ventricular ejection fraction (LVEF) and moderate to severe mitral regurgitation (MR), according to new findings from the Surgical Treatment for Ischemic Heart Failure trial [STICH; NCT00023595].

Marek A. Deja, MD, Medical University of Silesia, Katowice, Poland, reported results from a subanalysis of the STICH trial in patients with MR.

In the STICH study, 1212 patients with LVEF <35% who were suitable candidates for CABG were randomly assigned to CABG (n=610) or medical therapy alone (n=602). In the primary analysis, there was no difference in all-cause mortality between CABG and medical therapy alone (36% vs 41%; HR, 0.86; 95% CI, 0.72 to 1.04; p=0.12). While the primary result was neutral, CABG was associated with reductions in some secondary endpoints, including the risk of cardiovascular (CV) death (28% vs 33%; HR, 0.81; 95% CI, 0.66 to 1.00; p=0.05) and the composite endpoint of all-cause mortality or CV hospitalization (58% vs 68%; HR, 0.74; 95% CI, 0.64 to 0.85; p<0.001) [Velazquez EJ et al. *N Engl J Med* 2011].

At baseline, MR was present in 64% of patients and classified as mild, moderate, and severe in 46%, 15%, and 3% of the patients who were randomized in STICH, respectively, underscoring the high prevalence of MR in candidates for CABG. The decision of whether or not to treat MR was left to the surgeon. In the current analysis, investigators examined the relationship of MR severity and survival and compared outcomes in patients with moderate–severe MR who received mitral repair versus those who did not.

In patients who were randomized to medical treatment, mortality was higher in patients with increasingly more severe MR (30% with no/trace MR, 47% with mild MR, 55% with moderate–severe MR). Compared with patients with no or trace MR, patients with moderate or severe MR had nearly double the risk of death from all causes (HR, 1.97; 95% CI, 1.37 to 2.83), while those with mild MR had a 60% increase in all-cause mortality (HR, 1.60; 95% CI, 1.18 to 2.18).

After 6 years of follow-up, CABG was not associated with decreased mortality relative to medical therapy alone in patients with no or trace MR (28% vs 30%; HR, 0.87; 95% CI, 0.61 to 1.24); however, CABG was associated with a reduced risk of death in patients with mild MR (31% vs 47%; HR, 0.64; 95% CI, 0.48 to 0.85).

In the small subgroup of patients with moderate or severe MR (n=195), there was no survival advantage with CABG compared with medical therapy alone (HR, 0.86; 95% CI, 0.57 to 1.29) or with CABG and mitral repair (HR vs medical therapy 1.13, 95% CI, 0.69 to 1.86). However, after adjustment for baseline prognostic variables, the combination of CABG and MV repair was associated with a lower hazard of mortality compared with CABG alone (HR, 0.45; 95% CI, 0.23 to 0.90) and was associated with a trend toward lower mortality compared with medical therapy alone (HR, 0.66; 95% CI, 0.40 to 1.11).

The authors conclude that in patients with severe left ventricular dysfunction and mild MR, CABG alone improves survival, while in patients with moderate–severe MR, adding mitral repair to CABG tends to decrease perioperative risk and increase survival compared with CABG alone or medical therapy alone.

ASCOT-LLA: Statin Legacy Felt with Reduced Non-CV Death Eight Years After Trial End?

Written by Anne Jacobson

Prior treatment with atorvastatin is associated with a reduction in the risk of all-cause mortality compared with placebo 8 years after the early termination of the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-Lowering Arm (ASCOT-LLA) and 11 years after initial randomization, according to new findings from a long-term follow-up study.

In 2003, an interim analysis of ASCOT-LLA showed that atorvastatin significantly reduced the risk of coronary heart disease (CHD; RRR 36%) and stroke (RRR 27%) compared with placebo in patients with hypertension who were also receiving antihypertensive treatment, leading to an early termination of the trial [Sever PS et al. *Lancet* 2003]. The subgroup of patients who were enrolled in the United Kingdom (UK) cohort of ASCOT-LLA was then followed for an additional 8 years after trial termination on open-label therapy, as selected by the local health care provider. Peter S. Server, MD, FRCP, Imperial College, London, UK, presented mortality results for the entire 11-year follow-up period since initial randomization in ASCOT-LLA.

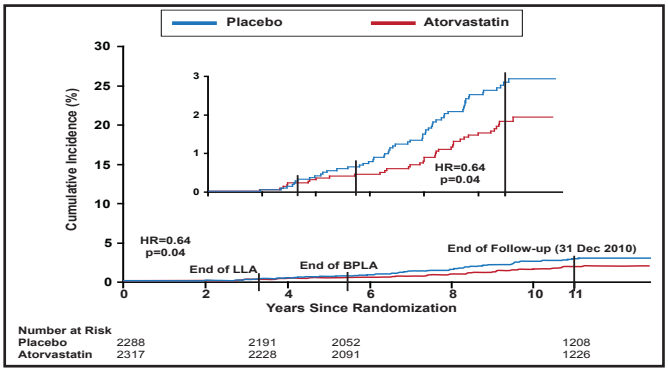
In the ASCOT-LLA randomized trial, 10,305 patients with hypertension and a total cholesterol level of ≤6.5 mmol/L (250 mg/dL) were randomly assigned to atorvastatin 10 mg or placebo. After a median follow-up of 3.3 years, the trial was terminated due to overwhelming benefit with atorvastatin, with a reduction in the primary endpoint of nonfatal myocardial infarction (MI) and fatal CHD of 36% compared with placebo (HR, 0.64; 95% CI, 0.50 to 0.83; p=0.0005). At that time, there was no significant difference between groups in terms of either all-cause mortality (HR, 0.87; 95% CI, 0.71 to 1.06) or cardiovascular (CV) mortality (HR, 0.90; 95% CI, 0.66 to 1.23).

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