Comment

Bringing JUPITER down to earth

In The Lancet today, Paul Ridker and colleagues present a much awaited subanalysis from the JUPITER trial. In the initial report, these investigators tested and validated the hypothesis that asymptomatic individuals with normal LDL cholesterol concentrations but with evidence of inflammation (increased C-reactive protein) would benefit from treatment with a statin. Results of the new a-priori analyses show that asymptomatic individuals randomly allocated to rosuvastatin for just less than 2 years benefited particularly from this drug if low concentrations of both LDL cholesterol and C-reactive protein were achieved. These findings add to evidence that cardiovascular disease has an inflammatory component and suggest that inflammation could become another target for primary prevention of cardiovascular disease.

Although, in many guidelines, LDL cholesterol is recommended as the most important target for lipid-lowering treatment, Ridker and his team have shown previously that other variables of the lipid profile—such as the cholesterol to HDL cholesterol ratio—are, when combined with C-reactive protein, better predictors of coronary heart disease risk than is LDL cholesterol alone. Therefore, although this prespecified analysis on the basis of achieved LDL cholesterol is relevant, we should pay attention to the additional results of the report, which indicate that irrespective of the lipid endpoint used (including the apolipoprotein B to apolipoprotein A1 ratio), a low concentration of C-reactive protein achieved with rosuvastatin treatment confers the best prognosis.

What do we do with these findings? Although JUPITER provides support to the lipid-inflammation target as proof of concept, Ridker and colleagues now need to put their work into a clinical and public health perspective. For instance, many groups around the world have shown that a sedentary lifestyle, poor level of fitness, abdominal obesity, smoking, insulin resistance, and metabolic syndrome are all predictive of raised concentrations of C-reactive protein. Although statins have enhanced greatly the ability to lower LDL cholesterol and thereby risk for cardiovascular disease, hopefully the findings of JUPITER will spark further discussion on appropriate use of these drugs.

The JUPITER results also indicate that we need to do a better job at global cardiovascular disease risk-assessment. Furthermore, despite the fact that regular exercise is a remarkable and cheap “polypill”, a comparison of the absolute reduction in risk for coronary heart disease that is gained after statin treatment versus that with a lifestyle-modification programme aimed at weight loss and improved fitness is unlikely to happen in the near future. A low level of cardiorespiratory fitness is a powerful predictor of cardiovascular disease independent of most studied risk factors.

This issue is important with respect to prophylactic use of a powerful statin such as rosuvastatin in primary prevention. The figure shows a behaviour that has unfortunately become the norm rather than the exception. It is not meant to make trivial the contribution of statins to cardiovascular disease prevention. However, before we recommend lifetime treatment with rosuvastatin for millions of presumably asymptomatic individuals, we should remember that we do not have long-term safety data for this drug.

Despite overwhelming evidence for the clinical benefits of statins in terms of relative-risk reduction, absolute reduction in risk is the clinically relevant outcome. For example, even if raised concentrations of C-reactive protein in an individual increase the relative risk threefold, the patient could be at low absolute risk in the absence of other risk factors.

From a pathophysiological standpoint, JUPITER provides key experimental data that inflammation...
is an important mediator of the clinical benefits of rosvuvastatin. However, to immediately translate these findings into clinical practice without appropriate and careful discussion of their implications is not prudent. Hopefully, focus on the JUPITER trial will spur constructive and responsible dialogues to prioritise clinical and public health actions for primary prevention of cardiovascular disease. How can we delineate the proper population to treat? When should we use C-reactive protein in clinical practice? These issues will have to be examined carefully.

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Fourth-generation fluoroquinolones in tuberculosis

Drug development against Mycobacterium tuberculosis has been an overlooked area of tuberculosis research for some time. The first breakthrough—to obtain an active antituberculosis agent—occurred in the mid-1940s with the seemingly reluctant discovery of the activity of streptomycin and the more focused path towards the synthesis of para-aminosalicylic acid. The second breakthrough came when three drug companies simultaneously and independently applied to patent isonicotinic acid hydrazide (now known as isoniazid), only to learn that this drug had already been synthesised 50 years earlier. The third and perhaps last specific attempt at finding an antituberculosis agent came with the isolation of an antibiotic from the rifamycin class, published in 1959. Almost two decades passed before a regimen based on isoniazid plus rifampicin underwent rigorous assessment.

Just 3 years after the identification of the rifamycins, nalidixic acid was synthesised. This agent was the starting point from which the later fluoroquinolones were developed. Fluoroquinolones were found to have activity against M tuberculosis and would become the first real competitors of the two most powerful classes of antituberculosis agents that are now in routine use. Although nearly all fluoroquinolones have antimycobacterial activity, the fourth generation, which includes gatifloxacin and moxifloxacin, have a particularly strong activity against M tuberculosis.

In The Lancet today, Marcus Conde and colleagues report the effect on sputum–culture conversion at 8 weeks of treatment with isoniazid, rifampicin, and pyrazinamide given in combination with either moxifloxacin or ethambutol (control). Ethambutol does not enhance, or only minimally enhances, the activity of the combination of isoniazid, rifampicin, and pyrazinamide against a fully susceptible strain. Indeed, so far, no drug has substantially enhanced the activity of this three-drug combination. The trial’s finding that culture conversion to negative occurred in 80% of patients in the moxifloxacin