Public Health Implications of the Inflammatory Concept of Atherosclerosis

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ABSTRACT

The inflammatory nature of atherosclerosis has long been postulated, and though currently widely accepted, the concept is difficult to disseminate and to translate into concrete public health measures. Through the years, it has been discerned that low density lipoprotein (LDL) cholesterol serves as the stimulus for the inflammatory response when it is deposited into the subendothelium. LDL stimulates the migration of the inflammatory cells into the subendothelium; a sequelae of cellular immune responses and a cascade of cytokines ensue, eventually resulting in the formation of a vulnerable plaque. Inflammatory cells, particularly macrophages and lymphocytes, and their cytokines play a role in all stages of the atherosclerotic process, modulating the vascular remodeling process as more LDL cholesterol is absorbed into the subendothelial space and forms an ever enlarging lipid core. When inflammatory cells release metalloproteinases into the fibrous cap separating the lipid core from the lumen, plaque becomes vulnerable to rupture especially with increased shear stress from luminal blood flow resulting in thrombosis; clinically acute coronary syndromes become manifest. The role of mast cells, macrophage apoptosis, and the role of the vasa vasorum in plaque progression has recently been delineated. Pharmacologic intervention to aggressively lower LDL cholesterol culminated in the discovery of statins which were proven in large landmark trials to lower the morbidity and mortality associated with the atherosclerotic process. Several generations of statins have evolved; however, residual mortality is observed despite aggressive therapy. A recent trial showing the beneficial effects of statins in patients with acceptable or normal lipid profiles but with elevated high sensitivity C reactive protein (hsCRP) augurs a change in the paradigm of treatment for atherosclerosis. Inflammatory biomarkers such as hsCRP and lipoprotein-associated phospholipase A2 (Lp-PLA2) are anticipated to change guidelines and treatment algorithms, and public health policy. The implication of infectious processes as triggers of inflammation in the atherosclerotic process is also discussed, particularly the role of periodontal disease, the role of flu vaccination, and the role of bacteria such as Chlamydia and Helicobacter.

Key Words: inflammation, atherosclerosis, C reactive protein

Introduction

The inflammatory nature of atherosclerosis has long been postulated,[1,2,3] and though currently widely accepted, the concept is difficult to disseminate and to translate into concrete public health measures. When the lay public was made to perceive that atherosclerosis or hardening of arteries was attributed solely to cholesterol deposition, it was easy to embark on programs to lower cholesterol through lifestyle change and dietary modification; it also made it easy to goad the pharmaceutical industry to embark on research to develop effective pharmacologic interventions to lower cholesterol. But both Anitschkov and Virchow not only described the atherosclerotic plaque as lipid laden, they also said that it was infiltrated with several types of cells: smooth muscle cells, macrophages, and lymphocytes.[4] While the discovery of cholesterol as an etiologic agent became historic, the role of inflammatory cells such as macrophages and lymphocytes in the atherosclerotic process was not elucidated until recently. The role of inflammatory cells is hard to translate into lay language and, clinically, the effect of their presence is hard to quantify, and intervention to thwart their effects is difficult to measure. It is only recently that measures of inflammation have come to the fore, and in the near future guidelines and a new database is forthcoming.

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Atherosclerosis is an Inflammatory Disease

Through the years, it has been discerned that cholesterol, particularly its subfraction known as low density lipoprotein (LDL), serves as the stimulus for the inflammatory response when it is deposited into the subendothelium.[5] LDL, by inducing the endothelium to express adhesion molecules and cellular migration factors, attracts inflammatory cells into the subendothelium. LDL is then oxidized and phagocytosed by migratory macrophages. Smooth muscle cells from the media also migrate towards the endothelium and, by laying down collagen, start the formation of the fibrous cap. Sequelae of cellular immune responses and a cascade of cytokines ensue, eventually resulting in the formation of a fatty streak and, with time, the formation of a lipid core. This eventually leads to the formation of a vulnerable plaque, i.e., a plaque likely to rupture and cause thrombosis and possibly infarction. Inflammatory cells and their cytokines play a role in all stages of the atherosclerotic process, modulating the vascular remodeling process as more LDL cholesterol is absorbed into the subendothelial space, forming an ever enlarging lipid core.[5] T-lymphocytes release interferon gamma which stimulates smooth muscle cells to release collagenase, which can dissolve collagen in the fibrous cap. The macrophages release metalloproteinases and dissolve the matrix composing the fibrous cap and surrounding matrix. This separates the lipid core from the

lumen. If released into areas other than the fibrous cap, these substances which dissolve matrix allow expansion of the plaque towards adventitia. This is the process of Glagovian or negative remodeling. In some cases, remodeling can also result in the expansion of the plaque inwards, towards the lumen, a process called positive remodeling. If the enzymes are released into the thinnest portion of the fibrous cap, the plaque becomes vulnerable to rupture especially with increased shear stress from luminal blood flow. This can result in thrombosis. If the point of rupture is small or limited in extent, the resulting thrombosis is limited and may lead to ischemic syndromes. If the extent of rupture is large, then thrombosis can be extensive. This thrombosis can cause luminal obstruction, and consequently infarction. Rupture of the fibrous cap allows tissue factor to initiate the coagulation cascade and platelet aggregation. This further propagates the thrombotic process.

Basic research into the inflammatory nature of atherosclerosis continues. Recent work by Libby[6] dwells on the putative functions of mast cells during atherogenesis. Libby's work shows that mast cells, once relegated to the adventitia, also inhabit the atherosclerotic intima. Mast cell precursors enter the arterial intima and can degranulate, releasing their granular contents, including autacoids, cytokines, proteinases, and heparin, among many other products. These mediators, in turn, can activate arterial endothelial and smooth-muscle cells, promote foam-cell formation by macrophages, and sensitize macrophages and smooth muscle cells to apoptosis. The proteases can contribute to extracellular matrix remodeling and can process matrix metalloproteinases and peptides like angiotensin into active forms. Mast cells may thus play a role in plaque rupture. Cytokines and autacoids such as histamine can promote the permeability of the endothelium, including that of the plaque's microvasculature, leading to the extravasation of erythrocytes and intraplaque hemorrhage. Intraplaque hemorrhage is common in advanced coronary atherosclerotic lesions as reported by the group of Kolodgie.[7] The relationship between hemorrhage and the vulnerability of the plaque to disruption may involve the accumulation of free cholesterol from erythrocyte membranes. By contributing to the deposition of free cholesterol, macrophage infiltration, and enlargement of the necrotic core, the accumulation of erythrocyte membranes within an atherosclerotic plaque may represent a potent atherogenic stimulus. These factors may increase the risk of plaque destabilization. The study by Tabas [8] dwelt on macrophage apoptosis in early and advanced atherosclerotic lesions. Early in the course, macrophage apoptosis decreases lesion cellularity; however, macrophage apoptosis in advanced lesions may contribute to necrotic core formation. In late lesions, however, a number of factors may contribute to defective phagocytic clearance of apoptotic macrophages, leading to secondary necrosis of these cells and a proinflammatory response. The cumulative effect of these late lesional events is the generation of a necrotic core, which, in concert with proatherogenic effects of residual surviving macrophages, promotes further inflammation, plaque instability, and thrombosis. Thus, the ability or lack thereof of lesional phagocytes to safely clear apoptotic macrophages may be an important determinant for acute atherothrombotic clinical events.

Another thrust of atherosclerosis research is the study of the vasa vasorum as they grow into and nourish the cellular contents of plaques. Several lines of evidence suggest that increased adventitial and plaque neovascularity, commonly observed in murine and human atherosclerosis, play an important role in progression and, possibly, destabilization of atherosclerotic plaques.[9] Increased plaque neovascularity may contribute to plaque progression by providing an entry point for inflammatory cells, and also as a source of intraplaque hemorrhage and plaque lipid. This line of research has led to interventions to control plaque neovascularity. In animal models, statins have been shown to eradicate plaque vasa vasorum. Antibodies against plaque angiogenic factors have also been tried.

Residual cardiovascular morbidity and mortality despite statins

Pharmacologic intervention to lower cholesterol culminated in the discovery of statins which have now been established as the agents of choice in lowering LDL. More than a decade since their introduction, statins have been proven to lower the morbidity and mortality associated with the atherosclerotic process.[10-15] Newer generations of statins, given at high dosages, have been used in large outcome trials as well and with good results.[16-19] These studies fortified the belief that statins were beneficial in controlling atherosclerosis by merely lowering LDL cholesterol. However, vascular biologists have long known that statins also have pleiotropic effects, specifically anti-inflammatory effects, i.e., they deplete the inflammatory cells within plaques, rendering them less likely to rupture. When a recent trial showed that a statin given to patients with normal lipid profiles lowered cardiovascular events by lowering inflammatory markers, particularly high sensitivity C reactive protein (hsCRP), a new horizon was opened in the management of atherosclerosis.[22,23] The trial indicated that something other than cholesterol could be targeted in the management of atherosclerosis.

In major landmark trials, a residual risk for cardiovascular events prevails despite treatment with statins, even at high doses, and despite reaching goals in lipid management: up to 7% residual risk in primary prevention, and 10-20% residual risk in secondary prevention trials.[10-15] This realization has led to strategies to further decrease the residual risk by measures aimed at other factors, such as increasing HDL, lowering non-HDL cholesterol, and, recently, markers of inflammation such as hsCRP.[20,21,24,25,26] Ridker has shown that other variables of the lipid profile—such as the cholesterol to HDL cholesterol ratio—are, when combined with hsCRP, better predictors of coronary heart

disease risk than LDL cholesterol alone.[25]

Risk factor evaluation has become more complex as the concept of atherosclerosis as an inflammatory disease translates into preventive interventions. A system of classification as proposed by Ridker classifies patients on the basis of their hsCRP level and LDL level, the highest risk for events in those with both parameters high, and the lowest for those whose levels for both were low. In between would be those with low LDL and high hsCRP, or low hsCRP and high LDL.[27]

Inflammatory biomarkers

A myriad of inflammatory markers have been studied as predictors of cardiovascular risk, including adhesion molecules, cytokines, acute phase reactants such as fibrinogen and hsCRP. Several of the markers are stable only when frozen, which limits their use to research settings. Only the acute phase reactants have widely available assays. Methods to measure low levels of CRP were devised as an index of chronic inflammation as seen in atherosclerosis. An assay for hsCRP is now readily available and has been found to conform to World Health Organization (WHO) standards; standardized across many commercial platforms, hsCRP has a proficiency testing program from the College of American Pathologists, and the Centers for Disease Control and Prevention has standardized CRP testing with acceptable coefficients of variation.[28] It needs to be emphasized that the above assays were for hsCRP with acceptable precision down to below 0.3 mg/L. It is within these lower previously normal ranges that hsCRP levels become predictive for cardiovascular events. Although new assays of other inflammatory markers may become available, the hsCRP assay represents the best candidate at this time, and is the most studied. Current evidence supports the use of hsCRP as the analyte of choice, after the consideration of the various analytes' stabilities: the analytes assay precision, accuracy, and the availability of standards for proper assay calibration. HsCRP is stable over long periods of time. It is unaffected by food intake and has no circadian variability. Variability in hsCRP levels is similar to that associated with cholesterol screening as long as hsCRP levels are within clinical range.

What is C-reactive protein? It is a protein that binds to the C-polysaccharide of the pneumococcal cell wall, a part of innate immunity that activates the classical complement pathway after aggregation and binding to ligands. It also binds to phospholipids of damaged cells with subsequent limited activation of the complement system and enhanced uptake of these cells by macrophages. CRP is a critical component of the immune system; an acute phase ß-globulin, its levels increase when the body is faced with infection or trauma. CRP has a long plasma half-life 18-20 hours. Composed of five 23 kDa subunits, CRP is primarily made in the liver.

Its other sources include smooth muscle cells and macrophages in atherosclerotic coronary arteries, the kidneys, neurons, alveolar macrophages, and adipose tissue. Its stable molecular structure is pentraxin; monomeric CRP has been seen deposited in atherosclerotic plaques,[29] and may be more atherogenic than the circulating pentraxin molecule. CRP is proatherogenic. It activates endothelial cells to express adhesion molecules, induces secretion of interleukin-6 (IL6), endothelin 1, decreases the expression and bioavailability of nitric oxide synthase, and activates macrophages to express cytokines, tissue factor, and enhances uptake of LDL.[31] A proinflammatory effect has been observed at 5 mg/L in animal studies and cell cultures; in humans, serum hsCRP conc of 1-3 mg/L has been associated with cardiovascular risk.

Data from Framingham indicate that circulating levels of hsCRP help to estimate risk for initial cardiovascular events and may be used most effectively in persons at intermediate risk for vascular events, offering moderate improvement in reclassification.[33] HsCRP retains an independent association with incident coronary events after adjusting for age, total cholesterol, HDL, smoking, BMI, history of hypertension, exercise level, and family history of coronary disease. In general most studies show a dose-response relationship between the level of hsCRP and the risk of incident coronary disease, sudden death, and peripheral arterial disease. Nonetheless, at this juncture, the entire adult population should not be screened for hsCRP for purposes of cardiovascular risk assessment. Little evidence supports a recommendation for widespread screening of hsCRP as a public health measure. It is the recommendation of the American Heart Association to determine hsCRP in patients without known cardiovascular disease but with an intermediate 10-20% risk of CHD over 10 years to guide considerations of further evaluation or therapy.[28]

It has also not yet been determined if serial hsCRP assessment provides incremental clinical value, although some enterprising medical centers have elected to offer hsCRP determination as part of annual physical examinations or "executive check-ups". More work needs to be done here. For instance, it would be useful if hsCRP levels were to be used in clinical decision-making for preoperative evaluation for non-cardiac surgery. Measurement of hsCRP can also be used to motivate persons with moderate or high risk to improve their lifestyle or to comply with drug therapies, particularly those with a history of revascularization. In fact, elevated baseline hsCRP portends high risk of 30-day death or myocardial infarction after coronary intervention. Coupled anatomic, clinical, and inflammatory risk stratification demonstrates strong predictive utility among patients undergoing percutaneous coronary intervention and may be useful for guiding revascularization strategies.[30] Indeed, hsCRP may be a marker for risk for restenosis after coronary angioplasty and stenting; however, more studies are needed in this regard. In patients with a history of acute coronary syndrome or post-myocardial infarction, the strongest associations with prognosis are with the levels of fibrinogen and hsCRP. HsCRP consistently predicts

new coronary events in patients with unstable angina and acute myocardial infarction independent of troponin. More recently, several studies have addressed the relationship between lesion morphology by new imaging modalities and hsCRP. In the study of Sano et al., using intravascular ultrasound (IVUS), the presence of a ruptured plaque has been related to elevated hsCRP, although no relation was found with the number of lesions.[36] In a prospective study that also used IVUS, hsCRP could not predict the extent of arterial remodeling.[37] However, other studies have shown that patients with elevated hsCRP have more severe plaque ruptures and more multiple plaque ruptures than the controls.[38] Accordingly, IVUS with virtual histology has shown a positive correlation between hsCRP and the size of the necrotic core in patients with acute coronary syndromes both in culprit and non-culprit lesions.[39] By using angioscopy, complex plaques revealed a higher intimal CRP and tissue factor expression than white / yellowplaques.[40] Studies using optical coherence tomography have correlated high levels of hsCRP with macrophage density and the presence of thin-cap-fibroatheromas.[41,42] However, the data concerning the extent and severity of coronary disease using novel imaging techniques and its correlation with biomarkers of inflammation remains very limited. More studies need to be done in this regard.

Proposed inflammatory biomarkers such as adhesion molecules and cytokines like IL6 are difficult to assay, a limitation for mass screening. Fibrinogen assays are available commonly, but there is a larger database with hsCRP. WBC count and ESR are generally too nonspecific as markers of inflammation. Another biomarker of inflammation which has revived excitement in the field is lipoprotein-associated phospholipase A2 (Lp-PLA2). Lp-PLA2 is strongly expressed within the necrotic core and surrounding macrophages of vulnerable and ruptured plaques and is associated with macrophage apoptosis, thereby promoting plaque instability.[43] Lp-PLA2 has been the recent focus of several epidemiologic studies involving primary and secondary prevention populations. Lp-PLA2 can be used to assess risk for future cardiovascular events, and like hsCRP is independent of traditional cardiovascular risk factors. Much work needs to be done before Lp-PLA2 becomes an acceptable inflammatory marker for mass screening. There are already some PLA2 inhibitors being tested in clinical trials with promising results.[89-92]

Is the role of inflammatory biomarkers in atherosclerotic progression instigated by infection?

The hypothesis that infectious agents may initiate or contribute to atherosclerosis is not new.[46] Recent appreciation of atherosclerosis as an inflammatory disease[47-49] has refocused efforts to define infection as a risk factor in cardiovascular disease. The association of hsCRP with infectious processes certainly reopens theories on the role of infectious and immunologic mechanisms in the progression of atherosclerosis, particularly in coronary heart disease. There have been probes into the role of infections in atherosclerosis and related diseases. *Chlamydia pneumoniae*, *Helicobacter pylori*, cytomegalovirus, herpes simplex virus and bacteria involved in dental infections are suspected to be the main infective agents involved in atherosclerotic disease. However, a causal relation between these microorganisms and atherosclerosis remains largely speculative.

The Third National Health and Nutrition Examination Survey (1989 to 1994), collected from over 10,000 people, has suggested that oral bacteria and periodontal inflammation can cause arterial inflammation as evidenced by elevated levels of hsCRP and fibrinogen.[50] Complementary to this, treating periodontal diseases successfully lowers levels of hsCRP and may thereby also lower the risk of heart disease.[51] The severity of periodontal disease has also been correlated with carotid plaque formation and with the incidence of ischemic stroke.[52] The question here is whether it is periodontal disease itself that predisposes to atherosclerosis progression or if in fact it is lifestyle and diet that affects both periodontal health and atherosclerotic progression. The pragmatic public health implication, i.e., the promotion of dental hygiene to prevent cardiovascular disease, is evident. However, the immunopathogenic mechanism by which oral bacteria that cause periodontal disease promote atherosclerosis is yet to be elucidated.

A spectrum of observational, cell biological, animal, and provocative preliminary human data suggest that the *Chlamydia pneumoniae* may have a role in atherogenesis.[53] Infection with *C. pneumoniae* is common, affecting up to 60-70% of adults. In animal models, *Chlamydia* has been demonstrated to have tropism for vascular tissue. The genus *Chlamydia* is composed of small, gram-negative, intracellular bacteria that depend on their host cell for growth and prolonged survival.[54] The organism's unique life cycle alternates between an infectious but nonreplicating elementary body and a noninfectious but metabolically active replicating reticulate body. *Chlamydia pneumoniae* is one of three chlamydial species that cause human disease.[55] It is a common human pathogen transmitted by aerosol droplets and can lead to upper respiratory tract infections, including pharyngitis, bronchitis, sinusitis, community-acquired pneumonia, and otitis media.[57] Humans encounter *C. pneumoniae* commonly with most individuals having several infections during their lifetime. Anti–*C. pneumoniae* antibodies, unusual in children younger than five years of age, occur in up to 50% of individuals by 20 years of age. The prevalence of antibody continues to increase with age among adults, reaching a peak in seropositivity of 80% in men and 70% in women by 65 years of age.[56] Vascular biologists have shown that circulating monocytes infected with *C. pneumoniae* adhere to and migrate through the endothelium, undergo cytolysis, release infectious elementary bodies, and establish chronic infection within the intima. Elementary bodies are capable of infecting and replicating within all atheroma cell types, including

resident macrophages, smooth muscle cells, and endothelial cells. *C. pneumoniae* modulates cell biology to trigger inflammatory cascades, release matrix metalloproteinases and procoagulant factors, recruit specific T-cell responses, alter cellular lipid metabolism, promote smooth muscle cell proliferation, induce endothelial leukocyte adhesion molecule expression, and impair arterial relaxation. Plaque destabilization may proceed through more direct mechanisms, *C. pneumoniae* enhances the production of matrix metalloproteinases which can weaken plaques and make them rupture more easily.[53]

Another microbe studied in this regard is *Helicobacter pylori*. *H. pylori* is a Gram-negative bacterium with a particular tropism for the gastric mucosa. Since 1994, several observational studies have been published testing an epidemiological association between *H. pylori* infection and coronary heart disease (IHD).[59-61] However, recent meta-analysis failed to demonstrate an increased risk of IHD among subjects infected by *H. pylori*.[62] A newly recognized determinant of *H. pylori* pathogenicity is the cytotoxin-associated gene-A (CagA).[58] CagA-positive strains of *H. pylori* have been shown to induce an inflammatory response in the gastric mucosa greater than that induced by CagA-negative strains. CagA seropositivity has also been associated with acute ischemic stroke and vascular diseases.[63,64] Anti-CagA antibodies recognize antigens localized inside the atherosclerotic plaque, in tibial arteries.[65]

The current consensus is that it is highly unlikely that *C. pneumoniae* or *H. pylori* or any other microbe is required for the initiation of atherosclerosis or can alone cause this complex disease. Compelling evidence comes from severely hyperlipidemic animals that develop atherosclerosis in germ-free conditions,[66] the capacity of current medical therapy to reduce cardiovascular mortality without antibiotics, and the observation that *C. pneumoniae* or *H. pylori* is not present in all atheromatous lesions.[53] It is likely that no one will be able to fulfill Koch's postulates in humans with either of these or any microbial agent.[53] Current clinical data do not warrant the use of antibiotics for prevention or treatment of CAD events, especially in view of the potential individual and collective risks of the reckless use of prophylactic antibiotics.[67] Nevertheless, the current body of evidence establishes that microbial pathogens are a plausible and potentially modifiable risk factor in cardiovascular diseases. Available evidence suggests that microbial agents such as *C. pneumoniae* or *H. pylori* may interact with defined factors, such as atherogenic lipid profiles, to modulate atheroma biology[68] and possibly with hypertension to dysregulate arterial function.[69] The chronic, often latent, nature of infections caused by these pathogens complicates examining its interactions with defined risk factors. Both infections may represent a potentially treatable risk factor for atherosclerosis. Unfortunately, available diagnostic methods to detect or monitor acute, chronic, or persistent *C. pneumoniae* or *H. pylori* infection lack sufficient reliability and standardization. Future work must define the interaction of infection with traditional risk factors for human atherosclerosis; for instance, whether or not infection serves as a trigger for plaque rupture.

The Role of Antibiotics and Vaccination

Antibiotic regimen to eradicate proatherogenic bacteria may not have been shown to alter the outcome in large scale trials on cardiovascular endpoints;[72] nonetheless, these negative studies do not disprove that infectious agents can play a role in atherosclerosis progression and indeed may prove to be one of the triggers initiating the cascade of events leading to plaque rupture.

Cardiovascular events are known to have a seasonal pattern, generally assumed to be related to influenza epidemics and increased rates of acute infectious respiratory diseases.[79-80] In fact, influenza vaccination has been shown to be associated with a decrease in recurrent coronary events.[81,82] Destabilization and rupture of the atherosclerotic plaque in proximity to an acute respiratory infection has been proposed as one of the possible mechanisms to explain this seasonality.[83-87] In an epidemiological study performed by Steinvil et al. of 8,110 asymptomatic adults undergoing a routine screening health program, concentrations of hsCRP and fibrinogen were correlated with the weekly epidemiological data for the incidence of acute respiratory tract infections in the community. It was demonstrated that an increase in the concentrations of the two inflammatory biomarkers can occur in completely asymptomatic adults at times of increased burden of acute respiratory tract infection in the general population. This raises the possibility that these microinflammatory changes represent occult and asymptomatic infections that could by themselves trigger acute atherothrombotic events.[88] Flu vaccination is now an accepted practice that is considered a preventive measure against cardiovascular disease.

The concept of atherosclerosis as an inflammatory process has public health ramifications which will unravel in the years to come. HsCRP and perhaps some other biomarkers of inflammation will probably become part and parcel of risk profiling of patients as well as healthy asymptomatic individuals. Recognizing that bacterial or viral infection can trigger plaque rupture or at the very least contribute to the progression of atherosclerosis should make us more vigilant in the overall care of patients with atherosclerotic disease. The public health implication of the success of statins in curbing mortality and morbidity in patients with currently acceptable lipid profiles remains to be explored. The role of inflammatory markers in screening of asymptomatic individuals will probably be the focus of new guidelines. Established markers of inflammation such as hsCRP may integrate the total inflammatory burden of an individual and obviate the need to add specific infectious variables to risk algorithms. The recognition of vaccination against influenza as a valid preventive measure in coronary care is a step in this direction. Vigilance must translate into action whether it be in the ordering of diagnostics to detect arterial

inflammation or at the very least to detect periodontal disease in the regular physical exam of cardiac patients. The challenge to translate the inflammatory concept of atherosclerosis into public health measures is needed if only to combat the aggressive ad campaigns of nutriceuticals of no known therapeutic value, which mislead the public into false hope with false science. Epidemiologically sound preventive measures in light of the inflammatory concept of atherosclerosis must be promoted. Statins in water, an enticing title of a symposium during the American Heart Association meetings last year is indeed thought-provoking, a parallelism with putting fluoride in water to combat tooth decay. This concept of making statins more available was put down in a recent *Lancet* editorial citing the lack of evidence for such a public health measure with good intentions, and the unknown unwanted side effects that can be unraveled were statins to be made more widely available.

Public health measures with regard to microinfections that can provoke inflammatory responses in arteries is what we need, not more medications. Already stirring a controversy in academic circles is the availability of the polypill from India, consisting of a ß-blocker, a diuretic, an ACE inhibitor, a statin, and aspirin.[94,95] Improved availability of flu vaccinations for the general public, and, for the clinics, a greater awareness among practitioners that vaccination against flu has beneficial cardiovascular consequences are among small measures that can perhaps put a dent in the epidemic of cardiovascular disease. So too will the promotion of dental health and gingival care. All these while awaiting more outcome trials using inflammatory biomarkers.

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