

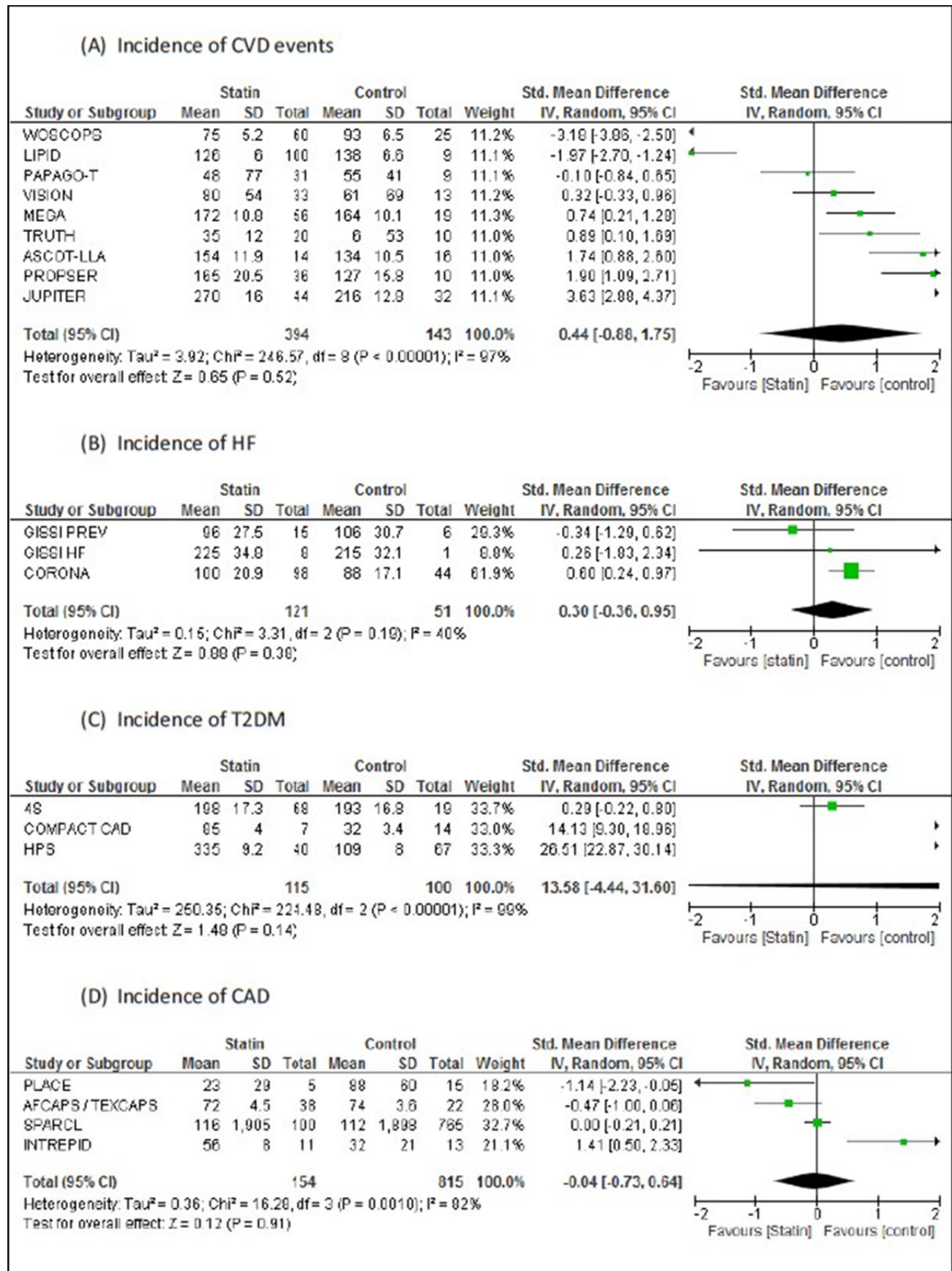
Figure 1: Over all meta-analysis of comparative studies in statin use and risk ratio of all cause mortality events.

### 3.1 Cardiovascular outcomes

On the referred studies based outcome result the control of risk factors with an overall effect of CVD events (IV random – 0.43; 95% CI –0.88, 1.75) heterogeneity 3.92; P=0.52; I<sup>2</sup>=97%, Heart Failure (IV random – 0.33; 95% CI –0.34, 0.99) heterogeneity 0.15; P= 0.34 I<sup>2</sup>=41%, Coronary Artery Disease (IV random – 0.14; 95% CI –0.65, 0.38) heterogeneity 0.17; P=0.61; I<sup>2</sup>=69%. The standard mean difference (SMD) funnel plot on each study trial notice the asymmetry in the illustrative simulations to influence the visual analytical detection by using empirical study data. The effect size in primary studies precise the false-positive results by measuring the reliable end points to conclude the sample size precision in the combined variations.

### 3.2 Outcome of T2DM

The assigned cases in the incidence of diabetes on receiving therapy (IV random – 0.29; 95% CI –4.64, 4.06) in the absolute terms, of significance shows the sources of heterogeneity 14.22; P=0.90; I<sup>2</sup>=98%. Likewise analysis of publication bias evidence.



**Figure 2:** (A) Forest plot standard mean difference evaluating statin therapy in the incidence of CVD events; (B) Incidence of heart failure; (C) Incidence of type 2 diabetes mellitus; (D) Incidence of coronary artery disease. Meta-analysis was performed using a random-effect model. CI= confidence interval; STD = standard mean difference.

### 3.3 Subgroup analysis

The consistent study characteristics as shown in Table 1 define the study of study design preceding the duration strategy prior to adults and old age group in randomizing the effect. As we discussed the median variables of cholesterol levels, glycated hemoglobin and glucose concentration the study provided different classes of drugs in the normal resistivity conditions with case-control studies.

Source	Study design	Intervention duration Follow up	Study Outcomes
Marchesini et al. 2001 [20]	Old adults	Statin + Metformin (4 months)	Prior CVD, ↓HbA1c, and ↓HTN 33%
Nair et al. 2004 [21]	Old adults	Statin + Metformin (12 months)	↓ ALT, ↓ AST, and Histology improved
Uygun et al. 2004 [22]	Old adults	Statin + Metformin (6 months)	Histology not improved
Bugianesi et al. 2005 [23]	Old adults	Statin + Metformin (12 months)	Histology improved, Diabetes ↓ 25%, and ↓ risk factors
Schwimmer et al. 2005 [24]	Sample	Statin + Metformin (6 months)	↓ insulin resistance, ↓ ALT, ↓ AST
De oliveira et al. 2008 (25)	Old adults	Statin + Metformin (12 months)	HTN improved 31% and mean SBP
Idilman et al. 2008 [26]	Randomized	Statin + Metformin (12 months)	↓insulin resistance, and ↑ LDL-C
Nobili et al. 2006 [27]	Old adults	Statin + Metformin (24 months)	Reduced HTN in smokers 12.5%
Shields et al. 2009 [28]	Randomized placebo	Placebo + Metformin (12 months)	Improved insulin resistance, ↓BMI , no significance
Loomba et al. 2009 [29]	Sample	Statin + Metformin (12 months)	Improved baseline lipids
Haukeland et al. 2009 [30]	Randomized placebo	Metformin + placebo (6 months)	No significance, control vs treatment

Wang et al. 2006 [31]	Old adults	TZDs vs Metformin (24 weeks)	Reduced HbA1c, AMTs, fasting glucose and insulin
Akyuz et al. 2007 [32]	Old adults	TZDs vs Metformin (12 months)	ECG abnormalities, and diabetes high risk in adults
Idilman et al. 2008 [33]	Old adults	TZDs vs Metformin (12 months)	↓ c- reactive protein, and ↓ insulin resistance
Belfort et al.	Randomized/placebo	TZDs vs placebo	↓ inflammatory

**Table 1:** Characteristic of included studies in clinical trials of statin vs placebo.

### 3.4 Trial sequential analysis

According to the qualitative studies, TNT [15] and IDEAL [16] the SSMD can be used on the fixed effects model if it produced the same results of randomized control Meta-analysis with onset pooled data. Mainly the aim is to achieve the expected consumption of controlling factor in preventions of CVD risk factors and additionally diabetic hypertension in the association of vascular disorders. Thus on calculating the hazard ratio on variance analysis the aim of nonstandard pharmacological drugs on a specific regimen in the correlation of cholesterol levels must evaluate the co-variable regression independently with the protocols of bringing better results on Randomized Controlled Trials.

## 4. Discussion

The present-day Meta-analysis affected the statin dosage of 50mg-80mg/day in several clinical trials discern the manifestation of CHD (1.112, 95%CI 1.04-1.22) [49] with a recurrent rhabdomyolysis in adults stated by American guidelines [12,13]. The interesting mechanistic phenomenon in the assessment of statins effectiveness possibly bring-up the unmatched statistical differences in controlling the underutilized insulin resistance with the progression of various consecutive dysfunctions sensitizing the immune cells in vitro [50, 51]. Therefore, the unknown evidence on literature reviewing 1000 patients/year of baseline recheck the drugs beneficial effect since 2004 [9] to scope the decreasing outcomes of adherence in terms of traditional risk factors as mentioned in fewer studies of fixed effect.

The American Health Care providers established a study treatment of statin drugs in the match of propensity score selecting the basic characteristic of new cases at potential risk on diabetic restrictions of HR (0.63, 95% CI 0.25-1.60). The affirmed outcomes on making knowledge gap empty exacerbate the complications of sudden death in maintaining the worsening of glycemia intensification. Regardless, the use of combined therapy including ACEIs or ARBs and  $\beta$  blockers or diuretics alleviate the potency on findings in each subgroup with the demographic results of high CRP, GI disturbances, disturbed lipid levels and cancer symptoms. Therefore, the survival bias on large analysis explains the confounding factors in the average modified conditions revealing the conditions of obesity and advanced aging. According to the following principles of Swerdlow et al. [9] examined the study of genetics which strongly concluded the amount of titrated dosing strike numerous micro-vascular and macro-vascular diseases on the

sites of skeletal muscles in the association of neurological disorders. The other studies of pharmacokinetics exposure to variability compose the IHD adequately in the prolonging T2DM diminish the homeostatic regulations of glucose activity, mitochondrial dysfunctions, beta cells death and metabolic blockade releasing the behavior of lipophilic state.

The recent US food and drug administration declare statins to be the first choice therapy by the majority of recommended physicians in the prevalence of adulthood diabetes onset irrespective of cardiac diseases. And also the designed National Health Insurance extrapolated the prospective and retrospective studies on Asian vs Americans clinical conditions similarity to verify the age reflux, social history, and multiple disorders on record of sampling cohort studies in making easier balanced population-based decisions accurately. Moreover, the published projects enrolled a large group of females with T2DM as follows MEGA, ASFA, TNT, IDEAL, SEARCH and JUPITER study trying atorvastatin and simvastatin with no appearance of current vascular disease ensure the morbid analysis on the strong inference of time duration curative symptoms. As also reported by PROPHER and WOSCOPS the results in the concerns of protection noted the reduction of malignancies deriving the uncertain side effects of myopathy and hepatotoxicity. At the examination of fibrinolytic carried out for decades with placebo testing reveal the vigilance of statins directly explaining the histology of cells and insulin action which already been attested on animal models to strengthen the relevance of powerful detection majorly in the intensive drugs bias evidences. Hence, altogether the negative and beneficial effects neutralize the glucose tolerance on the referred robust trial of (J-PREDICT) study in 2005. But still further to understand the clinical implications, the interpretations of previous studies are needed with several newly clinical diagnostic criteria for the authorized bias. In conclusion, the extended analyses about earlier findings require a perception of cholesterol observation in treating diabetogenicity to precede the subsequent life style modifications.

## 5. Limitations of Study

As already mentioned in the recruit exclusion of CVD related symptoms minimize the proportional outcomes of diabetes attribute the involvement of dyslipidemia with the critical magnitude of LVH. However, the guidelines respective to equal results no highly influenced the elderly as seemed earlier in the panels of collective data. The involvement of heterogeneity in risk ratio reduction across the ranges of increased survival rates on annual rates of 20%-30% with the stable CAD events in the consideration of PEACE study. But the contemporary significance of pooled study data in >65-year ages assumed an obvious high risk constitute describing a poor scoring system. Thus, the correct assessment of prognosis needs a long-term statin drugs for the auxiliary improvements in future in cardiovascular based on predictions at both the genders of identification in not denying the favorable experiments.

## 6. Conclusion

The Scientific literature demonstrates the consistent variations of each component generalized the contributable cardiovascular events in association of diabetes modified biological experimental statins in context of statistics. The importance of cholesterol lowering still unclear the analysis of insulin hypothesized complications in the detection of potential effect. Therefore, in the future necessarily to recognize the high risk outcome in comparative studies, the excluded studies must be added in the conduction of detection bias to clarify the differentiation of effective result.



## Conflicts of Interest Statement

The author declared that they have no competing interest.

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## References

1. Cornell JE, Mulrow CD, Localio R, et al. Random-effects meta-analysis of inconsistent effects: A time for change. *Ann Intern Med* 160 (2014): 267-270.
2. Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 343 (2011): d4002.
3. Furberg CD, Adams HP Jr, Applegate WB, et al. Asymptomatic Carotid Artery Progression Study (ACAPS) Research Group. Effect of lovastatin on early carotid atherosclerosis and cardiovascular events. *Circulation* 90 (1994): 1679-1687.
4. Knopp RH, d'Emden M, Smilde JG, Pocock SJ. Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the Atorvastatin Study for Prevention of coronary heart disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN). *Diabetes Care* 29 (2006): 1478-1485.
5. Furberg CD, Adams HP Jr, Applegate WB, et al. Asymptomatic Carotid Artery Progression Study (ACAPS) Research Group. Effect of lovastatin on early carotid atherosclerosis and cardiovascular events. *Circulation* 90 (1994): 1679-1687.
6. Downs JR, Clearfield M, Weis S, et al. Air Force/Texas Coronary Atherosclerosis Prevention Study. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. *JAMA* 279 (1998): 1615-1622.
7. Sever PS, Dahlöf B, Poulter NR, et al. ASCOT Investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): A multicentre randomised controlled trial. *Lancet* 361 (2003): 1149-1158.
8. Chan KL, Teo K, Dumesnil JG, Ni A, Tam J ASTRONOMER Investigators. Effect of lipid lowering with rosuvastatin on progression of aortic stenosis: results of the aortic stenosis progression observation: measuring effects of rosuvastatin (ASTRONOMER) trial. *Circulation* 121 (2010): 306-314.
9. Beishuizen ED, van de Ree MA, Jukema JW, et al. Two-year statin therapy does not alter the progression of intima-media thickness in patients with type 2 diabetes without manifest cardiovascular disease. *Diabetes Care* 27 (2004): 2887-2892.

10. Bone HG, Kiel DP, Lindsay RS, et al. Effects of atorvastatin on bone in postmenopausal women with dyslipidemia: a double-blind, placebo-controlled, dose-ranging trial. *J Clin Endocrinol Metab* 92 (2007): 4671-4677.
11. Colhoun HM, Betteridge DJ, Durrington PN, et al. CARDS Investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 364 (2004): 685-696.
12. Yusuf S, Bosch J, Dagenais G, et al. HOPE-3 Investigators. Cholesterol lowering in intermediate-risk persons without cardiovascular disease. *N Engl J Med* 374 (2016): 2021-2031.
13. Anderssen SA, Hjelstuen AK, Hjermann I, Bjerkan K, Holme I. Fluvastatin and lifestyle modification for reduction of carotid intima-media thickness and left ventricular mass progression in drug-treated hypertensives. *Atherosclerosis* 178 (2005): 387-397.
14. Ridker PM, Danielson E, Fonseca FAH, et al. JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 359 (2008): 2195-2207.
15. Salonen R, Nyssönen K, Porkkala E, et al. Kuopio Atherosclerosis Prevention Study (KAPS): A population-based primary preventive trial of the effect of LDL lowering on atherosclerotic progression in carotid and femoral arteries. *Circulation* 92 (1995): 1758-1764.
16. Nakamura H, Arakawa K, Itakura H, et al. MEGA Study Group. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA study): a prospective randomised controlled trial. *Lancet* 368 (2006): 1155-1163.
17. Crouse JR III, Raichlen JS, Riley WA, et al. METEOR Study Group. Effect of rosuvastatin on progression of carotid intima-media thickness in low-risk individuals with subclinical atherosclerosis: the METEOR Trial. *JAMA* 297 (2007): 1344-1353.
18. Asselbergs FW, Diercks GFH, Hillege HL, et al. Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND IT) Investigators. Effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria. *Circulation* 110 (2004): 2809-2816.
19. Shepherd J, Cobbe SM, Ford I, et al. West of Scotland Coronary Prevention Study Group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 333 (1995): 1301-1307.
20. Marchesini G, Bianchi G, Tomassetti S, et al. Metformin in non-alcoholic steatohepatitis. *Lancet* 358 (2001): 893-894.
21. Nair S, Diehl AM, Wiseman M, Farr GH, et al. Metformin in the treatment of non-alcoholic steatohepatitis: A pilot open label trial. *Aliment. Pharmacol Ther* 20 (2004): 23-28.
22. Uygun A, Kadayifci A, Isik AT, et al. Metformin in the treatment of patients with non-alcoholic steatohepatitis. *Aliment Pharmacol Ther* 19 (2004): 537-544.
23. Bugianesi E, Gentilcore E, Manini R, et al. A randomized controlled trial of metformin versus vitamin E or prescriptive diet in nonalcoholic fatty liver disease. *Am J Gastroenterol* 100 (2005): 1082-1090.
24. Schwimmer JB, Behling C, Newbury R, et al. Histopathology of pediatric nonalcoholic fatty liver disease. *Hepatology* 42 (2005): 641-649.

25. De Oliveira CP, Stefano JT, De Siqueira, et al. Combination of N-acetylcysteine and metformin improves histological steatosis and fibrosis in patients with non - alcoholic steatohepatitis. *Hepatol Res* 38 (2008): 159-165.
26. Idilman R, Mizrak D, Corapcioglu D, et al. Clinical trial: Insulin-sensitizing agents may reduce consequences of insulin resistance in individuals with non-alcoholic steatohepatitis. *Aliment Pharmacol Ther* 28 (2008): 200–208.
27. Nobili V, Marcellini M, Devito R, et al. NAFLD in children: A prospective clinical-pathological study and effect of lifestyle advice. *Hepatology* 44 (2006): 458-465.
28. Shields WW, Thompson KE, Grice GA, et al. The Effect of Metformin and Standard Therapy versus Standard Therapy alone in Nondiabetic Patients with Insulin Resistance and Nonalcoholic Steatohepatitis (NASH): A Pilot Trial. *Ther Adv Gastroenterol* 2 (2009): 157-163.
29. Loomba R, Lutchman G, Kleiner DE, et al. Clinical trial: Pilot study of metformin for the treatment of non-alcoholic steatohepatitis. *Aliment Pharmacol Ther* 29 (2009): 172-182.
30. Haukeland JW, Konopski Z, Eggesbo HB, et al. Metformin in patients with non-alcoholic fatty liver disease: A randomized, controlled trial. *Scand J Gastroenterol* 44 (2009): 853-860.
31. Wang CH, Leung CH, Liu SC, et al. Safety and effectiveness of rosiglitazone in type 2 diabetes patients with nonalcoholic Fatty liver disease. *J Formos Med Assoc* 105 (2006): 743-752.
32. Akyuz F, Demir K, Ozdil S, et al. The effects of rosiglitazone, metformin, and diet with exercise in nonalcoholic fatty liver disease. *Dig Dis Sci* 52 (2007): 2359-2367.
33. Idilman R, Mizrak D, Corapcioglu D, et al. Clinical trial: Insulin-sensitizing agents may reduce consequences of insulin resistance in individuals with non-alcoholic steatohepatitis. *Aliment Pharmacol Ther* 28 (2008): 200–208.
34. Belfort R, Harrison SA, Brown K, et al. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. *N Engl J Med* 355 (2006): 2297-2307.
35. Aithal GP, Thomas JA, Kaye PV, et al. Randomized, placebo-controlled trial of pioglitazone in nondiabetic subjects with nonalcoholic steatohepatitis. *Gastroenterology* 135 (2008): 1176-1184.
36. Ratziu V, Giral P, Jacqueminet S, et al. Rosiglitazone for nonalcoholic steatohepatitis: One-year results of the randomized placebo-controlled Fatty Liver Improvement with Rosiglitazone Therapy (FLIRT) Trial. *Gastroenterology* 135 (2008): 100-110.
37. Omer Z, Cetinkalp S, Akyildiz M, et al. Efficacy of insulin-sensitizing agents in nonalcoholic fatty liver disease. *Eur J Gastroenterol Hepatol* 22 (2010): 18-23.
38. Tushuizen ME, Bunck MC, Pouwels PJ, et al. Incretin mimetics as a novel therapeutic option for hepatic steatosis. *Liver Int* 26 (2006): 1015-1017.
39. Klonoff DC, Buse JB, Nielsen LL, et al. Exenatide effects on diabetes, obesity, cardiovascular risk factors and hepatic biomarkers in patients with type 2 diabetes treated for at least 3 years. *Curr Med Res Opin* 24 (2008): 275-286.
40. Kenny PR, Brady DE, Torres DM, et al. Exenatide in the treatment of diabetic patients with non-alcoholic steatohepatitis: A case series. *Am J Gastroenterol* 105 (2010): 2707-2709.

41. Iwasaki T, Yoneda M, Inamori M, et al. Sitagliptin as a novel treatment agent for non-alcoholic Fatty liver disease patients with type 2 diabetes mellitus. *Hepatology* 58 (2011): 2103-2105.
42. Ito M, Kawaguchi T, Taniguchi E, et al. Dipeptidyl peptidase IV inhibitor improves insulin resistance and steatosis in a refractory nonalcoholic fatty liver disease patient: A case report. *Case Rep Gastroenterol* 6 (2012): 538-544.
43. Yilmaz Y, Yonal O, Deyneli O, et al. Effects of sitagliptin in diabetic patients with nonalcoholic steatohepatitis. *Acta Gastroenterol Belg* 75 (2012): 240-244.
44. Armstrong MJ, Houlihan DD, Rowe IA, et al. Safety and efficacy of liraglutide in patients with type 2 diabetes and elevated liver enzymes: Individual patient data meta-analysis of the LEAD program. *Aliment Pharmacol Ther* 37 (2013): 234-242.
45. Nelson A, Torres DM, Morgan AE, et al. A pilot study using simvastatin in the treatment of nonalcoholic steatohepatitis: A randomized placebo-controlled trial. *J Clin Gastroenterol* 43 (2009): 990-994.
46. Athyros VG, Tziomalos K, Gossios TD, et al. Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study: A post-hoc analysis. *Lancet* 376 (2010): 1916-1922.
47. Foster T, Budoff MJ, Saab S et al. Atorvastatin and antioxidants for the treatment of nonalcoholic fatty liver disease: The St Francis Heart Study randomized clinical trial. *Am J Gastroenterol* 106 (2011): 71-77.
48. Pramfalk C, Parini P, Gustafsson U, et al. Effects of high-dose statin on the human hepatic expression of genes involved in carbohydrate and triglyceride metabolism. *J Intern Med* 269 (2011): 333-339.
49. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ* 327 (2003): 557-560.
50. Shepherd J. The West of Scotland Coronary Prevention Study: A trial of cholesterol reduction in Scottish men. *Am J Cardiol* 76 (1995): 113C-117C.
51. Ridker PM, Danielson E, Fonseca FAH, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 359 (2008): 2195-2207.

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