A CLUSTER RANDOMIZED TRIAL OF OBJECTIVE RISK ASSESSMENT VERSUS STANDARD CARE FOR ACUTE CORONARY SYNDROMES

David B. Brieger MBBS, MMed, PhD, FESC

On behalf of the Australian GRACE Risk Intervention Study (AGRIS) investigators

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HEALTH SYSTEMS RESEARCH

Declaration of interest

- Research contracts (Sanofi Aventis, Astra Zeneca)
- Consulting/Royalties/Owner/ Stockholder of a healthcare company (BMS/Pfizer, Aspen Pharmaceuticals, Boehringer Ingelheim)

BACKGROUND

- Assessing risk and weighing the potential benefits of therapies is an essential clinical process for optimizing care for acute coronary syndromes (ACS)

- Routine use of objective risk scores, such as the Global Registry of Acute Coronary Events (GRACE) score, is strongly advocated in international guidelines

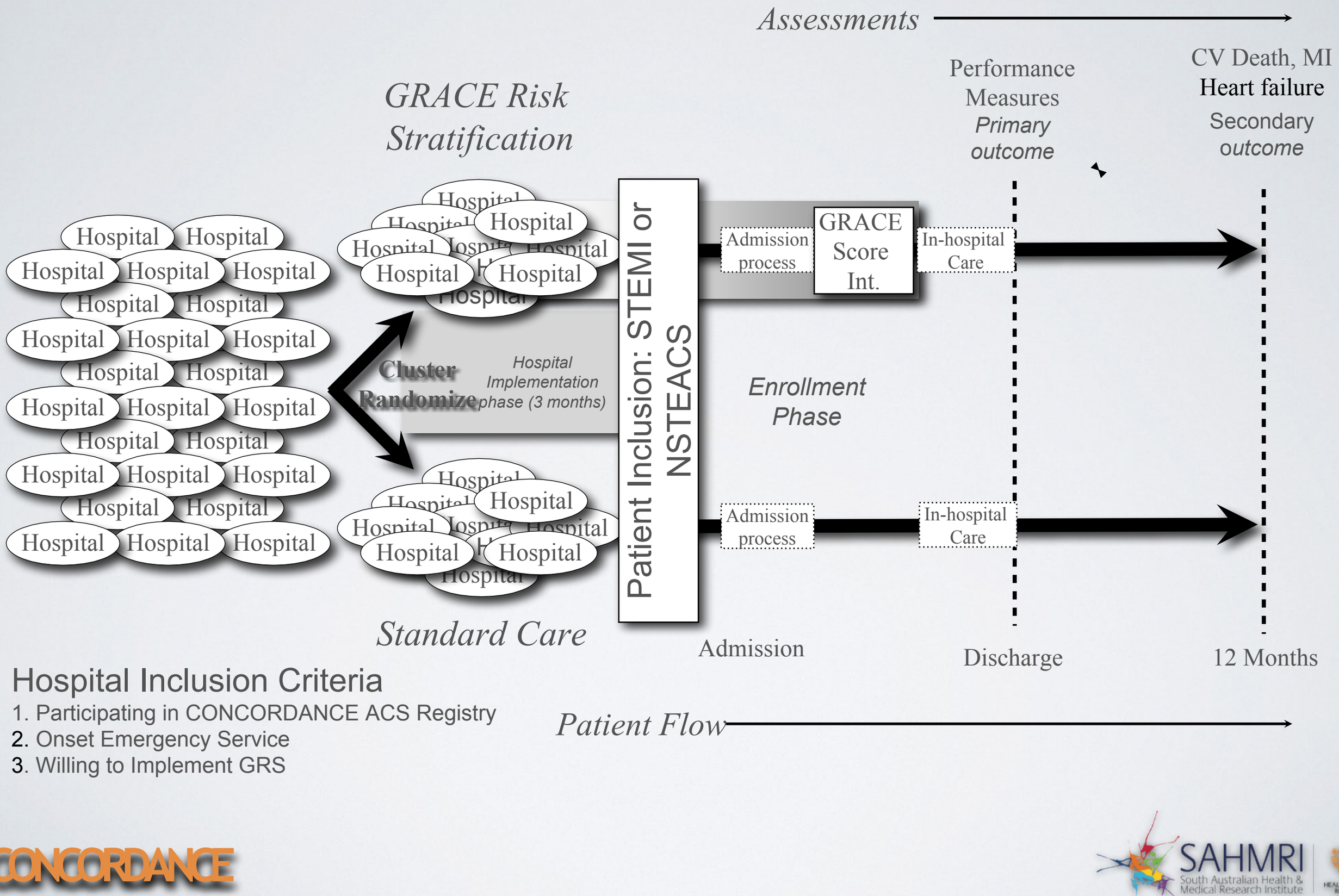
- The value of the GRACE risk score (GRS) in improving care and outcome has not been prospectively tested

AGRIS HYPOTHESES

- **Primary:** Objective risk stratification and simple decision support using the GRACE Risk Score improves hospital adherence with evidence based treatment among high risk ACS patients.

- **Secondary:** Objective risk stratification and simple decision support using the GRACE Risk Score results in a reduction in cardiac death, recurrent myocardial infarction or worsening heart failure among high risk ACS patients at 12 months

AGRIS STUDY SCHEMATIC



Hospital Inclusion Criteria

1. Participating in CONCORDANCE ACS Registry
2. Onset Emergency Service
3. Willing to Implement GRS

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STUDY ORGANISATION

- **Data Collection**

Australian CONCORDANCE ACS Registry (Pragmatic Clinical Trial)

- **Consent**

Organisational Consent (for AGRIS intervention)
Patient level opt out consent (for data collection and follow-up)

- **Funding**

Astra Zeneca Investigator Sponsored Research Grant

- **International Design**

Study design was developed collaboratively with investigators running companion studies in the UK and Canada

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AGRIS STUDY: SAMPLE WORKSHEET

Hospital Name

AGRIS Study Worksheet Page 1

URN: 012345678
SURNAME
First Name
DOB: 01/02/34

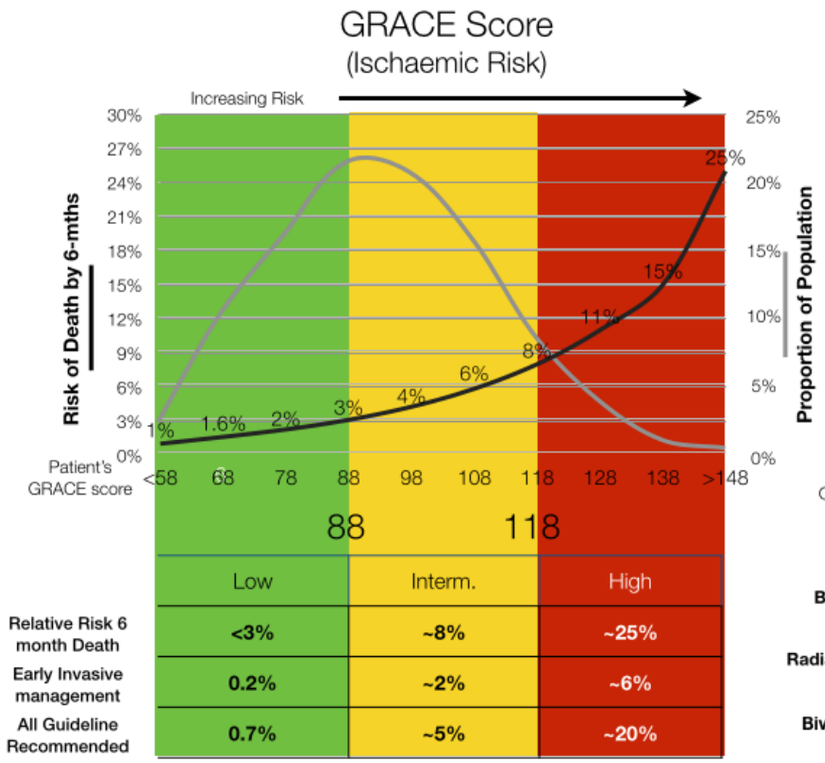
Step 1: Use the following table to calculate patient's GRACE Risk Score and CRUSADE Bleeding Risk Score

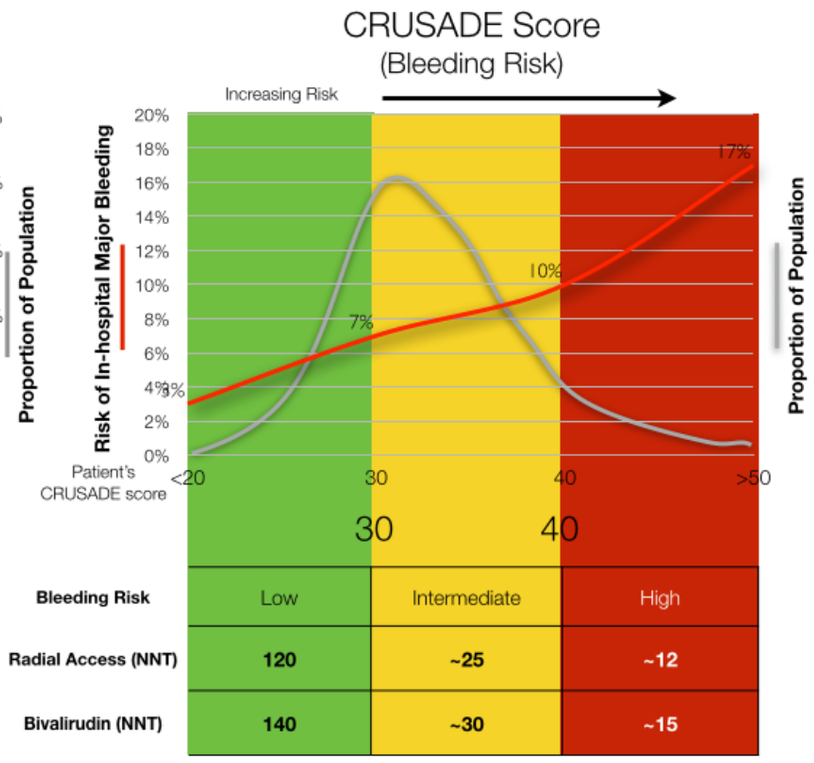
Age (years)	points	Patient
<40	0	
40-49	18	
50-59	36	
60-69	55	
70-79	73	
80+	91	
HR (bpm)	**points**	
<70	0	
70–89	7	
90–109	13	
110–149	23	
150–199	36	
>200	46	
SBP (mmHg)	**points**	
<80	63	
80–99	58	
100–119	47	
120–139	37	
140–159	26	
160–199	11	
>200	0	
Creatinine (umol/L)	**points**	
0–34	2	
35–70	5	
71–105	8	
106–140	11	
141–176	14	
177–353	23	
≥354	31	
Clinical	**points**	
Killip Class I	0	
Killip Class II	21	
Killip Class III	43	
Killip Class IV	64	
ST Deviation	30	
Troponin (+)	15	
Cardiac Arrest	43	
GRACE Score		

Base Hct%	points	Patient
<31	9	
31-33.9	7	
34-36.9	3	
37-39.9	2	
≥40	0	
eGFR (ml/min)	**points**	
≤15	39	
>15-30	35	
>30-60	28	
>60-90	17	
>90-120	7	
>120	0	
Heart Rate (bpm)	**points**	
≤70	0	
71-80	1	
81-90	3	
91-100	6	
101-110	8	
111-120	10	
>120	11	
SBP (mmHg)	**points**	
≤90	10	
91-100	8	
101-120	5	
121-180	1	
181-200	3	
>200	5	
Clinical	**points**	
Female	8	
CCF	7	
Vasc Disease	7	
CRUSADE		

Notes on using scores:
- Use heamodynamic characteristics at the time of presentation
- Killip Class I= Clear lung fields,
- Killip Class II= Crepitations in lower ones
- Killip Class III= Creps in the Upper Zones
- Killip Class IV: Pulmonary Oedema or Cardiogenic Shock
- ST deviation= ST elevation or Depression >1mm
- STEMI and NSTEMI in Bleeding score are mutually exclusive. Score STEMI if there is any ST elevation.

Step 2: Use the nomograms below to estimate the patient specific risk and estimated benefit from guideline recommended therapies





ARR: Absolute Risk Reduction in 6 month death associated with provision of therapy

The GRACE Score is: .....

The Risk Strata is: (circle one)

- Low (≤88)
- Intermediate (89-118)
- High (>118)

The CRUSADE Score is: .....

The Risk Strata is: (circle one)

- Low (≤30)
- Intermediare (31-40)
- High (>40)

Hamm CW, Bassand JP, Agewall S, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. European Heart Journal. 2011;32:2999–3054.

Fox KAA, Dabbous OH, Goldberg RJ, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). BMJ. 2006;333:1091–1091.

Subherwal S, Bach RG, Chen AY, et al.. Baseline Risk of Major Bleeding in Non-ST-Segment-Elevation Myocardial Infarction: The CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) Bleeding Score. Circulation. 2009;119:1873–1882.

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AGRIS STUDY: SAMPLE WORKSHEET

Hospital Name

AGRIS Study Worksheet Page 2

Please File in Medical Record

URN: 012345678
SURNAME
First Name
DOB: 01/02/34

Step 3: Specific recommendations to consider based on scores

Step 4: Confirm intended therapies
Please tick (✓) intended utilisation for guideline recommendations below

LOW	INTERMEDIATE	HIGH	Commentry	Intended	Not Intended	Contra-indicated(Please state reason)
Aspirin	Aspirin	Aspirin	Unless contraindicated, allergy, high bleeding risk			
Ischaemia testing			Reserve for low risk			
	Clopidogrel or Ticagrelor with aspirin	Clopidogrel or Ticagrelor with aspirin	Initiate soon after establishing diagnosis			
	Prasugrel with aspirin	Prasugrel with aspirin	May consider in Primary PCI for STEMI, and NSTEACS for undergoing PCI			
	Low molecular weight heparin or UF heparin	Low molecular weight heparin or UF heparin	Consider in patients with biomarker elevation and/or dynamic ECG changes			
	Coronary Angiography	Coronary Angiography	If Intermediate risk (GRS≥89) and no contra-indication to coronary angiography, consider angiography within 96 hours (NICE guidance)			
		Coronary Angiography within 24 hours	If very high risk (GRS>140) and no contra-indication to coronary angiography, , consider angiography within 24hours of admission			
	Bivalirudin	Bivalirudin	For patients undergoing coronary angiography if at high risk of bleeding			
		Glycoprotein IIb/IIa inhibitors	Consider at the time of PCI, but balance against bleeding risk			
Assessment of left ventricular function	Assessment of left ventricular function	Assessment of left ventricular function	All patients unless recently performed			
ACE inhibition/ARB	ACE inhibition/ARB	ACE inhibition/ARB	Indicated in Hypertension, Diabetes, LV dysfunction			
B Blockers	B Blockers	B Blockers	Indicated in all MI, UA with LV dysfunction			
Statins	Statins	Statins	All patients unless not tolerated			
Cardiac rehabilitation	Cardiac rehabilitation	Cardiac rehabilitation	Give advice on follow-up, management of cardiovascular risk factors, management/information concerning their medications, life style changes			

Signature (Medical): .....

Role: Date:

Signature (Nursing): .....

Role: Date:

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IMPLEMENTATION OF GRACE RISK TOOL

- Overseen by Health Systems Research, South Australian Health and Medical Research Institute and Flinders University

- Education of clinical staff on use of GRACE Risk tool and introduction into practice

- Recruitment in sites randomised to intervention did not commence until tool was used in 90% of eligible patients

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PRIMARY OUTCOME

- Among patients alive at hospital discharge with high risk ACS (GRS of > 118), composite of:
    - Receipt of inpatient angiography
    - Prescription of at least 4 of 5 clinical guideline advocated therapies (Aspirin, P2Y12 inhibitor, HMG-CoA reductase inhibitor, beta-blocker, ACE inhibitor or ARB)
    - Referral to cardiac rehabilitation services
- Criteria were evaluated separately and aggregated to a **Performance Score** (maximum possible score of 3)

SECONDARY OUTCOME

- Among patients alive at hospital discharge with high risk ACS (GRS of > 118) and followed for 12 months, composite of:
  - Post discharge cardiac mortality
  - Admission for (re)MI
  - Admission for heart failure

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SAMPLE SIZE CALCULATION

Sample size estimated following evaluation of pre-existing CONCORDANCE data (patients recruited from 2009-2013). Among these 2326 patients, 44.7% were receiving all components of evidence based care, and the mean Performance Score was 2.10

A sample size of 12 sites per group with 28 high risk patients per site (336 patients per arm) was calculated to have 80% power to detect a difference in the mean Performance Score of 0.5 when the intracluster coefficient (ICC) was 0.176 with a significance level of 0.05.

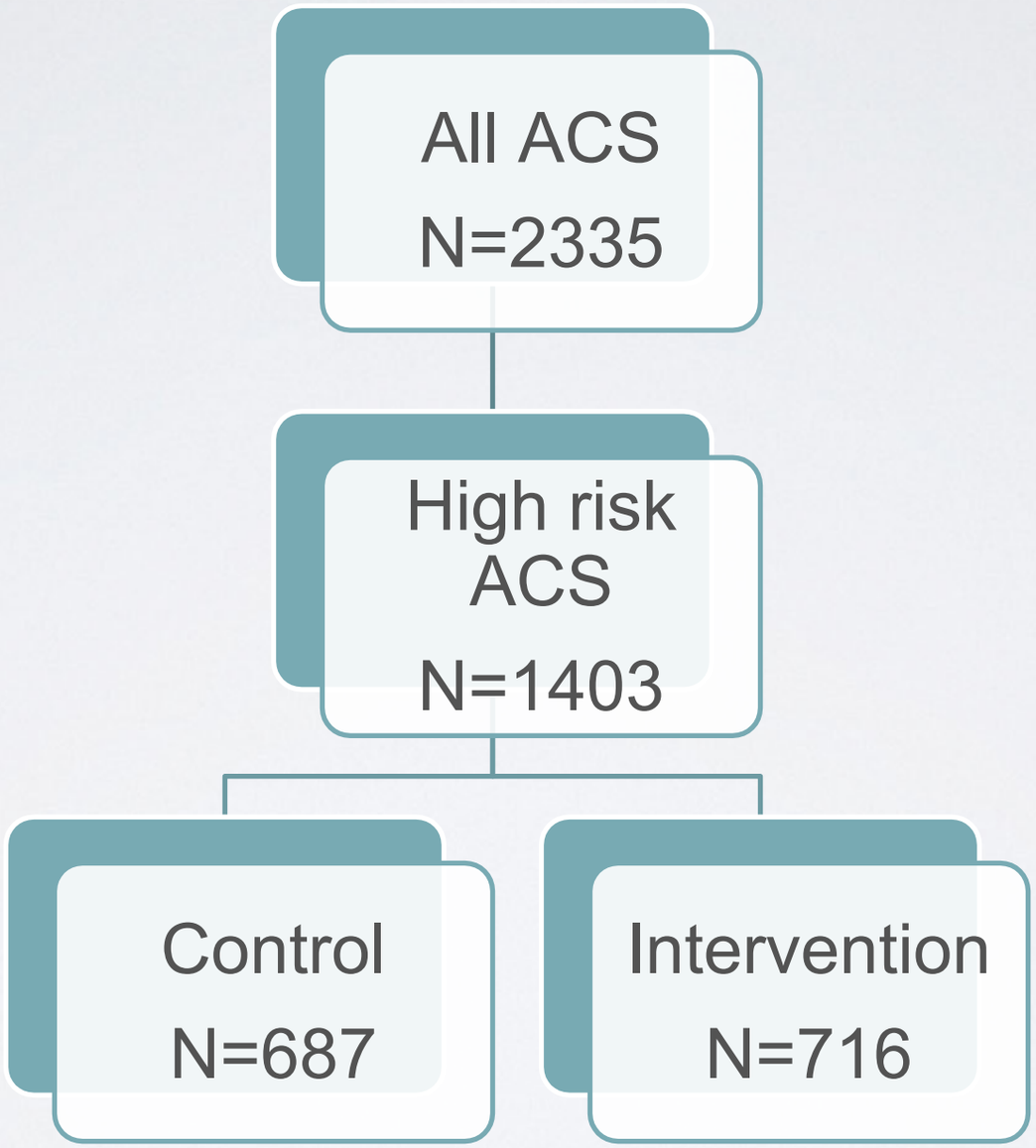
INTERIM STATISTICAL ANALYSIS

- The statistical plan was predicated on a minimum number of high risk patients from each hospital. The majority of sites exceeded their target while several hospitals recruited poorly.

- The Study Executive committee requested that the DSMB perform an assessment of the trial's likelihood of detecting difference in the primary endpoint after the study had been running for 4.5 years and 1403 high risk patients had been recruited.

- Based on observed differences in the primary endpoint, the DSMB recommended discontinuation of the study.

CONSORT DIAGRAM



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BASELINE CHARACTERISTICS

Factor		Control	Active	P-value
N		687	716	
Age, median (IQR)		70 (62, 67)	71 (63, 78)	0.12
Female Sex, n (%)		215 (31)	212 (30)	0.62
Diagnosis, n (%)	STEMI	244 (36)	292 (41)	0.45
	NSTEMI	379 (55)	376 (53)	
	UA	64 (9)	48 (7)	
GRS, median (IQR)		147 (132,167)	150 (133,168)	0.24
Diabetes, n (%)		247 (36)	228 (32)	0.12
Killip class, n (%)	1	565 (82)	588 (82)	0.90
	2	89 (13)	101 (14)	
	3	26 (4)	19 (3)	
	4	7 (1)	8 (1)	
Cardiac arrest on admission, n (%)		16 (2)	31 (4)	0.20
Prior MI, n (%)		210 (31)	199 (28)	0.55
Congestive heart failure, n (%)		60 (9)	62 (9)	0.97
Previous CABG, n (%)		90 (13)	91 (13)	0.83
Previous PCI, n (%)		146 (21)	131 (18)	0.34
Previous atrial fibrillation, n (%)		90 (13)	87 (12)	0.71
Peripheral arterial disease, n (%)		49 (7)	38 (5)	0.31
Serum creatinine, median (IQR)		88 (72, 108)	88 (73, 107)	0.74

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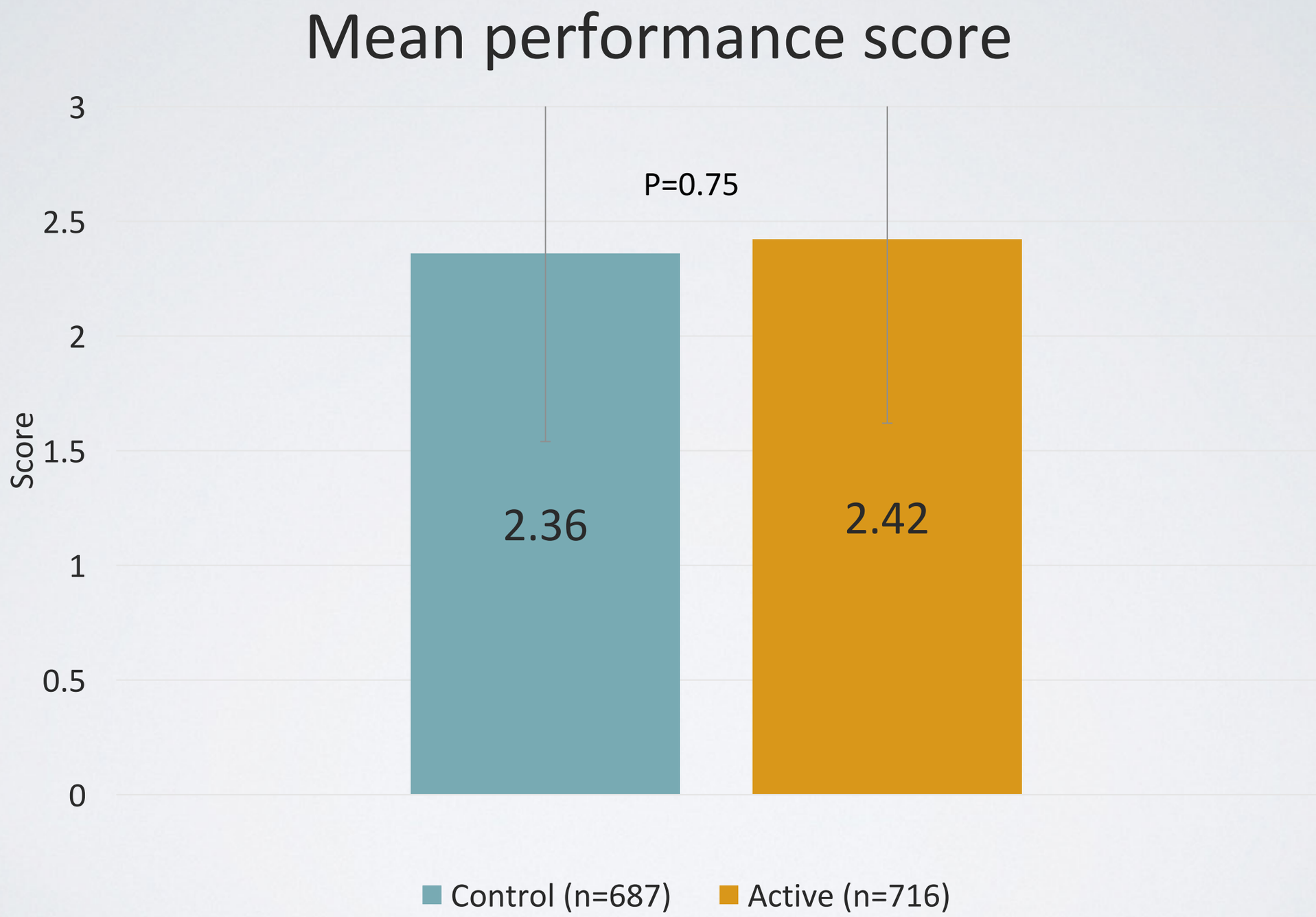
PRIMARY ENDPOINT



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COMPONENTS OF PRIMARY ENDPOINT

Factor	Control	Active	p-value
N	687	716	
Angiography, n (%)	581 (85)	650 (91)	0.01

COMPONENTS OF PRIMARY ENDPOINT

Factor	Control	Active	p-value
N	687	716	
Angiography, n (%)	581 (85)	650 (91)	0.01
Medication Compliance, n (%)	518 (75)	533 (74)	0.79

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COMPONENTS OF PRIMARY ENDPOINT

Factor	Control	Active	p-value
N	687	716	
Angiography, n (%)	581 (85)	650 (91)	0.01
Medication Compliance, n (%)	518 (75)	533 (74)	0.79
ASA at discharge, n (%)	609 (89)	647 (90)	0.44
P2Y12 at discharge, n (%)	518 (75)	524 (73)	0.55
Betablocker at discharge, n (%)	529 (77)	561 (78)	0.58
Statin at discharge, n (%)	638 (93)	653 (91)	0.37
ACE-I/ARB at discharge, n (%)	413 (73)	388 (67)	0.07

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HEALTH SYSTEMS RESEARCH

COMPONENTS OF PRIMARY ENDPOINT

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Statin at discharge, n (%)	638 (93)	653 (91)	0.37
ACE-I/ARB at discharge, n (%)	413 (73)	388 (67)	0.07
Rehab Referral, n (%)	520 (76)	551 (77)	0.87

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COMPONENTS OF PRIMARY ENDPOINT

Factor	Control	Active	p-value
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Angiography, n (%)	581 (85)	650 (91)	0.01
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P2Y12 at discharge, n (%)	518 (75)	524 (73)	0.55
Betablocker at discharge, n (%)	529 (77)	561 (78)	0.58
Statin at discharge, n (%)	638 (93)	653 (91)	0.37
ACE-I/ARB at discharge, n (%)	413 (73)	388 (67)	0.07
Rehab Referral, n (%)	520 (76)	551 (77)	0.87
Complete adherence, n (%)	373 (54)	423 (59)	0.43

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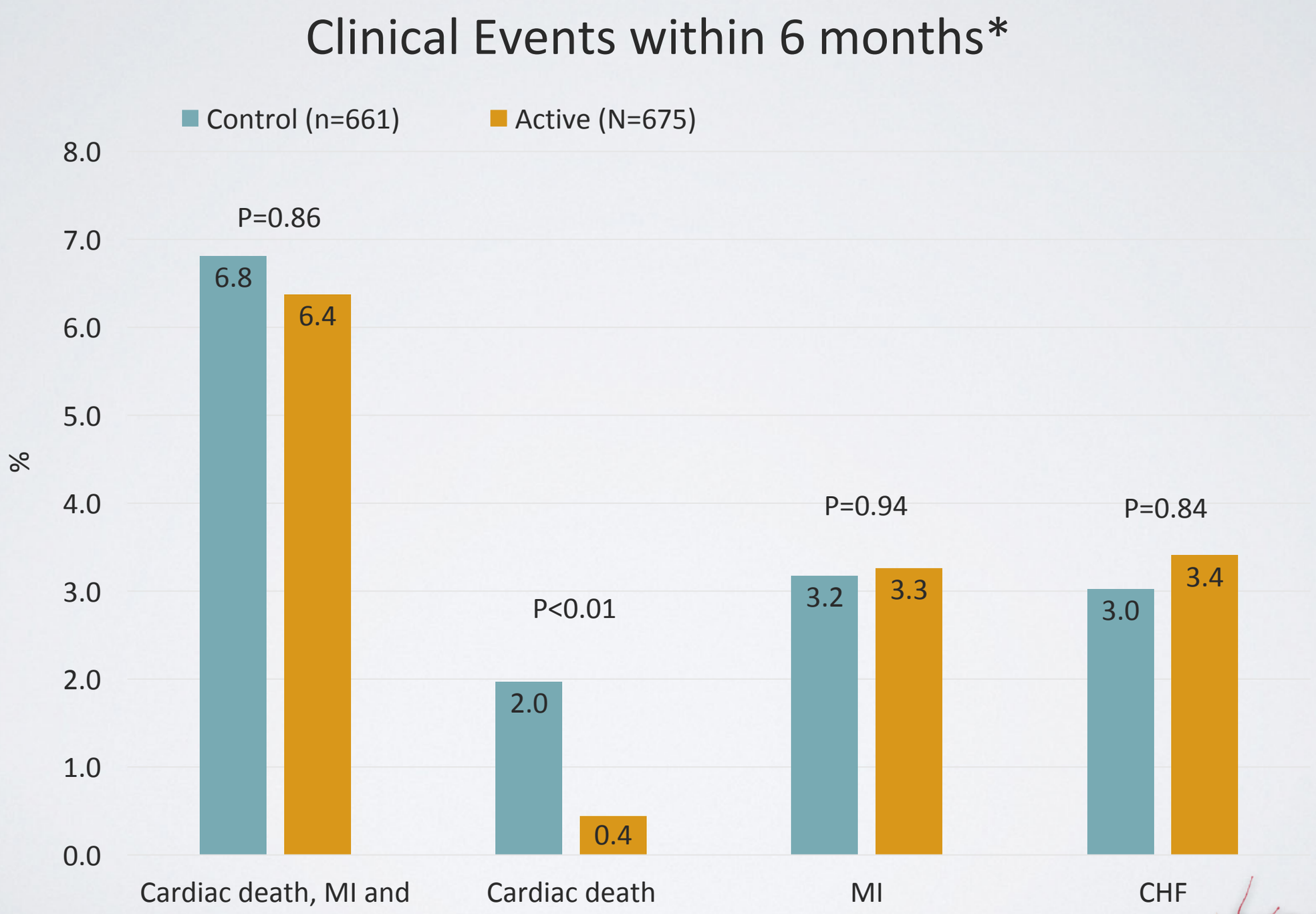
SECONDARY (CLINICAL) ENDPOINT



*based on a follow up rate of 95.2%

CONCLUSIONS (1)

- Routine implementation of the GRACE risk score coupled with decision support recommendations did not increase use of guideline recommended treatment
- This was largely explained by better than expected performance in control hospitals and a failure of the intervention to impact on medication prescription or rehabilitation referral

CONCLUSIONS (2)

- Ongoing international efforts to show the value of objective risk stratification and decision support should ensure adequate representation of sites with demonstrated gaps in evidence based practice

ACKNOWLEDGEMENT

Thank you to the investigators, study coordinators and study participants who contributed to the AGRIS study