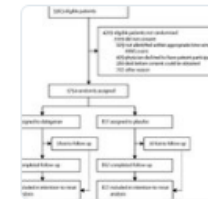
3. Difficult area of research; i) patients probably more concerned about surgical pathology than MINS (which is predominantly asymptomatic) hence high non-compliance. ii) doctors scared of bleeding, hence difficulty in recruitment. But now MANAGE evidence suggests benefits >> risks

2 1 1



Bruce Biccard @BruceBiccard · Jun 9

4. Conclusion. Patients with MINS should get statin, aspirin, and anticoagulation should be considered as a potentially important part of the proposed management strategy. #MANAGE



Dabigatran in patients with myocardial injury after ...

Among patients who had MINS, dabigatran 110 mg twice daily lowered the risk of major vascular complications, with no significant increase in major bleeding. Patients... thelancet.com

1 1 2



Rupert Pearce @rupert_pearce · Jun 9

....how long for?

2 1



Bruce Biccard @BruceBiccard · Jun 10

I am not sure how long one should continue anticoagulation after #MINS, but if background cardiovascular protection from anticoagulation extends out to just over a year, I would think that maybe this should be the minimum. #MANAGE



Summary

- In the developing world
 - Perioperative cardiovascular events are important
 - Cardiovascular risk stratification guidelines are needed
 - Treatment of perioperative cardiovascular events must be prioritized