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**Journal**

Journal of Clinical Lipidology, 10(5)

**ISSN**

1933-2874

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**Publication Date**

2016-09-01

**DOI**

10.1016/j.jacl.2016.06.013

Peer reviewed

# Mortality reduction in patients treated with long-term intensive lipid therapy: 25-year follow-up of the Familial Atherosclerosis Treatment Study - Observational Study

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## Abstract

**BACKGROUND**—Cardiovascular disease (CVD) begins early in life and is associated with both the number of risk factors present and length of exposure to these risk factors including hyperlipidemia.

**OBJECTIVES**—The clinical benefit of intensive lipid therapy over 25 years was investigated in the Familial Atherosclerosis Treatment Study – Observational Study (FATS-OS).

**METHODS**—Of 175 CAD subjects with mean LDL-C of 191 mg/dl and mean age of 50 years, who completed the randomized and placebo-controlled FATS, 100 choose receiving lipid management by their physicians (UC) and 75 elected to receive an intensive lipid therapy (IT) with lovastatin (40mg/day), niacin (2.5g/day) and colestipol (20g/day) from 1989 to 2004, followed by double therapy with simvastatin (40–80mg/day) and niacin from 2005 to 2006 and by triple therapy of ezetimibe 10 mg and simvastatin 40–80 mg/day plus niacin during 2007–2012. Death from CVD, non-CVD and any cause were compared between UC and IT using Cox proportional hazards model.

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**RESULTS—**UC and IT groups were similar in risk factors with the exception that IT had more sever CAD. Mean LDL-C levels were 167 mg/dl from 1988 to 2004, 97 from 2005 to 2006, and 96 from 2007 to 2012 in surviving subjects receiving UC. IT lowered LDL-C to 119 mg/dl, 97, and 83 in the 3 time periods. Compared to UC, IT significantly reduced total mortality (11.1 vs. 26.3 per 1,000 PY, HR=0.45, 95% CI: 0.26–0.77, p=0.003) and CVD mortality (10.6 vs. 27.7 per 1,000 PY, HR=0.34, 95% CI: 0.15–0.80, p=0.009). The non-CVD mortality was also reduced, but was not of statistical significance (6.8 vs. 12.7 per 1,000 PY, HR=0.55, 95% CI: 0.27–1.14, p=0.11).

**CONCLUSIONS—**Long-term intensive lipid therapy significantly reduced total and cardiovascular mortality in FATS-OS. These results support the importance of lifetime risk management to improve long-term outcome.

## Keywords

cardiovascular disease; mortality; lifetime risk; lipid-lowering therapy

## INTRODUCTION

Population studies have indicated that an increase in lifetime risk of cardiovascular disease (CVD) and mortality is associated with both the number of CVD risk factors present and length of exposure to these risk factors [1–3]. Data from randomized clinical trials have demonstrated that lowering LDL-C results in CVD event reduction [4, 5] and have led to recommendations by current guidelines [6,7] to select the appropriate intensity of statin therapy in patients most likely to benefit. However, none of these trials lasted more than 7 years. We designed a 25-year observational study (OS) following the Familial Atherosclerosis Treatment Study (FATS) [8] to investigate the long-term clinical benefit of intensive lipid therapy.

## METHODS

### The FATS Randomized Trial

The study design and results for the first 146 enrollees in FATS have been previously described [8]. In brief, between January 1984 and Dec 1986, a total of 176 patients without diabetes were enrolled in this randomized, doubly-blinded angiographic comparison of two intensive lipid-altering regimens with a proven conventional approach. Participants were men aged 62 years or younger with established coronary artery disease, elevated apolipoprotein B (apo B) levels and a family history of premature vascular events. They were randomly assigned to a 2.5 year period of one of three arms: lovastatin (20 mg bid) and colestipol (10 gm tid); niacin (1 gm qid) and colestipol; or conventional therapy of diet and colestipol for those with LDL-C ≥ 90th percentile for age (or colestipol placebo for those with lower LDL-C) [8]. All received dietary counseling at American Heart Association Level I or II by a dietitian blinded to treatment. Clinic visits for counseling, blood sampling, clinical monitoring and medication supplies occurred monthly for one year and bimonthly thereafter. Plasma lipids, lipoproteins, and apolipoproteins were determined at pretreatment base line and at specified time-points during and after therapy [8]. Coronary angiography

was performed at base line and after 2.5 years. Coronary stenosis severity was measured as described previously [8]. The primary study endpoint was per-patient mean change in proximal stenosis severity over the 2.5-year treatment interval. Results were reported in 1990 [8].

### The FATS Observational Trial

**Subjects**—As illustrated in Figure 1, prior to 1988, all those completing or quitting the randomized trial were thanked for their participation and advised to return to the usual care of their physicians who were, at that time, given full details of their randomized regimen and their clinical, lipoprotein and angiographic outcomes. No specific treatment recommendations were made at the time of returning to the usual care.

Between June 1986 and December 1988, a pilot study (n=9) of triple-drug therapy (niacin 1000 mg bid, lovastatin 20 mg bid, and colestipol 10 gm bid) was conducted in order to gain experience with this regimen [9] as FATS continued (Figure 1). The lipid response to this regimen was impressive [9]; average responses to this regimen were: total cholesterol change from 300 mg/dl to 170, LDL-C from 215 to 95 mg/dl, HDL-C from 46 to 56 mg/dl, and triglyceride from 190 to 120 mg/dl.

Therefore, we decided, in late 1988 to invite all those finishing the randomized phase to continue indefinitely on the triple-therapy regimen, with dose adjustment for ambitious lipid targets of LDL-C    100 mg/dl and HDL-C    50 mg/dl or to the highest dose tolerated without side-effects. In all, 75 of 86 patients who were invited to continue triple-therapy did so (including nine pilot study patients) and formed the intensive treatment (IT) group. The remaining 11 plus previous 89 subjects who finished FATS prior to 1988 returned to the usual care of their physicians, a total of 100 these subjects formed the usual care (UC) group as shown in Figure 1.

**Intensive Therapy**—From 1989 to 2004, IT consisted of triple-combination therapy revised from the pilot doses to lovastatin (40mg/day), niacin (2.5g/day) and colestipol (20g/day). From 2005 to 2006, IT became a double-combination therapy due to the availability of colestipol and transitioned to simvastatin (40–80mg/day) and niacin, either slow-release (2g/day) or immediate-release (4g/day). Beginning 2007 and through 2012, triple therapy of Vytorin (ezetimibe 10/simvastatin 40–80 mg/day) plus niacin (same type and dosage in 2006) was used for more effectively lowering of LDL-C.

Subjects continuing very intensive therapy were seen every 6 months for clinical evaluation, dietary counseling (20 minutes at AHA step I or II, as desired), blood sampling, medication resupply and compliance assessment. Medication dosage was adjusted based on in-treatment lipid response and clinical or laboratory side effects. Slow-release niacin was given twice daily at meal times. Immediate-release niacin was recommended to be taken 3 times daily with meals. Aspirin 81 mg once or twice daily was recommended 30 minutes prior to niacin to help reduce the flushing side effect.

Plasma lipids and lipoproteins were measured at baseline and every six months throughout the study at the Northwest Lipid Research Laboratory. Also, creatinine, uric acid, glucose,

serum aspartate aminotransferase, and creatinine kinase were measured to detect possible adverse side effects.

**Usual Care**—Those subjects who returned to the usual care of their physicians were mailed questionnaires every 3 years. In addition to an informed consent to request data, the following points of information were included in the questionnaires: 1. Alive or dead and cause of death. 2. Clinical or cardiovascular event since leaving study. 3. Nature of the event, and treating physician/hospital. 4. Under lipid therapy at any point since leaving the study. 5. If so, what drug(s), date started, date stopped, and lipid values on therapy. 6. Name, address of physician managing lipids. In subjects who did not return the questionnaires and respond to our follow-up phone calls, their family members were contacted to confirm the survival status.

By questionnaire and direct phone contact, the temporal sequence of drug therapy and the treating physician were established for every UC patient. This sequence was confirmed by the treating physician, who provided one or more estimates of total cholesterol, triglyceride, LDL-C, and HDL-C for each period of therapy with given drug(s) and dosage. For periods in which lipid drugs were not used, lipid levels obtained by the physician were recorded, if available. If not, the most recent off-treatment FATS estimates of these four parameters were used. On average, we obtained 7±6 lipid assessments among the UC subjects.

### Mortality Determination

Death was either reported by the subject family or identified using the State fatal statistics database. In the event of death, a death certificate was obtained from the local department of health with any associated hospital records if possible. Each death was classified as cardiovascular or non-cardiovascular based on the primary cause of death indicated by the death certificate. Cardiovascular causes included sudden cardiac death, fatal myocardial infarction or stroke, or heart failure due to ischemic heart disease. The non-cardiovascular deaths included cancer, infection and accidents.

### Statistical Analysis

In comparison of lipids, the linear mixed models were used to adjust for the different timing of lipid measurements in different subjects over time. For example, subjects in IT group had their lipid measurements every 6 months compared to those in UC group had available data on lipids between 6 and 36 months. The lipid comparisons between the 2 treatment groups were further adjusted for multiple periods and for multiple variables. Statistically significance was denoted when $p<0.001$ with Bonferroni adjustment.

Cox proportional hazards model was used to compare CVD mortality, non-CVD mortality and all-cause mortality over 25 years between IT and UC groups.

Cox regression models were use to identify clinical and laboratory variables that were associated with total, CVD and non-CVD mortality. Multivariate analysis was performed including variables with $p<0.05$ in the univerate analysis to identify the independent factors associated with total, CVD and non-CVD mortality.

All statistical calculations were conducted with the R statistical software package [10].

## RESULTS

### Baseline patient characteristics

Clinical variables and coronary stenosis as assed by quantitative angiography are presented in Table 1. Compared to UC, subjects in IT had significantly more severe mean coronary stenosis at baseline of FATS (39% vs. 30%, p<0.001). All other factors were well balanced between UC and IT groups.

### Lipid and lipoprotein levels

As described in Table 2, UC represented an increased intensity of LDL-C lowering influenced by national cholesterol treatment guidelines over time. For example, the mean LDL-C levels were 167 mg/dl from 1988 to 2004, 97 from 2005 to 2006, and 96 from 2007 to 2012 in surviving subjects. Subjects in the IT group were under aggressive treatment and monitoring for their lipid management. The mean LDL-C levels were 119 mg/dl from 1988 to 2004, 97 from 2005 to 2006, and 83 from 2007 to 2012. Significant differences in lipid levels between UC and IT groups were primarily found during the first 16 years of the study from 1988 to 2004.

### Mortality over 25 years

Of a total of 70 deaths identified in FATS-OS over 25 years, 52 were in UC and 18 in IT. Table 3 provides the detailed mortality information and causes. Compared to UC group, IT had significantly lower total mortality (11.1 vs. 26.3 per 1,000 PY, HR=0.45, 95% CI: 0.26–0.77, p=0.003) (Figure 2A).

**Cardiovascular death**—Compared to UC, IT group had significantly lower cardiovascular mortality (10.6 vs. 27.7 per 1,000 PY, HR=0.34, 95% CI: 0.15–0.80, p=0.009) as shown in Figure 2B.

**Non-cardiovascular death**—IT group also had lower non-cardiovascular mortality compared to UC, but this did not reach statistical significance: 6.8 vs. 12.7 per 1,000 PY, HR=0.55, 95% CI: 0.27–1.14, p=0.11 (Figure 2C).

### Factors associated with mortality

IT, history of MI and history of ischemic leg pain were identified as independent factors associated with total mortality by multivariate analysis including all clinical factors and biomarkers that were correlated with mortality in the univariate analysis (Table 4). IT independently reduced total mortality risk by 53% (HR=0.47, 95% CI: 0.26–0.85, p=0.01), risk of CVD death by 70% (HR=0.30, 95% CI: 0.12–0.74, p=0.01) and risk of non-CVD death by 29% (HR=0.71, 95% CI: 0.32–1.55, p=0.4).

## DISCUSSION

In our 25-year follow-up study of FATS, we found that prolonged intensive combination lipid therapy is associated with significant reductions in cardiovascular mortality and total mortality in men with a history of hypercholesterolemia and coronary atherosclerosis. There was a non-significant trend towards reduction in non-cardiovascular mortality. Multivariate regression analysis showed that intensive therapy independently predicted a lower risk of cardiovascular mortality and total mortality.

Atherosclerosis is a chronic disease process that begins early in life and is associated with exposure to a number of risk factors including hypercholesterolemia [11]. Analysis of longitudinal epidemiologic studies has shown that the burden of these risk factors is a significant predictor of the lifetime risk of atherosclerotic vascular disease [1,3] and its related death [2]. Based on the lifetime risk model [2], the projected 25-year cardiovascular mortality in FATS-OS was 30%. We observed 27% cardiovascular death over 25 years in the usual care group and 9% in subjects with a greater burden of angiographic coronary disease received intensive lipid therapy for 25 years. The data indicate that an early and long-term adequate control of hyperlipidemia can lead to 18% absolute or 66% relative risk reduction in cardiovascular mortality over 25 years.

Studies of genetic-based cholesterol disorders have confirmed both the risk and benefit of life-long exposure to abnormal levels of cholesterol. For example, patients with familial hypercholesterolemia (FH) are chronically exposed to severely elevated serum cholesterol levels from birth and have accelerated atherosclerosis with premature manifestations of clinical cardiovascular events proportional to both the level and duration of their exposure to high cholesterol [12]. This risk is attenuated with aggressive lowering of LDL-C, primarily with statins [13]. On the contrary to FH, patients born with loss of function mutations in the PCSK (proprotein convertase subtilisin/kexin) 9 gene have life-long exposure to low serum LDL-C which is associated with significant reductions in the incidence of coronary heart disease [14]. The duration of treatment in previously published randomized clinical trials of lowering cholesterol have all been relatively short, lasting less than 7 years, and insufficient to evaluate the question of whether life-long lipid therapy does translate to reduction of CVD death risk. In FATS-OS we were able to follow a cohort of intensively treated subjects for 25 years.

The potential long-term clinical benefits of lipid therapy have been noted previously in the 10-year follow up study of the West of Scotland Coronary Prevention Study (WOSCOPS) [15] and recently in its 20 years of follow-up [16], and the 11-year follow-up in the Heart Protection Study (HPS) [17]. During a 10-year follow up, subjects with hypercholesterolemia that were initially randomized to pravastatin for 5 years in WOSCOPS [18] experienced a significant 27% relative risk reduction in coronary heart disease death or non-fatal myocardial infarction as compared to placebo treated subjects (HR = 0.73; 95% CI, 0.63–0.83, P<0.001). The risks of total mortality and coronary heart disease death were reduced by 13% and 27% at the 20 years of follow-up despite equal proportions of subjects (31%) subsequently receiving statin therapy after the 5-year randomized phase in the original placebo and pravastatin groups. The 11-year follow up study of HPS showed that

vascular mortality and morbidity reduction during the 5 years of in-trial period persisted largely unchanged during the subsequent 6 years of post-trial follow-up [17]. In our study, we demonstrated that continued treatment with intensive therapy for 25 years as compared to usual care in subjects with hyperlipidemia and coronary atherosclerosis is associated with a 55% risk reduction in total mortality and 66% risk reduction in cardiovascular mortality. These data together indicate that further reduced exposure to hyperlipidemia can result in further reduction in cardiovascular mortality and morbidity. These results support the importance of lifetime cardiovascular risk management by early and long-term interventions.

Apart from intensive therapy, multivariate regression analysis in our study showed that a history of myocardial infarction or ischemic leg pain were independent predictors of total mortality. Both the diagnosis of myocardial infarction or symptoms of peripheral artery disease are clinical endpoints of the atherosclerotic cardiovascular disease (ASCVD) process and once identified, place patients at high risk of future atherosclerotic cardiovascular events [19,20]. Therefore, recent treatment recommendations by the American College of Cardiology and American Heart Association for high ASCVD risk patients include intensive lipid therapy with the hope that long-term treatment would lower their substantial CVD risk [6]. While we did find that prolonged intensive lipid therapy was associated with reduced mortality in our study, the continued association between clinically evident coronary and peripheral atherosclerosis and mortality despite intensive lipid therapy for 25 years suggests the presence of underlying residual cardiovascular risk and the importance of primary prevention in high-risk patients.

Given the observational nature and a small number of highly selected subjects in our study, our results are limited by the influence of known and unknown confounders. For example, the subjects who initially elected to enroll in FATS-OS and continued with intensive therapy may represent individuals who were more tolerant and compliant with combination lipid therapy. Also, they may be more motivated to maintain on triple lipid therapy due to more severe coronary atherosclerosis as compared to those subjects who returned to the usual care of their primary providers. While there has never been a randomized controlled trial of lipid therapy for 25 years addressing these limitations, our results are consistent with data from clinical trials (5–7 years) demonstrating benefit of intensive lipid therapy in high risk subjects [4,5] and genetic data showing the CV benefit of life-long exposure to low serum cholesterol associated with polymorphisms of cholesterol controlling genes [14,21,22].

In conclusion, our study demonstrated significant reductions in cardiovascular and total mortality in men with hypercholesterolemia and history of coronary atherosclerosis who were treated with intensive lipid therapy for 25 years.

## Acknowledgments

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### Highlights

- This observational study describes the long-term clinical benefit of intensive lipid therapy.

- Intensive lipid therapy for 25 years significantly reduced total mortality.

- Intensive lipid therapy for 25 years significantly reduced cardiovascular mortality.

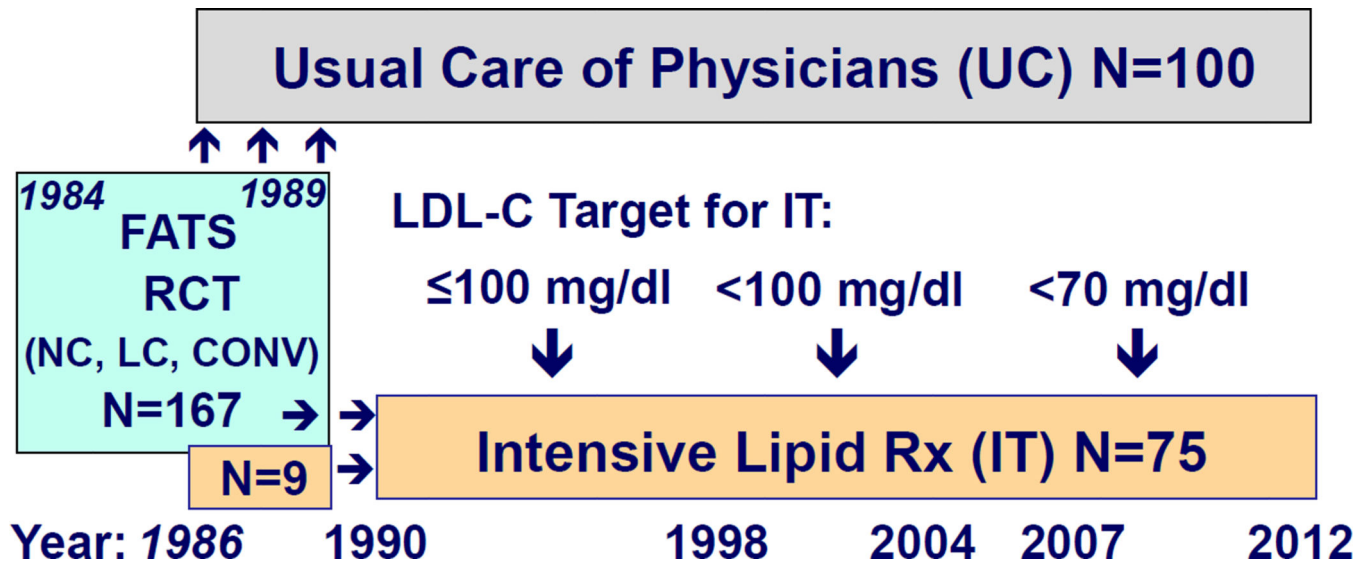- These findings support lifetime atherosclerotic vascular disease risk management.

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**Figure 1.**
Study design of the 25-year observational study (OS) following the Familiar Atherosclerosis
Treatment Study (FATS). After original FATS, 75 subjects choose to continued intensive
lipid therapy (IT) and 100 others decided to return to the usual care (UC) of their physicians.
The intensity of lipid treatment in the IT group was achieved based on the targeted LDL-C
levels recommended by the National Cholesterol Education Program guidelines.
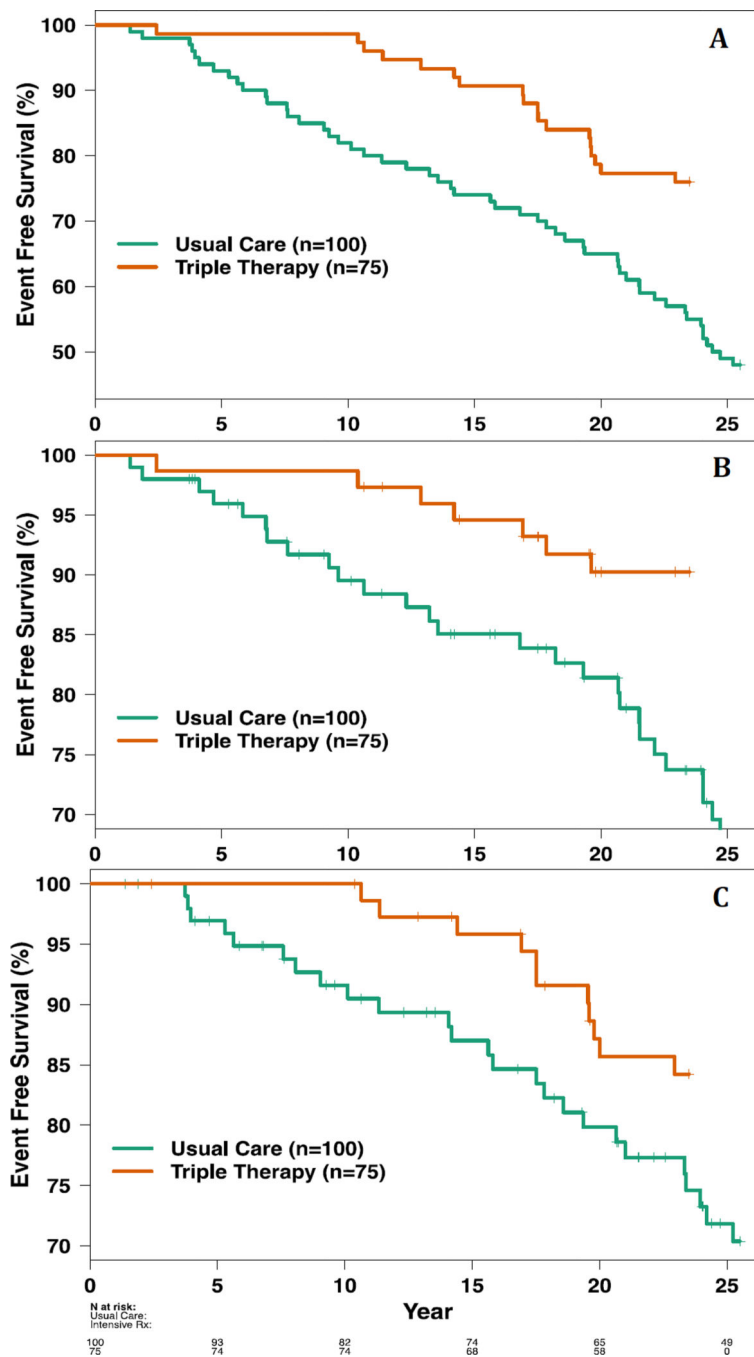
**Figure 2.**
Kaplan-Meier estimated event-free survival over 25 years in FATS-OS by treatment. Panel A: survival from any death. HR (IT/UC) = 0.45 (95% CI 0.26–0.77), P=0.003 using log-rank test. Panel B: survival from cardiovascular death. HR (IT/UC) = 0.34 (95% CI 0.15–0.80), P=0.009. Panel C: survival from non-cardiovascular death. HR (IT/UC) = 0.55 (95% CI 0.27–1.14), P=0.11.

**Table 1**

Baseline characteristics in FATS-OS

| | UC | IT | P-value |
|---|---|---|---|
| Number of subjects | N=100 | N=75 | |
| Age at FATS entry, years, mean±SD | 46±9 | 47±8 | 0.3 |
| BMI, mean±SD | 28±4 | 27±4 | 0.5 |
| Hypertension, n (%) | 36 (36) | 30 (40) | 0.5 |
| History or current smoking, n (%) | 53 (53) | 32 (43) | 0.3 |
| History of myocardial infarction, n (%) | 40 (40) | 36 (49) | 0.3 |
| History of angina, n (%) | 70 (70) | 57 (77) | 0.3 |
| History of leg pain due to ischemia, n (%) | 7 (7) | 4 (5) | 0.7 |
| Type of lipid abnormality | | | 0.13 |
| Familial hypercholesterolemia, n (%) | 7 (7) | 12 (16) | |
| Familial combined hypercholesterolemia, n (%) | 39 (39) | 30 (40) | |
| High apoB, n (%) | 54 (54) | 33 (44) | |
| Number of coronary arteries with 50% stenosis, mean±SD | 1.2±0.8 | 1.7±0.9 | 0.001 |
| Mean percent coronary stenosis, %, mean±SD | 30±12 | 39±10 | 0.001 |
| Number of subjects with coronary stenosis progression in FATS, n (%) | 38 (38) | 29 (38) | 0.9 |

**Table 2**

Mean lipid levels in FATS-OS by treatment groups and periods

| | Total Chol., mg/dl, Mean (95% CI) | Log$_{10}$Triglycerides[*] Mean (95% CI) | LDL-C, mg/dl Mean (95% CI) | HDL-C, mg/dl Mean (95% CI) |
|---|---|---|---|---|
| *1988–2004* | | | | |
| UC | 247 (238–256) | 2.25 (2.21–2.30) | 167 (157–176) | 40 (37–42) |
| IT | 196 (186–205) | 2.10 (2.06–2.14) | 119 (109–129) | 47 (44–50) |
| *P-values[**]* | *(p<0.001, p<0.001)* | *(p<0.001, p<0.001)* | *(p<0.001, p<0.001)* | *(p<0.001, p=0.001)* |
| *2005–2006* | | | | |
| UC | 166 (148–184) | 2.02 (1.94–2.10) | 97 (80–113) | 47 (43–51) |
| IT | 175 (163–186) | 2.00 (1.94–2.05) | 97 (85–109) | 55 (51–58) |
| *P-values[**]* | *(p=0.8, p=1)* | *(p=0.9, p=1)* | *(p=1, p=1)* | *(p=0.01, p=0.04)* |
| *2007–2012* | | | | |
| UC | 163 (146–180) | 2.09 (2.02–2.17) | 96 (80–111) | 44 (40–48) |
| IT | 163 (152–173) | 1.96 (1.92–2.01) | 83 (72–94) | 57 (54–60) |
| *P-values[**]* | *(p=1, p=1)* | *(p=0.01, p=0.052)* | *(p=0.4, p=1)* | *(p<0.001, p<0.001)* |

[*]: The log-transformed triglycerides were used due to their skewed distribution.

[**]: The first p-values adjust for the multiple comparisons (multiple periods) within the same outcome. The second p-values also adjust for the multiple outcomes. (by an additional Bonferroni adjustment).

**Table 3**

Total, CVD and non-CVD Mortality in FATS-OS

| | UC (n=100) | IT (n=75) |
|---|---|---|
| *Total death, N=70* | 52 | 18 |
| *Cardiovascular death, n=34* | 27 | 7 |
|   - Vascular | 6 | 0 |
|   - Coronary related | 21 | 7 |
| *Non-cardiovascular death, n=36* | 25 | 11 |
|   - Cancer | 10 | 7 |
|   - Respiratory disease | 4 | 1 |
|   - Infection | 5 | 0 |
|   - Accident | 4 | 2 |
|   - Liver failure | 1 | 0 |
|   - Suicide | 1 | 1 |

**Table 4**

Independent factors associated with total, CVD or non-CVD Mortality in FATS-OS by multivariate models

| | All cause death | | CVD death | | Non-CVD death | |
|---|---|---|---|---|---|---|
| | HR (95% CI) | p | HR (95% CI) | p | HR (95% CI) | p |
| Intensive therapy | 0.47 (0.26–0.85) | 0.01 | 0.30 (0.12–0.74) | 0.01 | 0.71 (0.32–1.55) | 0.4 |
| History of myocardial infarction | 2.13 (1.29–3.52) | 0.003 | 1.87 (0.91–3.85) | 0.09 | 2.59 (1.28–5.23) | 0.008 |
| History of leg pain due to ischemia | 2.37 (1.13–4.96) | 0.02 | 2.30 (0.84–6.30) | 0.11 | 2.48 (0.83–7.42) | 0.1 |
| Number of coronary arteries with 50% stenosis, per 1 | 1.12 (0.82–1.53) | 0.5 | 1.57 (1.02–2.42) | 0.04 | 0.78 (0.49–1.25) | 0.3 |