Editorial

Residual Cardiac Risk Reduction Beyond Lipid Lowering

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Even after targets for low-density lipoprotein cholesterol (LDL-C) levels, blood pressure and HbA_{1c} have been achieved in accordance with current guidelines and standards of care, patients with dyslipidaemia remain at high risk for vascular events (i.e. residual risk).[1] Indeed, in the prospective, randomised, double-blind, active treatment-controlled, secondary prevention Treating to New Targets (TNT) trial, patients randomised to 10 mg/d of atorvastatin had a 5-year rate of major cardiovascular disease (CVD) events of 10.9%, while those randomised to 80 mg/d of atorvastatin had an 8.7% event rate (residual risk), despite the CVD risk reduction by 22% ($p<0.001$) compared with atorvastatin 10 mg/d, and the achievement of LDL-C levels of 77 mg/dl (well below those suggested by guidelines).[2] Atherogenic dyslipidaemia, characterised by elevated triglyceride (TG) and low high-density lipoprotein cholesterol (HDL-C) levels, is common in patients with established CVD, type 2 diabetes mellitus (T2DM), or the metabolic syndrome (MetS) and contributes to both macrovascular and microvascular residual risk.[1,3] The Residual Risk Reduction Initiative (R3i)[4] is an institution launched to address this significant clinical issue. The aims of R3i were: (1) to highlight the evidence that atherogenic dyslipidaemia is associated with residual macrovascular and microvascular risk in patients at high CVD risk, despite the implementation of the current standards of care for dyslipidaemia and T2DM; and (2) to propose therapeutic interventions for reducing this residual vascular risk according to the existing evidence and expert consensus. Although lifestyle modification is an important initial step, effective drug intervention (high dose of effective statins, niacin, fibrates, omega-3 fatty acids) aiming at the achievement of all lipid targets is also often required either as monotherapy or (in most cases) as a combination treatment.[3]

However, this approach focuses only on vascular events and does not consider other components of the total cardiac risk, including sudden cardiac death (SCD), ventricular arrhythmias (VA), atrial fibrillation (AF), and heart failure (HF). Hypolipidaemic drugs might also be useful for the management of the residual risk for the latter aspects of the total cardiac risk; our efforts should aim at total cardiac risk reduction rather than at vascular risk alone.

Despite the substantial improvement in the management of CVD, SCD remains

an important global health concern,[5,6] causing 300,000 to 400,000 deaths annually in the US[5] and more than 3 million deaths worldwide.[6] Arrhythmias are the commonest cause of SCD, with ventricular tachycardia (VT) or fibrillation (VF) implicated in the majority (83.4%) of cases.[6,7] Coronary artery disease (CAD) is to blame for approximately 80% of these fatal VAs and the others are attributed to hypertrophic or dilated cardiomyopathy (DCM), congenital heart disease, primary electrophysiological abnormalities, valvular heart disease, bradyarrhythmias and electromechanical dissociation.[7,8]

Omega-3 fatty acids (FAs) have been shown to reduce the incidence of SCD.[9] The largest prospective, randomised, placebo-controlled trial that assessed the efficacy of omega-3 FAs in secondary CVD prevention was the GISSI Prevenzione Study.[10] This study included 11,324 patients with a recent myocardial infarction (MI), who were randomised to receive either 850 mg of omega-3 FAs—46% pure eicosapentaenoic acid (EPA) + 36% pure docosahexaenoic acid (DHA) + 6% polyunsaturated fatty acids (PUFA)—daily or usual care, on top of other secondary prevention interventions. Treatment with omega-3 significantly reduced all-cause mortality by 28% after only 4 months and this benefit was mainly driven by the reduction of SCD risk by 45% ($p<0.001$). The benefit remained significant for the entire duration of the study (3.5 years).[8] The Japan EPA lipid intervention study (JELIS)[11] included 18,645 patients with hyperlipidaemia (more than 3500 of whom had a history of a CVD event). Patients were randomly assigned to statin alone or a combination of statin and 1.8 g of EPA daily. After 5 years, combination treatment was associated with a significant 19% reduction of the primary composite endpoint comprising death, revascularisation, MI and unstable angina, compared with statin monotherapy. A very recent *post hoc* analysis of this trial showed similar beneficial effects of the statin+EPA combination on CVD outcomes in the secondary prevention subgroup; in these patients, relative risk (RR) was reduced by 23% ($p=0.033$, number needed to treat [NNT]=19).[12] The greatest RR reduction (53%, $p=0.043$) was recorded in primary prevention patients with increased TG and low HDL-C levels[13] and in secondary prevention patients with peripheral arterial disease (PAD) (57%, $p=0.041$).[14] Regarding the mechanism of action, several experimental studies showed positive effects of omega-3 FAs on lipid metabolism, coagulation, platelet and endothelial function, arterial stiffness, inflammation and atherosclerotic plaque stability.[15]

The American Heart Association suggests that increased consumption of food rich in omega-3 FA (e.g. oily fish) is advisable for primary CVD prevention.[16] However, in patients with CAD, the recommended daily intake of omega-3 FAs (1 g/d) may be greater than what can readily be achieved through diet alone.[16] Accordingly, these patients, in consultation with their physician, could consider omega-3 FA supplements for CAD risk reduction. Omega-3 FA supplements could also be part of the medical management of hypertriglyceridaemia, where larger doses of omega-3 FAs (2 to 4 g/d) are required.[16]

Very recently, the results of the Alpha Omega Trial were reported. This is a prospective, double-blind, placebo-controlled trial that included 4837 patients, 60-80 years of age (78% men), who had had an MI and were receiving state-of-the-art antihypertensive, antithrombotic and lipid modifying therapy. Patients were randomised to receive in the form of a margarine for 40 months a combination of EPA + DHA (total 400 mg/d), 2 g/d of alpha-linolenic acid (ALA), EPA+DHA plus ALA, or placebo.[17] During the follow-up period neither EPA+DHA ($p=0.93$) nor ALA ($p=0.20$) reduced the incidence of the primary endpoint (major CVD events). In the pre-specified subgroup of women, EPA+DHA was associated with a reduction in the rate of major CVD events compared with placebo, which approached significance ($p=0.07$).[17] It is possible that the low doses of omega-3 FAs used in this study are the reason for the lack of benefit. Indeed, the antiarrhythmic effects of omega-3 FAs appear to emerge at 750-800 mg/d (46% EPA+38% DHA) and are consistent up to the dose of 2500 mg/d.[18]

Treatment with omega-3 FAs can also be beneficial in patients with heart failure (HF).[19] In the GISSI HF trial there was a 9% reduction in all-cause mortality (hazard ratio [HR] 0.91, 95% confidence interval [CI] 0.833-0.998, $p=0.041$) and an 8% reduction in all-cause mortality plus hospitalisation in patients with HF (adjusted HR 0.92, 99% CI 0.849-0.999, $p=0.009$).[19] Although the benefit of omega-3 FAs was smaller than expected in this study, we should consider that it was observed in a population receiving optimal background treatment and was consistent across all predefined subgroups.[19] Moreover, there were no adverse effects of omega-3 FAs. In terms of NNT, 4.6 lives were saved/1000 patient-years with omega-3 Fas,[19] while in the Heart Protection Study, where high CVD risk patients were treated with 40 mg of simvastatin versus placebo, 3.6 lives

were saved/1000 patient-years.[20] Finally, it should also be taken into consideration that, in the same study, rosuvastatin 10 mg/d did not improve the outcome of patients with HF.[21] Despite the benefits of omega-3 FAs, very few patients with CAD or HF are receiving this treatment.

Another way to reduce residual cardiac risk is treatment with statins. Statins slow the progression (and possibly induce regression) of atherosclerosis and reduce clinical events significantly.[22,23] Slowing coronary atherosclerosis progression might reduce myocardial ischaemia, a potential trigger for VAs, and this might result in a reduced risk for SCD. However, it is also possible that statins possess other, more direct, antiarrhythmic properties.[24] The majority of patients with non-ischaemic DCM or CAD experience recurrent episodes of VA, which are the most frequent cause of SCD in this population.[25] Treatment with angiotensin-converting enzyme inhibitors (ACE-I) and/or statins is associated with a reduced incidence of VAs (HR 0.4, p=0.01 and HR 0.1, p=0.03, respectively).[25,26] Fatal VAs generally require an arrhythmogenic substrate and a trigger event. Acute myocardial ischaemia is often the trigger for fatal VT/VF in patients with CAD: it leads to ionic imbalances and a decrease in tissue pH, which result in slowed conduction, reduced excitability, prolonged repolarisation, cell-to-cell uncoupling and spontaneous electrical activity.[5,25] Other triggering mechanisms include metabolic and haemodynamic shifts, neurohormonal and neuropsychological factors, as well as exogenous pharmacological or toxic effects.[5] The presence of such triggers in an abnormal electrophysiological substrate (prior MI or cardiomyopathy) may lead to fatal VT or VF. Thus, therapies that can prevent these triggers or stabilise the underlying arrhythmogenic substrate might reduce the incidence of SCD.[5] The only proven therapies for preventing SCD are an implantable cardioverter-defibrillator (ICD) and beta-adrenergic blockers.[25,27] Statins might also reduce the incidence of these arrhythmias.[28,29]

Several observational studies assessed the effects of statins on the risk of death in >10,000 patients with HF and almost all showed significant reductions in mortality with statin treatment. The second Multicenter Automatic Defibrillator Implantation Trial (MADIT-II)[30] enrolled patients with ischaemic cardiomyopathy (ICM) and left ventricular ejection fraction (LVEF) ≤30%. A 28% reduction in the risk of a first VA (95% CI 0.52-0.99, p=0.046) and a significant reduction in SCD (p<0.01) were observed in those receiving statin therapy for ≥90% of the follow-up period compared with those receiving statins for ≤10% of the follow-up period.[30] Whether statins have a specific effect on life-threatening VAs or they reduce the risk of VAs through their anti-ischaemic actions was addressed in the DEFIbrillators in Non-Ischaemic cardiomyopathy Treatment Evaluation (DEFINITE) study,[31] which evaluated the benefits of an ICD in the primary prevention of VA in patients with non-ICM and LVEF ≤35%. Statin use was associated with a 78% reduction in all-cause mortality (HR 0.22, 95% CI 0.09-0.55, p<0.001). One patient of 110 (0.9%) on statin therapy died of SCD compared with 18 of 348 (5.2%) not on statins (p=0.04). Although the difference was not significant, patients in the statin group had lower numbers of appropriate ICD shocks (HR 0.78, 95% CI 0.34-1.82). These data suggest that statins may directly suppress VAs, beyond their anti-ischaemic effects. The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT)[32] enrolled patients with ICM or non-ICM and LVEF ≤35% (1187 on statin at the last visit, including 371 with non-ICM). During a mean follow up of 45.5 months, statin use was associated with a reduced risk for all-cause mortality, independent of HF aetiology, suggesting that statins are beneficial in both non-ICM and ICM. In addition, the reduction in all-cause mortality with statin treatment was observed both in patients who had an ICD and in those who did not.[32] A meta-analysis of 10 randomised clinical trials (n=22,275) showed that statin treatment was associated with a significant 19% risk reduction for SCD in patients with either CAD or non-ICM (95% CI 0.71-0.93, p=0.003). The benefit of statins was independent of the changes in lipid levels.[33] It is unclear from these studies whether all statins have antiarrhythmic effects in all high risk patients and whether these effects are dose-dependent.[34]

Indices of heart rate variability (HRV) appear to be useful in the prediction of arrhythmic events and SCD.[35] Low HRV is a predictor of subsequent arrhythmias and is associated with increased CVD morbidity and mortality in post-MI patients.[6] On the other hand, hypercholesterolaemia is associated with decreased HRV in men with or without CAD.[6] Long-term treatment of hypercholesterolaemic patients with atorvastatin (20 mg/d) improved sympathovagal balance and increased HRV.[36] Patients with a prior history of MI treated with atorvastatin showed a larger increase in HRV compared with patients with-

out a history of CAD, despite similar LDL-C levels.[36] These effects of statins on HRV might reduce the risk of VA/VT and SCD. Indeed, atorvastatin therapy was associated with a decreased incidence of SCD in patients with advanced HF and LVEF <30%.[37] In another study, simvastatin did not affect HRV in patients with non-ICM.[38] However, a modest correlation between LDL-C reduction and an improvement in the sympathetic responsiveness to stress were recorded.[38] The potential antiarrhythmic actions of statins have also been evaluated by assessing their effects on QT dispersion, another non-invasive predictor of the risk for SCD and VA/VT. A pilot study evaluated in 23 hypercholesterolaemic patients the effects on lipid levels and QT dispersion of treatment with 40 mg/d of fluvastatin for 12 months.[39] QT dispersion decreased from 39 ± 8 to 34 ± 8 ms ($p<0.05$). These results suggest that fluvastatin might improve the heterogeneity of ventricular repolarisation and this might reduce the risk of VAs.[39] The reduced mortality risk of patients with non-ICM during statin treatment might be related to the anti-inflammatory actions of these agents.[40] In a study of patients with non-ICM, New York Heart Association (NYHA) class II or III and LVEF ≤40%, atorvastatin 10 mg/d reduced C-reactive protein (CRP) levels by 37% ($p=0.0002$).[41] Studies of patients with acute coronary syndromes showed an association between the anti-inflammatory effects of statins and the restoration of the sympathovagal balance.[42] In another study, administration of atorvastatin 40 mg/d for 2 months and 10 mg/d for the next 4 months in patients with DCM (LVEF <40%) improved NYHA class and reduced the risk for hospitalisation.[43]

Observational data suggest that statins might also reduce the risk for AF in patients with CAD.[44,45] In a prospective observational cohort study, the incidence of new-onset AF was evaluated in 449 patients with stable CAD and without previous AF over an average follow up of 5 years.[46] AF occurred in 12% of all patients. Those receiving statin therapy were less likely to develop AF (odds ratio [OR] 0.48, 95% CI 0.28-0.83). This risk reduction remained significant after adjustment for potential confounders, including age, hypertension, LVEF, occurrence of heart failure or acute ischaemic events, baseline LDL-C levels, and changes in LDL-C levels (adjusted OR 0.37, 95% CI: 0.18-0.76).[46]

An analysis of the US National Registry to Advance Heart Health (ADVANCENT),[47] a multicentre registry of 25,268 patients with LVEF ≤40%, showed a reduced risk for new onset AF in patients who were taking lipid-lowering medications (92% a statin) compared with either patients with untreated hyperlipidaemia, or patients without hyperlipidaemia (25 vs. 33 vs. 33%, respectively; $p<0.001$ for both comparisons). The association between lipid-lowering therapy and reduced risk for AF persisted after multivariate adjustment (OR 0.69, 95% CI 0.64-0.74).[47] In the Atorvastatin for Reduction of Myocardial Dysrhythmia After Cardiac Surgery (ARMYDA-3) study,[48] patients undergoing cardiac surgery who were not treated with statins and had no history of AF were randomly assigned to atorvastatin 40 mg/d or placebo starting 7 days before the operation. There was no difference between the 2 groups in the type of surgery (most patients underwent coronary artery bypass grafting). Preoperative atorvastatin treatment resulted in a 61% reduction in the risk of postoperative AF (35 vs. 57% in the placebo group; adjusted OR 0.39, 95% CI 0.18-0.85, $p=0.017$) and reduced the duration of hospitalisation (6.3 ± 1.2 vs. 6.9 ± 1.4 d in the placebo group, $p=0.001$). Peak postoperative high sensitivity CRP (hs-CRP) levels were higher in patients who developed AF postoperatively. Atorvastatin, treatment with beta blockers, and combination treatment with these 2 agents were the only independent predictors of freedom from AF in this study.[48] In another randomised trial,[49] patients with AF persisting for at least 48 hours were randomised to either atorvastatin (10 mg/d) or placebo prior to electrical cardioversion. Patients receiving atorvastatin were more likely to spontaneously convert to sinus rhythm prior to electrical cardioversion (25% vs. 8.3%, $p<0.05$) and were less likely to have recurrence of AF in the 3 months following electrical cardioversion (12.5% vs. 45.8%, $p=0.01$).[49]

Several large observational studies showed that statin treatment is associated with improved outcomes in patients with HF[50,51] and reduces the risk for HF after MI,[53] possibly because of the pleiotropic effects of these agents.[54] Although small prospective randomised controlled trials (RCTs) also showed a benefit in mortality, LVEF and HF symptoms[55] with atorvastatin, the results of 2 recent large RCTs have challenged these findings.[56,57] In the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) trial,[56] 5011 patients with moderate to severe systolic ischaemic HF were randomly assigned to rosuvastatin 10 mg/d or placebo. Rosuvastatin did not reduce the primary composite outcome of death from CVD causes, nonfatal MI, or nonfatal stroke. There were fewer hospitalisations for CVD causes or for

worsening HF in the rosuvastatin group than in the placebo group, but rosuvastatin did not improve the functional status as assessed by the NYHA classification.[56] It has been suggested that the CORONA study did not show a benefit with statin treatment because it enrolled very old patients (mean age 73 years) with advanced HF (NYHA class III-IV or class II with LVEF ≤35%).[57] It is also possible that the CORONA study population might have had CAD that was too advanced to modify and it was too optimistic to expect a low rosuvastatin dose (10 mg/d) to provide substantial clinical benefits on top of optimal treatment for HF.[57] However, the GISSI-HF trial, which had a similar design and included younger patients with earlier stages of HF, yielded similar results.[21] In this prospective, double-blind study, patients aged 18 years or older with HF, irrespective of cause and LVEF, and NYHA class II-IV, were randomly assigned to rosuvastatin 10 mg/d (n=2285) or placebo (n=2289). Rosuvastatin did not affect the clinical outcome (mortality and hospitalisations).[21]

In a meta-analysis of 10 randomised, placebo-controlled statin studies (10,192 patients with HF followed up for 3 to 47 months), statins had no effect on all-cause or CVD mortality, but reduced the risk of hospitalisation for worsening HF (OR 0.67, p=0.008).[58] Patients randomised to statins also showed a 4.2% increase in LVEF during follow up (95% CI 1.3-7.1, p=0.004). Furthermore, *post hoc* analyses suggested a heterogeneity among different statins; atorvastatin significantly reduced all-cause mortality (OR 0.39, p=0.004) and the risk for hospitalisation for worsening HF (OR 0.30, p<0.0001), randomisation to atorvastatin and simvastatin improved the LVEF, whereas these benefits were not observed in patients randomised to rosuvastatin.[58] These results are in agreement with our findings from the GREek Atorvastatin and Coronary heart disease Evaluation (GREACE) study.[59] This was a "real life", secondary prevention, target-driven study that randomised 1600 patients with CAD to receive either atorvastatin or "usual" medical care. The dose of atorvastatin was titrated up to 80 mg/d, aiming at LDL-C levels <100 mg/dL (mean study dose, 24 mg/day). The follow-up period was 3 years. In GREACE, 118 patients had HF at baseline (63 in the atorvastatin group vs. 55 in the usual care group; mean age 61 years). In these patients, atorvastatin reduced CVD events by 45% (p=0.0062). Moreover, in the entire study population, atorvastatin significantly reduced the risk of new-onset HF or of worsening of pre-existing HF by 50% (p=0.021). Patients with pre-existing HF showed the greatest reduction in HF-related hospitalisations.[59,60] Based on the existing evidence, the Food and Drug Administration (FDA) suggests that in patients with clinically evident CAD, atorvastatin is indicated to reduce the risk of hospitalisation for HF.[61]

These results were confirmed by the TNT study.[62] TNT randomised 10,001 patients with stable CAD to atorvastatin 80 or 10 mg/d and followed them up for a median period of 4.9 years. Patients with known LVEF <30% or advanced HF were excluded from the study. At baseline, 7.8% of patients had a history of HF. The incidence of hospitalisation for HF, a predefined secondary endpoint of the study, was 2.4% in the atorvastatin 80 mg/d arm and 3.3% in the 10 mg/d arm (HR 0.74, 95% CI 0.59-0.94, p=0.0116). The benefit of the higher atorvastatin dose was greater in patients with a history of HF; in this subgroup, the incidence of hospitalisation for HF was 17.3% and 10.6% in the 10- and 80 mg/d arms, respectively (HR 0.59, 95% CI 0.4 to 0.88, p=0.009).[62]

It is possible that the beneficial effects of statins on renal function, serum uric acid levels and aortic elasticity might also contribute to the reduction in the risk for HF.[63-66]

In conclusion, residual cardiac risk reduction can be achieved by administering statins and omega-3 FAs. Both statins and omega-3 FAs have direct and/or indirect antiarrhythmic properties. Statins also appear to exert anti-inflammatory actions, they improve HRV and reduce the risk for ventricular arrhythmias after MI. Data from trials in patients with CAD suggest that statins reduce the risk of recurrent VT/VF in patients with ICM, but more studies are needed to determine whether statins also have antiarrhythmic effects in patients with non-ICM. In addition, current guidelines do not recommend statin treatment for its antiarrhythmic effects *per se*. On the other hand, omega-3 FAs, despite their antiarrhythmic properties and their proven benefit in patients with HF, are considerably under-prescribed, and this therapeutic gap needs to be addressed if we aim at residual cardiac risk reduction.

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