Methods: In this double-blind, placebo-controlled trial, we randomly assigned 15,526 patients with a recent ACS to receive twice-daily doses of either 2.5 mg or 5 mg of rivaroxaban or placebo for a mean of 13 months and up to 31 months. The primary efficacy end point was a composite of death from cardiovascular causes, myocardial infarction (MI), or stroke.

Results: Rivaroxaban significantly reduced the primary efficacy end point, as compared with placebo, with respective rates of 8.9% and 10.7% (hazard ratio in the rivaroxaban group, 0.84; 95% confidence interval [CI], 0.74–0.96; $P=0.008$), with significant improvement for both the twice-daily 2.5-mg dose (9.1% vs 10.7%, $P=0.02$) and the twice-daily 5-mg dose (8.8% vs 10.7%, $P=0.03$). The twice-daily 2.5-mg dose of rivaroxaban reduced the rates of death from cardiovascular causes (2.7% vs 4.1%, $P=0.002$) and from any cause (2.9% vs 4.5%, $P=0.002$), a survival benefit that was not seen with the twice-daily 5-mg dose. As compared with placebo, rivaroxaban increased the rates of major bleeding not related to coronary artery bypass grafting (2.1% vs 0.6%, $P<0.001$) and intracranial haemorrhage (0.6% vs 0.2%, $P=0.009$), without a significant increase in fatal bleeding (0.3% vs 0.2%, $P=0.66$) or other adverse events. The twice-daily 2.5-mg dose resulted in fewer fatal bleeding events than the twice-daily 5-mg dose (0.1% vs 0.4%, $P=0.04$).

Conclusion: In patients with a recent ACS, rivaroxaban reduced the risk of the composite end point of death from cardiovascular causes, MI, or stroke. Rivaroxaban increased the risk of major bleeding and intracranial haemorrhage but not the risk of fatal bleeding.

Perspective

Since coronary artery disease especially in the form of ACS is a prothrombotic state, it makes great logic to use long-term oral anti-coagulation. However, in the presence of dual antiplatelet therapy, the so called triple therapy it is fraught with high-risk of bleeding complications but in settings like a patient with atrial fibrillation who undergoes stenting, it becomes mandatory to use triple therapy for variable periods of time. Earlier meta-analysis revealed improved cardiovascular outcomes with addition of warfarin to aspirin in ACS patients but with increased bleeding complications. The ATLAS ACS TIMI 51 trial is a further extension to use triple therapy in patients with recent ACS in general. Rivaroxaban is an oral anti-coagulant that directly and selectively inhibits factor Xa. Aspirin was used in 98% of the patients and thienopyridin in 93% of patients. Rivaroxaban added to dual antiplatelet therapy following ACS significantly reduced the primary end point of cardiovascular death, myocardial infarction and stroke at a mean follow-up of 13 months. The lower dose (2.5 mg twice daily) used in one arm also showed a survival benefit. Although there was increased incidence of major bleeding including intracranial haemorrhage, there was no fatal bleeding with use of add-on rivaroxaban. The result was irrespective of the mode of presentation (ST-segment elevation myocardial infarction [STEMI], non-STEMI [NSTEMI] or unstable angina). Index event was a STEMI in 50.3% of the patients, an NSTEMI in 25.6% and unstable angina in 24.0%. The mean time from the index event to randomisation was 4.7 days. The mean duration of treatment was 13.1 months. Rivaroxaban reduced the risk of stent thrombosis as well. The benefit with rivaroxaban was consistent among the sub-groups except for patients with a history of stroke or transient ischaemic attack. There was no evidence of increased liver toxicity. Earlier in the ATLAS ACS TIMI 46 and APPRAISE 1 trials, rivaroxaban and apixaban showed trends towards a reduction in cardiovascular events. However, further studies are required to have this reproducible result in varied subset of ACS patients with other co-morbid conditions. We need a large trial which compares rivaroxaban to warfarin in the presence of dual antiplatelet therapy in post ACS patients before this new idea is accepted.

2. Effect of two intensive statin regimens on progression of coronary disease. Nicholls SJ, Ballantyne CM, Barter PJ. N Engl J Med 2011;365:2078–87. doi: 10.1016/S0019-4832(12)60038-8

Background: Statins reduce adverse cardiovascular outcomes and slow the progression of coronary atherosclerosis in proportion to their ability to reduce low-density lipoprotein (LDL) cholesterol. However, few studies have either assessed the ability of intensive statin treatments to achieve disease regression or compared alternative approaches to maximal statin administration.

Methods: We performed serial intravascular ultrasonography in 1039 patients with coronary disease, at baseline and after 104 weeks of treatment with either atorvastatin, 80 mg daily, or rosuvastatin, 40 mg daily, to compare the effect of these two intensive statin regimens on the progression of coronary atherosclerosis, as well as to assess their safety and side-effect profiles.

Results: After 104 weeks of therapy, the rosuvastatin group had lower levels of LDL cholesterol than the atorvastatin group (62.6 mg/dL vs 70.2 mg/dL [1.62 mmol/L vs 1.82 mmol/L], $P<0.001$), and higher levels of high-density lipoprotein (HDL) cholesterol (50.4 mg/dL vs 48.6 mg/dL [1.30 mmol/L vs 1.26 mmol/L], $P=0.01$). The primary efficacy end point, percent atheroma volume (PAV), decreased by 0.99% (95% confidence interval [CI], –1.19 to –0.63) with atorvastatin and by 1.22% (95% CI, –1.52 to –0.90) with rosuvastatin ($P=0.17$). The effect on the secondary efficacy end point, normalised total atheroma volume (TAV), was more favourable with rosuvastatin than with atorvastatin: –6.39 mm³ (95% CI, –7.52 to –5.12), as compared with –4.42 mm³ (95% CI, –5.98 to –3.26) ($P=0.01$). Both agents induced regression in the majority of patients: 63.2% with atorvastatin and 68.5% with rosuvastatin for PAV ($P=0.07$) and 64.7% and 71.3%, respectively, for TAV ($P=0.02$). Both agents had acceptable side-effect profiles, with a low incidence of laboratory abnormalities and cardiovascular events.

Conclusion: Maximal doses of rosuvastatin and atorvastatin resulted in significant regression of coronary atherosclerosis. Despite the lower level of LDL cholesterol and the higher level of HDL cholesterol achieved with rosuvastatin, a similar degree of regression of PAV was observed in the two treatment groups.

Perspective

The favourable effects of statins in reducing cardiovascular events are well established and have been shown to be effective irrespective of baseline LDL cholesterol levels. In addition to the pleotropic effects, statins have been well demonstrated to reduce the rate of progression of coronary atheroma and in some studies even regression. The LDL cholesterol has directly been correlated with amount of atherosclerosis burden in coronary arteries. Rosuvastatin has been shown to be more potent and effective than atorvastatin in reducing LDL cholesterol and increasing HDL cholesterol.

The SATURN trial was done to study and establish the effects of high dose statins on progression of coronary atherosclerosis. This trial revealed that both rosuvastatin and atorvastatin in high doses are equally effective in regressing plaque burden (percent atheroma volume) in coronary arteries when used for over 2 years.

The improvement in lipid profile (reducing LDL cholesterol level and increasing HDL cholesterol levels) was seen more with rosuvastatin which may have resulted in significant but modest reduction in total atheroma volume in coronary arteries. The frequency of cardiovascular events was low (approximately 7% over 2 years) and similar with the use of both regimens.

The overall regression of atherosclerosis was observed in approximately 65% of the study patients over 2 years of statin therapy and was equal in both groups. This implies that approximately one third of patients had disease progression despite the use of high dose statin therapy. This leaves a scope for a novel therapeutic agent which may be more effective either by improving lipid profile or by a different pathway to modify disease activity.

The overall incidence of adverse effects was similarly low with both regimen of statin. Elevation of serum transaminases was slightly higher in atorvastatin arm whereas proteinuria was slightly higher with rosuvastatin therapy. Overall incidence of diabetes was not affected by use of either statin over 2 years in the study.

The SATURN trial goes on to demonstrate that it is the dose of the statin which is more important than the nature of the statin in achieving the treatment goal. Naturally a less powerful statin has to be given in appropriate doses to achieve a given target when compared to a more powerful statin.

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Cardiac magnetic resonance imaging pericardial late gadolinium enhancement and elevated inflammatory markers can predict the reversibility of constrictive pericarditis after antiinflammatory medical therapy: a pilot study. Feng D, Glockner J, Kim K, et al. *Circulation* 2011;124:1830–7.
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The diagnosis of constrictive pericarditis has been an enigma since long and continues to present as a diagnostic challenge. Once the diagnosis has been made it is even more challenging to decide which patient benefits from therapy. It is in this context that this study looked at 89 patients over a 7 years period with documented constriction by cardiac magnetic resonance imaging (MRI) with gadolinium. Twenty-nine patients received anti-inflammatory medications after CMR. A subset of 14 patients had resolution of constrictive pericarditis (defined by improvement by one New York Heart Association [NYHA] grade), whereas 15 patients had persistent disease after 13 months. The group with reversible constrictive pericarditis had greater pericardial thickness (4 ± 1 mm vs 2 ± 1 mm, $P=0.001$), had increased intensity of gadolinium (93% vs 33%), higher C-reactive protein (59 ± 52 mg/L vs 12 ± 14 mg/L, $P=0.04$), respectively and erythrocyte sedimentation rate (ESR) (49 ± 25 mm/hr vs 15 ± 16 mm/hr, $P=0.04$) compared to the persistent group. Anti-inflammatory therapy was associated with a reduction in C-reactive protein, ESR, and pericardial late gadolinium enhancement (LGE) in the group with reversible constrictive pericarditis, but not in the persistent disease group.

Perspective

Constrictive pericarditis is challenging both in terms of diagnosis and response to treatment. This small but focused study shows the adjunctive role of cardiac MRI in making the diagnosis, plan therapy and prognostication. This study demonstrated an association between systemic inflammatory markers and gadolinium enhancement with improvement in NYHA functional class following anti-inflammatory therapy among patients with clinical evidence of constrictive pericarditis. Further large studies will help in establishing this technique as the gold standard in differentiating reversible from persistent constrictive pericarditis.

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