Impact of Resting Heart Rate on Mortality, Disability and Cognitive Decline in Patients after Ischemic Stroke

Data from PROFESS

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Disclosures

Authors were members of the PROfESS Steering Committee or received honoraria and research grants from Boehringer Ingelheim as well as fees from other major cardovascular pharmaceutical companies

Background: Psychosocial Stress is CV Risk Indicator

Association of psychosocial risk factors with risk of acute myocardial infarction in 11 119 cases and 13 648 controls from 52 countries (the INTERHEART study): case-control study

*Annika Rosengren, Steven Hawken, Stephanie Ôunpuu, Karen Sliwa, Mohammad Zubaid, Wael A Almahmeed, Kathleen Ngu Blackett, Chitr Sitthi-amorn, Hiroshi Sato, Salim Yusuf, for the INTERHEART investigators**

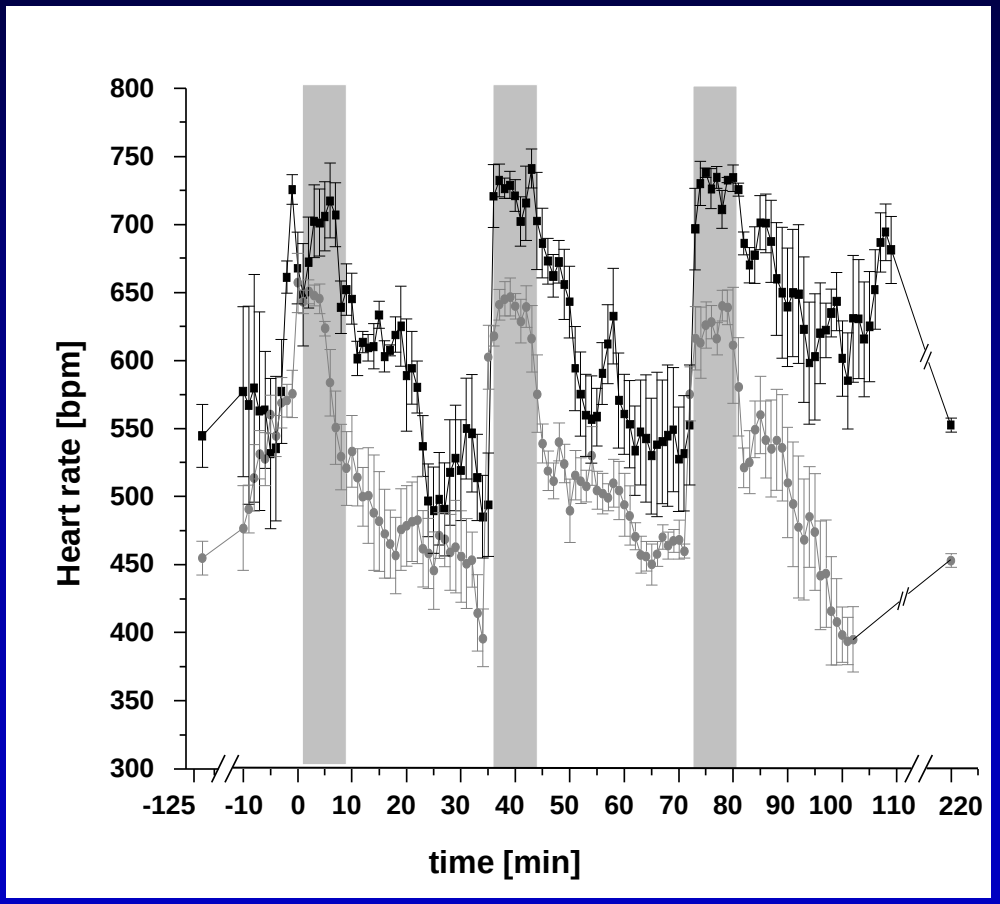
	Odds ratio (99% CI)
General stress* (n=24 767)	
Never	1
Some period, home or work	1·05 (0·96–1·14)
Several periods, home or work	1·45 (1·30–1·61)
Permanent, home or work	2·17 (1·84–2·55)
Financial stress (n=24 767)	
Little or none	1
Moderate	1·19 (1·11–1·29)
Severe	1·33 (1·19–1·48)
Stressful life events (n=24 767)	
None	1
1	1·23 (1·13–1·34)
2 or more	1·48 (1·33–1·64)

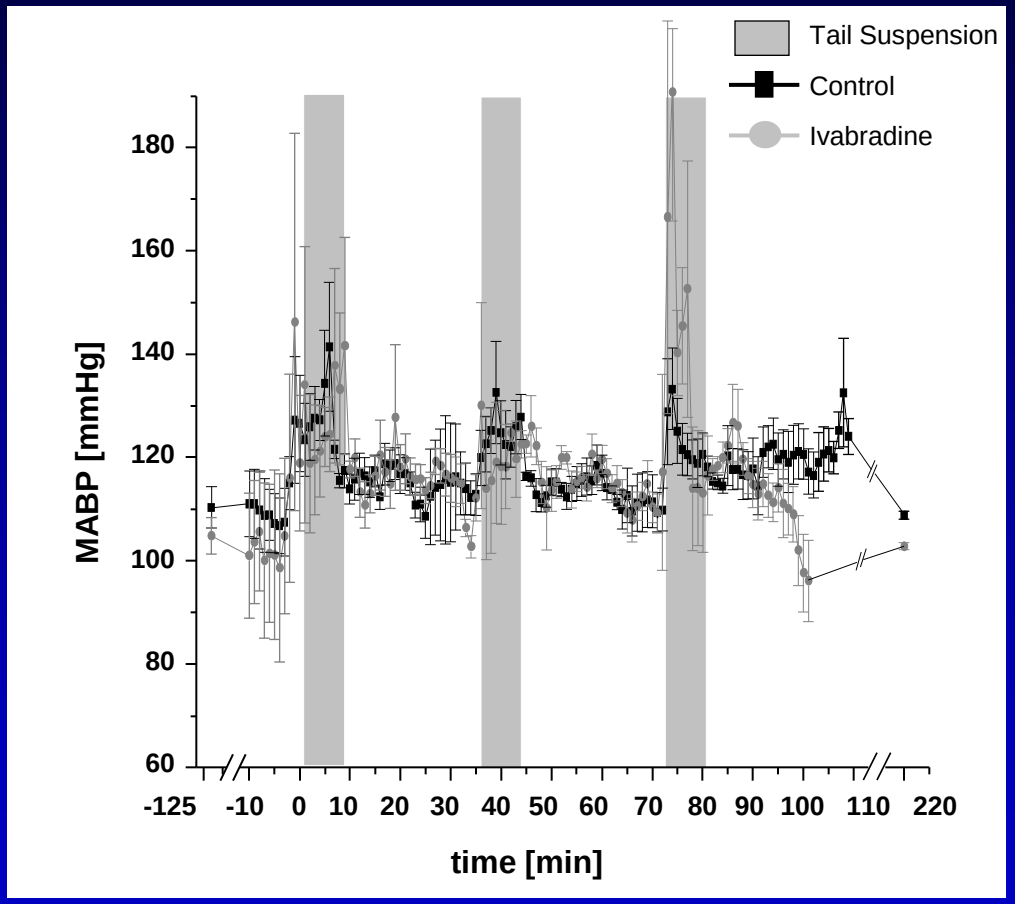
Rosengren et al, Lancet 364 (2004): 953-962

Background: Stress Produces a Vascular Phenotype

Custodis et al,
Stroke 42: 1742-1749, 2011

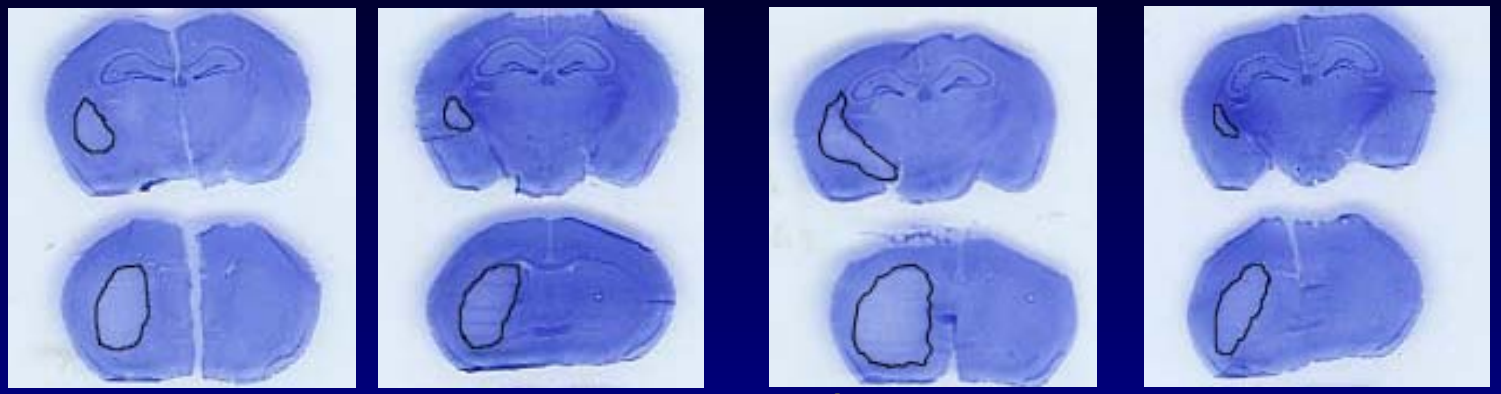
Background: Stress Reaction Involves Heart Rate

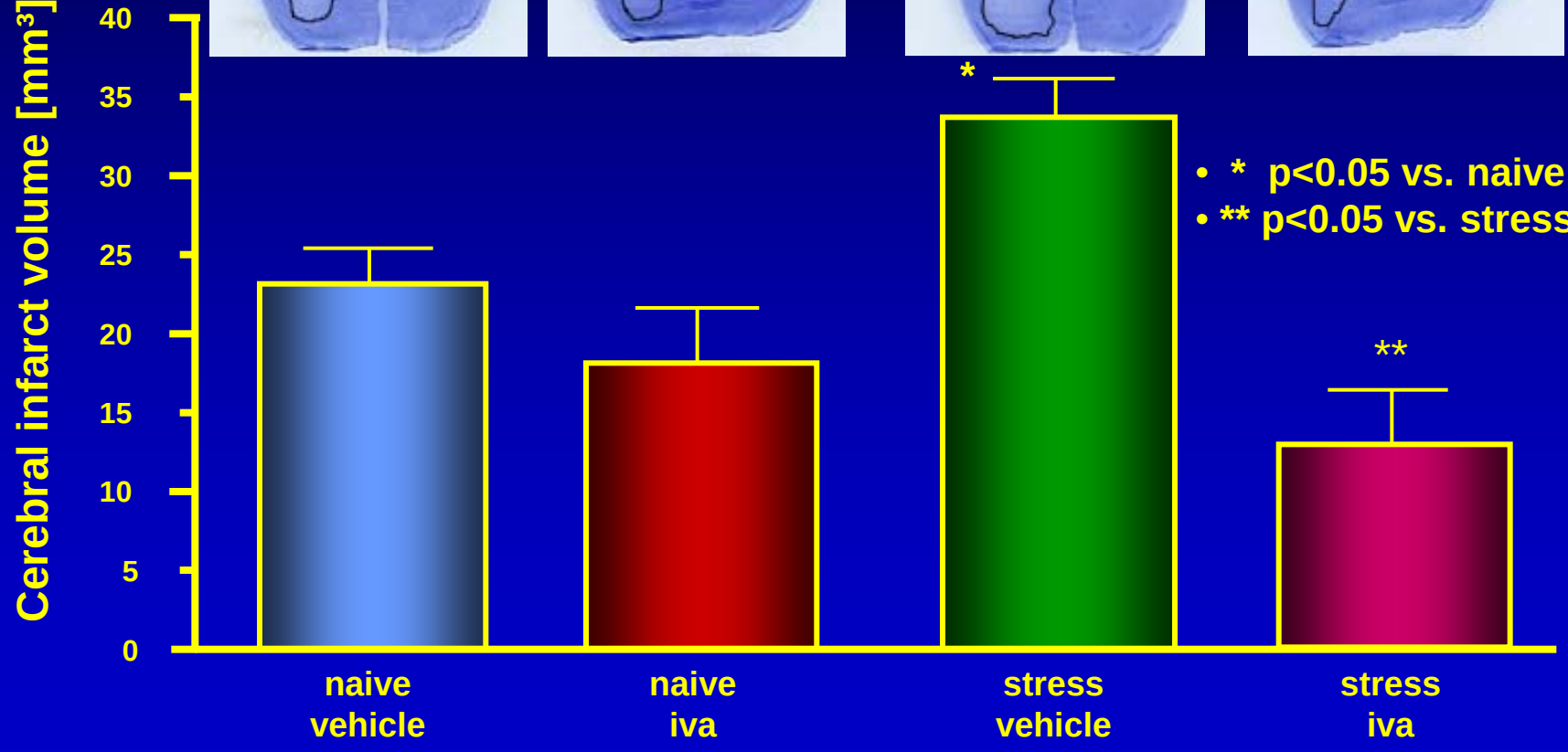




Custodis et al, Stroke 42: 1742-1749, 2011

Background: Stroke Size in Chronic Stress is HR Dependent





Custodis et al, Stroke 42: 1742-1749, 2011

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Study Design

2x2 Factorial design 20,332 stroke patients over age 50

	ER-DP+ASA	Clopidogrel*
Telmisartan	ER-DP+ASA + clopidogrel placebo + Telmisartan	Clopidogrel + ER-DP+ASA placebo + Telmisartan
Telmisartan placebo	ER-DP+ASA + clopidogrel placebo + Telmisartan placebo	Clopidogrel + ER-DP+ASA placebo + Telmisartan placebo

20,332 pts

Diener et al., Cerebrovasc Dis 17: 253-261, 2004

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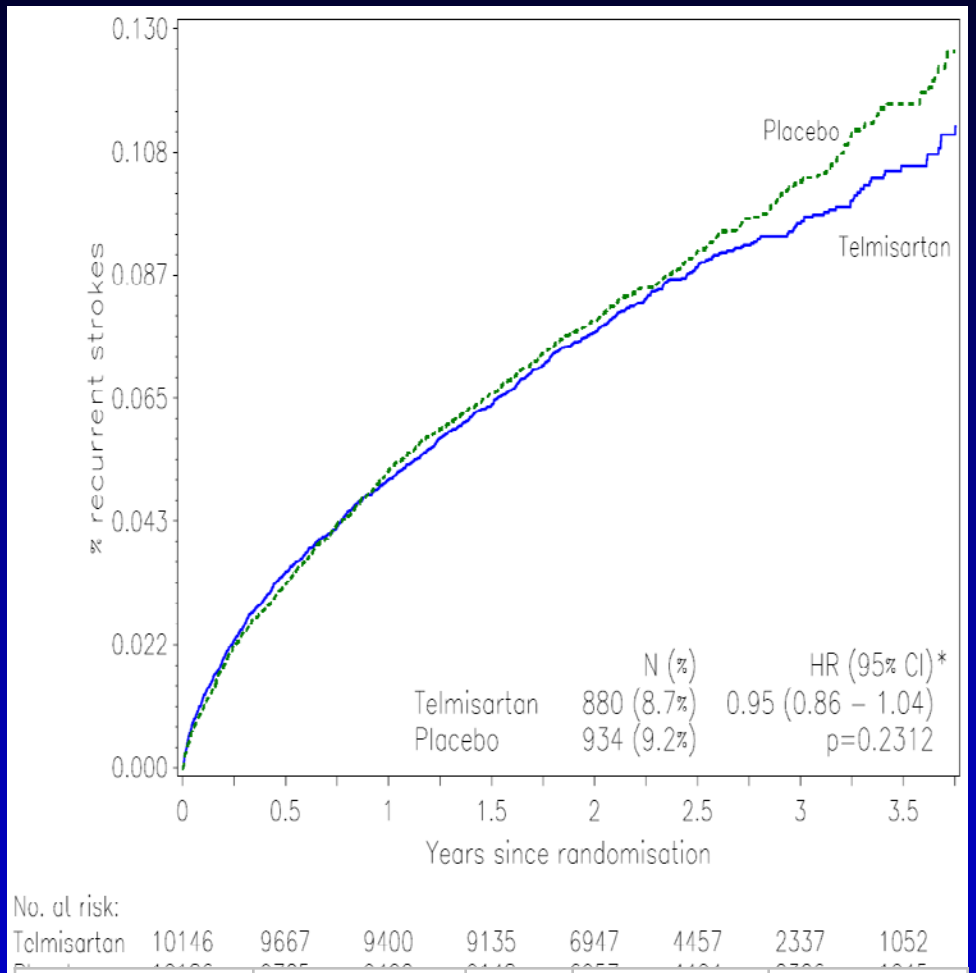
Objectives:

- To compare the efficacy and safety of the combination of extended-release dipyridamole and aspirin to clopidogrel (non-inferiority first then superiority)
- To compare telmisartan to placebo in the prevention of recurrent stroke (superiority)

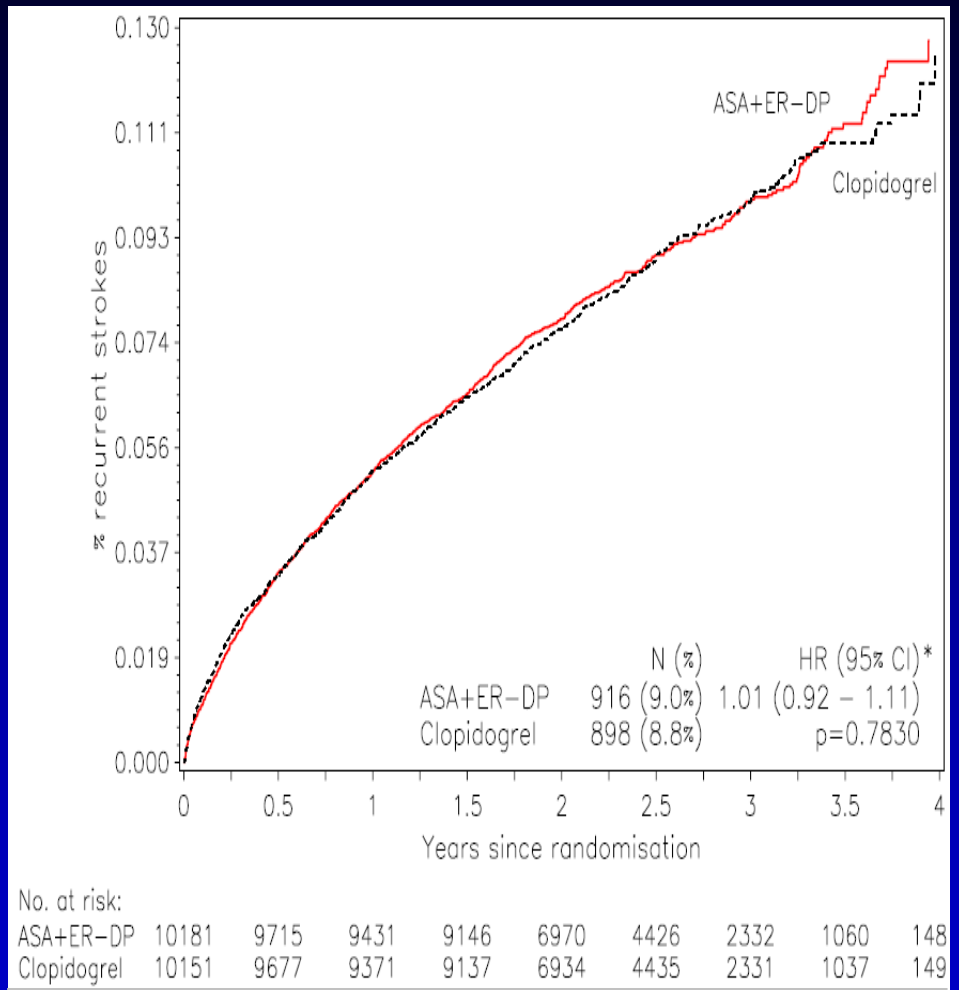
PROFESS Primary Outcome: Recurrent Stroke

** Covariates in Cox model are age, baseline ACE-inhibitor use, Modified Rankin, and baseline diabetes status.



Telmisartan	Placebo	HR	95% CI	p-value
880 (8.7%)	934 (9.2%)	0.95	0.86, 1.04	0.231

Yusuf et al., NEJM 359: 1225-1237 , 2008

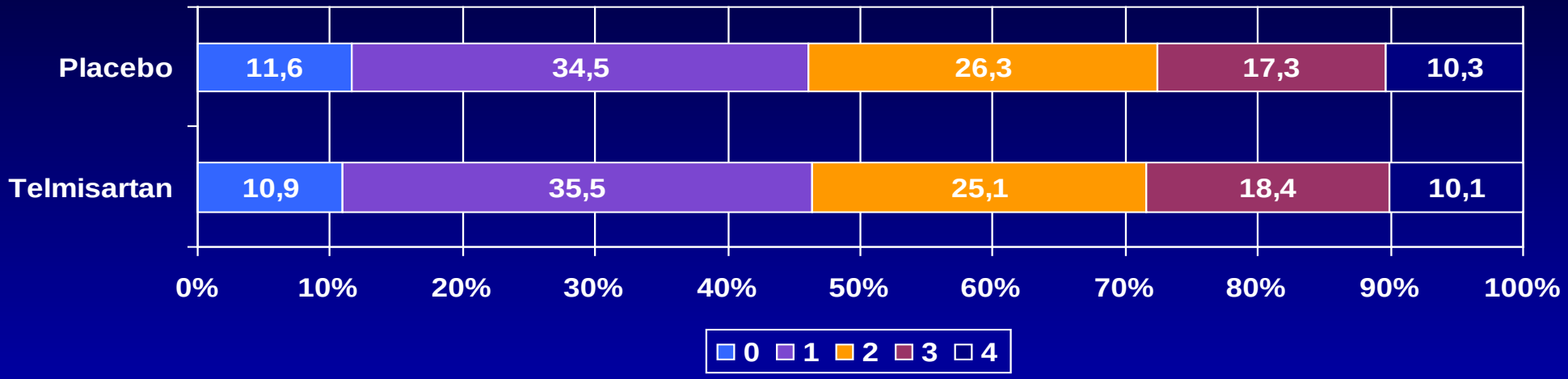


ASA+ER-DP	Clopidogrel	HR	95% CI	p-value
916 (9.0%)	898 (8.8%)	1.01	0.92, 1.11	0.783

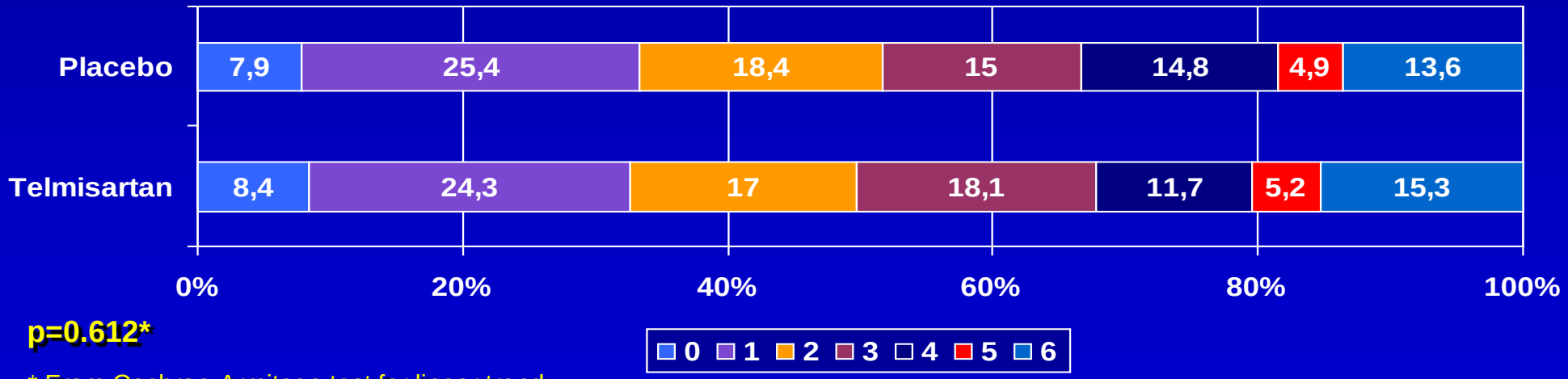
Sacco et al., NEJM 359: 1238-1251, 2008

mRS Among Subjects with Recurrent Strokes – ARB Comparison

Baseline



3 months post recurrent stroke



p=0.612*

* From Cochran-Armitage test for linear trend.

Diener et al., Lanct Neurol 7: 875-884, 2008

Objectives of Current Analysis (1)

- HR predict CV events along the cardiovascular continuum
- In stress models, HR reduction reduces stroke size

- It s not known whether HR in patients after stroke

  - predicts recurrent stroke, MI, CHF or death after stroke
  - is associated with functional outcome or cognitve decline after recurrent stroke

Objectives of Current Analysis (2)

Association of Resting Heart Rate to

- Recurrent Stroke, Myocardial Infarction and CHF

- Total CV and non CV-Mortality

- Disability after recurrent stroke as measured by mRS
- Disability of recurrent stroke as measured by Barthel Index
- Decline in cognitive function as measured by Mini Mental State Examination (MMSE)

According to: Cummings, JAMA 269 (1993): 2420-2421 ; Crum et al, JAMA 269 (1993): 2386-2391

Mahoney and Barthel, Maryland State Medical Journal 21 (1965): 61-65

Definitions and Methods

Statistical Analysis:

- 20,165 Pts, 695 centers, 35 countries

- differences tested by Chi-square (categorical) or Kruskal Wallis test (continuous)

- Cox propotional hazard model

- multiple regression

- $p<0.01$

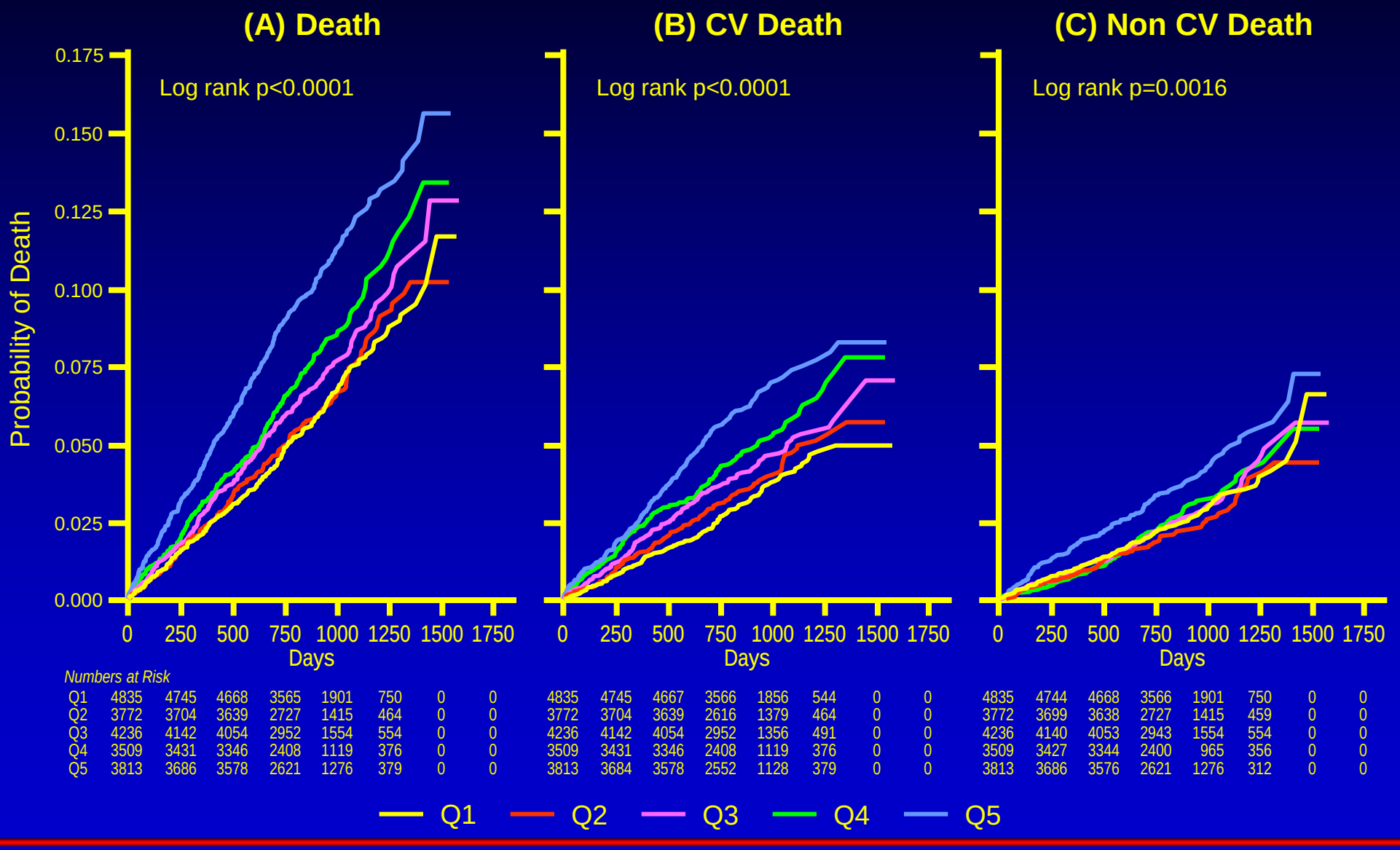
Baseline Characteristics Divided by Quintiles of Heart Rate

	Q1 (≤ 64)	Q2 (65 to ≤ 70)	Q3 (71 to ≤ 76)	Q4 (77 to ≤ 82)	Q5 (> 82)	P
Age in years	67.36 (8.50)	66.19 (8.48)	65.90 (8.55)	65.46 (8.52)	65.46 (8.63)	<0.0001
Female sex (%)	30.82	34.62	38.05	37.25	40.05	<0.0001
Hypertension (%)	75.68	72.53	73.87	73.07	74.48	0.0095
Diabetes mellitus (%)	21.80	25.85	29.04	30.92	35.43	<0.0001
Hyperlipidemia (%)	50.49	45.86	46.08	44.40	45.21	<0.0001
Use of Statin (%)	51.23	46.37	45.14	44.74	47.76	<0.0001
Use of Diuretic (%)	23.10	20.97	20.35	18.50	20.85	<0.0001
Use of Beta-blocker (%)	35.76	21.45	17.19	14.79	10.81	<0.0001
Baseline SBP	145.42 (17.15)	143.45 (16.40)	143.73 (16.25)	143.64 (15.95)	143.93 (16.70)	<0.0001

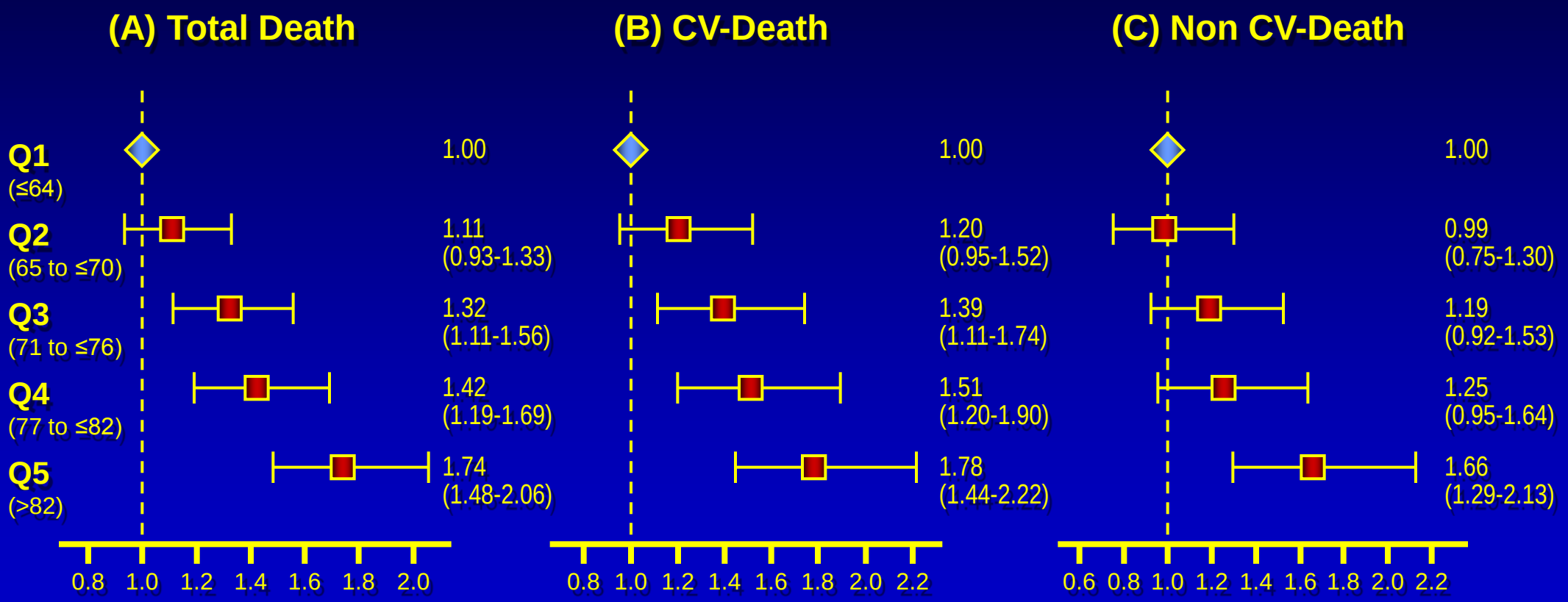
Baseline Characteristics Divided by Quintiles of Heart Rate

	Q1 (≤ 64)	Q2 (65 to ≤ 70)	Q3 (71 to ≤ 76)	Q4 (77 to ≤ 82)	Q5 (> 82)	P
TOAST classification Large-artery atherosclerosis	27.36	28.69	26.65	29.67	31.31	<0.0001
Modified Ranking scale score 0 – 2	81.43	77.55	77.86	73.55	69.24	<0.0001
Baseline NIHSS score 0 – 1	45.60	40.27	40.08	35.77	35.04	<0.0001
MMSE score at 1 month	27.16 (3.77)	27.14 (3.86)	27.05 (3.98)	26.86 (4.35)	26.54 (4.61)	<0.0001

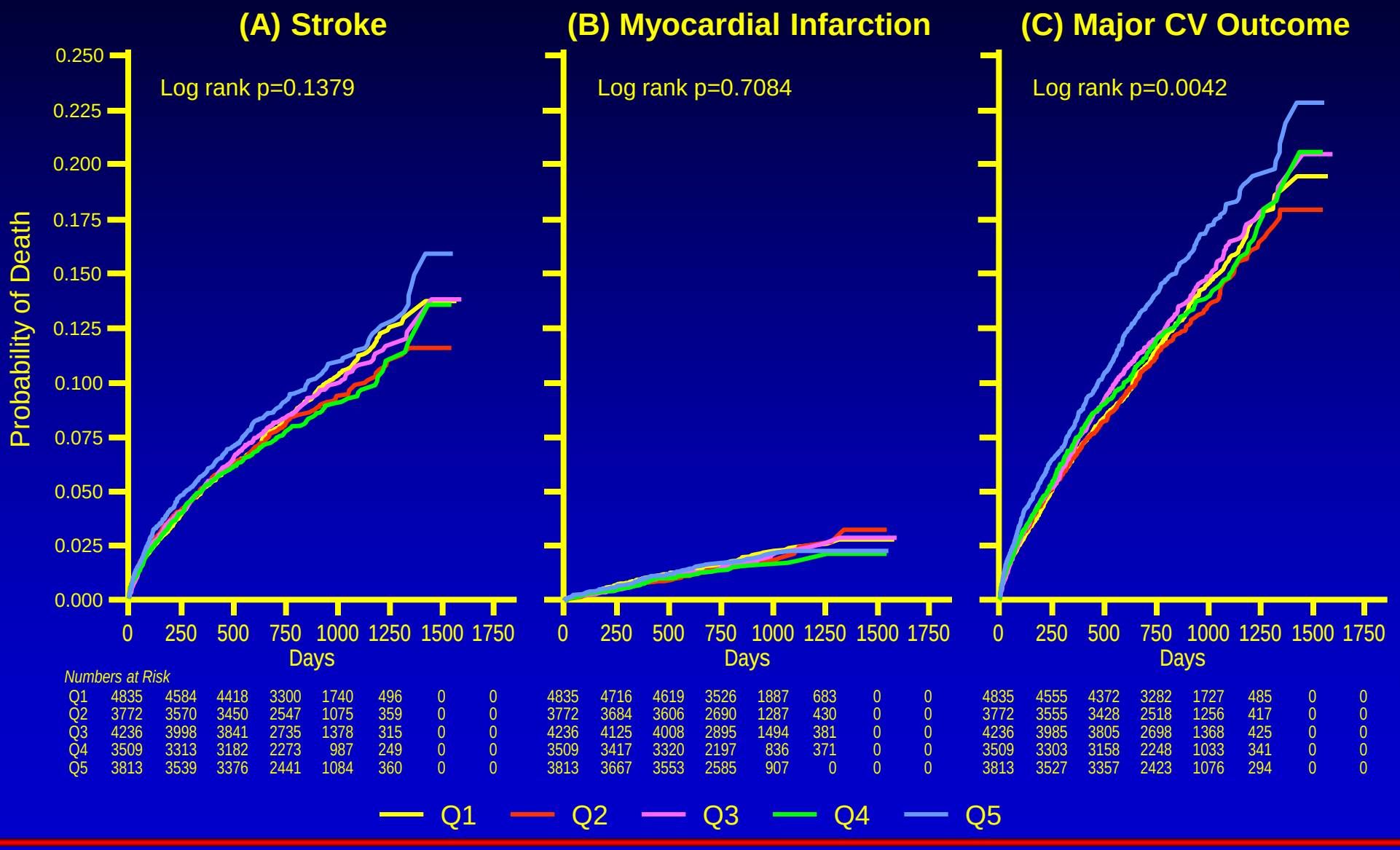
Cardiovascular Outcomes



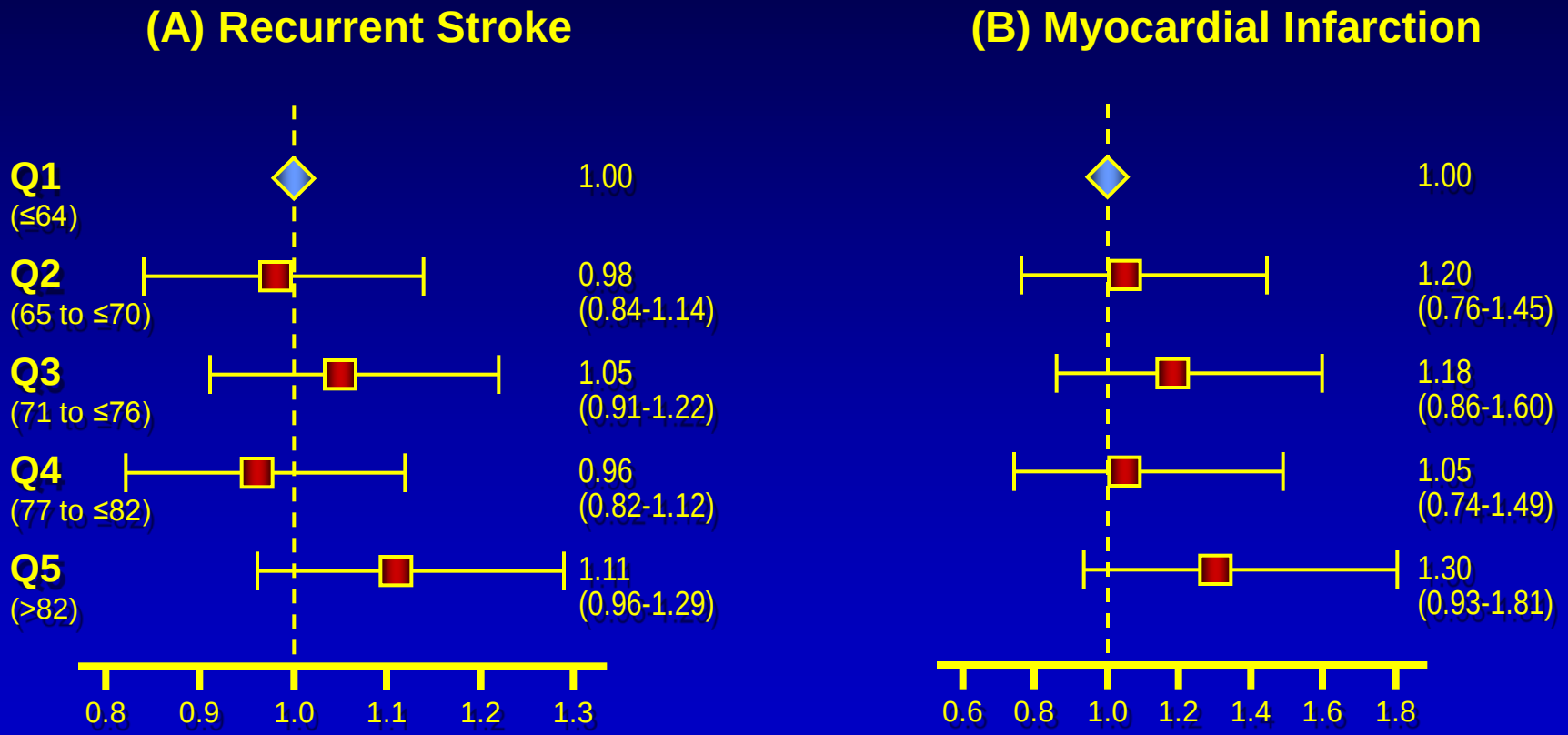
Cardiovascular Outcomes



Cardiovascular Outcomes



Cardiovascular Outcomes



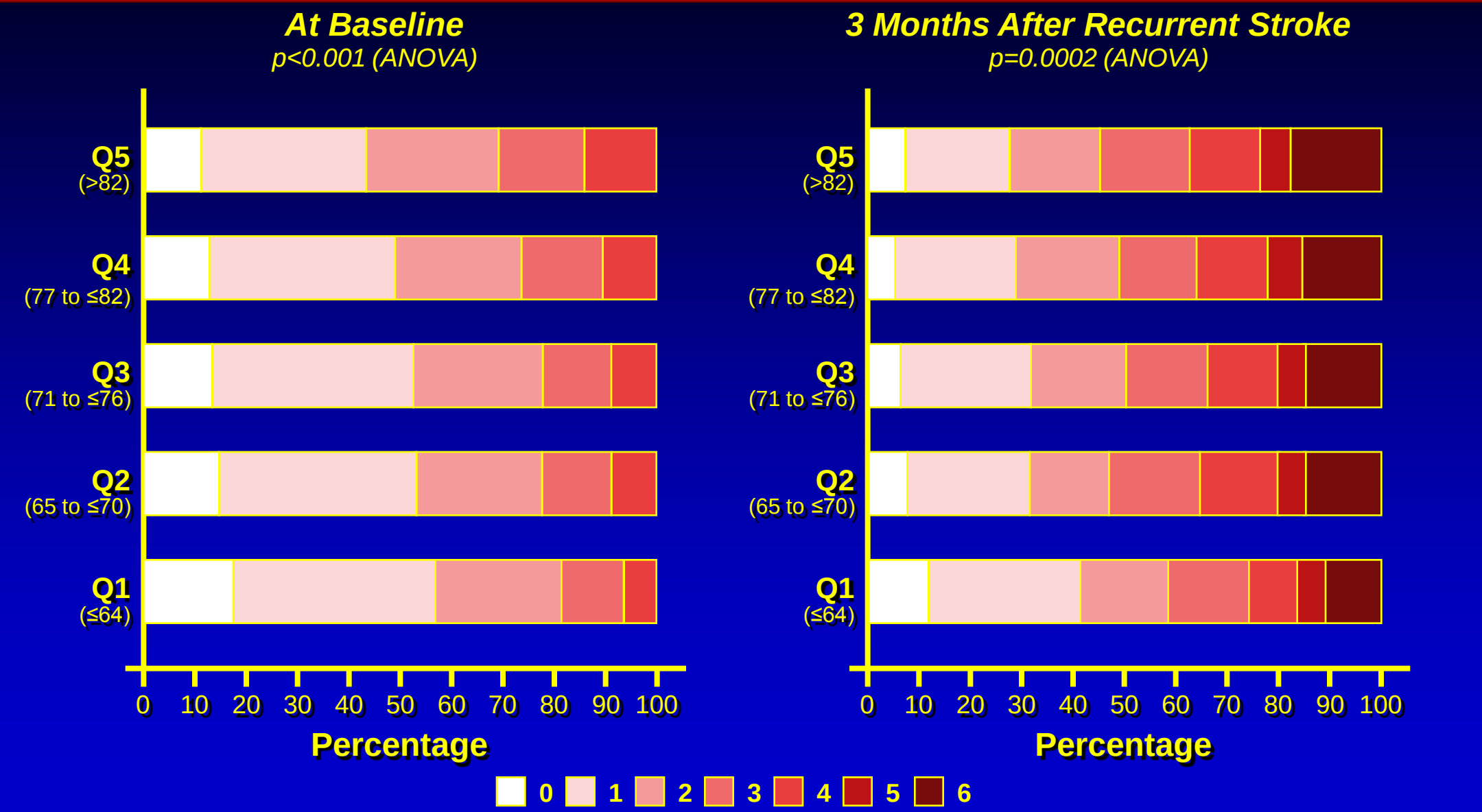
Neurological Outcomes

- Disability after recurrent stroke as measured by mRS
- Disability of recurrent stroke as measured by Barthel Index
- Decline in cognitive function as measured by Mini Mental State Examination (MMSE)

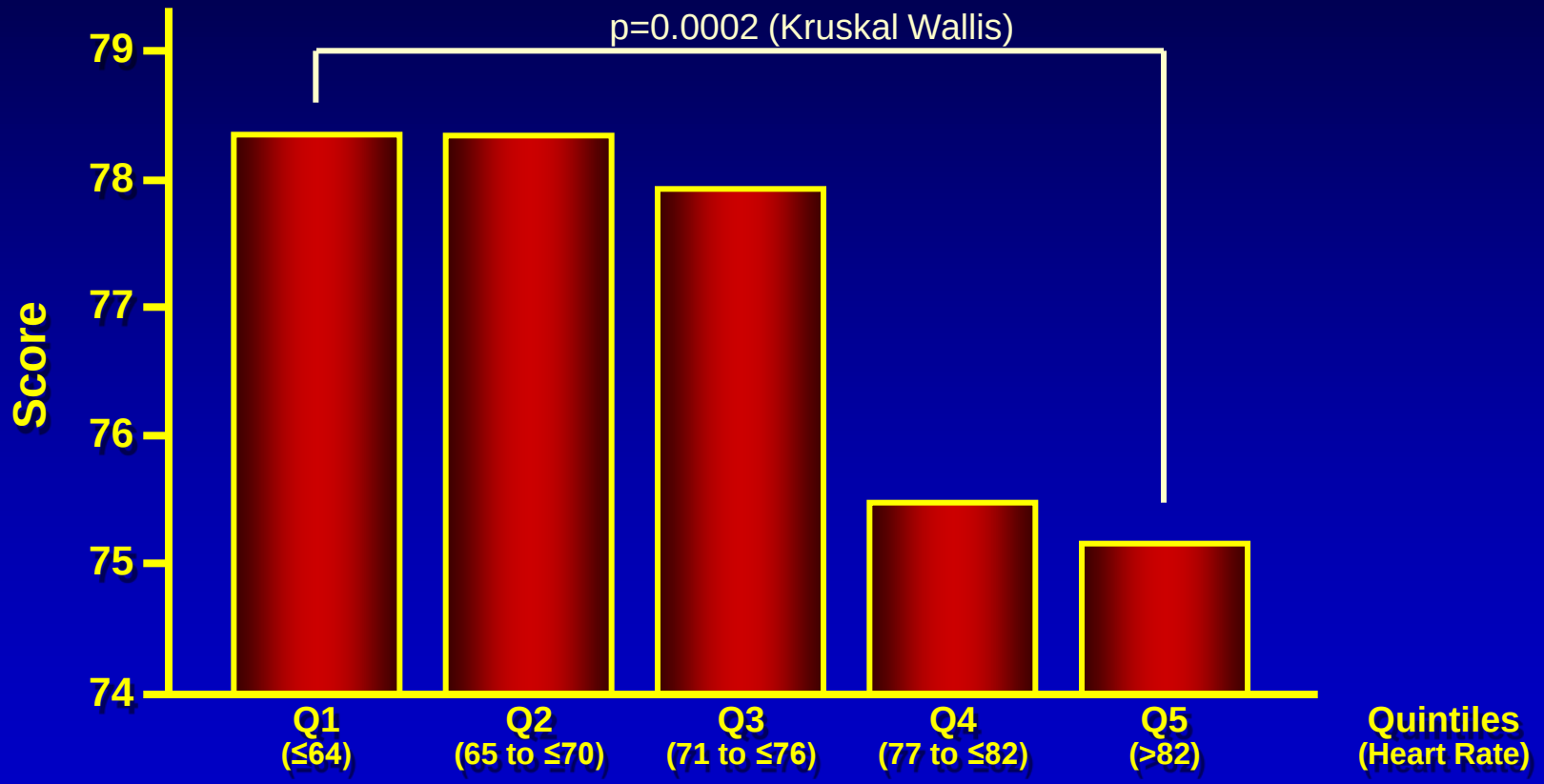
According to: Cummings, JAMA 269 (1993): 2420-2421 ; Crum et al, JAMA 269 (1993): 2386-2391

Mahoney and Barthel, Maryland State Medical Journal 21 (1965): 61-65

Modified Rankin Scale Scores

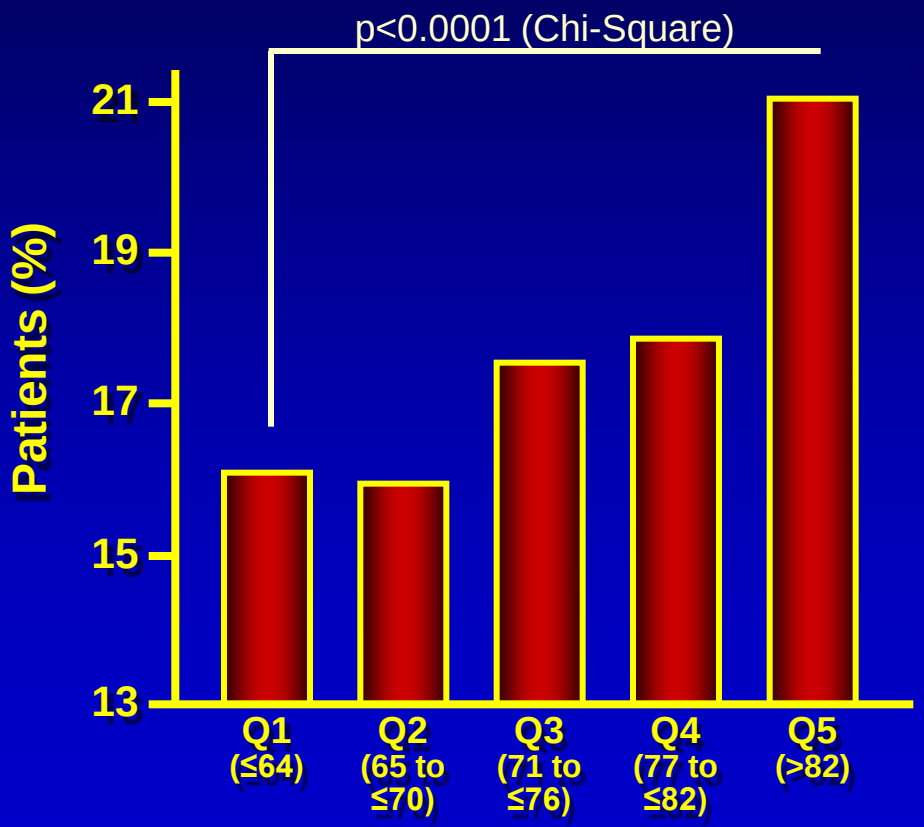


Barthel Index (Self Care) After Recurrent Stroke

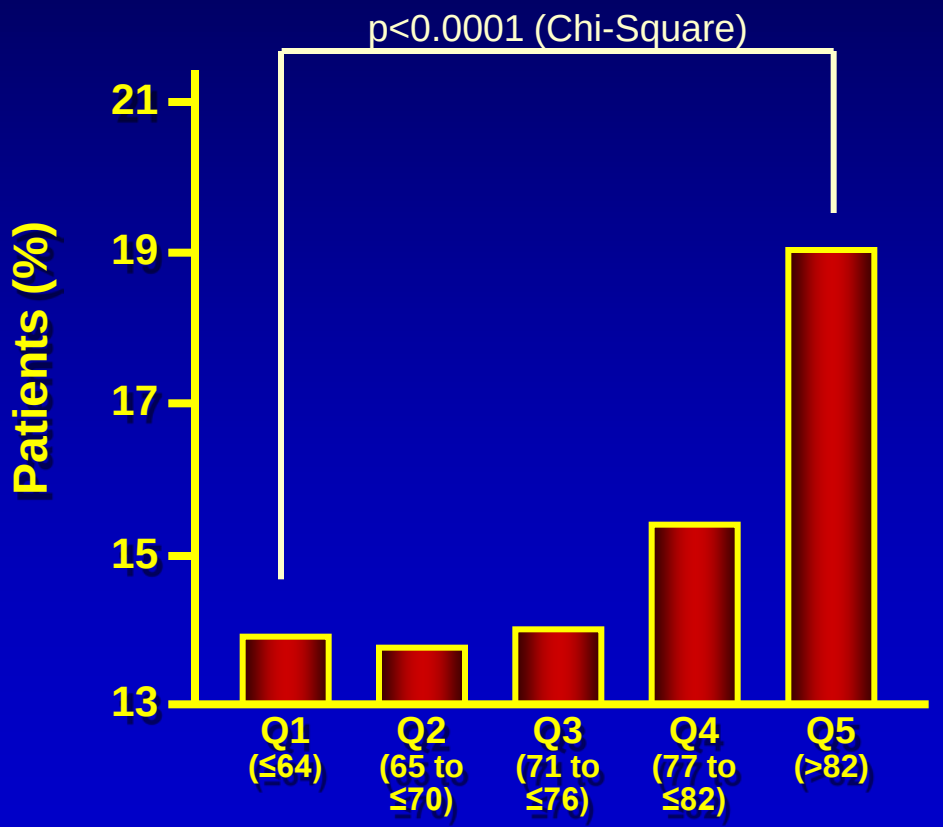


Mini Mental State Exam (MMSE) ≤ 24 (Dementia)

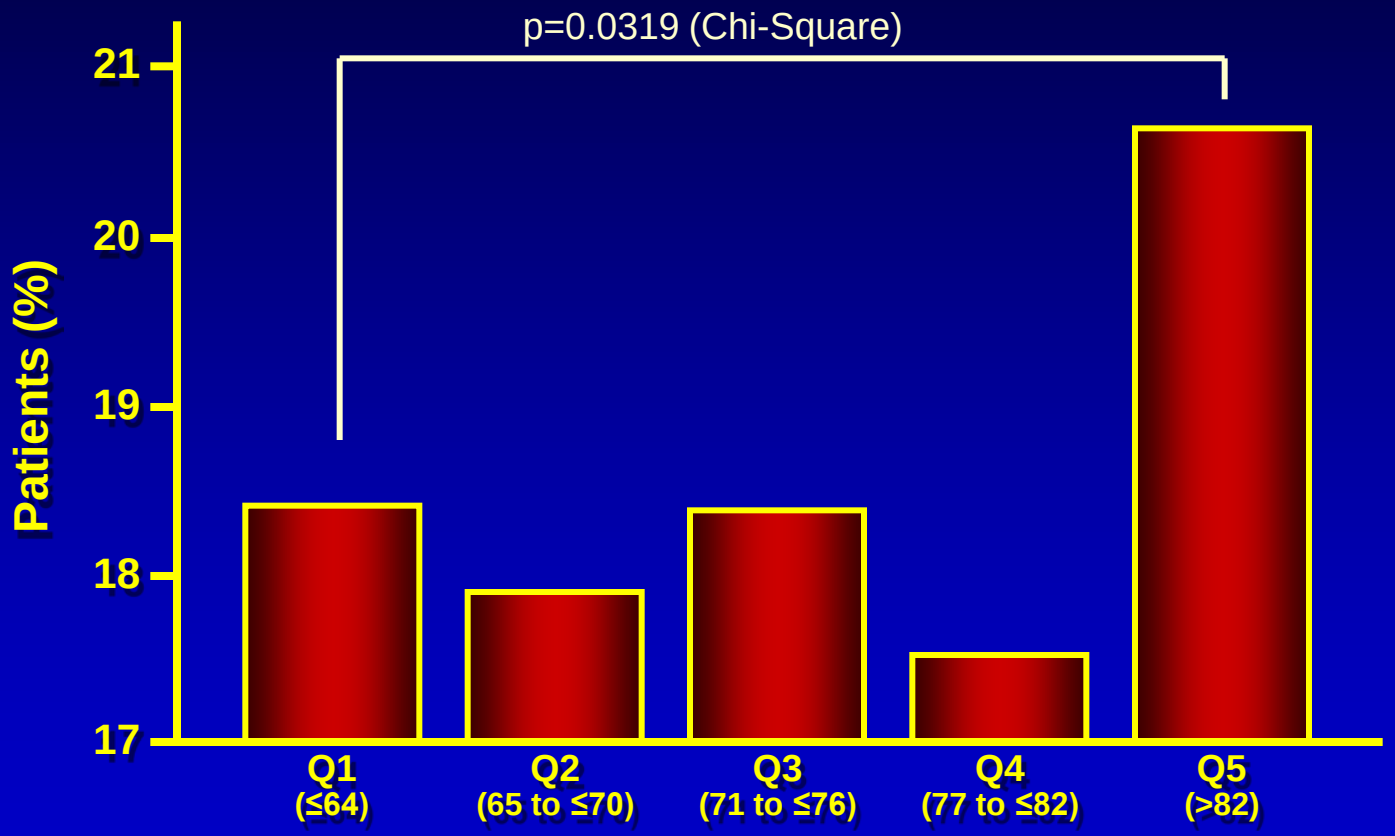
MMSE at month 1



MMSE from month 1 to penultimate visit



> 2pt Decrease in Mini Mental State Exam (MMSE) (One Month vs. Penultimate)



Conclusion (1)

Cardiovascular Outcomes

- No association of resting heart rate to recurrent stroke and myocardial infarction

- Resting heart rate is predictive of mortality after a first stroke

- total CV and non CV-mortality have different heart rate thresholds

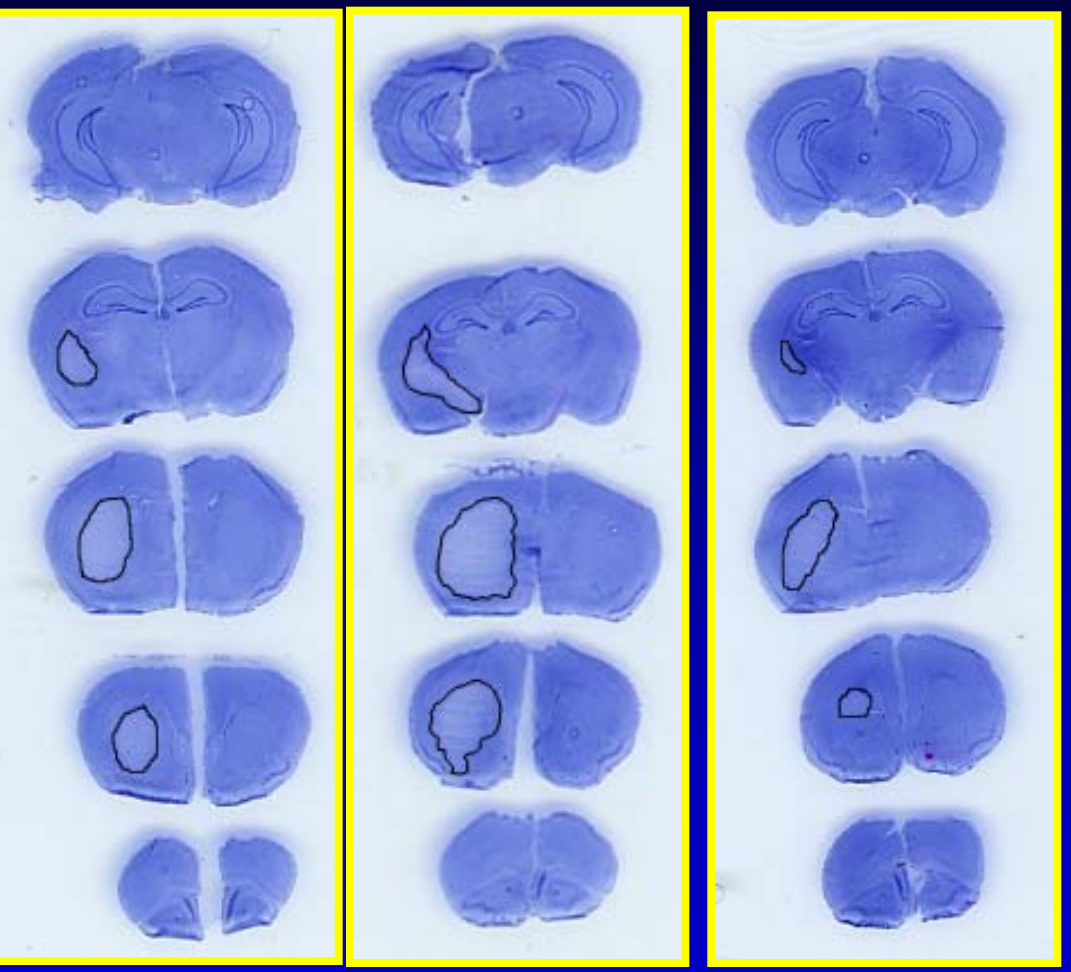
Conclusion (2)

Measures of neuroprotection are associated to low resting HR

- Disability after recurrent stroke as measured by mRS
- Disability of recurrent stroke as measured by Barthel Index
- Decline in cognitive function as measured by Mini Mental State Examination (MMSE) i.e. less patients

  > 26 or 2 Pts decline

Interpretation



naive vehicle | stress vehicle | stress iva

- Low heart rates might be associated to smaller strokes rather then to lower numbers of recurrent strokes to improve functional outcomes.

- Heart rate could be a therapeutic target after a first stroke.

Custodis et al, Stroke 42: 1742-1749, 2011

European Heart Journal
doi:10.1093/eurheartj/ehs250

Impact of resting heart rate on mortality, disability and cognitive decline in patients after ischaemic stroke

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Received 29 June 2012; revised 17 July 2012; accepted 23 July 2012

Aims Recurrent stroke is a frequent and disabling event. A high heart rate is associated with cardiovascular outcomes. We investigated the effects of the resting heart rate on cardiovascular and neurological outcomes after recurrent stroke in the high-risk population of the PRoFESS study.

Methods and results A total of 20 165 patients after ischaemic stroke (mean age 66.1, SD 8.6 years) assigned to the treatment arms of the PRoFESS trial were pooled divided by quintiles of the baseline heart rate and analysed according to cardiovascular and functional outcomes after stroke: recurrent stroke and major cardiovascular outcomes such as stroke, myocardial infarction, and worsening or new-onset heart failure as well as death from cardiovascular and non-cardiovascular causes. Pre-defined endpoints were disability after a recurrent stroke, assessed with the modified Rankin scale (mRS) and the Barthel index at 3 months, and cognitive function, assessed with the Mini-Mental State Examination (MMSE) score at 4 weeks after randomization and at the penultimate visit. Patients in the two highest quintiles of heart rate (77–82 and >82 b.p.m.) were at a higher risk for total death [hazard ratio (HR) 1.42, 95% CI 1.19–1.69 and HR 1.74, 95% CI 1.48–2.06, $P < 0.0001$] compared with the lowest quintile. Similar results were observed for vascular death [71–≤76 b.p.m., HR 1.39 (1.11–1.74), $P < 0.0001$] and non-vascular death [from >82 b.p.m., HR 1.66 (1.29–2.13), $P = 0.0016$]. Myocardial infarction ($P = 0.7084$) and recurrent stroke ($P = 0.1379$) were not significantly associated with the baseline heart rate. Hazard ratios were adjusted to multiple confounders including the baseline blood pressure. In the group of patients with a recurrent stroke, an association of a lower heart rate to better outcomes was measured with the Barthel index across all heart rate groups. In addition, there was a significant association of the baseline heart rate to the occurrence of significant cognitive decline according to an MMSE score ≤24 points at 1 month and at the penultimate visit or a decline of ≥2 points between these two time periods. Better independence score at a low heart rate were observed.

Conclusion The heart rate is a risk indicator for mortality in patients with stroke and, importantly, a low heart rate is associated with a better functional outcome and less cognitive decline after an ischaemic stroke.
Trial registration: ClinicalTrials.gov, number NTC00153062.

Keywords Heart rate • Stroke • Cardiovascular outcomes • Cognitive decline • Dementia

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Thank You!

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