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Inflammation and infection as risk factors of coronary artery disease: What is the evidence?

JOSEPH B. MUHLESTEIN, M.D.

Over the past several decades, atherosclerosis and its complications has become the major health problem in the Western world with more than 50% of deaths attributed to its complications. The exact causes of atherosclerosis are not clearly known, although multiple risk factors (eg, hypertension, hyperlipidemia, diabetes, family history, and smoking) have been well described. However, these risk factors alone account for only about 50% of the total risk of experiencing cardiovascular disease. Consequently, an ongoing search is under way to discover new risk factors for atherosclerosis, as well as the basic underlying causes of progression.

A variety of new and potentially significant novel "non-traditional" risk factors have been found to be associated, to some degree, with coronary atherosclerosis, including genetic risk factors, uric acid, homocysteine or iron levels, and chronic inflammatory or infectious factors. Although each of these potentially novel risk factors may play a role in the development and progression of atherosclerosis, the exact mechanisms of their influence and how these can be modified are still under intensive study. The purpose of this review is to discuss currently available epidemiologic and basic scientific evidence relating the potential risk factors of inflammation and chronic infection for atherosclerosis.

Inflammation and heart disease: A historical perspective

Inflammation, as demonstrated by elevations of white blood cell count, C-reactive protein (CRP), or serum amyloid, has long been known to be associated with acute myocardial infarction (MI).[1] It is well known that after a patient presents with an acute MI, these systemic markers of inflammation will rise significantly over the subsequent several days, and as the patient recovers, will return closer to baseline. Recently, elevated markers of inflammation (ie, CRP and serum amyloid) have also been found in patients presenting with acute unstable angina, even in the absence of significant myocardial necrosis.[2] The question is, however: "Which is the 'chicken' and which is the 'egg'?" The increased inflammation that occurs during an acute MI has often been presumed to be secondary to myocardial necrosis which acts as a potent pro-inflammatory stimulant to the body. It has been thought that this may also be a secondary phenomenon in the case of unstable angina as well. Therefore, the presumption by some has been that acute ischemic syndromes lead to the enhancement of the inflammatory state within the body, rather than inflammation contributing to atherosclerosis.

Further support for the concept that inflammatory markers provide an independent measure of risk for atherosclerotic events comes from a prospective analysis by Ridker et al of CRP levels and risk of first MI in apparently healthy men within the Physician's Health Study.[3] In this study, mild to moderate elevations of CRP (generally all within the normal range) at baseline were found to be highly predictive of an increased relative risk of MI over the subsequent long term follow-up of the study, thus providing new evidence that low levels of chronic inflammation may predate, as well as predict, the development of ischemic heart disease.

The importance of CRP and other markers of chronic inflammation in the prediction of coronary artery disease (CAD) and MI has also been demonstrated in other studies. In an angiographic case control

BRIGHAM AND WOMEN'S HOSPITAL

A Teaching Hospital of

HARVARD MEDICAL SCHOOL

Brigham and Women's Hospital
75 Francis Street
Boston,Massachusetts 02115
Fax:(617) 732-5291
Cardiovascular Division Website:www.heartdoc.org

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study at the LDS Hospital,when compared to normal controls,[4] baseline CRP levels were significantly elevated, not only in post-MI patients, but also in patients with stable CAD and no prior history of MI. Other studies have also demonstrated that CRP is a predictor of future ischemic events in patients with known atherosclerotic heart disease.[5]

What is the underlying cause of chronic inflammation?

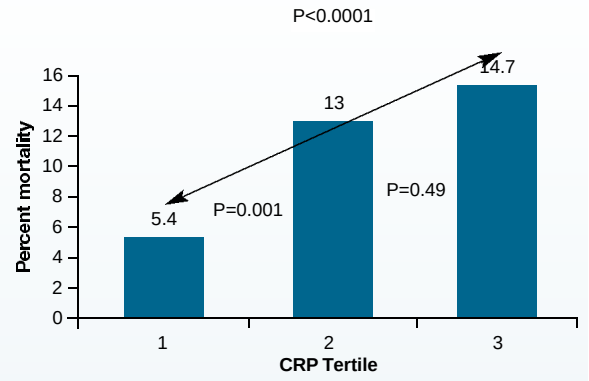
With the understanding of the significance of chronic inflammatory markers as predictors of the development and progression of atherosclerosis, a search for potential underlying causes of this chronic inflammation has begun. Two major hypotheses have been proposed: The first hypothesis is that chronic inflammation occurs as a result of the pro-inflammatory effect of a variety of lipid products, especially oxidized LDL;[6] the second is that chronic inflammation occurs as a result of some form of a chronic infectious process. Indeed, a variety of chronic infectious pathogens have been reported to be associated with coronary atherosclerosis, including:

- *Chlamydia pneumoniae*, shown to be serologically associated in case control studies,[7] as well as being present in atherosclerotic plaque.[8] In animal models, *C. pneumoniae* has been used to induce or accelerate the development of atherosclerosis.[9]
- *Helicobacter pylori*, reported to be associated through case control serologic studies[10]
- cytomegalovirus (CMV), shown to be associated in case control serologic studies[11] and directly found in atherosclerotic plaque,[12]
- a variety of other chronic viral infectious agents including herpes simplex virus one (HSV-1), herpes simplex virus two (HSV-1), and hepatitis A (HA).

However, these serologic associations are not always reproducible and there have been well-controlled negative studies for each of these proposed agents. Therefore, further studies are required to determine if and how chronic infectious agents may play a significant etiologic role in the development and progression of coronary atherosclerosis.

We recently studied 985 patients with angiographically-defined severe CAD (at least one major vessel with ≥70% stenosis) to determine whether CRP, as well as seropositivity to *C. pneumoniae*, CMV, or *H. pylori* predicts future mortality.[13] Each patient had baseline blood samples drawn at the time of their diagnostic coronary angiogram and was then followed for an average of 3 years, at which time survival status was obtained. Figure 1 shows differing mortality rates based on tertiles of CRP levels, and reveals a step-wise increase in risk of mortality based on levels. Although patients presenting with stable or unstable angina, or acute MI were included in this study, sub-analysis showed similar findings in all three groups. Figure 2 shows mortality rates based on seropositivity to *C. pneumoniae*, *H. pylori*, or CMV. Interestingly, seropositivity to either *H. pylori* or *C. pneumoniae* did not predict an increased risk of future death, whereas seropositivity to CMV was related to a three-fold increase in mortality rate. This finding was confirmed to be independent from other important determinants of risk such as age and ejection fraction by multivariable Cox regression analysis. These findings further strengthen the association between an infection-inflammatory process and CAD progression.

Figure 1. Mortality, after 3 years follow-up, of patients with known CAD, based on baseline C-reactive protein level tertiles.



The "total pathogen burden" hypothesis

Although multiple infectious agents have been serologically associated (to some degree) with CAD, none of these associations are extremely strong and they generally have odds ratios that are <2.0. Therefore, it seems unlikely that any single infectious agent is the single cause of atherosclerosis in most patients. However, as in a variety of other infectious processes, more than one agent may cause an atherosclerotic host response. With this in mind, Dr. Stephen Epstein at the Washington Hospital Center proposed this question: "Might the risk of coronary disease be associated, not only with individual infectious agents, but also with the total number (pathogen burden) of agents as well?" To test this hypothesis, he evaluated 233 study subjects undergoing coronary arteriography of whom 68% had evidence of CAD.[14] He tested them for seropositivity to 5 potential pathogens: CMV, *C. pneumoniae*, Hepatitis A (HAA), Herpes simplex virus-1 (HSV-1), and Herpes simplex virus-2 (HSV-2). Figure 3 shows the adjusted odds ratios for the diagnosis of CAD based on the number of pathogens to which each patient was seropositive.

Figure 2. Mortality, after 3 years follow-up, of patients with known CAD based on baseline seropositivity to CMV, *Chlamydia pneumoniae* (C pn) or *H. pylori* (H py).

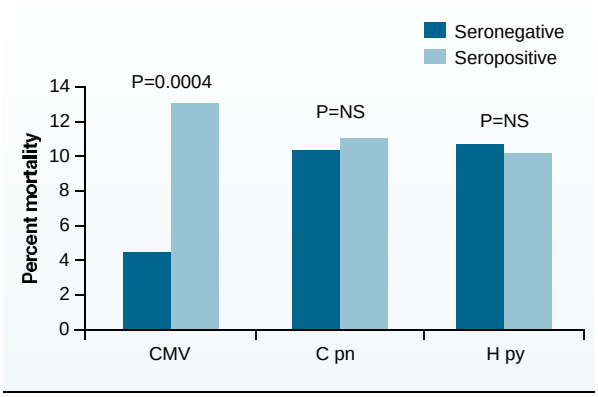
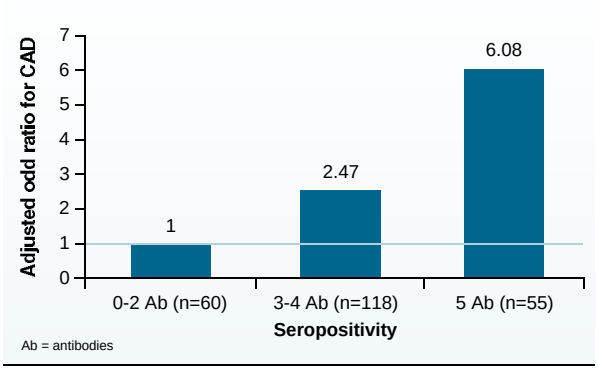


Figure 3. Adjusted odds ratio for the angiographic diagnosis of CAD based on total pathogen burden (see text for details).



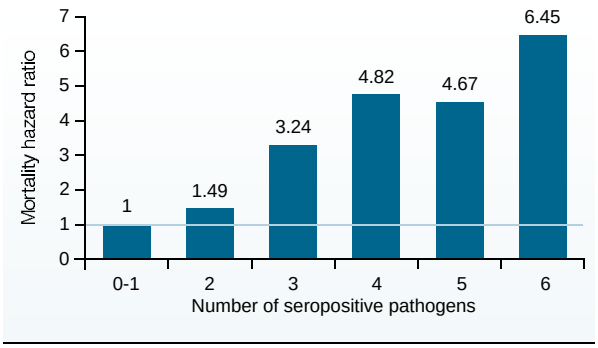
As total pathogen burden rose, a significant step-wise increase in risk of CAD diagnosis was noted.

With these findings in mind,we embarked upon a collaborative project between Washington Hospital Center, John Hopkins University, and LDS Hospital.[15] The previously described 985 patients with angiographically diagnosed CAD who were followed for long-term clinical outcome at LDS Hospital were tested for baseline seropositivity to 6 potential pathogens including CMV, *H. pylori*, *C. pneumoniae*, HSV-1, HSV-2, and HA. Figure 4 shows the hazard ratios for future mortality over 3 years follow-up based on the number of seropositive pathogens detected. Again, a step-wise increase in the risk of mortality was noted with increasing pathogen burden. These findings appear to strengthen the hypothesis that chronic infectious processes from a variety of pathogens might influence the development, or progression, of atherosclerosis.

How infections exert an effect on atherosclerosis: Potential mechanisms

Although the slow steady progression of an atherosclerotic plaques may result in symptoms such as stable angina, major ischemic complications such as unstable angina or MI generally occur after a plaque becomes acutely unstable and ruptures, the result of rapid plaque expansion due to intraplaque hemorrhage or acute coronary thrombosis. The major distinguishing features of an unstable plaque include a thin fibrous cap and the presence of inflammatory cells. Studies by

Figure 4. Hazard ratio of mortality, based on total pathogen burden (see text for details), of patients with known CAD.



Libby at the Brigham and Women's Hospital and others[16-18] demonstrate the critical role that inflammation plays in plaque destabilization. Activated T cells in the atheroma stimulate the activation of plaque macrophages which then release matrix metalloproteinase and other enzymes that have the potential to degrade interstitial collagen and weaken the critical intimal cap.[19-20] In addition, activated T cells in human atheroma also secrete the lymphokine IFN-γ, an inhibitor of the production of interstitial collagen.[21] The combination of these two processes can result in further thinning and ultimate rupture of the fibrous cap. Although inflammatory processes play a critical role in plaque destabilization, how these inflammatory processes are initiated and perpetuated still remains unclear.

Other pathogenic mechanisms have been proposed to explain how chronic infectious agents may contribute to the initiation and perpetuation of the inflammatory process that results in plaque destabilization. For instance, it has been shown *C. pneumoniae* infection significantly accelerates the development of foam cells and permits this transformation to occur at much lower levels of LDL cholesterol.[22] Therefore,it is possible that infection with *C. pneumoniae* enhances the susceptibility of the vessel wall to toxic damage from oxidized LDL. It has also been shown in tissue culture that *C. pneumoniae* infection of endothelial cells significantly enhances their pro-coagulant state through a decrease in the production of tissue plasminogen activator and an increase in production of tissue factor.[23] Possibly, infection of endothelial cells with *C. pneumoniae* stimulates the local coagulation system of the vessel wall and increases the potential for coronary thrombosis. Recently, Libby and colleagues[24] documented the co-localization of chlamydial heat shock protein 60 (HSP-60) within human atherosclerotic tissue. They also documented a correlation between HSP-60 and the production, in atherosclerotic foam cells, of matrix metalloproteinase enzymes.[25] Therefore, another potential mechanism whereby *C. pneumoniae* might induce the development or progression of atherosclerosis is through its production of HSP-60 within atherosclerotic plaque. Similar potential mechanisms by other chronic infectious agents that may contribute to the development or progression of atherosclerosis are also being discovered. Although a positive role of chronic infection in the atherosclerotic process has still not been definitively verified, these findings further contribute to the body of knowledge that strengthens these associations.

Atherosclerosis prevention/treatment based on the inflammation/infection hypothesis

Treatment with antibiotics

Because there are antibiotic agents that are effective against some of these infectious agents,especially *C. pneumoniae*, a variety of secondary prevention antibiotic treatment trials – designed to test the hypothesis that antibiotic therapy reduces recurrent clinical events in patients with CAD – have been performed, or are now ongoing.

• In a relatively small study from London,[26] 60 stable *C. pneumoniae* seropositive post-MI male patients were randomized to either azithromycin or placebo and followed for

18 months. Although the numbers were small, there was a statistically significant reduction in the number of ischemic events in the group receiving antibiotic treatment (25% versus 8%, p=0.03).

• In another study from Argentina,[27] 202 patients presenting with unstable angina were randomized to receive a 30-day course of roxithromycin or placebo. At the end of the 30-day follow-up, a statistically significant reduction in recurrent cardiovascular events was found in the group receiving antibiotic therapy (9% versus 2%, p=0.03).

• A third small study of 302 seropositive CAD patients randomized to receive 3 months of continuous azithromycin therapy or placebo was reported by our group at LDS.[28] Blood samples were drawn at baseline, at 3 months, and at 6 months, and markers of inflammation, including CRP and interleukin-6 were measured at each time course. At 3 months, immediately after the cessation of antibiotic therapy, no statistically significant differences between the levels of markers of inflammation were detected between the treatment or control groups. However, by 6 months, a statistically significant reduction in levels of both CRP and interleukin-6 were noted in the antibiotic treatment group.

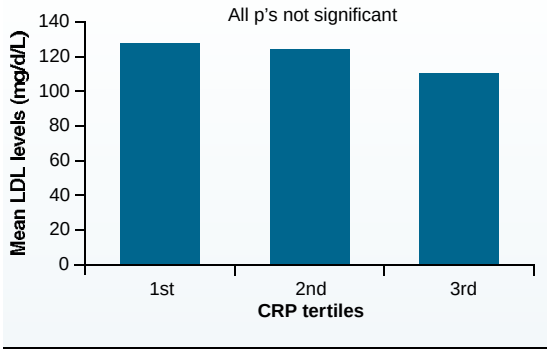
• Based on the epidemiology mechanistic studies and these preliminary results, several large clinical trials have now begun. The first trial (expected to be completed in 2001) is the WIZARD study. In this trial, >3,000 patients with a history of MI and documented presence of seropositivity to *C. pneumoniae* are being randomized to either placebo or 3 months treatment with azithromycin. The primary clinical endpoint is death, MI, admission for unstable angina, and need for repeat revascularization at 3 years.

• Another study, the ACES (Azithromycin and Coronary Events) Study, sponsored by the NIH, will enroll >4,000 patients with known CAD; they will be randomized to receive a full year of chronic azithromycin treatment versus placebo and followed for >4 years. Until the results of these studies are available, it is not recommended that patients be routinely prescribed antibiotics for the secondary prevention of CAD.

Potential anti-inflammatory effects of statins

Because of the well-documented association between hyperlipidemia and the development of CAD, lipid modification through dietary and pharmacologic approaches has been a mainstay of risk factor reduction in the management of atherosclerosis for many years. Starting in 1994, when the Scandinavian Simvastatin Survival Study[29] documented a 30% reduction in mortality in patients randomized to simvastatin, multiple large long-term secondary (as well as primary) prevention studies have documented the benefits of statin therapy in patients with modestly elevated or average LDL levels. The presumption has been that this benefit occurred through stabilization of plaques, mainly or exclusively through the lipid lowering effects of the agents. However, besides their ability to lower serum cholesterol levels, statins are also known to have at least some potential direct anti-inflammatory effects.[30] The possibility therefore exists that some of the beneficial effects attributed to statin therapy might arise from non-lipid related effects. We analyzed potential interactions between lipid levels, statin use, and markers of inflammation in patients with significant CAD in our long-term cohort study.[31] The mean baseline LDL levels of the patients stratified according to CRP levels were not significantly different (Figure 5). Additionally, after controlling for age, sex, ejection fraction, and other potential co-morbid confounders, multivariable regression analysis showed no independent predictive value of total cholesterol, LDL, or HDL levels on mortality in this study population. Despite the absence of a predicative value of baseline lipid levels, an important effect of treatment by statin agents was noted. The mortality rates of the patients prescribed statin therapy at the time of initial hospital discharge was >50% lower than in patients not discharged on a statin (Figure 6). Interestingly, in this study population, the benefit of statin therapy was also independent of baseline of LDL levels.

Figure 5. Mean levels of baseline LDL, based on baseline C-reactive protein level tertiles, of patients with angiographically diagnosed significant CAD.



These findings raise a number of questions including:

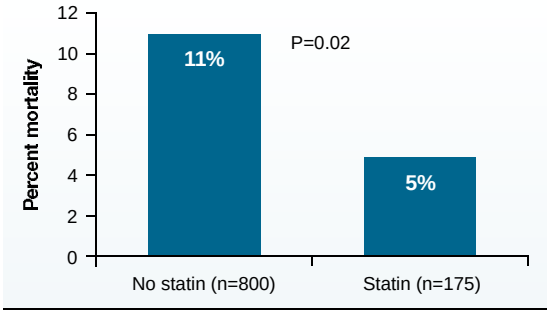
• Why were baseline lipid levels not predictive of mortality in this population?

• Why was a similar benefit of statins observed in all patients regardless of their baseline lipid levels?

• Why was the prescription of statins upon hospital discharge so valuable?

Because of the observational nature of this study, absolute answers are not available, and the possibility of mere chance results must also be considered. In an attempt to address some of these questions, we related statin use, CRP, and mortality rates. Using tertiles of baseline CRP levels in our study population, we found that the vast majority of the benefit of statins occurred in patients with the higher levels of this inflammatory marker (Figure 7). A similar finding has also been

Figure 6. Mortality, after 3 years follow-up, of patients with known CAD based on the presence of a statin prescription at discharge.



reported from the CARE study by Ridker, et al.[32] Therefore, the presence of chronic inflammation, as evidenced by elevated CRP levels, more effectively predicts the beneficial effect of statin therapy than does baseline lipid levels. We found a similar relationship in our study population using seropositivity to CMV, another marker of potential inflammation/infection (Figure 8). Once again, in patients discharged on a statin, a survival benefit was found mainly in those who were seropositive to CMV.[33]

An even closer relationship between statin efficacy and inflammation was found by Ridker et al in the CARE trial which revealed that long-term pravastatin administration significantly lowered CRP levels.[34] Pravastatin use was associated with reductions in CRP levels not accounted for by LDL lowering. In other words, in patients not randomized to pravastatin whose LDL levels lowered anyway (either by diet or other mechanisms), CRP levels did not decrease to the same degree as patients on pravastatin. Therefore, although the findings are observational and not definitive,evidence is mounting to substantiate a proposal that at least some statin agents possess an anti-inflammatory effect that is independent of their lipid lowering effect and this may contribute to beneficial mortality reductions in patients with known CAD.

Figure 7. Mortality, after 3 years follow-up, of patients with known CAD based on the presence of a statin prescription at discharge, stratified by tertile of baseline C-reactive protein levels.

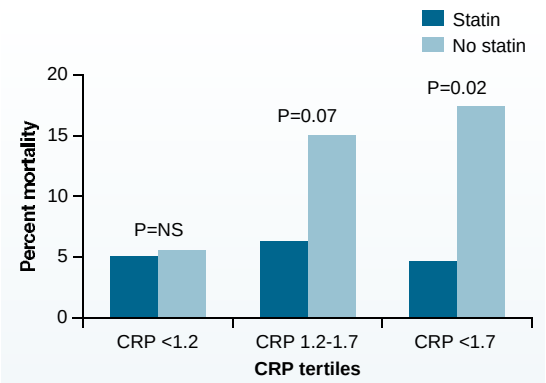
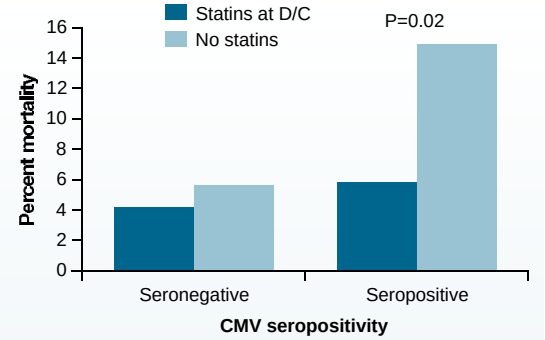


Figure 8. Mortality, after 3 years follow-up, of patients with known CAD based on the presence of a statin prescription at discharge, stratified by seropositivity to CMV.



Summary

On a variety of fronts, chronic inflammation/infection has been found to be significantly associated with the development of atherosclerosis and the clinical complications of unstable angina, MI, and stroke. For the most part, these are still just associations. As well,potential mechanisms whereby chronic infections may play a role in atherogenesis are myriad though none are directly proven in man. The infectious agents with the most evidence to support an etiologic role in atherosclerosis include *C. pneumoniae* and CMV. However, evidence is mounting for a variety of other potential agents. Future studies are expected to further elucidate the pathophysiologic relationship between chronic inflammation/infection and atherosclerosis and to evaluate the potential of a variety of treatment approaches, including antibiotics. In the meantime, there is mounting evidence that statin therapy, already proven to be an effective in the secondary prevention of CAD, may produce at least some of its beneficial effects through direct, non-lipid related, anti-inflammatory effects. It is important to use proven agents and consider new mechanisms that may generate novel therapies for this multifaceted disease process.

Editors note: *The recent announcement of the PROVE-IT (TIMI 22):PRavastatin OratorVastatin Evaluation and Infection Treatment is particularly relevant to this Grand Rounds topic. PROVE-IT will be a 2x2 factorial, randomized, double-blind trial designed to demonstrate equivalence of pravastatin and atorvastatin and to demonstrate the superiority of an antichlamydial antibiotic over placebo in reducing major cardiovascular events in patients with acute coronary syndromes. The trial will be coordinated by the TIMI office with Eugene Braunwald, M.D.,Study Chairman and Christopher Cannon, M.D.,Principal Investigator. In addition,mechanistic studies prospectively relating lipids, inflammatory markers and clinical outcomes will undoubtedly address many of the key issues in this evolving area.*

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Joseph Brent Muhlestein, MD, graduated from Brigham Young University and received his medical degree from the University of Utah, in Salt Lake City. After completing a fellowship at Duke University and remaining as a junior faculty member there for a time, he joined the cardiology faculty of the University of Utah and became Director of Research for the Cardiac Catheterization Laboratory at LDS Hospital in Salt Lake City. He currently is Director of Cardiology Research for Intermountain Health Care, a consortium of hospitals in the Intermountain West that includes LDS Hospital. He is also Associate Professor at University of Utah School of Medicine.

Dr. Muhlestein's research interests includes investigation of the underlying etiologies of atherosclerosis, emphasizing inflammatory, infectious and genetic factors. He participates as principal investigator on a variety of multi-center randomized clinical trials centered around ischemic heart disease and interventional cardiology. He also supervises a large cardiac catheterization laboratory clinical database and participates in cardiovascular clinical outcomes research.

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