tion did not reduce time to a 90 days break in treatment with either an ACE-I/ARB (Hazard ratio (HR): 0.82, 95% Confidence Interval (CI): 0.34-1.97, P=0.650), a BB (HR: 1.09, 95% CI: 0.53-2.66, P=0.820) or an ARRA (HR: 1.30, 95% CI: 0.85-2.00, P=0.298). No interaction between adherence, the HF clinic intervention, any high-risk subgroup was observed (NT-proBNP > 1000 pg/ml, eGFR < 60 ml/min/1.73 m², NYHA class III, high doses of diuretics, elderly, low educational level, low income or living alone) (P>0.05 for all). At follow up end adherence was 90% for ACE-I/ARB’s, 88% for BB’s and 75% for ARRA’s and did not differ between treatment arms (LogRisk > 0.05 for all).

Conclusions: Extended follow up in an outpatient HF clinic did not improve long-term adherence to guideline based therapy and adherence did not deteriorate when follow up was shifted from the HF clinic to primary care. However, novel strategies to improve long term adherence for aldosterone receptor antagonists are needed.

807 | BEDSIDE
Trimetazidine improves exercise tolerance and left ventricular function in patients with contemporary treatment of chronic ischemic heart failure
P. Pagorek, T. Rudzinski, L. Chrzanowski, J.D. Kasprzak. Chair and Department of Cardiology, Medical University., Lodz, Poland
Purpose: To prospectively evaluate the effect of modified-release trimetazidine, as an addition to standard therapy, on functional class, exercise tolerance and left ventricular function in patients with ischemic heart failure.
Methods: 48 patients with chronic heart failure were randomized in a cross-over study to placebo or trimetazidine (modified release pill, 35 mg t.i.d.) for two periods of 90 days. At the end of each period, all patients underwent ergospirometry, 2D echocardiography and physical examination. New York Heart Association (NYHA) class, left ventricular ejection fraction, plasma concentrations of NT-proBNP, interleukin-8 and adiponectin were evaluated. The patients were treated according to current standards, with -90% rate of beta-blocker and RAA-blockade use.
Results: Compared with placebo, exercise time (trimetazidine (TMZ) 452.5 ± 145.6 s vs. 413.3±167.5 s, p=0.039) and load (TMZ 117.5±44.9 vs 104.8±43.8 Watt, p=0.046) during ergospirometry test, increased in the trimetazidine group. Left ventricular ejection fraction increased 30.7±6.4% in patients treated with trimetazidine compared with 28.8±6.1% in those receiving placebo, p=0.043. On trimetazidine NYHA class decreased from 2.76±0.4 to 2.53±0.50, p=0.03. Plasma levels of NT-proBNP decreased significantly in trimetazidine compared with placebo (TMZ 2507.2±1957.9 vs 2962±1950.3 pg/ml, p=0.048).
Conclusions: The addition of trimetazidine to modern multidrug treatment improves exercise tolerance and left ventricular ejection fraction in patients with ischemic heart failure. This is accompanied by a significant decrease in the levels of NT-proBNP.

808 | SPOTLIGHT 2013
Interaction between statins and fibrates regarding cardiovascular outcomes
E. Salahaddeen, C. Torp-Pedersen. Gentofte Hospital, Department of Cardiology, Copenhagen, Denmark
Purpose: There are contradicting reports of the safety and effectiveness of combining statins and fibrates. We used the large Sibu-trimazidine Cardiovascular OUTcomes (SCOUT) trial to further explore this relation.
Methods: Combining statins and fibrates for treatment of dyslipidemia. We used the large Sibu-trimazidine Cardiovascular OUTcomes (SCOUT) trial to further explore this relation.
Results: 9804 patients were randomized. Mean age was 63.2±6.1 (min-max 51-81) years and 42% were women. 333 (3.4%) patients received combination therapy including statins and fibrates. Risk of cardiovascular death and all-cause mortality, respectively, were analyzed using multivariate Cox regression models.
Results: 9804 patients were randomized. Mean age was 63.2±6.1 (min-max 51-81) years and 42% were women. 333 (3.4%) patients received combination therapy including statins and fibrates. Risk of cardiovascular death and all-cause mortality were increased in patients using combination therapy compared to statin monotherapy: HR (for primary endpoint) was 1.40 (95% CI 1.05-1.88), HR for cardiovascular death was 1.63 (1.04-2.55) and HR for all-cause mortality was 1.67 (1.21-2.32). Patients receiving fibrate monotherapy had increased risk of cardiovascular death compared to those receiving statin monotherapy: HR was 1.57 (1.10-2.22). Incidence Rate (IR) and 95% Confidence Interval (CI) of primaryendpoint, cardiovascular death and all-cause mortality for the combination therapy treatment class vs. statin monotherapy were 3.83 (2.90-5.05) vs. 2.57 (2.38-2.77) 1.61 (1.05-2.46) vs. 1.01 (0.90-1.14); and 3.06 (2.24-4.17) vs. 1.94 (1.78-2.12), respectively. Incidence rate of cardiovascular death for fibrate only treatment class was 1.50 (1.10-2.04). No significant association of gender was observed (P-for interaction for primary endpoint, cardiovascular death and all-cause mortality were 0.81, 0.16 and 0.49, respectively).
Conclusion: In obese or overweight patients with cardiovascular disease and/or type 2 diabetes, the combination therapy with statins and fibrates was associated with an increase risk of cardiovascular adverse events, including cardiovascular death, and all-cause mortality.

809 | BEDSIDE
Mishap opportunities: low use of evidence-based treatment with eplerenone after myocardial infarction - a nationwide study
S.M. Sollien Berger, M. Schou, M.D. Schmiegelow, L.K. Nume, S. Christensen, L. Koebber, C. Torp-Pedersen, G. Gislason. 1. Gentofte University Hospital, Department of Cardiology, Copenhagen, Denmark; 2. Rigshospitalet - Copenhagen University Hospital, Heart Centre, Department of Cardiology, Copenhagen, Denmark; 3. Aalborg University, Department of Health Science and Technology, Aalborg, Denmark
Purpose: The aldosterone antagonist eplerenone reduces mortality and readmissions after acute myocardial infarction (MI) in patients with LVEF ≤40% and either symptomatic heart failure or diabetes mellitus, and is recommended by ESC guidelines. We investigated evidence-based use of eplerenone in a nationwide cohort of patients after first-time MI in Denmark.
Methods: From national registers we included all patients with MI, aged ≥30 years and surviving ≥30 days. Indication for eplerenone was defined as claimed prescription of loop-diuretics in addition to either ACE-inhibitor or anti-diabetic drugs, within 90 days after discharge. Use of eplerenone and other aldosterone antagonists was identified, and survival compared by Kaplan-Meier analysis.
Results: We included 49,479 patients (63% men, mean age 68.1±13.6 years) with a median follow-up of 1003 (IQR 420-1716) days. Treatment with eplerenone was indicated in 9,115 (18.4%) patients, of which 93 (1.02%) received eplerenone, and 2,157 (23.7%) received spironolactone. Mortality rates for groups with and without indication for eplerenone at one-year were 1,096 (16.0%) and 3,115 (8.1%), and at end-of-follow-up 2,871 (41.8%) and 8,680 (22.5%), respectively (Figure). Applying the evidence-based mortality benefit effect of eplerenone to our results, a potential of 164 and 431 deaths within the first year, and during long-term follow-up, respectively, could have been saved by guideline-recommended use of eplerenone.

Survival by eplerenone indication

Conclusions: In a nationwide cohort of post-MI patients, a low use of eplerenone was observed in patients with indication for treatment. Our findings suggest an unexploited potential in the treatment of high-risk group of patients, and therefore focus on initiation of evidence-based treatment is warranted.

810 | BEDSIDE
The effect of heart rate reduction with ivabradine on renin function in patients with chronic heart failure: an analysis from SHIFT
A.A. Voors, D.J. Van Veldhuisen, M. Robertson, I. Ford, J. Borre, M. Boehr, M. Komada, K. Swedberg, L. Tavazzi. on behalf of the SHIFT investigators. 1. University Medical Center Groningen, Groningen, Netherlands; 2. University of Glasgow, Glasgow, United Kingdom; 3. State University of New York, Downstate Medical Center, New York, United States of America; 4. Saarland University Hospital, Department of Internal Medicine III, Homburg-Saar, Germany; 5. University Pierre & Marie Curie (UPMC), Paris, France; 6. The Cardiovascular Institute, Sahlgrenska University Hospital, Göteborg, Sweden; 7. Maria Cecilia Hospital-GVM Care and Research, Eltore Sansavini Health Science Foundation, Cotignola, Italy
Background: In patients with chronic systolic heart failure and sinus rhythm, heart rate reduction with ivabradine reduces mortality and morbidity. We studied the relationship between heart rate and renal function and the effects of heart rate reduction with ivabradine in patients with and without renal dysfunction.
Methods and results: From the 6558 patients that were randomized in SHIFT, baseline creatinine and at least one follow-up measurement were available in 6160 patients. Median follow-up was 22.9 months. Renal dysfunction was defined as an eGFR <60 ml/min/1.73 m² and was present in 1579 out of the 6160 patients (26%). Worsening renal function (WRF) was defined as a creatinine increase in excess of >0.5 mg/dL and >25% from the baseline value. Risk of WRF was directly related to baseline heart rate, with an incremental risk of 5% for every 5 bpm heart rate increment (HR 1.05/5bpm, 95% confidence interval 1.02-1.08, p=0.003). WRF developed in 1029 (17%) patients and significantly
predicted the primary endpoint of hospitalisation for worsening HF or cardiovas-
ccular death (HR 1.38; 95% CI 1.15–1.64; p<0.001) and of all-cause mortality (HR 1.42; 95% CI 1.16–1.72; p<0.001). Ixabradine use was associated with a reduc-
tion of the primary composite endpoint both in patients with (HR, 0.81, 95% CI, 0.68 to 0.97), and without renal dysfunction (HR, 0.81, 95% CI, 0.71 to 0.91) (P-
value interaction, 0.89). No differences were found in changes in renal function over time between ivabradine and placebo treated patients.

Conclusion: In chronic stable systolic heart failure patients, heart rate was di-
rectly and independently associated with risk of WRF, but reduction in heart rate by ivabradine had a neutral effect on renal function during 2 years of follow-up. The effects of ivabradine were maintained both in patients with and without renal dysfunction.

**STATIN FOR EVERYONE EVERY TIME – IS IT RIGHT?**

**831 I BEDSIDE**

**Efficacy of AMG 145, a fully human monoclonal antibody to PCSK9: data from 1252 patients in four phase 2 studies**

F. Rael1, R.P. Giugliano2, M.J. Koren3, D. Sullivan4, E.M. Roth5, R. Weiss6, J.B. Kim7, J. Yang8, M.S. Sabatine8, E.A. Stein9, 1University of the Witwatersrand, Johannesburg, South Africa; 2Brigham and Women’s Hospital, Department of Medicine, Cardiovascular Division, TIMI Study Group, Boston, United States of America; 3Jacksonville Center For Clinical Research, United States of America; 4Royal Prince Alfred Hospital, Camperdown, New South Wales, Australia; 5Sterling Research Group, Cincinnati, United States of America; 6Maine Research Associates, Auburn, Maine, United States of America; 7Amgen Inc., Thousand Oaks, United States of America; 8Metabolic & Atherosclerosis Research Center, Cincinnati, United States of America

Purpose: In 4 recent randomized phase 2 trials, 12 weeks of AMG 145, a fully human monoclonal antibody to PCSK9, demonstrated robust reductions in LDL cholesterol (LDL-C), with favorable changes in other lipids. In a prespecified analy-
sis, we pooled data from the 4 studies into a single database to assess the efficacy of AMG 145.

Methods: The 4 trials enrolled 1359 patients. This pooled analysis included 1252 patients who received various doses of AMG 145 subcutaneously (SC) and 301 received placebo SC; 107 patients who received ezetimibe were excluded. In each trial, treatment duration was 12 weeks and the primary end point was per-
centage change in LDL-C by ultracentrifugation (UC) from baseline to week 12. Three of the 4 trials of AMG 145 permitted stable background statin therapy. Results: Of 1252 patients, 44% were male, mean age 56±12 years. Mean pre-
treatment LDL-C by UC was 3.6±1.0 mmol/L. Mean changes in LDL-C from base-
line at week 12 ranged from −40% to −59% across AMG 145 doses vs. 0.1% to 0.5% for placebo, P<0.001 for all dose groups. Favorable changes were also ob-
served in apolipoprotein B, lipoprotein(a), triglycerides, HDL-C, and apolipopro-
tein A1. The highest doses, AMG 145 140 mg Q2W (N=123) and 420 mg Q4W (N=213) vs placebo Q2W (N=123) and Q4W (N=178), produced the greatest ef-
ficacy (Table).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AMG 145 mean treatment difference vs placebo, %</th>
<th>140 Q2W (N=123)</th>
<th>420 mg Q4W (N=213)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td>(by ultracentrifugation)</td>
<td>−52.9%</td>
<td>−52.6%</td>
</tr>
<tr>
<td>Apolipoprotein B</td>
<td></td>
<td>−52.01%</td>
<td>−43.51%</td>
</tr>
<tr>
<td>Lipoprotein(a)</td>
<td></td>
<td>−55.37%</td>
<td>−56.79%</td>
</tr>
<tr>
<td>Triglycerides</td>
<td></td>
<td>−25.89%</td>
<td>−15.62%</td>
</tr>
<tr>
<td>HDL-C</td>
<td></td>
<td>8.8%</td>
<td>5.93%</td>
</tr>
<tr>
<td>Apolipoprotein A1</td>
<td></td>
<td>3.99%</td>
<td>3.86%</td>
</tr>
</tbody>
</table>

*p<0.001; **p<0.05.

Conclusions: In this large pooled analysis of 4 phase 2 studies, AMG 145 dosed either Q2W or Q4W showed marked and significant reductions in LDL-C and favorable changes in other pro-atherogenic and anti-atherogenic lipids in diverse patient populations.

832 I BEDSIDE

**HDL cholesterol, size, particle number, and residual vascular risk after potent statin therapy: the JUPITER trial**

S. Mora, R. Glynn, P. Ridker. Brigham and Women’s Hospital, Boston, United States of America

Purpose: Chemically-measured high-density lipoprotein cholesterol (HDL-C) may not be the best clinical measure of HDL. Little is known about alternative HDL measures such as HDL size or particle number (HDL-P) as determinants of residual risk after potent statin therapy.

Methods: In JUPITER, HDL size and HDL-P were measured by nuclear magnetic resonance spectroscopy and HDL-C was chemically assayed at baseline and after random allocation to rosuvastatin 20 mg/day or placebo. Levels were related to first CVD events.

Results: Rosuvastatin lowered LDL cholesterol (by 49%) and raised HDL-C (6.1%), HDL size (1.2%), and HDL-P (3.8%); all p<0.0001. Among placebo-
allocated individuals, on-treatment HDL-C and HDL-P had similar inverse as-
soations with CVD (risk factor-adjusted hazard ratio per 1-standard deviation: 0.79, 95% CI 0.63-0.98, and 0.81, 95% CI 0.67-0.97, respectively). By contrast, among rosuvastatin-allocated individuals, on-treatment HDL-P was statistically significantly associated with CVD (0.73, 0.57-0.93; p=0.01) but HDL-C was not (0.82, 0.63-1.08, p=0.17). Among rosuvastatin-allocated individuals, on-treatment HDL-P remained significant (0.72, 0.53-0.97, p=0.03) after additionally adjusting for HDL-C. In risk factor-adjusted models, HDL size showed no significant asso-
ciation with CVD. However, after additionally adjusting for HDL-C, on-treatment HDL size conferred increased risk for the secondary combined endpoint of CVD and all-cause death.

Conclusions: In the setting of potent statin therapy, HDL particle number may be a better marker of residual risk than chemically-measured HDL-C. This has potential implications for evaluating novel therapies targeting HDL.

833 I SPOTLIGHT 2013

**Statins prevent cataracts: a meta-analysis**

J.B. Kostis, J.M. Dobrzynski. UMDNJ-Robert Wood Johnson Medical School, New Brunswick, United States of America

Purpose: To investigate the occurrence of cataract among statin users.

Methods: We performed a systematic search of the MedLine, Web of Knowledge, Cochrane database and ClinicalTrials.gov and identified 363 records of all titles pertaining to statins and cataract. After exclusion of 296 titles based on reading the abstracts, we examined 68 full text articles. Fifty-three were excluded because of the absence of controls or cataract as an outcome, were duplicate reports from the same study, reviews, nutrition studies, animal studies or basic science stud-
ies. The meta-analysis included 13 clinical trials, two of which had separate data for clinical cataract and for ophthalmologist detected opacities. Using random ef-
fects models, we examined all studies and separately studies of clinical cataracts and opacities detected by ophthalmologists. Publication bias was examined by studying funnel plots.

Results: Use of statins was associated with lower rate of cataract (odds ratio [OR] 0.81, 95% confidence interval [CI] 0.72, 0.92, p=0.0009). The effect was statistically significant for studies examining clinical cataract (OR 0.81, CI 0.71, 0.92, p=0.0016), while only a trend was seen in studies examining opacities de-
tected by ophthalmologists (OR 0.84, CI 0.60, 1.17, p=0.20). Meta-regression indicated an increase in benefit of statins with longer duration of use with OR varying from 0.45 for a treatment duration of 13 years to 0.90 for a treatment du-
ration of 6 months. Also, older age was associated with lower benefit (OR 0.90 for persons in their 70s [who probably already had cataract] to 0.50 for persons in their 40s).

Conclusions: Statins have a protective effect for cataract and this effect is magni-
nified with longer use and among younger individuals.

834 I BEDSIDE

**Benefits of statins in elderly subjects without established cardiovascular disease. a meta-analysis**

G. Savarese1, S. Paolillo2, C. D’Amore3, T. Losco4, F. Musella1, O. Scala1, G. Rengo5, D. Leosco2, B. Trimmarano2, P. Perrone Filardi2, 1Department of Advanced Biomedical Sciences: Federico II University, Naples, Italy, Naples, Italy; 2Department of Medical Translational Sciences; Federico II University, Naples, Italy, Naples, Italy

Background: Since ageing of the population is steadily raising, prevention of Car-
 dovascular disease in the elderly is relevant. In elderly patients with previous CV events, use of statins is recommended by guidelines, whereas the employ of these drugs in elderly subjects without previous CV events is still debated. The aim of the present study was to verify whether statins reduce all-cause mortality and CV events in elderly people without previous established CV disease.

Methods: MEDLINE, Cochrane, indexed resources: MEDLINE, Cochrane. 1979-2012 years. 1029 studies were searched for articles about statin treatment in patients without CV disease
ease until December 2012. Study inclusion criteria were: randomized allocation to statin or placebo; age at randomization – ≤65 years or report of outcomes in the subgroup of patients with age – <65 years; report of at least 1 clinical event among all-cause death, CV death, Myocardial Infarction (MI), coronary revascularization, stroke and new cancer onset; report of outcomes separately for patients without established CV disease. Meta-analysis was performed to assess the influence of