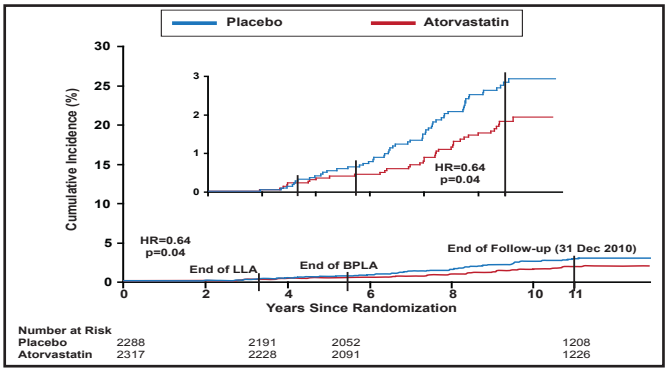
After ASCOT-LLA was terminated, investigators continued to collect mortality data in the UK cohort (n=4605) for a total median follow-up of 11 years from initial randomization. Mortality data were available from the UK Office for National Statistics and General Register Office for Scotland, and the cause of death was identified in death certificates.

By the end of the ASCOT-LLA extension study, most patients who were initially randomized to atorvastatin therapy continued to take atorvastatin (63%), while a minority (4%) took another statin. Likewise, most patients in the placebo group also switched to atorvastatin (56%), with a small number initiating therapy with another statin (7%).

Through 11 years of median follow-up in the ASCOT-LLA extension group, the risk of all-cause mortality was 14% lower for those who were initially assigned to atorvastatin compared with placebo (HR, 0.86; 95% CI, 0.76 to 0.98; p=0.02). The survival benefit was driven by a reduction in non-CV deaths (HR, 0.85; 95% CI, 0.73 to 0.99; p=0.03). In particular, patients who were initially randomized to atorvastatin had a lower long-term risk of death due to infections and respiratory illness (HR, 0.64; 95% CI, 0.42 to 0.97; p=0.04; Figure 1). By comparison, there was no difference in the risk of death due to CV causes (HR, 0.89; 95% CI, 0.72 to 1.11; p=0.32).

Figure 1. Cumulative Incidence of Mortality Due to Combined Infection and Respiratory Disease.



Reproduced with permission from Oxford University Press. The Anglo-Scandinavian Cardiac Outcomes Trial: 11-year mortality follow-up of the lipid-lowering arm in the UK. Sever PS et al. *Eur Heart J. 28 Aug* 2011.

These observations from the ASCOT-LLA extension study may suggest a legacy benefit in terms of a reduction in mortality with atorvastatin, further underscoring the benefit of statins. The mechanism by which statin therapy may reduce the risk of infection and non-CV death over the long term is unclear and needs verification in additional studies, given the limitations of this nonrandomized comparison. Future prospective studies may determine if statins can reduce the risk of sepsis or death from infectious illness, Prof. Sever concluded.

Additional reading: Sever PS et al. *Eur Heart J* 2011.

An Exploratory Analysis from IRIS

Written by Anne Jacobson

The Immediate Risk Stratification Improves Survival (IRIS) trial compared the safety and efficacy of the early insertion of an implantable cardiac defibrillator (ICD) or medical treatment alone in 898 patients who were at high risk for sudden cardiac death (SCD) after myocardial infarction (MI). The primary analysis of the IRIS trial showed significantly fewer deaths due to SCD in the ICD group compared with medical therapy alone (27 vs 60 deaths; p=0.049). However, this was offset by an increase in non-SCD (68 vs 39 deaths; p=0.001), resulting in a neutral effect on total mortality after 72 months (HR, 1.04; p=0.76) [Steinbeck G et al. *New Engl J Med* 2009].

Gerhard Steinbeck, MD, University of Munich, Munich, Germany, presented results from an exploratory post hoc analysis of the IRIS trial, designed to elucidate predictors and mechanisms that contribute to the observed increase in non-SCD in the ICD group.

In the current analysis, investigators applied different statistical tools—the kernel method for smoothed hazard curve estimation—to examine daily mortality risk over time. They found that ICD use decreased the risk for SCD but only within the first 2 years following implantation. Conversely, ICD use was associated with a steady increase in the risk of non-SCD after implantation, particularly after 3 years of follow-up.

In a multivariate analysis, mortality risk patterns were consistent across 30 subgroups, with early ICD associated with decreased risk of SCD and increased risk of non-SCD in each subgroup, except for a small group of 91 patients with STEMI who did not undergo reperfusion (interaction p<0.001). Further prospective data are needed to better understand this observation in a small subgroup whose characteristics may differ from the overall cohort.

Independent of ICD use, five factors predicted total mortality: older age (HR, 1.49; p<0.001), left main or three-vessel disease (HR, 1.48; p=0.004), QRS ≥120 ms (HR, 1.60; p=0.001), New York Heart Association class 3 or 4 heart failure (HR, 2.00; p<0.001), and ejection fraction <35% (HR, 2.18; p<0.001). Conversely, use of an angiotensin receptor-converting inhibitor or angiotensin receptor blocker (HR, 0.56; p=0.003) and administration of clopidogrel (HR, 0.64; p=0.001) are associated with lower mortality risk.

Right ventricular pacing was associated with increased total mortality (HR, 2.1; p<0.001) due to an elevated risk of non-SCD (HR, 3.8; p<0.001). Periods of appropriate or

inappropriate shocks were associated with a particularly high risk of total mortality (HR, 4.7; p<0.001) due to increased non-SCD (HR, 9.9; p<0.001).

Current guidelines for primary prevention exclude ICD implantation in patients within the first 40 days after MI. However, this restriction excludes a vulnerable population, given that the SCD is significantly higher immediately post-MI, especially in patients with low left ventricular ejection fraction.

Discussant Christophe Leclercq, MD, Rennes University Hospital, Rennes, France, said that the new IRIS analysis did not answer the question of why ICD fails to reduce total mortality early after MI. As such, there is no evidence to support changes to the current guidelines for ICD implantation, he concluded.

Increased Bleeding Risk with Concomitant Use of Antiplatelet Therapy: Dabigatran vs Warfarin

Written by Maria Vinall

The RE-LY trial compared two doses of dabigatran (110 mg BID and 150 mg BID) with open label warfarin (target INR 2 to 3) in 18,113 patients with nonvalvular atrial fibrillation (AF). The primary results demonstrated that treatment with the 110-mg dose was associated with rates of stroke and systemic embolism (SSE) that were similar to those seen with warfarin but with a lower rate of major bleeding. Meanwhile, dabigatran, at a dose of 150 mg, reduced the rate of SSE compared with warfarin but had a similar rate of major bleeding [Connolly SJ et al. *N Engl J Med* 2009]. Antonio Miguel Dans, MD, University of the Philippines, Manila, Philippines, presented the results of post hoc subanalyses from RE-LY, comparing the efficacy and safety of dabigatran with warfarin in patients dependent upon use of concomitant antiplatelet therapy (APT).

Many patients who are on oral anticoagulant therapy also require APT. The specific objectives of these analyses were to compare the efficacy (SSE) and safety (major bleeding, as defined by the International Society of Thrombosis and Hemostasis) of each dose of dabigatran versus warfarin in subgroup of patients with and in the subgroup of patients without concomitant antiplatelet use and to determine the effect of concomitant APT on rates of bleeding. Other efficacy and safety endpoints included all stroke, hemorrhagic stroke, ischemic stroke, cardiovascular (CV) death, minor bleeding, major + minor bleeding, intracranial bleeding, and extracranial bleeding.

A total of 6952 (38.2%) patients received concomitant APT during the study, and in the majority of cases, this consisted of aspirin with or without clopidogrel. The hazard ratio of the primary efficacy endpoint (SSE) was significantly lower for the 150-mg dabigatran dose compared with warfarin both for patients who were not on APT (HR, 0.52; 95% CI, 0.38 to 0.72) and for those who were on APT (HR, 0.80; 95% CI, 0.59 to 1.05). However, the p-value for interaction was 0.058 indicating evidence of attenuation in the benefit of dabigatran in the group on APT. Meanwhile, the hazard ratio of the primary efficacy endpoint for the 110 mg dose was not significantly different than that for warfarin in either those who received or did not receive APT, and the p-value for interaction (p=0.74) indicated no effect modification by concomitant APT on the effect of the lower dose of dabigatran. Other findings were consistent for both doses across all efficacy endpoints that were evaluated.

Overall, the risk of major bleeding was higher for patients who were on concomitant APT, even after adjustment for important clinical factors (adjusted HR, 1.60; 95% CI, 1.41 to 1.81), that attempted to account for the higher risk profile of patients who require APT. The hazard for major bleeding was lower for dabigatran 110 mg compared with warfarin, regardless of the use of concomitant APT with no evidence of effect modification due to the use of concomitant APT (interaction p-value 0.79). Similarly, there was no evidence of an interaction (p = 0.87) between APT and the risk of major bleeding with dabigatran 150 mg, which was similar to that of warfarin. Thus, the findings with regard to major bleeding that were observed in the main trial (less bleeding with dabigatran 110 mg compared with warfarin, similar bleeding with 150 mg dabigatran compared with warfarin) also apply, whether concomitant APT was administered or not.

Results from this study underscore the increased risk of bleeding associated with the concomitant use of APT and anticoagulant therapy with an observed 60% increase in the adjusted hazard of bleeding in this post-hoc analysis. While the lowest rates of bleeding for patients taking concomitant APT were observed with dabigatran 110 mg, whether it is the optimal choice for patients with AF who need APT requires confirmation in a prospective randomized trial. Clinicians should note that the 110 mg dose is not commercially available in all countries (eg, USA). An additional limitation of the current analysis was that there was no assessment of different APT regimens (eg, aspirin monotherapy vs dual APT with aspirin +