CONCLUSION:

The clinical manifestations of atherosclerosis range from CHD to cerebrovascular disease. Atherosclerosis is highly prevalent in Western society, and is the single greatest cause of mortality. A steady escalation in prevalence of CHD is being reported from developing countries, especially India. Although many risk factors for atherosclerosis are known (smoking, hypertension, diabetes, hyperlipidaemia), much of the attributable risk remains unexplained. A search for newer cardiovascular risk factors continues.

The recognition that atherothrombosis is inflammatory has raised the intriguing question of the inflammatory triggers. Indeed, inflammation underlies atherothrombosis at each stage, including initiation, progression, and advanced disease where plaque instability and disruption lead to ACS.

Although non infectious factors (eg. Oxidized LDL) clearly play a proinflammatory role\textsuperscript{2,3}, interest has been renewed regarding the possibility that infection might be among these triggers\textsuperscript{7,47}.

Chronic infections might initiate and perpetuate vascular endothelial damage\textsuperscript{53}.

It has been suggested that infectious agents may directly or indirectly trigger the cascade of biological and biochemical reactions leading to inflammation, atherosclerosis, and vascular thrombotic events\textsuperscript{113}. The idea that microorganisms may
cause inflammatory or immune-mediated, 'non-infectious' disease is now acceptable.53.

The finding of C.pneumoniae within human atherothrombotic tissue has kindled renewed interest in the issue of infection for human atherothrombotic disease and has begged the question of "innocent bystander versus dangerous pathogen". Certainly, cellular and molecular studies have demonstrated that infectious agents CAN activate the major pathways involved in atherothrombosis and vascular thrombosis. Animal models, beginning with Marek's disease, also show the potential for infections to accelerate and anti-infective treatment to suppress atherothrombosis. C.pneumoniae can stimulate inflammation, facilitate lipid accumulation and matrix degradation, provoke endothelial dysfunction, promote thrombosis, and promote smooth muscle accumulation—all well recognized atherogenic mechanisms.

Serologic studies have shown high antibody prevalence for C.pneumoniae among those with coronary and other vascular diseases.21 Nevertheless, seropositivity indicates past exposure, not active infection; prevalence is high among general population; associations have been variables; and confounding has been a concern. Aggregate exposure to many candidate infectious agents ("pathogen burden") appears to be a strong and in some studies, a consistent risk marker.16,18

Several serological methods previously reported have yielded conflicting results about the association of C.pneumoniae with CHD possibly due to lack of uniformity in methods used (i.e. different classes of antibodies tested, different methods, and different cut-off points). This has resulted into reporting of diverging results from
several studies. To obviate this anomaly, the precise titer and the specific antibody for chronic chlamydial infection has now been defined\textsuperscript{83}. All the same, all the methods of diagnosis, including PCR and ICC, need to be properly standardized.

The present consensus of research workers is that better markers than serology of active or latent, as opposed to past, resolved infection are clearly needed. Heat shock proteins and anti heat shock proteins antibodies are promising possibilities. Identification of chlamydial DNA in the cells of atheromatous tissue may be more revealing than positive serologic studies.

Antichlamydial antibiotic like azithromycin, in different doses and different durations, have been administered to entire spectrum of patients with CHD, who were seropositive to C.pneumoniae or to patients of CHD irrespective of their serological status.

Data from laboratory studies and clinical trials seem to divulge. More evidence of a role of C.pneumoniae emerged from basic laboratory studies, where as clinical trials of patients with stable and unstable CHD failed to demonstrate a significant benefit of antibiotic therapy\textsuperscript{66}.

Effects of antibiotic on future adverse cardiovascular events, chlamydial antibody titer and inflammatory markers have been variable. The present study revealed beneficial effects of azithromycin as seen by reduction in the occurrence of adverse cardiovascular events at the end of 6 months follow up. These results confirm the
findings of previous workers\textsuperscript{20,117-120}, but are at variance with the work published by others\textsuperscript{56,113,116,122}.

In the next few years, anti-infective and vaccine trials targeted against C.pneumoniae will be added to adequately powered antibiotic trials to better assess the therapeutic potential against this potentially atherogenic infective agent. These will provide additional insight into role of infection in atherothrombosis and its therapy. However, these trials also will have their limitations.

As we await the outcome of future investigations, it has been suggested to preferentially select antibiotics that are effective against C.pneumoniae, when they are also appropriate agents for treating inter current illness such as bronchitis and bacterial pneumonia in patients who are also at risk of developing or are known to have CHD\textsuperscript{19}.

Correlation of the data of the present study may indicate that in the natural history of C.pneumoniae infection, the primary prevention of cardiovascular disease might be effected with antibiotics or vaccination, thereby demonstrating the ultimate criterion of causality – the cessation of the exposure followed by a reduction of disease.

\textbf{Very importantly, the present study is the first of its kind in our country.} The observation should stimulate other workers from different parts of our country to carry out larger and longer clinical trials, and to perform preclinical research, to explore the intriguing but as yet unproved hypothesis that C.pneumoniae
may play a role as causal factor in at least a subgroup of patients with CHD, who might be amenable to antibiotic or preventive therapies.

Additional clinical trials should be considered to determine more fully the potential clinical and public health implications of the associations reported herein.

In the link between "inflammation, infection and atherosclerosis", the current research will, therefore, demand a true multidisciplinary approach.

The findings of the present study imply that nearly half of the current CHD in our population is statistically attributable to C.pneumoniae infection. It will be important to prove or disprove the "infectious" basis to atherosclerosis in the 50% of patients without traditional risk factors. Innovative research efforts need to be encouraged.