




**What to do when you don't wear Lead:
Managing Chronic Stable Angina**

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**Chronic Stable Angina (CSA)
Case Presentation**

- 72 yo WM with c/o chest pressure
- 6 month history of CP when walking up a long hill. Resolves with rest.
- Hx HTN, former smoker, +FH
- Had neighbor who knew someone who “died getting an angiogram”
- Creatinine 2.3

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VI. *Some Account of a Disorder of the Breast.* By WILLIAM HEBERDEN, M. D. F. R. S.

Read at the COLLEGE, JULY 21, 1768.

THERE is a disorder of the breast, marked with strong and peculiar symptoms, considerable for the kind of danger belonging to it, and not extremely rare, of which I do not recollect any mention among medical authors. The feat of it, and sense of strangling and anxiety with which it is attended, may make it not improperly be called Angina pectoris.

Those, who are afflicted with it, are seized, while they are walking, and more particularly when they walk soon after eating, with a painful and most disagreeable sensation in the breast, which seems as if it would



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would take their life away, if it were to increase or to continue: the moment they stand still, all this uneasiness vanishes. In all other respects the patients are at the beginning of this disorder perfectly well, and in particular have no shortness of breath, from which it is totally different.

W. Heberden, *Medical Transactions, Royal College of Physicians of London.* 1768



“The rigidity of the coronary arteries may act, proportionally to the extent of the ossification, as a mechanical impediment to the free motion of the heart; and though a quantity of blood may circulate through these arteries, sufficient to nourish the heart, yet there may be less than what is requisite for ready and vigorous action. Hence, though a heart so diseased may be fit for the purposes of common circulation, during a state of bodily and mental tranquility, and of health otherwise good, yet when any unusual exertion is required, it’s powers may fail, under the new and extraordinary demand.”

C.H. Parry, Lancet 1799



CSA: Incidence

- Estimates range from 7-17 million Americans with angina**
- 3-3.5% Patients with angina have an MI each year**
- 21% men aged 65-69yr and 27% aged 80-84 have angina**
- 14% women aged 65-69 yrs and 25% aged 80-84yrs have angina**



Pathophysiology

Inadequate myocardial blood flow



Decreased systolic and diastolic function



Abnormal lactate production



ECG changes



Symptoms

Pathophysiology: supply

- Predominately related to a decrease in maximal coronary blood flow due to a fixed stenosis
- Additional factors include a variable degree of focal vasospasm, lack of endothelial dependent vasodilatation, and likely some degree of vasoconstriction of coronary resistance vessels (microscopic)

Pathophysiology: demand

- Anything that increases Heart Rate
- Anything that increases Blood Pressure
- Anything that increases contractility (e.g. medications or pre-load)



Angina

- Probably related to production of noxious chemical stimuli
- In chronic stable angina, adenosine can recreate the symptoms but does not result in ECG changes
- In some patients with CSA, aminophylline (which blocks adenosine receptors) improved exercise symptoms but did not affect ECG changes



Does angina=ischemia?

- Not necessarily
- In CASS 62% of women with definite angina had CAD, 89% of men
- For a given degree of angiographically identified CAD, patients who are Asx or mildly symptomatic have better prognosis
- When angina is improved so is silent ischemia.



Does ischemia=angina?

- NO
- Women have more atypical Sx (possibly related to an increase in spasm and microvascular angina)
- At least 75% of ischemic episodes in CSA are silent
- The number and duration of silent ischemic episodes correlates with outcomes
- Dyspnea and fatigue are also symptoms of myocardial ischemia (possibly more common in patients with a several year duration of chronic ischemia).
- Prognosis of patients with these symptoms is unclear relative to those with angina or who are truly asymptomatic.



What defines stable?

- Longer than 2-3 months
- Not a changing pattern
- Can occur at rest or nocturnally



CSA Patterns

- 5125 Pts with CSA
- 50% women
- Most had > 1 CVRF and at least 2 episodes/week
- 90% had it with exercise
- ~50% had it at rest
- ~33% had it with mental stress
- ~25% had angina at night



Canadian Cardiovascular Society Classification

CCS I: Only with strenuous activity

CCS II: Slight limitation with vigorous activity such as walking up a hill

CCS III: Marked limitation and symptoms during ADLs

CCS IV: Inability to do ADLs and may occur at rest



CSA Evaluation: ETT

- To correlate symptoms with ischemia for diagnosis
- To provide exercise prescription (limited prospective data)
- To evaluate efficacy of therapy
- To define risk of future events



ETT: to define future risk Hi Risk Features

- Inability to complete 6 min. of Bruce Protocol
- Early Positive (3 min)
- > 2mm ST depression
- Persistently elevated HR after 1 min rest
- Downsloping ST depression
- Ischemia at < 120bpm
- Flat or lowered BP response
- Serious ventricular arrhythmia at HR < 120



CSA Therapy

- To reduce risk
- To improve symptoms



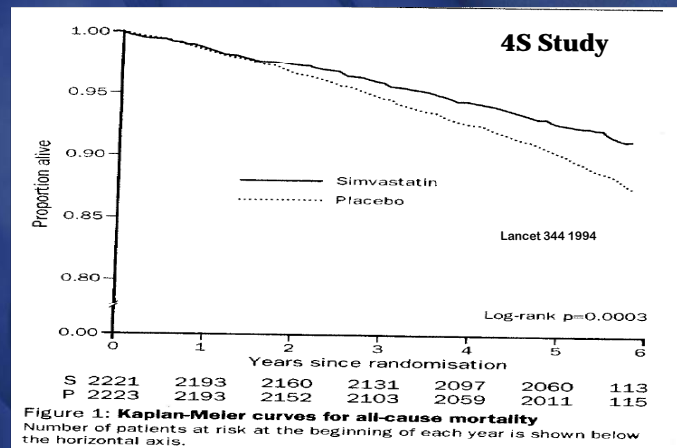
CSA Therapy to reduce future risk: Aspirin

Swedish Angina Pectoris Aspirin Trial

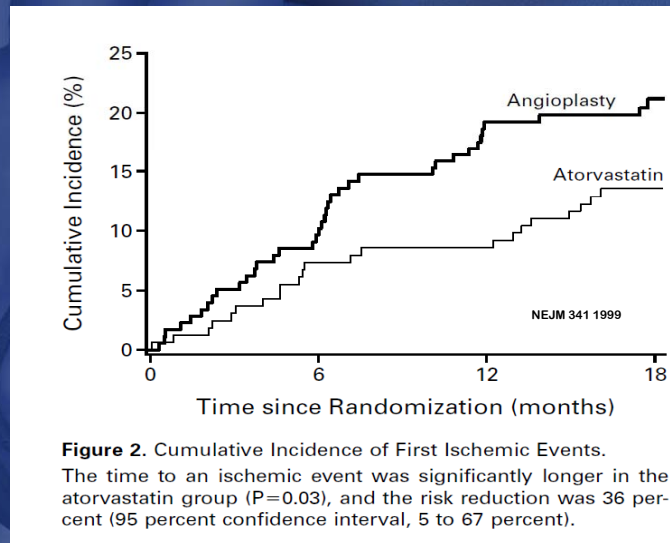
- 2035 patients with CSA treated with BB
- 75 mg ASA versus placebo
- 34% reduction in death and MI
- 32% reduction in secondary vascular events
- No data of superiority of higher dose
- No improvement in symptoms



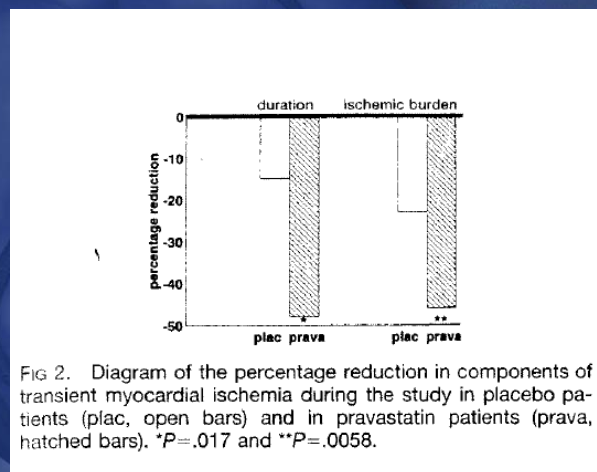
CSA Therapy To reduce future risk: Statins



CSA Therapy: Statins



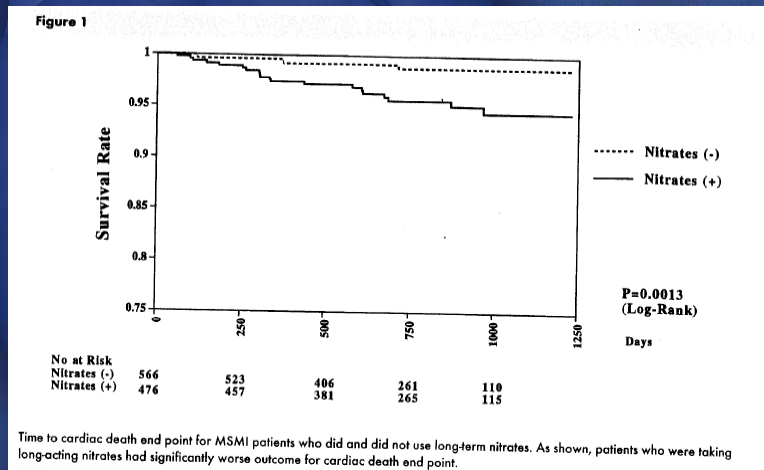
CSA Therapy to reduce future risk: Statins



CSA Therapy to reduce future risk: Nitrates



CSA Therapy to reduce future risk: Nitrates?



CSA Therapy to reduce future events: Calcium Channel Blockers



CSA Therapy: to reduce future events Calcium Channel Blockers (?)

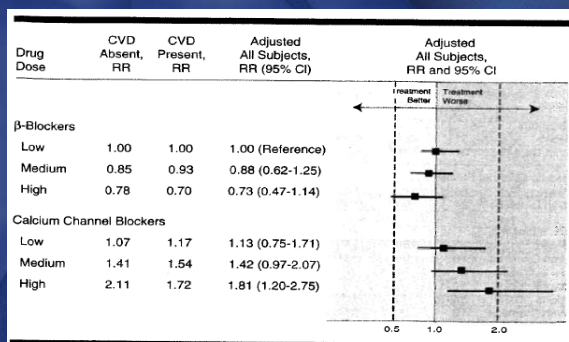


Figure 3.—Association between myocardial infarction and use of calcium channel blockers compared with the low-dose users of β-blockers: dose-response analysis stratified by the presence or absence of clinical cardiovascular disease (CVD). RR indicates risk ratio (boxes); CI, confidence interval (cross bars). Among subjects without CVD, the RRs were adjusted for the factors listed in the legend of Figure 1. Among subjects with CVD and among all subjects, the RR was adjusted not only for age, sex, calendar year, smoking, diabetes, pretreatment systolic blood pressure, duration of hypertension, physical activity, and education, but also for the clinical CVD characteristics of angina, stroke, claudication, coronary angioplasty, coronary bypass surgery, peripheral vascular surgery, carotid endarterectomy, and recent use of nitroglycerin. For all subjects, P values for the tests for trend were .035 for β-blockers and .003 for calcium channel blockers.



CSA Therapy to reduce future events Calcium Channel Blockers (?)

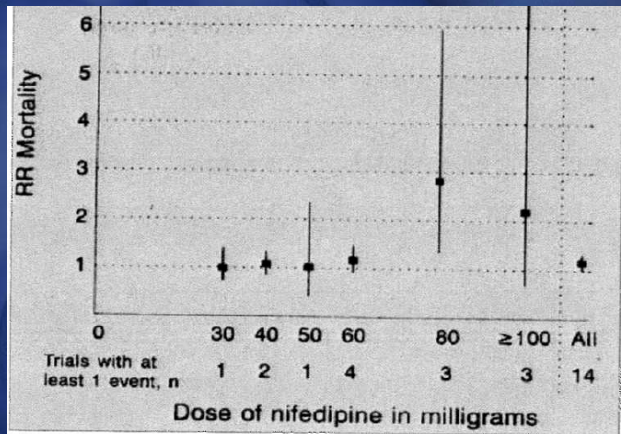


Figure 1. Graph showing risk or mortality according to daily dose of nifedipine. RR indicates risk ratio



CSA Therapy to reduce future risk: Beta Blockers

TABLE 3. Outcomes During Treatment

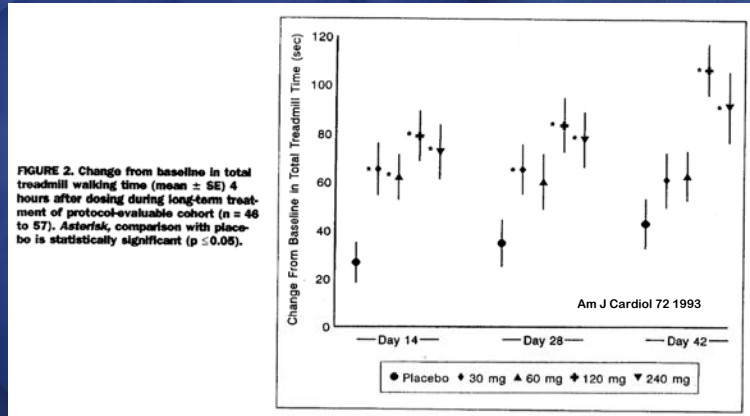
Outcomes at 1 Year	Placebo (n=154)	Atenolol (n=152)	RR (95% CI)	P
Death or resuscitated VT/VF	4	1		
Nonfatal MI	3	2		
Hospitalized for unstable angina	6	4		
Death, VT/VF, MI, or hospitalization	13	7	0.55 (0.22 to 1.33)	.175
Aggravation of angina	26	9	0.35 (0.17 to 0.72)	.003
Revascularization	0	1		
Any adverse event	39	17	0.44 (0.26 to 0.75)	.001

RR indicates relative risk; CI, confidence interval; VT, ventricular tachycardia; VF, ventricular fibrillation; and MI, myocardial infarction.

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CSA Therapy to improve symptoms: Nitrates



CSA Therapy: CCB Mechanism of Action

- Inhibition of intracellular Calcium uptake resulting in less binding of actin to myosin
- Relaxation of smooth muscle
 - peripheral vasodilatation (afterload reduction)
 - Decreased contractility
 - Coronary vasodilatation
 - Inhibition of exercise induced coronary vasoconstriction

CSA Therapy to improve symptoms BB vs CCB

Table 3. Outcomes in Stable Angina for β -Blockers vs Calcium Antagonists*

Outcomes	No. of Trials	β -Blockers, No.		Calcium Antagonists, No.		Measures	Effect Size	95% CI	P Value	References
		Patients	Events	Patients	Events					
Cardiac death or MI	61	3000	57	3054	59	Odds ratio (<1 favors β -blockers)	0.97	0.67 to 1.38	.85	10-26, 28-41, 48-56, 59-64, 66-78, 80-84, 86-90
Angina episodes per week	32	1127	NA	1107	NA	Mean difference (<0 favors β -blockers)	-0.31	-0.62 to 0.00	.05	10-50
Nitroglycerin use per week	25	736	NA	726	NA	Mean difference (<0 favors β -blockers)	-0.14	-0.41 to 0.32	.32	10, 22-24, 26, 27, 29-35, 37-41, 43-47, 49, 50
Time to 1-mm ST depression	20	567	NA	557	NA	Standardized mean difference (>0 favors β -blockers)†	0.06	-0.06 to 0.18	.33	23, 26, 30-32, 34, 36, 37, 40-42, 49, 51-58
Total exercise time	32	840	NA	831	NA	Standardized mean difference (>0 favors β -blockers)†	-0.10	-0.20 to 0.00	.05	10, 23, 24, 27-33, 35, 36, 40-42, 47-49, 51-54, 56, 57, 59-66
Withdrawal for adverse events	51	2811	239	2778	317	Odds ratio (<1 favors β -blockers)	0.72	0.60 to 0.86	<.001	19, 20, 22-26, 28, 30, 32, 33, 35, 37-41, 49-51, 53-56, 58, 59, 61, 63, 64 66-87

*CI indicates confidence interval; MI, myocardial infarction; and NA, not applicable. No statistical evidence of trial heterogeneity was observed for any of the outcomes listed (Q statistic, $P > .20$).
†Standardized mean differences were calculated as mean exercise time (β -blockers) - mean exercise time (calcium antagonists)/pooled SD.



CSA Therapy to improve symptoms: BB vs NTG

Table 5. Outcomes in Stable Angina for β -Blockers vs Nitrates*

Outcomes	No. of Trials	β -Blockers, No.		Calcium Antagonists, No.		Measures	Effect Size	95% CI	P Value	References
		Patients	Events	Patients	Events					
Cardiac death or MI	6	129	1	129	1	Odds ratio (<1 favors β -blockers)	1.0	0.21 to 4.70	>.99	104-109
Angina episodes per week	5	86	NA	84	NA	Mean difference (<0 favors β -blockers)	-0.83	-4.70 to 3.10	.68	104, 106-109
Nitroglycerin use per week	3	53	NA	53	NA	Mean difference (<0 favors β -blockers)	-1.90	-0.40 to 0.20	.08	104, 108, 109
Time to 1-mm ST depression	1	27	NA	27	NA	Standardized mean difference (>0 favors β -blockers)†	0.12	-0.42 to 0.65	.66	104
Total exercise time	1	21	NA	21	NA	Standardized mean difference (>0 favors β -blockers)†	0.29	-0.90 to 0.32	.35	109
Withdrawal for adverse events	5	124	6	124	13	Odds ratio (<1 favors β -blockers)	0.47	0.18 to 1.18	.11	104-107, 109

*CI indicates confidence interval; MI, myocardial infarction; and NA, not applicable. Statistical evidence of trial heterogeneity (Q statistic) was observed for the outcomes of angina episodes ($P = .003$) and nitroglycerin use ($P = .04$).
†Standardized mean differences were calculated as [mean exercise time (β -blockers) - mean exercise time (nitrates)]/pooled SD.



CSA Therapy to reduce symptoms: NTG vs CCB

Table 4. Outcomes in Stable Angina for Nitrates vs Calcium Antagonists*

Outcomes	No. of Trials	Nitrates, No.		Calcium Antagonists, No.		Measures	Effect Size	95% CI	P Value	References
		Patients	Events	Patients	Events					
Cardiac death or MI	10	377	0	376	0	Odds ratio (<1 favors nitrates)	NA	NA	NA	92-101
Angina episodes per week	5	143	NA	143	NA	Mean difference (<0 favors nitrates)	0.52	-0.12 to 1.2	.10	93, 95, 97, 98, 100
Nitroglycerin use per week	5	143	NA	143	NA	Mean difference (<0 favors nitrates)	0.19	-0.23 to 0.60	.38	93, 95, 97, 98, 100
Time to 1-mm ST depression	3	81	NA	81	NA	Standardized mean difference (>0 favors nitrates)†	-0.19	-0.50 to 0.11	.22	93, 97, 100
Total exercise time	5	126	NA	126	NA	Standardized mean difference (>0 favors nitrates)†	-0.11	-0.36 to 1.40	.39	93, 97, 100, 102, 103
Withdrawal for adverse events	9	340	12	339	9	Odds ratio (<1 favors nitrates)	1.34	0.57 to 3.10	.50	92-97, 100, 101, 103

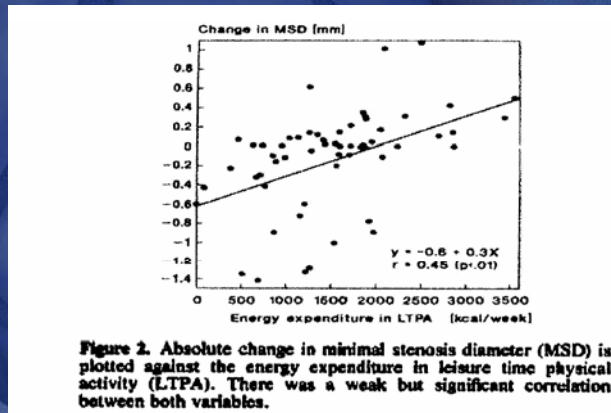
*CI indicates confidence interval; MI, myocardial infarction; and NA, not applicable. No statistical evidence of trial heterogeneity was observed for any of the outcomes listed (Q statistic, P>.20).

†Standardized mean differences were calculated as [mean exercise time (nitrates) - mean exercise time (calcium antagonists)]/pooled SD.



CSA Therapy: Other Therapies to think of

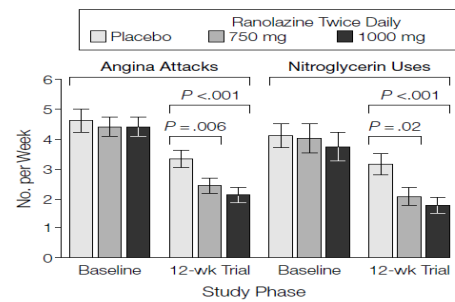
- Exercise



CSA Therapy: Other therapies to think about

- Ranolazine

Figure 4. Angina Frequency and Nitroglycerin Consumption in the Intent-to-Treat Population



Data are presented as means (SE). P values are for comparisons of each ranolazine group vs placebo.



CSA Therapy: Other therapies to think about

- Testosterone?

TABLE 3. Changes in Exercise Parameters in Active and Placebo Groups

	Baseline	Week 6	Week 14	P
Time to 1-mm ST-segment depression, s				
Active	309 ± 27	343 ± 26	361 ± 22	0.02*
Placebo	267 ± 25	284 ± 23	292 ± 24	
P	0.25	0.09	<0.05*	
Rate-pressure product at 1-mm ST-segment depression				
Active	16 870 ± 986	16 040 ± 1070	16 800 ± 939	0.59
Placebo	18 990 ± 853	17 160 ± 835	18 100 ± 939	
P	0.1	0.4	0.3	
Raw change in time to 1-mm ST-segment depression, s				
Active		34 ± 17	52 ± 17	0.02*
Placebo		18 ± 17	25 ± 11	
P		0.5	0.2	
Change in time to 1-mm ST-segment depression, %				
Active		26 ± 16	37 ± 20	0.02*
Placebo		13 ± 9	15 ± 6	
P		0.5	0.3	

All values are expressed as mean ± SEM. Probability values between the 2 groups with time were calculated with ANCOVA; between the 2 groups at a single time point, with student's unpaired t tests.
*Statistically significant.



CSA Therapy: Other therapies to think about

- **EECP**

Table 2. Exercise Treadmill Test

	Inactive CP				Active CP				Between-Group p Value
	n	Pre-CP	Post-CP	p Value	n	Pre-CP	Post-CP	p Value	
Exercise duration (s)	58	432 ± 22	464 ± 22	< 0.03	57	426 ± 20	470 ± 20	< 0.001	< 0.31
Time to ≥1-mm ST-segment depression (s)	56	326 ± 21	330 ± 20	< 0.74	56	337 ± 18	379 ± 18	< 0.002	= 0.01

Duration in seconds, mean ± SEM.

Pre-CP: baseline, before counterpulsation; Post-CP: follow-up, postcounterpulsation. p values are computed based on adjusted change in duration from baseline to follow-up.



CSA Case Presentation Continued

- Started ASA, Statin, and BB immediately. PRN NTG
- Echo normal
- ETT: 9 minutes, stopped because of CP, ST segment depression at 8 minutes
- 2 weeks later, improved but still limited
- BP still elevated so added LA CCB and LA NTG
- 2 weeks later, Asx. ETT: 11 minutes, no CP or ST segment changes

