A randomized, controlled trial comparing the effect of differing education strategies on adherence to HMG CoA reductase inhibitors for primary prevention

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A. Study Purpose and Rationale

The purpose of the study is to determine if two differing educational strategies, one comprehensive and one which is specifically targeted at relaying information on the low toxicity and favorable side effect profile of HMG CoA reductase inhibitors (statins) has an effect on adherence to therapy for primary prevention.

Coronary disease is the leading cause of death worldwide and increased levels of cholesterol, in particular low density lipoprotein cholesterol (LDL-C), have been shown to be risk factors in predicting adverse cardiac events. Statin therapy has been shown to be beneficial in secondary prevention by reducing coronary events and mortality in patients with known disease[1, 2]. But, given the profound morbidity and mortality associated with CAD, methods of primary prevention are critically important and several large trials have shown the benefit of statin therapy in this regard. The West Scotland Coronary Prevention Study (WOSCOPS) showed lipid lowering therapy (LLT) was associated with a 32 percent reduction in rate of coronary events and a 22 percent reduction in total mortality [3]. The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) also showed benefit of therapy in patients with no history of coronary disease, and reported a similar 37 percent reduction in composite endpoint which included fatal or nonfatal myocardial infarction, sudden death or unstable angina [4].

However, despite the overwhelming benefit, good safety profile and low cost of statin therapy, the rates of non-adherence are high even in patients with known disease [5]. Not surprisingly, this rate is even higher in patients targeted for primary prevention, and on average is reported to be near 50 percent [5-7]. A large retrospective study using a health maintenance organization database showed the risk of discontinuation of therapy in the clinic setting is highest in the first 6 months, estimating that about 20 percent of patients stop during this time period. This study also showed that significant predictors of discontinuation were age less than 50 years, female sex and previous LLT [8]. Another prospective trial, from a large academic medical center in New York City, again found similarly poor adherence. In this study, veterans self-reported discontinuation at a rate of 55 percent at 6 months and after analysis of questionnaires regarding reasons for stopping the medication, the following were found to be predictive: expected short treatment duration, low perceived risk of myocardial infarction, concern about potential harm from statins, being Hispanic and younger age [9].

Given these concerns of non-adherence, multiple studies have been done to try to identify strategies which may improve compliance. For instance, physician follow-up and provider continuity have been shown to improve adherence [10], as have follow-up lipid testing and physician visits within first 3 months of initiation [11]. In fact, those who then showed early reduction in LDL-C with early testing, went on to have higher rates of long term adherence at 3 years [12].

In addition to close follow-up, initial studies also suggest that educating patients has an impact on adherence. A randomized trial of patients on statins, primarily for secondary prevention, showed a program of education involving discussion of efficacy, pharmacokinetic profile, side effects, expected duration of treatment, and mortality and morbidity benefit, resulted in an almost two-fold increase in likelihood of adherence at 15 months [13]. The above results highlight the possible benefit of such educational strategies, and this study hypothesizes that discussing above key topics with patients will improve adherence in a population of patients on therapy for primary prevention, as well. Additionally, given high observational reports that concern for toxicity is the primary reason for discontinuation of statins in this particular population, we further believe that a more targeted educational strategy addressing this issue may give comparable or more favorable results as the comprehensive education.

B. Study Design and Statistical Analysis

The study will be longitudinal, interventional and prospective involving three groups which will be randomized either to (1) control group (2) comprehensive education group (3) targeted education group.

All groups will have a run-in period of 4 to 12 weeks in which patients will receive comprehensive education about lipid lowering therapy and drug will be initiated and titrated up in increments of 20 percent as needed until patients reach LDL levels within 10 percent of goal as indicated by ATP III guidelines [14]. Patients will then be randomized to one of the three groups and return for follow-up visit at 6 months.

The control group will receive no additional formalized education at the 6 month check-up and lipid level check. The comprehensive education group will receive a three tiered approach at 6 month check-up that will specifically reinforce the following topics: the real risk of coronary events and the benefits of statins in preventing coronary artery disease, the need to continue therapy indefinitely, and the low risk of toxicity and side-effects. The targeted education group will only have the last topic of toxicity and side-effects discussed at 6 month check-up. Education will be provided by the primary care physician at regular follow-up visits and they will be responsible for documenting discussion of three vs. one topic in their Webcis clinical note of the visit. If patients are primarily Spanish speaking, documentation of use of interpreter will also be necessary.

All groups would then return again for lipid level check at 12 and 24 months.

Primary outcome will be percent change in LDL level from time of randomization to follow-up at 12 months. Secondary outcome will be this change at 24 months and percent change in total cholesterol, HDL cholesterol and triglycerides.

CURVES study showed treatment with atorvastatin resulted in an average 45 percent reduction in LDL with a standard deviation of 10 percent [15] . Estimating a 5 percent minimum success rate, power analysis estimates 65 patients per group (195 patients total) would be needed to detect a 5 percent difference in primary outcome with a power of 80 percent and an alpha value of 0.05. Estimating attrition rate of 50 percent pre-randomization 400 patients will be recruited. Statistical analysis will be made using analysis of variance. A multi-variate regression analysis will be done at the completion of the study to investigate the effect of age, gender, race and previous LLT on percent change.

C. Study Procedure

All subjects will have fasting lipid panel, which includes total cholesterol, HDL, LDL and triglyceride levels, checked at outpatient phlebotomy during initial titration as needed to obtain goal and then at 6, 12 and 24 months. In addition, hepatic panel will be drawn at initiation if no baseline value is available in the last 6 months and will be repeated at 12 weeks as per FDA notes. Per CPMC laboratory manual, Olympus enzymatic measurement of total cholesterol, HDL cholesterol, and triglycerides are done and a calculated value for LDL are used in reported data. This testing is not beyond the scope of normal initiation of statin therapy and in fact represent standard of care as described in ATP III Guidelines and FDA.

***Visit 0: (0 weeks)** Eligible and interested study subjects sign informed consent. Coronary disease risk factors are assessed and documented. Baseline demographic data is collected including age, gender, self-described race or ethnicity, and previous history of LLT. All patients at this time will be given comprehensive education regarding therapy in accordance with ATP III guidelines [14]. If no hepatic panel is available within the last 6 months, patient will be sent to outpatient phlebotomy to have sample drawn for analysis. Patients will also be given laboratory slip to have repeat lipid panel drawn at outpatient phlebotomy, 2 to 4 weeks after initiation of therapy.

Visit 1: (4-6 weeks) Subjects will return to primary care provider, or be informed over phone, of results of repeat lipid testing and will have dose of statin titrated as needed to obtain goal LDL. Patients not at goal will be given another laboratory slip to have repeat lipid panel drawn as described above.

Visit 3: (12 weeks) If patients were not at goal they will return to primary care provider again after repeat lipid testing and will again be informed of levels and have their medication titrated as needed to obtain goal LDL. All patients will have hepatic panel repeated at this point to assess for any elevation in transaminases over baseline.

***Visit 4: (6 months)** Patients within 10 percent of goal LDL will be randomized to one of three groups at this visit. Control group will have only lipid level checked. Comprehensive and targeted educational groups will receive teaching as described previously by their primary care physician. All groups will have lipid levels reviewed with patient and be given laboratory slip for follow-up lipid testing at 12 months.

***Visit 5: (12 months)** Patients will have 12 month lipid levels reviewed with primary care physician and be given laboratory slip for follow-up lipid testing at 24 months.

***Visit 6: (24 months)** Patients will have 24 month lipid levels reviewed with primary care physician. Study wrap-up.

***All of these visits will be regular follow-up visits for patients and thus other medical issues and relevant care issues will be discussed with primary care physician as per usual follow-up visit.**

D. Study Drugs

Study drugs will be any HMG CoA reductase inhibitor, or statin, as prescribed by primary care physician. Prescription of a particular statin maybe influenced by insurance formularies, provider preference, etc. However, in general as a class, they are competitive inhibitors of HMG CoA reductase, which is the rate-limiting step in cholesterol biosynthesis thereby resulting in a reduction in intrahepatic cholesterol and an increase in LDL receptor turnover thus a reduction in LDL.

Rare, but accepted side effects are hepatic dysfunction, muscle injury and renal dysfunction [16].

E. Study Subjects

Patients will be included in the study if they receive care from "Associates in Internal Medicine"(AIM) outpatient clinic, are within 18-80 years of age, and are starting statin therapy for first time, or if patients are resuming therapy after at least one year of self-reported non-adherence and meet ATP III guidelines for requiring lipid lowering medication.

Patients will be excluded if they have history of hospitalization for myocardial infarction or unstable angina, current anginal symptoms, or documented cardiac catheterization or stress test showing ischemic disease. In addition, they will be excluded if they are unable to achieve LDL levels within 10 percent of goal during run-in period or have had history of adverse events with prior statin therapy.

F. Recruitment of Subjects

Subjects will be recruited by their own physicians, practicing at Columbia Presbyterian Medical Center. Since subjects are recruited directly from their regular outpatient provider, it is assumed that the primary physician agrees that the patient is suitable for the study, as stipulated by above criteria and current practice guidelines.

G. Confidentiality of Study Data

To insure confidentiality of all trial participants, all study data will be coded using a unique code number. Data will be stored in a secure location, accessible only to investigators.

H. Potential Conflict of Interest

No potential conflict of interest.

I. Location of Study

This study will be conducted in the AIM outpatient clinic located at Vanderbilt Clinic, second floor of Presbyterian Hospital which is part of the Columbia University Medical Center (622 West 168th Street New York, New York 10032).

J. Potential Risks

Potential risks include those accepted with initiation of statin therapy as previously described in study drug section

K. Potential Benefits

Potential benefits include reduction of cardiovascular events and possible improvement in mortality as described in study rationale.

L. Alternative Therapies

As discussed in ATP III Guidelines, alternative therapies for primary prevention include lifestyle changes such as: (1) reduced intakes of saturated fat and cholesterol, (2) increased physical activity, and (3) weight control. But, after these methods have failed additional medical therapy is standard of care and only those who meet criteria for medication will be included in this study. In addition, while other classes of medications have shown to modestly reduce LDL, statins are by far considered first line therapy.

M. Compensation to Subjects

Patients will not be compensated for participation.

N. Costs to Subjects

There are no additional costs to subjects.

O. Minors as Research Subjects

N/A

P. Radiation or Radioactive Substances

N/A

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