
# Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) Trial

## CGA Ancillary Data (Case-Cohort Design for Chromogranin A) Limited Access Data Set Documentation

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# 1 Overview of the CGA Ancillary Limited Access Data Set

This CD contains documentation and data comprising the CGA Ancillary Limited Access Data Set for the Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) trial. This data release includes data collected as ancillary data to the main PEACE trial. These data include the biomarker, chromogranin A. The commercial purpose data set is the same as the non-commercial data set, so only one data set is provided.

# 2 Overview of the Main Study Limited Access Data Set

The Limited Access Data Set for the Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) trial is available as a separate data set. Data from the main study includes baseline and follow-up data collected from initiation of the trial (November 1996) through the conclusion of the trial (December 2003).

# 3 PEACE Publications and Ancillary Studies Committee

The PEACE Publications and Ancillary Studies Committee plans to remain active and requests that investigators share their proposals/analysis plans with the Committee so that the Committee can encourage collaborations and avoid redundancies. Please send an e-mail to Drs. Eugene Braunwald, Marc Pfeffer and Bernard Gersh, expressing your interest in and your proposed use of the PEACE limited access data set. Their e-mail addresses are: EBraunwald@partners.org, MPfeffer@rics.bwh.harvard.edu, Gersh.Bernard@mayo.edu

# 4 Description of the Trial

## 4.1 Purpose

The goal of the PEACE trial was to test whether ACE-inhibitor therapy, when added to modern conventional therapy, would reduce the rate of nonfatal myocardial infarction, death from cardiovascular causes, or coronary revascularization in low-risk patients with stable coronary artery disease and normal or slightly reduced left ventricular function.

## 4.2 Overall Study Design

The trial was a double-blind, placebo-controlled study in which 8290 patients were randomly assigned to receive either trandolapril at a target dose of 4 mg per day (4158 patients) or matching placebo (4132 patients). Patients underwent randomization from November 1996 to June 2000 and were followed at six-month intervals for up to 7 years (median, 4.8 years) through December 2003.

## 4.3 Inclusion Criteria

- Age 50 years or older
- Coronary artery disease documented by at least one of the following:
  - Myocardial infarction at least 3 months before enrollment

- Coronary-artery bypass grafting or percutaneous transluminal coronary angioplasty at least 3 months before enrollment
- Obstruction of ≥50% of the luminal diameter of at least one native vessel on coronary angiography

- Left ventricular ejection fraction >40% on contrast or radionuclide ventriculography or echocardiography, a qualitatively normal left ventriculogram, or the absence of left ventricular wall-motion abnormalities on echocardiography (a subgroup of echocardiograms was reviewed by a core laboratory to confirm eligibility)
- Toleration of the medication and successful completion of the run-in phase, with ≥80% compliance with the medication

## 4.4 Exclusion Criteria

- Current use of or a current condition requiring use of an ACE inhibitor or a contraindication to ACE inhibitors
- Current use of an angiotensin II–receptor antagonist
- Hospitalization for unstable angina within the preceding 2 months
- Valvular heart disease deemed to require surgical intervention
- Coronary-artery bypass grafting or percutaneous transluminal angioplasty within the preceding 3 months
- Planned elective coronary revascularization
- Serum creatinine >2.0 mg/dl (177 μmol/liter)
- Serum potassium >5.5 mmol/liter
- Limited chance of 5-yr survival
- Psychosocial condition precluding long-term adherence
- Unable or unwilling to give consent
- Female sex and of childbearing potential and not using contraception
- Current use in a research trial of medication not approved by the U.S. Food and Drug Administration or the Health Protection Branch of the Canadian Department of National Health and Welfare

## 4.5 Study Organization

The PEACE trial was sponsored by the National Institutes of Health (NIH), National Heart, Lung, and Blood Institute (NHLBI). An independent data and safety monitoring board reviewed patient safety data and interim results. An executive committee and a steering committee provided scientific leadership and a clinical and statistical coordinating center coordinated all elements of the trial. An Italian coordinating center oversaw the data collection process in Italy. Patients were enrolled from 187 clinics in the United States (including Puerto Rico), Canada, and Italy. Study medication was distributed by a central pharmacy. All specimens went to a central laboratory and a morbidity and mortality review committee adjudicated outcomes. A publications and ancillary studies committee reviewed and approved proposals, manuscripts and presentations.

## 4.6 Outcomes Documentation and Adjudication

The following outcomes were classified by centrally-trained, local staff and confirmed by outcomes staff at the coordinating center through review of medical records:

- Coronary-artery bypass grafting

- Percutaneous coronary intervention
- Hospitalization for unstable angina
- Peripheral vascular disease requiring angioplasty, bypass grafting, or aneurysm repair
- Hospitalization for congestive heart failure
- Hospitalization for cardiac arrhythmia

A morbidity and mortality review committee conducted a further review of medical records, and classified and adjudicated the following outcomes:

- Cardiovascular death
- Non-cardiovascular death
- Death from unknown causes
- Myocardial infarction

Further review of medical records by one of the morbidity and mortality review committee members was conducted for the following outcome:

- Stroke

All reviews were blinded to the study intervention.

The following outcome was ascertained by patient self-report:

- New-onset diabetes

# 5 Description of the CGA Ancillary Data

## 5.1 Purpose

To examine whether the concentration of chromogranin A (CgA) is associated with outcomes in PEACE patients who provided EDTA plasma specimens.

## 5.2 Overall Biospecimen Collection in PEACE

Blood and urine samples (serum, EDTA plasma, citrate plasma and urine) were obtained at the clinical centers. Blood samples were centrifuged at room temperature, processed per standard laboratory methods, then frozen within 90 minutes of collection at -20°C at the individual centers. Within 2 weeks (clinics with a -20°C freezer) or 2 months (clinics with a -70°C freezer) of collection, samples were shipped on dry ice via over-night delivery to the PEACE central laboratory for storage at -70°C. A baseline blood sample was obtained in approximately 3786 participants. A follow-up blood sample was obtained in approximately 2081 participants whom also had a baseline blood sample and in 696 participants whom did not have a baseline blood sample. A baseline urine sample was obtained in approximately 3414 participants. A follow-up urine sample was obtained in approximately 1891 participants whom also had a baseline urine sample and in 606 participants whom did not have a baseline urine sample. The follow-up sample was not standardized with regards to time since randomization and was obtained in a time period from just after randomization to 6 years, 3 months from randomization; for a median

of 3 years. Sample collection was not standardized with regards to time of day or time since last meal. All participants from the US and Canada were eligible for biospecimen collection.

## 5.3 Biomarker Information

Biomarker measurements were performed by personnel blinded to clinical outcomes and treatment allocation.

A never before thawed tube of EDTA plasma was shipped frozen from the PEACE central laboratory on dry ice to the University of Oslo, Norway. EDTA plasma was then thawed and aliquots shipped frozen from the University of Oslo on dry ice to the University of Aarhus, Denmark, where samples were analyzed for CgA. CgA was measured by a commercially available ELISA-assay (Code no. K0025, DakoCytomation, Glostrup, Denmark) in accordance with the instructions of the manufacturer. The detection limit of the assay was 7.0 U/L, and the intra- and interassay coefficients of variance (CV) were below 5 and 10%, respectively.

Baseline CgA was measured in 1331 participants selected for a nested case-cohort analysis.

## 5.4 Study Design

The study design is a nested case-cohort study design, conducted among patients providing EDTA plasma samples.

### 5.4.1 The case-cohort approach

The case-cohort design was proposed by Prentice (1986) as an efficient sub-sampling mechanism for survival studies. It is used when data cannot be collected on all patients within a cohort. It is also particularly useful when more than one case group will be studied.

This approach uses a two-step sampling process. First, patients are randomly selected from the study cohort regardless of their event status (sub-cohort). Then a second group of patients are selected with the event of interest (cases). Some of the patients in this second group may also be in the first group. The two groups are analyzed together in a Cox regression model. Modifications to the parameters (β-hat and the variance estimators) are made to correct for the sampling design. Therneau and Li (1998) summarize these methods, which are described below.

Self and Prentice (1988) derived an appropriate parameter estimate β-hat and variance estimator for the design described in Prentice (1986) and proved results on their asymptotic distribution. The β-hat is estimated from the random sub-cohort. The variance estimate is algebraically complex as it must correct for over sampling of cases with an event (the usual estimate of the variance will overestimate the precision of β-hat).

Lin and Ying (1993) discussed Cox regression with incomplete covariate measurements and treated the case-cohort design as a special case of their general results. The method uses all members of the sub-cohort and all failures outside the sub-cohort who are "at risk."

Barlow (1994) gives a robust variance estimate based on the approximate jackknife. This method uses a survey sampling approach to allow for more complicated sampling mechanisms. The betas are estimated using sampling weights.

### 5.4.2 Methods for this PEACE case-cohort biomarker study

- ***Inclusion criterion for this case-cohort biomarker study:***
  - Provided baseline EDTA plasma

  Based on this criterion, 3780 PEACE patients were eligible for this case-cohort biomarker study.

- Additional criteria for the case group (outcomes):
  - Death from cardiovascular causes (adjudicated), or
  - Non-fatal myocardial infarction (adjudicated), or
  - Non-fatal congestive heart failure (reviewed), or
  - Non-fatal stroke (reviewed)

- ***Sub-cohort selection (representative sample of the cohort)***
  We randomly selected a sub-cohort from the N=3780 pool of patients with a baseline EDTA plasma sample. This sub-cohort contains patients without events and also contains patients with events as well (i.e. this sub-cohort is representative of the cohort from which it came).

- ***Case group selection (patients with the outcome)***
  A second group includes all patients with the outcomes of interest (death from cardiovascular causes, non-fatal myocardial infarction, non-fatal congestive heart failure or non-fatal stroke) among the N=3780 pool of patients. Note that some of the patients in this case group are also in the sub-cohort.

- ***Results of the sub-cohort and case selection***
  - N=1331 individual patients providing data for this case-cohort biomarker study
  - N=1455 in the analysis data set:
    - 1025 in the sub-cohort (901 controls and 124 cases treated as controls)
    - 430 in the case group (death from cardiovascular causes, non-fatal myocardial infarction, non-fatal congestive heart failure or non-fatal stroke)

### 5.4.3 Analysis

The Self and Prentice estimate of B-hat can be computed using PHREG (proportional hazards regression) with an offset term in the model.

Note that patients who are in both the sub-cohort and the case group are entered as two separate observations. These patients will have status = censored for the observation in the sub-cohort, and status=event for the observation in the case group. The variances are corrected by adding a correction term to the variance terms returned by the Cox model. The correction term uses the dfbeta residuals multiplied by the proportion of cases sampled.

### 5.4.4 Case-cohort references

Barlow, W.E. Robust variance estimation for the case-cohort design. Biometrics 1994 50, 1064-1072.

Binder, D.A. Fitting Cox's proportional hazards models from survey data. 1992 Biometrika 79, 139-47.

Lin, D.Y. and Ying, Z. Cox regression with incomplete covariate measurements. J. American Statistical Association, 88, 1341-9.

Prentice, R.L. A case-cohort design for epidemiologic cohort studies and disease prevention trials. Biometricka 1986 73 1-11.

Self, S.G. and Prentice, R.L. Asymptotic distribution theory and efficiency results for case-cohort studies. Annals Statistics 1988 16, 64-81.

Therneau, Terry M. and Hongzhe Li. Computing the Cox model for Case Cohort Designs. Technical Report Series, Section of Biostatistics, Mayo Clinic, Rochester, Minnesota June 1998. (Subsequently published in lifetime Data Analysis 1999 Jun; 5(2):99-112).

# 6 Files and Documents on the CD

## 6.1 Limited Access Data Set as a SAS CPORT Transport Library

- *CGA.LADS* (SAS CPORT transport library)
    - This transport library can be imported into any system (PC, Unix, Mainframe OS, etc.). For instructions on importing the file, please see Section 8 "***Installing the SAS Files.***" Conversion of the files using CIMPORT is required.

## 6.2 Limited Access Data Set as a PC SAS Data Set

- *CGA.sas7bdat*
    - For investigators that use PC SAS, this file can be read in directly by PC SAS versions 7, 8 and 9. No import program is necessary.

## 6.3 Import Program

- *PEACE_Import.sas* (SAS program that can be used to import the file)

## 6.4 Readme Document (this document)

- *PEACE readme CGA.pdf* (pdf document)

# 7 Description of System Requirements

- CD-ROM drive
- A working installation of the SAS system version 8 or later

# 8 Installing the SAS Files

## 8.1 PC SAS Users:

- Copy the PC SAS data set from the CD to a directory on the system running the SAS software. The PC SAS format file can be read in directly by PC SAS versions 7, 8 and 9. No import program is necessary.

## 8.2 All Other Users (Unix, Mainframe OS, etc.):

- Transfer the SAS CPORT transport library from the CD to a directory on the system running the SAS software. The transfer must be made using binary format.

- Execute a program such as the one below to read the transport library and convert it to a native SAS library format suitable for your operating system. Remember to change the directory and file names appropriately. This program is included on the CD, called "*PEACE_Import.sas*"

```
filename xin 'C:\Peace\SAS Data\CGA.LADS';
LIBNAME CGA 'C:\Peace\SAS Data';
PROC CIMPORT LIBRARY= CGA INFILE=XIN MEMTYPE=ALL;
run;
```

- The imported data set is:
  - *CGA.sas7bdat* (SAS data file)

# 9 Contents of the CGA Ancillary Limited Access Data Set

The table below lists all variables in the CGA ancillary limited access data set. The data set file includes a participant ID (NEW_ID) that links all data set files. Merge data files by this variable.

| Variable | Comments |
|---|---|
| NEW_ID | Merge data files by this variable |
| B_CGA | Baseline CgA<br>Units = U/L<br>Recoded CgA > 120.0 = 228.0 |
| CASE_CVDEATH | Cardiovascular (CV) death case group |
| CASE_MI | Non-fatal myocardial infarction (MI) case group |
| CASE_CHF | Non-fatal congestive heart failure (CHF) case group |
| CASE_STROKE | Non-fatal stroke case group |
| SUB_COHORT | Sub-cohort group |