Framingham Risk Prediction of Coronary Heart Disease in Inflammatory Bowel Disease: a Retrospective Analysis

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A. Study Purpose and Rationale

Goals

The goal of this study is to determine whether global coronary heart disease (CHD) risk models such as those derived by the Framingham Heart Study predict CHD risk in patients with inflammatory bowel disease.

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is an immune-mediated chronic disorder of the gastrointestinal tract consisting primarily of Crohn's disease (CD) and ulcerative colitis (UC). It affects nearly 1.4 million US citizens with a peak age of onset between 15 - 30 years and prevalence ranges of 37-246 cases per 100,000 persons for UC and 26-199 cases per 100,000 persons for CD.[1] The pathophysiology of IBD has not been determined; however, current theories suggest the presence of maladaptive inflammatory response in a genetically susceptible host.[2] IBD can exert effects outside the gastrointestinal tract. Population based studies have detailed such extra-intestinal manifestations which most often include eye, skin, biliary and joint involvement.[3]

Inflammation and Heart Disease

Many inflammatory diseases are associated with premature cardiac events namely, rheumatoid arthritis and systemic lupus erythematosis.[4,5] Furthermore, inflammation has a primary role in coronary artery disease (CAD).[6] It is therefore plausible to assume other chronic inflammatory diseases would accelerate cardiac disease. However, the association between IBD and heart disease is not clear. In fact, population studies do not report such an association.[,7] There is also conflicting data on the relationship between IBD and surrogate markers of heart disease such as increased intimal thickness.[8,9]

Framingham Heart Study

The landmark Framingham Heart Study identified characteristics associated with heart disease and derived predictive mathematical models. These factors include sex, age, blood pressure, total cholesterol, low-density lipoprotein, high-density lipoprotein, smoking status and diabetes status to determine coronary heart disease over a five or ten year period.[10] National panels advise physicians to utilize global heart disease risk score assessments for their patients.[11]

IBD and Heart Disease

Shekhar et. al, compared the Framingham risk score in patients with IBD and CAD versus patients with CAD alone. Their results suggest an increased Framingham risk score in patients in the CAD group when compared with IBD + CAD and adjusted for age and sex.[12]

Another study demonstrated increased angina (stable, unstable) and acute myocardial infarction in IBD patients despite lower rates of traditional CAD markers such as hypertension, dyslipidemia and diabetes.[13] Furthermore, transthoracic echocardiographic analysis of 68 patients found structural echocardiographic changes, mitral valve prolapse and pericardial effusion more often in Crohn's disease without any change in ejection fracture.[14] While IBD is associated with increased venous thrombotic events[15], a retrospective IBD cohort study demonstrated evidence for increased arterial thrombotic events namely acute mesenteric ischemia and for women with IBD above 40 an increased myocardial infarction risk.[16]

The goal of this study is to compare the Framingham risk score prediction in IBD patients with actual CHD events in that population. Our hypothesis is that IBD independently confers a CHD risk not accounted by the Framingham calculation.

Limitations of the study include the cross-sectional data obtained from a retrospective analysis, other heart disease risk factors not assessed in the Framingham Risk Calculator such as chronic kidney disease, cardiac side effects of IBD therapies and the presence of additional inflammatory illnesses. Patients with chronic illnesses also are evaluated by physicians more frequently and may undergo more testing which may identify a cardiac illness prematurely. For this reason coronary imaging is not considered as an end point.

Additionally, the Framingham study was designed for age ranges from 30-74 with heart disease strictly defined to include myocardial infarction, CHD death, angina and coronary insufficiency.[10]

B. Study Design and Statistical Analysis

Study Design

This retrospective cohort study will consist of a medical chart review of 289 patients with documented IBD. The patients will be analyzed for predicted cardiac events based on the Framingham risk calculator and compared to observed events in the same cohort. As such, the observed cardiac events will serve as the cases and the Framingham predicted cardiac events would serve as the controls. The primary outcome will be cardiac events identified by chart analysis. Patients will be excluded from the study if they are less than 30 or greater than 74 years of age at initial report of an IBD diagnosis or have

incomplete data to calculate the Framingham score. The Framingham Risk Calculation for CHD can determine risk from 4-12 years and requires patient age, gender, smoking status, presence of diabetes, left ventricular hypertrophy (by EKG criteria), systolic blood pressure, total cholesterol and high-density lipoprotein levels.[17]

Definition of variables

- Cardiac events are defined as myocardial infarction, CHD death, angina, or coronary intervention such as PCI or CABG.
- Framingham definition of CHD includes myocardial infarction, CHD death, angina, and coronary insufficiency.
- IBD is defined as either ulcerative colitis or Crohn's disease based on endoscopic, histologic or pathology data

Statistical Analysis

The data will compare the expected, control event rate based on the Framingham risk calculator with the observed, experimental event rate at 5 years by utilizing a one sample Chi-square test for categorical data. Using prior studies as a point of reference we postulate a 7% control event rate and expect to find a 5% effect or a 12% observed, experimental event rate in the IBD population. A sample size of 289 subjects will power the study at 80% with a P value of 0.05 to detect a statistically significant difference. Demographic data can be further analyzed using t-test analysis for continuous variables and Chi-square analysis for categorical data. Subgroup analysis will be performed based on Framingham risk criteria, number of IBD flares, active IBD treatment and the presence of other identified chronic inflammatory illnesses.

C. Study Procedure

The study will utilize systematic chart review of medical records of patients with known diagnosis of IBD, as previously defined. Patients will have their initial Framingham risk score calculated and then compared to actual cardiac events at a 5-year follow up.

D. Study Drugs:

No drugs will be used in this study.

E. Medical Device:

No medical devices will be used in this study.

F. Study Questionnaires:

No questionnaires will be used in this study

G. Study Subjects

Medical record data from 289 patients from the Columbia Presbyterian Medical Center (CPMC), Division of Digestive and Liver Disease with endoscopic evidence of IBD will be further classified for 5-year CHD risk based on the Framingham risk score. All patients will be between 30 and 74 years of age in concordance with the validity of the Framingham risk calculator. Subjects will be analyzed with at least 5-year follow-up data. This would limit the study to patient entry at 2005.

Inclusion criteria

- Individuals aged 30 to 74 years
- Patients seen in consultation for IBD at CPMC
- Endoscopic or biopsy documentation of IBD
- Availability of patient data for Framingham risk calculation

Exclusion criteria

- Persons not meeting the above criteria and incomplete data necessary to calculate the Framingham risk score.

H. Recruitment of Subjects

Patient data will be obtained from medical chart review and no additional patient recruitment will be required as part of this study.

I. Confidentiality of Study Data:

Study data will be coded without the use of names, medical record numbers, social security numbers, initials, birthdates, demographic or other identifiable personal information. A unique code number will be generated for each study subject and data will be stored at a secure location available only to the study investigators.

J. Potential Conflict of Interest:

None of the investigators has any proprietary interest in any portion of the study.

K. Location of the Study:

All analysis will be conducted at the Columbia-Presbyterian Medical Center.

L. Potential Risks:

Patients will not incur any additional risk by participating in this study.

M. Potential Benefits:

Patients will not have any direct benefit by participating in this study.

N. Alternative Therapies:

No experimental studies are included in this study.

O. Compensation to Subjects:

Subjects are not eligible for any compensation as part of this study.

P. Costs to Subjects:

Subjects will not incur any costs due to this study.

Q. Minors as Research Subjects:

Minors will be excluded from study participation.

R. Radiation or Radioactive Substances:

No radiation will be used in this study.

References

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