

Online Appendix

Supplemental Data

Cyclosporine A in reperfused myocardial infarction: results of the multicenter, controlled, open-label CYCLE trial

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EVENT VALIDATION COMMITTEE CHARTER

INTRODUCTION

Multicenter, randomized, open label, blinded end point, study. The purpose of the study is to test the hypothesis that the administration of a single in dose of 2.5mg of CsA right before primary PCI could improve the outcome of AMI patients, by improving myocardial reperfusion.

Primary end point: Improvement of myocardial reperfusion, measured with ST-segment resolution $\geq 70\%$ 1 hour after PCI.

Secondary endpoints: High sensitive troponin T (hsTnT) at day 4 after PCI. All-cause mortality, HF or shock within 6 months of randomization; re-hospitalization for CV reasons within 6 months of randomization; left ventricular remodeling.

ROLE AND RESPONSIBILITIES

The main responsibility of the Event Validation Committee is to review and validated reported clinical events included in the secondary end point in a blind manner.

The Event Validation Committee will work in accordance with the procedures as defined in this manual independently from the Steering Committee (SC) and the Data and Safety Monitoring Board (DSMB).

The primary role of the CEC is to classify death and to define and adjudicate the following reported outcome events

- Cardiovascular hospitalizations,
- Heart failure (requiring hospitalizations).

The Committee will receive documentations of the events by the Coordinating Center and will meet on a regular basis. During its first meeting the Events Validation Committee will elect a chair, will discuss the definitions of the events and approved this charter.

The objective for the committee is to utilize a consistent and unbiased classification system. For each event the CEC will adjudicate whether they meet the criteria of an outcome event as defined in this manual. The CEC will be blind regarding any information relating to randomization group.

To perform their activities the CEC members will review the outcome events forms (Death, Hospitalizations, Heart Failure) completed by the investigative site together with the required documentation.

The CEC will not responsible for any safety assessment of the study. The responsibility for safety assessment will remain with the DSMB.

OUTCOME EVENT DEFINITIONS AND DOCUMENTATION

All cause death. Death will be classified as cardiovascular, non cardiovascular or unknown. Only deaths due to a clearly documented non cardiovascular cause such as cancer, trauma, infection, respiratory failure are non cardiovascular. Multi organ failure as a result of cardiovascular disease should be adjudicated as a cardiovascular death.

Cardiovascular death. Cardiovascular death includes sudden cardiac death, unwitnessed unexpected death, fatal MI, death from heart failure, death related to invasive diagnostic or therapeutic procedures, death from stroke, death from non cerebral embolism, arrhythmic death, death due to presumed cardiovascular cause and death due to other cardiovascular cause.

Sudden cardiac death. Death that occurs suddenly, unexpectedly and includes the following:

- Death witnessed within 60 minutes of the onset of new or worsening symptoms,
- Identified arrhythmia captured on an ECG recording or witnessed on a monitor by a health professional (lasting less than 60 min),
- Cardiac arrest or successfully resuscitated cardiac arrest with death within 24 hours without identification of non cardiac etiology,
- Witnessed and instantaneous death without new or worsening symptoms.

The diagnosis of sudden death excludes subjects with a known diagnosis such as myocardial infarction, pulmonary edema, stroke.

Unwitnessed unexpected death. death without other cause that occurs unexpectedly and is unwitnessed. This includes patients who are found dead where there is no other explanation.

Death from stroke. Death occurring within 30 days from a stroke without any evidence of other cause contributing to the event (for definition see page 7 “**Non fatal stroke**”).

Death from non cerebral embolism. Death occurring within 7 days from a systemic arterial embolism (for definition see page 8 “**Systemic arterial embolism**”).

Fatal MI. Death occurring within 7 days after a documented/validated myocardial infarction (for definition see pages 6-7 “**Myocardial Infarction**”) in which there is no evidence of an another cause of death.

- Autopsy evidence of a recent infarct without other evidence of another cause of death.
- A fatal myocardial infarction may be adjudicated for a death that has suggestive criteria for infarct but does not meet the strict definition of MI. Suggestive criteria are:
 - ECG changes indicative of acute injury,
 - Abnormal markers without evolution (patient died before a subsequent lab draw),
 - Other evidence of wall motion abnormality.

Death from Heart Failure/Cardiogenic shock. Death that occurs within the context of clinical symptoms/signs of heart failure (even if the terminal event was an arrhythmia) (for definition see page 6 “**Heart failure**” and “**Cardiogenic shock**”). Cardiogenic shock without another cause of shock (sepsis, anaphylaxis) is included.

If heart failure is secondary to MI, then MI should be listed as the primary cause of death given the patient suffered a MI in the 7 days of death (see above).

Death related to invasive procedures. Cardiovascular death occurring within 30 days of any cardiovascular or non cardiovascular surgery or within 7 days of angiography evaluation, angioplasty, atherectomy, stent placement, ablation or other invasive vascular intervention.

Arrhythmic death. Death due to documented arrhythmia (complete A-V block, ventricular tachyarrhythmia) not occurring suddenly or unexpectedly without any evidence of other cause contributing

to the event. An example of death from arrhythmia is a subject who is admitted with tachyarrhythmias and dies 5 hours later.

Death due to presumed cardiovascular cause. Death not attributed to the categories of cardiovascular death and not attributed to a non cardiovascular cause.

Death from other cardiovascular cause. Refers to death due to pericardial tamponade, valve thrombosis or other causes not mentioned above.

NON CARDIOVASCULAR DEATH

Non cardiovascular death is defined as any death clearly due to a non cardiovascular cause and categorized as follows.

Malignancy. A documented malignant neoplasia in the absence of a new evidence of deterioration of the cardiac disease (absence of new ischemic events, worsening HF, cerebrovascular disease etc).

Infective (including sepsis). All causes of death from infection *that cannot be classified as cardiovascular* will be included in this category.

Accidental/Trauma. Cases of death from suicide, violence or accident will be classified as a separate category with the option of considering the three categories separately.

Other non cardiovascular cause. Other serious non cardiovascular disease in the absence of a new evidence of deterioration of the cardiac disease (absence of new ischemic events, worsening HF, cerebrovascular disease etc).

Unknown cause of death. Not determinable cause of death. Lack of specific documentation despite any effort to obtain it.

HOSPITALIZATIONS

Hospitalization means unplanned or elective admission to a hospital for at least an overnight stay or resulting in death.

All hospitalizations will be classified as cardiovascular or non cardiovascular; prolongation of a non cardiovascular hospitalization for a cardiovascular cause may be considered as cardiovascular hospitalization if there is a clear documentation that the cardiovascular diagnosis prolonged the hospitalization for at least two consecutive dates (overnight). Day care admission for the management of heart failure will be considered as a hospitalization. Hospitalization for heart failure will receive special attention and additional information about this will be collected. For scheduled multiple day care admissions a single hospitalization form will be filled reporting the number of days of admission.

CAUSES OF CARDIOVASCULAR HOSPITALIZATION

Heart failure. Patients presenting with at least two of the following signs or symptoms and requiring intravenous medications (diuretics or vasodilators or inotropes) or initiation or increase in dosage (if previously prescribed for another cause, i.e. hypertension) of loop diuretic, ACE-inhibitor/ARB therapy, or evidence-based beta-blocker therapy.

- increased dyspnea on exertion,
- orthopnea,
- nocturnal dyspnea,
- increasing peripheral edema,
- pulmonary edema,
- increasing fatigue/decreasing exercise tolerance,

- renal hypoperfusion (worsening renal function),
- elevated jugular venous pressure,
- radiological sign of CHF,
- new evidence of left ventricular systolic dysfunction,
- new evidence of BNP ≥ 400 pg/mL, NT-proBNP 1500 pg/ml

Cardiogenic shock: Cardiogenic shock is decreased cardiac output and evidence of tissue hypoxia in the presence of adequate intravascular volume.

Hemodynamic criteria for cardiogenic shock are sustained hypotension (systolic blood pressure < 90 mm Hg for at least 30 min) and a reduced cardiac index (< 2.2 L/min/m²) in the presence of elevated pulmonary capillary occlusion pressure (>15 mm Hg).

The diagnosis of cardiogenic shock can be made at the bedside by observing hypotension and clinical signs of poor tissue perfusion, which include oliguria, cyanosis, cool extremities, and altered mentation. These signs usually persist after attempts have been made to correct hypovolemia, arrhythmia, hypoxia, and acidosis.

Myocardial infarction: Non periprocedural MI. Myocardial infarction will be diagnosed if the subject has detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following:

- Symptoms of ischemia,
- ECG changes indicative of new ischemia (see ST elevation/ST depression and T wave changes)*,
- Development of pathological Q waves in the ECG,
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

*[**ST elevation** = new ST elevation at the J point in two contiguous leads with the cut off points: ≥ 0.2 mV in men or ≥ 0.15 mV in women in leads V₂ – V₃ and/or 0.1 mV in other leads. **ST depression and T-wave changes** = new horizontal or down sloping ST depression ≥ 0.05 mV in two contiguous leads; and/or T inversion ≥ 0.1 mV in two contiguous leads with prominent R-wave or R/S ratio >1].

Myocardial infarction: Periprocedural MI.

- For percutaneous coronary interventions (PCI) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of periprocedural myocardial necrosis. By convention, increases of biomarkers greater than 3x99th percentile URL have been designated as defining PCI-related myocardial infarction
- For coronary artery bypass grafting (CABG) in patients with normal baseline troponin values, elevation of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 5x 99th percentile URL plus either new pathological Q waves or new LBBB or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium, have been designed as defining CABG - related myocardial infarction.

Non fatal stroke. Stroke is defined as the presence of acute neurological deficit thought to be of vascular origin with signs or symptoms lasting greater than 1 hour. Subarachnoid hemorrhage may not cause focal deficit.

On the basis of clinical symptoms, autopsy and/or CT/MRI, strokes will be classified as:

- a) definite or probable ischemic stroke,

- b) definite hemorrhagic stroke, (for both, a & b, confirmed by CT, MRI scan),
- c) subarachnoid hemorrhage, (a CT scan or cerebrospinal fluid report must be available showing evidence of bleeding in the subarachnoid space),
- d) uncertain or unknown type of stroke.

Hemorrhagic stroke does not include hemorrhage secondary to cerebral infarct, into a tumor, into a vascular malformation or post-traumatic hemorrhage.

Transient Ischemic Attack (TIA). Acute disturbance of focal neurological or monocular (amaurosis fugax) function with symptoms lasting less than 24 hours and thought to be due to vascular mechanism.

Major hemorrhage. Major bleeding is defined as bleeding associated with any of the following:

- Drop in hemoglobin of at least 5g/dl,
- Significant hypotension with the need for inotropic agents,
- Intraocular bleeding leading to significant loss of vision,
- Requirement for a transfusion of at least of 2 units of red blood cells or equivalent whole blood.

Minor hemorrhage. Minor bleeding is defined as any other bleeding requiring modification of the drug regimen of the patients. Bleeding clearly due to trauma or to some other factors e.g. peptic ulcer would not be a cardiovascular admission.

Systemic arterial embolism. Clinical history consistent with acute loss of blood flow to a peripheral artery which is supported by evidence of embolism from surgical specimens, autopsy, angiography or other objective testing.

Unstable angina. Cardiac biomarkers are negative for myocardial necrosis. Clinical presentation (one of the following) with cardiac symptoms considered to be myocardial ischemia on final diagnosis:

- Rest angina,
- New onset severe angina (CCS grading scale \geq III),
- Increasing angina (intensity, duration and/or frequency) with an increase in severity of at least 1 CCS class.

AND

New or worsening ST or T wave changes on ECG. ECG changes should satisfy the following criteria for acute myocardial ischemia in the absence of LVH and LBBB:

- ST elevation,
- New transient (known to be less than 20 minutes) ST elevation at the J-point in two contiguous leads with the cut-off point,
- ≥ 0.2 mV in men or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads,
- ST Depression and T wave changes,
- New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads and/or T inversion ≥ 0.1 mV in two contiguous leads with prominent R-wave or R/S ratio >1 ,

OR

- Need of urgent coronary revascularization.

Other cardiovascular causes

- Coronary Angiography
- CABG/PTCA
- Atrial/Ventricular arrhythmias
- PM implantation
- ICD Implantation
- Biventricular pacing implantation
- Pulmonary embolism

- Other causes

Non cardiovascular causes

- Neoplasia
- Diabetes
- Renal Failure
- Bronchopulmonary
- Sepsis
- Thoracic pain

Other non cardiovascular causes.

Supplemental Table 1. Coronary angiography and procedures.

	Total (N= 410)	CsA (N= 207)	Control (N= 203)	P value
Catheter access artery				0.82
Femoral	85 (20.7)	42 (20.3)	43 (21.2)	
Radial	325 (79.3)	165 (79.7)	160 (78.8)	
Culprit lesion TIMI-flow				0.44
0/1	2 (0.5)	2 (1.0)	0 (0.0)	
LM	198 (48.4)	99 (48.1)	99 (48.8)	
LAD	53 (13.0)	27 (13.0)	26 (12.8)	
LCX	133 (32.5)	64 (31.1)	69 (34.0)	
RCA	3 (0.7)	3 (1.5)	0 (0.0)	
PDA	6 (1.5)	4 (1.9)	2 (1.0)	
DIAG	13 (3.2)	7 (3.4)	6 (3.0)	
OM	1 (0.2)	0 (0.0)	1 (0.4)	
others				
TIMI-flow before PCI				0.09
0	342 (83.4)	179 (86.5)	163 (80.3)	
1	68 (16.6)	28 (13.5)	40 (19.7)	
PCI performed	406 (99.0)	204 (98.6)	202 (99.5)	0.32
Time from symptom onset to time first antegrade flow	180 ±67	178 ±69	183 ±65	0.52

No. of stents implanted				0.70
0	13 (3.2)	6 (2.9)	7 (3.5)	
1	271 (66.7)	138 (67.7)	133 (65.8)	
2	93 (23.0)	47 (23.0)	46 (22.8)	
3	25 (6.1)	10 (4.9)	15 (7.4)	
4	4 (1.0)	3 (1.5)	1 (0.50)	
Type of stent				0.28
Drug eluting	290 (71.4)	153 (75.0)	137 (67.8)	
Bare metal	102 (25.1)	45 (22.0)	57 (28.2)	
None	14 (3.5)	6 (3.0)	8 (4.0)	
Max pressure (atm) balloon dilation	15.1 ± 3.5	15.0 ± 3.7	15.2 ± 3.2	0.56
Total inflation time (s)	30 [20-50]	30 [20-45]	30 [20-50]	0.44
Thrombus aspiration, %	275 (67.7)	144 (70.6)	131 (64.9)	0.22
TIMI – flow after PCI				0.28
0	6 (1.5)	3 (1.5)	3 (1.5)	
1	3 (0.7)	3 (1.4)	0 (0.0)	
2	35 (8.6)	20 (9.8)	15 (7.4)	
3	362 (89.2)	178 (87.3)	184 (91.1)	
Rentrop grade 0	382 (96.2%)	195 (97.5%)	187 (94.9%)	0.04
1	9 (2.3%)	5 (2.5%)	4 (2.0%)	
2	6 (1.5%)	0	6 (3.1%)	
3	0	0	0	
Patients with myocardial blush grade 2-3 at coronary angiography*	322 (81.1%)	159 (79.5%)	163 (82.7%)	0.41

LM=left main; LAD=left anterior descending; LCX=left circumflex; RCA=right coronary artery; PDA=posterior descending artery; DIAG=first diagonal; OM=obtuse marginal.

*400 recordings of the final control coronary angiography were readable.

Supplemental Table 2. Echocardiographic data from intention to treat population.

	Day 4				Month 6			
	Total (n=392)	CsA (n=197)	Control (n=195)	P value	Total (n=354)	CsA (n=176)	Control (n=178)	P value
Heart rate (bpm)	68.7± 10.8	68.5±10.3	68.8±11.3	0.79	63.1±9.7	63.5±9.5	62.8±9.8	0.48
Systolic blood pressure (mmHg)	117.7±15.3	117.3±15.0	118.1±15.6	0.65	127.1±14.7	126.7±14.6	127.4±14.8	0.66
Diastolic blood pressure (mmHg)	70.7±9.9	71.7±9.3	69.8±10.4	0.09	76.4±8.8	76.7±8.1	76.2±9.4	0.61
LV end-diastolic volume (mL)	98.3±26.9	99.9±27.2	96.7±26.5	0.26	106.8±35.5	109.3±37.1	104.3±33.7	0.20
LV end-systolic volume (mL)	48.1±19.5	49.8±19.3	46.4±19.6	0.10	50.4±27.3	51.9±27.9	48.8±26.6	0.30
LV end-diastolic volume index (mL*m ⁻²)	51.8±12.9	52.4±12.9	51.2±12.8	0.37	56.2±17.7	57.2±18.2	55.1±17.1	0.29
LV end-systolic volume index (mL*m ⁻²)	25.4±9.9	26.1±9.7	24.6±10.2	0.15	26.5±14.1	27.2±14.2	25.8±14.0	0.38
LV ejection fraction (%)	50.6±9.4	50.1±9.1	51.1±9.7	0.29	54.1±9.6	53.7±9.5	54.4±9.6	0.50
Mean LV wall motion score	1.46 ±0.29	1.47±0.28	1.44±0.30	0.34	1.35±0.34	1.35±0.35	1.34±0.34	0.78
LV akinetic/dyskinetic segments (%)	17.4±14.8	17.6±14.9	17.2±14.9	0.77	12.2±14.2	11.8±14.4	12.6±14.0	0.59

Data are presented as mean±standard deviation.

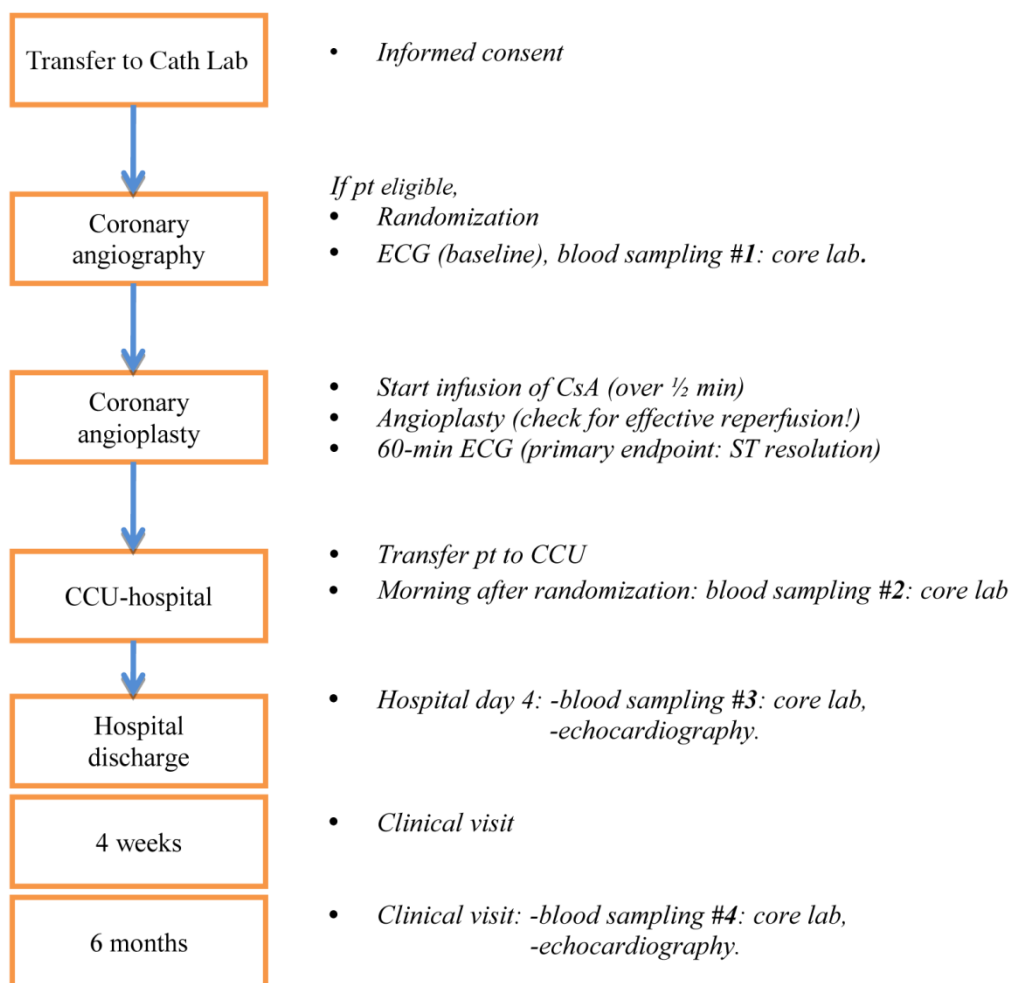
Supplemental Table 3. Echocardiographic data in the sub-analysis .

	Day 4				Month 6			
	Total (n=348)	CsA (n=171)	Control (n=177)	P value	Total (n=314)	CsA (n=153)	Control (n=161)	P value
Heart rate (bpm)	68.4± 11.0	68.4± 10.6	68.5± 11.4	0.97	63.1± 9.6	63.5± 9.3	62.8± 9.9	0.55
Systolic blood pressure (mmHg)	118.0± 15.2	117.9± 14.8	118.2± 15.6	0.86	127.7± 14.4	127.4± 14.1	127.9± 14.7	0.77
Diastolic blood pressure (mmHg)	71.0± 9.6	72.2± 8.8	69.9± 10.2	0.06	76.7± 8.7	76.9± 7.9	76.4± 9.3	0.59
LV end-diastolic volume (mL)	97.4± 26.3	99.4± 27.2	95.5± 25.3	0.17	105.5± 33.9	109.9± 36.2	101.2± 31.1	0.03
LV end-systolic volume (mL)	47.1± 18.5	49.2± 18.9	45.0± 17.9	0.04	49.2± 26.6	52.2± 28.1	46.3± 25.0	0.06
LV end-diastolic volume index (mL*m ⁻²)	51.5± 12.4	52.3± 12.8	50.6± 11.9	0.22	55.5± 16.9	57.5± 17.9	53.5± 15.7	0.04
LV end-systolic volume index (mL*m ⁻²)	24.8± 9.3	25.8± 9.6	23.9± 9.1	0.06	25.9± 13.8	27.3± 14.4	24.5± 13.1	0.08
LV ejection fraction (%)	51.1± 9.0	50.4± 9.0	51.8± 9.0	0.17	54.5± 9.5	53.9± 9.8	55.1± 9.3	0.24
Mean LV wall motion score	1.4± 0.3	1.5± 0.3	1.4± 0.3	0.21	1.3± 0.3	1.4± 0.4	1.3± 0.3	0.33
LV akinetic/dyskinetic segments (%)	16.9± 14.5	17.4± 14.8	16.4± 14.3	0.54	11.7± 14.0	11.8± 14.7	11.6± 13.3	0.88

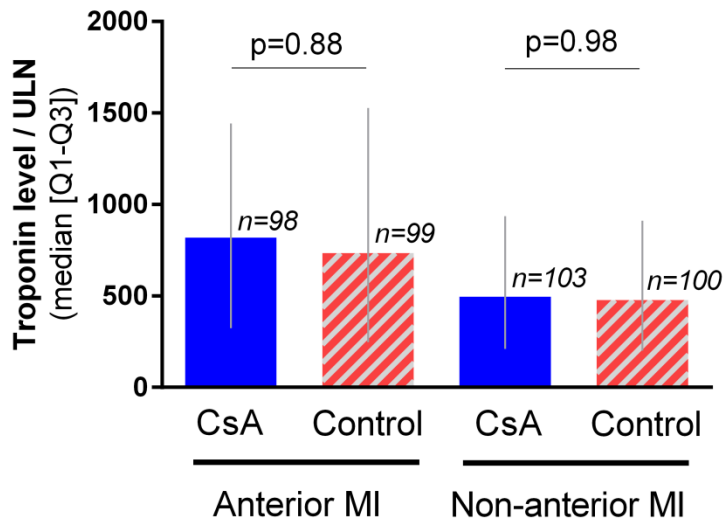
Data are presented as mean±standard deviation.

‡ patients included in the sub-analysis were those without protocol violations and optimally reperfused (TIMI=3) after PCI

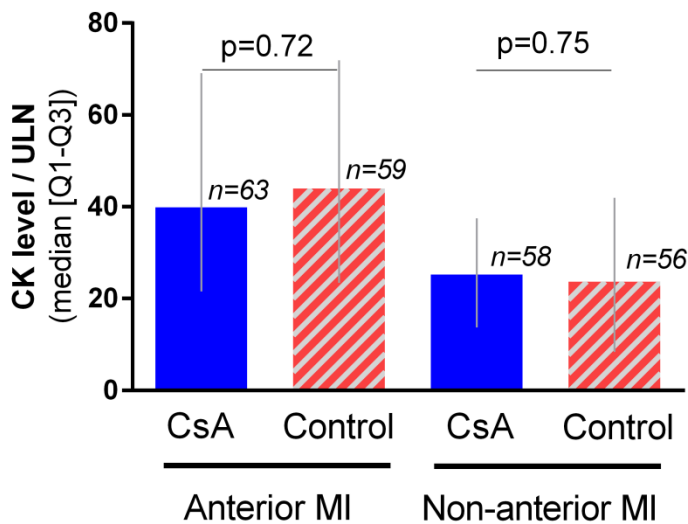
Supplemental Figure 1. Flow chart of the CYCLE study.



Supplemental Figure 2. Effect of cyclosporine A on circulating peak levels of cardiac troponins (upper panel) and creatine kinase (lower panel) measured locally at the clinical centers. Patients have been stratified by MI site. Peak levels of cardiac troponins and CK are normalized by the upper limit of normal at each site. The number of patients in each group is shown above corresponding bars. P for Wilcoxon test.



2-way ANOVA
 Treatment: p=0.91
 Site of MI: p=0.004
 Interaction treatment*site:p=0.89



2-way ANOVA
 Treatment: p=0.63
 Site of MI: p<0.0001
 Interaction treatment*site:p=0.99

Supplemental Figure 3. Effect of cyclosporine A on circulating levels of (a) cardiac troponins and (b) creatine kinase measured locally at the clinical centers. Values have been normalized by the ULN of individual clinical chemistry laboratories and shown as median [Q1-Q3].

