# 行政院國家科學委員會專題研究計畫　成果報告

## 對非糖尿病合併型血脂肪過高患者使用 PPARg agonist、PPARa agonist、或 HMGCoA 還原酶對各種嶄新心血管疾病危險因子之影響

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**中文摘要：**

**關鍵詞：血脂肪異常，內皮細胞，發炎，胰島素阻抗**

**背景：在臨床上，血液中總膽固醇及中性脂肪濃度同時不正常升高（又稱合併型血脂肪異常「**combined hyperlipidemia**」），往往合併有所謂的『胰島素阻抗』症狀。目前的觀念，認為『胰島素阻抗』可能是造成與其相關的包括高血壓、高血脂、內皮細胞功能異常等病狀的根本及共通原因。邇來，已有提昇人體對胰島素反應的藥物（**PPARγ agonist**，如** rosiglitazone**）發展出來；雖然這類藥物目前主要使用於糖尿病病人，然而已有相關研究指出，這類藥物使用於非糖尿病的胰島素阻抗病人亦有提升人體胰島素反應性的療效，且並無低血糖的副作用。由於合併型血脂肪異常也是胰島素阻抗症候群的典型表現之一，因此我們想要探究** PPARγ agonist **這類胰島素增敏劑是否對這類病人也有降低心血管疾病的療效。此外，對於合併型血脂肪異常病人的降血脂肪藥物使用，一直有「究竟該先使用** statin **類藥物或** fibrate **類藥物」的爭論。到目前為止，還沒有一個大型研究針對合併型血脂肪異常患者使用** statin **類或** fibrate **類藥物究竟在降低心血管疾病方面何者效果較好的研究發表。在本研究中，我們計畫針對合併型血脂肪異常患者，以其血管內皮細胞功能及發炎指標（包括** hs-CRP**，**IL-1**，**IL-6**，**sCD40**，及** sCD40L **等）作為預測未來心血管疾病發生的指標，評估使用** PPARγ agonist**、**statin **單一治療、或** fibrate **單一治療的效果孰優孰劣。此外，我們也將受試者依照其基礎狀態的血脂肪及發炎指標數值加以分組，試圖找出是否不同的血脂肪或發炎指標數值會使受試者對藥物的反應產生具有差別性的影響。除了血脂肪及發炎指標之外，我們也試圖分析** eNOS **基因型態多型性（**4a/b **和** $Glu_{298}Asp$**）對藥物反應的影響。**

**實驗方法：年齡在十八至八十歲，且血清中性脂肪數值介於** 200 **至** 500mg/dL**，總膽固醇**=200mg/dL **且總膽固醇/**HDL **膽固醇比值**.>5 **者皆可進入本試驗。受試者先接受八個星期的飲食治療，在此期間內，停止使用所用降血脂肪藥物。在完成了八個星期的藥物清除期後，受試者隨機分配為接受** rosiglitazone **（**4 mg/day**），**simvastatin**（**20 mg/day**）或接受** micronized fenofibrate **（**200 mg/day**）三組。所有的受試者皆接受八個星期的藥物治療。在接受藥物治療前，每位受試者均接受兩次血液抽驗（藥物清除期前及隨機分配前一週）；藥物治療後受試者亦接受兩次血液抽驗（七週半及八週）。此外，在隨機分配前一週及接受八週的藥物治療後，進行右肱動脈的血管內皮細胞功能檢驗。我們利用超音波機器評估與內皮細胞功能相關的血流引致血管擴張（**flow-mediated vasodilation**）現象及硝化甘油引致的血管擴張（**nitroglycerin-induced vasodilation**）現象作為內皮細胞功能的指標。本試驗預計約需一百二十名受試者。**

**結果及臨床意義：本研究首次顯示使用** simvastatin**，**fenofibrate**，或** rosiglitazone **均能有效降低合併型血脂肪異常患者的體內發炎程度、及改善內皮細胞功能異常狀況。若就內皮細胞功能改善程度細加分析，可以發現** Fenofibrate **對於基礎** HDL **膽固醇數值小於** 40 mg/dL **者特別有效，而** simvastatin **則對於基礎** HDL **膽固醇數值大或等於** 40 mg/dL **者特別有效。本研究的另一貢獻為，首次證明對於非糖尿病合併型血脂肪異常病患使用** rosiglitazone **不僅沒有低血糖的副作用，且能明顯的改善其內皮細胞功能及體內胰島素阻抗性。惟所測試之** eNOS **基因多型性無法作為預測病患對於藥物反應之指標。**

## 英文摘要：

**Keywords:** endothelium, fibrate, insulin sensitizer, hyperlipidemia, statins

**Background:** Combined hyperlipidemia is characterized by elevated levels of total cholesterol, low-density lipoprotein cholesterol (LDL-C) and triglycerides and decreased levels of high-density lipoprotein cholesterol (HDL-C). It is the pathognomonic dyslipidemia observed in individuals with insulin resistance syndrome. However, it is still uncertain whether PPARγ agonist (e.g. rosiglitazone) had beneficial effects on the prevention of coronary heart disease (CHD) in individuals with combined hyperlipidemia. Moreover, given that combination therapy with fibrate plus statin confers a risk of rhabdomyolysis, it is also worthwhile to determine whether optimal therapy for patients with combined hyperlipidemia should consist of fibrate monotherapy or statin monotherapy. Until now, however, no head-to-head comparison of the therapeutic effects (on CHD events) of fibrate monotherapy with statin monotherapy in individuals with combined hyperlipidemia has been published. In this study, we will compare the effects of PPARγ agonist, statin monotherapy and fibrate monotherapy on both endothelial function and markers of inflammation (hs-CRP, IL-1, IL-6, sCD40, and sCD40L), as surrogate indicators of future CHD, in patients with combined hyperlipidemia. We will further examine the therapeutic effects of these agents in subgroups stratified by various baseline characteristics and genotypes of eNOS (4a/b and $Glu_{298}Asp$) to see if there were any differential effects among these agents.

**Methods:** Eligible patients, aged 18 to 80 years with plasma triglyceride levels between 200 and 500 mg/dL, total cholesterol level =200 mg/dL, and total cholesterol/HDL cholesterol ratio>5, will be instructed to adhere to the AHA Step 1 diet throughout the study and undergo an 8-week run-in period during which previous lipid-lowering therapy will be discontinued. After the run-in phase, patients will be randomized to receive rosiglitazone (4 mg/d)(n = 40), simvastatin (20 mg/d)(n = 40) or micronized fenofibrate (200 mg/d)(n = 40) for 8 weeks. The patients will be seen at the screening visit (i.e. before the 8-week run-in), 1 week before randomization, at entry (randomization), and 4 and 8 weeks of treatment. Two fasting blood samples will be obtained at baseline 7 days apart and at the end of the 8-week drug-therapy phase (weeks 7.5 and 8). Endothelium-dependent flow-mediated vasodilation in response to reactive hyperemia and nitroglycerin-induced vasodilation will be evaluated in the right brachial artery 1 week before randomization and after 8 weeks of active treatment.

**Results and Clinical Significance:** Our study for the first time demonstrated that simvastatin, fenofibrate, and rosiglitazone markedly reduced plasma levels of high-sensitivity CRP, IL-1, and sCD40L, and improved endothelium-dependent FMD without mutual differences. The improvement in FMD with fenofibrate treatment correlated inversely with baseline HDL-C levels, whereas the improvement in FMD with simvastatin treatment was positively related to HDL-C levels. Accordingly, in the subgroup with a baseline HDL-C of ≤ 40 mg/dl, only fenofibrate significantly improved the endothelium-dependent FMD. On the other hand, in the subgroup with HDL-C > 40 mg/dl, only treatment with simvastatin achieved significant improvement in FMD. Furthermore, we demonstrated the safety and benefits of rosiglitazone use in ameliorating endothelial dysfunction and inflammation, reversing insulin resistance, and lowering blood pressures in non-diabetic patients with the metabolic syndrome. The predictive value of eNOS polymorphisms studied on pharmacological responses has not been proved.

# 報告內容

## 前言：

Combined hyperlipidemia is characterized by elevated levels of total cholesterol, low-density lipoprotein cholesterol (LDL-C) and triglycerides and decreased levels of high-density lipoprotein cholesterol (HDL-C), and accounts for up to 33% of those with elevated cholesterol levels.[1]. It is the pathognomonic dyslipidemia observed in individuals with insulin resistance syndrome. Insulin resistance has been speculated to be the underlying cause of various pathological manifestations associated with insulin resistance syndrome. One recent study has demonstrated that treatment with PPARγ agonist, rosiglitazone, in non-diabetic insulin resistant individuals was associated with improvement in endothelial function.[2] There was no hypoglycemia observed in that study. However, it is still uncertain whether rosiglitazone had beneficial effects on endothelial function in individuals with combined hyperlipidemia. On the other hand, in both observational studies and clinical trials, patients with combined hyperlipidemia and low HDL-C had disproportionately higher risk for coronary heart disease (CHD) compared with those with elevated LDL-C levels alone.[3,4] In substudy analyses of the Helsinki Heart Study[5] and the Bezafibrate Infarction Prevention study,[6] patients with combined hyperlipidemia received the greatest benefit on CHD event reduction with fibrate therapy. Besides, in the post hoc analysis of the Scandinavian Simvastatin Survival Study,[7] patients with combined hyperlipidemia also had significantly greater reduction of major coronary events with simvastatin compared with patients with isolated LDL-C elevation. Given that combination therapy with fibrate plus statin confers a risk of rhabdomyolysis,[8] it is worthwhile to determine whether optimal therapy for these high-risk individuals should consist of fibrate monotherapy, statin monotherapy, or PPARγ agonist. Until now, however, no head-to-head comparison of these therapeutic agents in patients with combined hyperlipidemia has been published.

Endothelial dysfunction is considered an early manifestation of atherosclerosis and independently predicts cardiovascular events.[9,10] As a consequence, endothelial function is currently being regarded as a potential tool for prediction of the risk of CHD events. Treatment with statins or fibrates alone has been demonstrated to improve endothelial function in hypercholesterolemic individuals.[11,12] Nevertheless, there are only few studies comparing the effects of both lipid-lowering agents on endothelial function in combined hyperlipidemia and the results are inconsistent.[13,14]

Recent evidence indicates that atherosclerosis is a chronic inflammatory process. Several acute phase reactants and cytokines have been implicated in this process, with their plasma concentrations increased in a variety of atherosclerotic diseases.[15] C-reactive protein (CRP), an acute phase reactant, is a sensitive marker of systemic inflammation and represents an independent risk factor for cardiovascular events in numerous prospective epidemiological studies.[16] In addition, studies have demonstrated that CRP confers risk above that of an

abnormal lipid profile.[17] Treatment with statins not only reduce LDL-C, but also reduce CRP in an LDL-independent manner.[18,19] However, the effects of fibrates on levels of CRP are still controversial.[13,14]

Among the numerous proinflammatory cytokines, studies have recently demonstrated that the multipotent immunomodulator CD40 ligand (CD40L) and its receptor CD40 play an important role in the various stages of atherogenesis.[20] In accord with the predicted role of the CD40/CD40L dyad in atherogenesis, disruption of CD40 signaling significantly diminished lesion formation and progression in hypercholesterolemic mice.[21] In addition to the 39-kDa, cell-associated form, CD40L also occurs in a soluble, biologically fully active form (sCD40L). It has been shown that patients with unstable angina have elevated plasma levels of sCD40L.[22] Moreover, elevations of circulating sCD40L predict future CHD, irrespective of plasma levels of lipid profile and CRP, in apparently healthy women participating in the Women's Health Study.[23] There is paucity of data regarding the effects of statins, fibrates, or PPARγ agonist on plasma levels of sCD40L and CD40.

## 研究目的：

In this study, we compared the effects of statin monotherapy, fibrate monotherapy, and PPARγ agonist on both endothelial function and markers of inflammation, as surrogate indicators of future CHD, in patients with combined hyperlipidemia. We further examined the therapeutic effects of all three agents in subgroups stratified by various baseline characteristics to see if there were any differential effects in different pre-existing clinical scenarios. Moreover, we tried to explore the predictability of genetic polymorphisms of eNOS on the therapeutic effects of different agents. These findings provide us a rational basis in considering insulin sensitizer, statins or fibrates as the first-line agent for combined hyperlipidemia.

## 研究方法：

### Subjects and Study Design

Patients were recruited from the Clinics at the National Taiwan University Hospital, without restriction to sex or socioeconomic status. Inclusion criteria included the following: age 18 to 80 years, plasma triglyceride levels between 200 and 500 mg/dL, total cholesterol levels =200 mg/dL, total cholesterol/HDL cholesterol ratio >5, and insulin resistance phenotype according to the diagnostic criteria set in the Adult Treatment Panel III. Major exclusion criteria are acute coronary event, stroke, or coronary revascularization within the preceding 3 months; insulin-dependent diabetes mellitus or poorly controlled non-insulin-dependent diabetes mellitus ($HbA_{1c}$ >8%); severe obesity; overt liver disease; chronic renal failure; hypothyroidism; myopathy; alcohol or drug abuse; several other significant diseases; or use of other lipid-lowering therapy, immunosuppressants, erythromycin and/or neomycin, ketoconzaole, and hormone-replacement therapy. All subjects gave written informed consent.

Eligible patients were instructed to adhere to the American Heart Association Step 1 diet throughout the study and underwent an 8-week run-in period during which previous lipid-lowering therapy was discontinued. After the run-in phase, patients were randomized to receive rosiglitazone (4 mg/d)(n = 40), simvastatin (20 mg/d)(n = 40) or micronized fenofibrate (200 mg/d)(n = 40) for 8 weeks. The patients were seen at the screening visit (i.e. before the 8-week run-in), 1 week before randomization (baseline laboratory and vascular studies), at entry (randomization), and 4 and 8 weeks of treatment. At week 8, physical examinations, laboratory assessments, and vascular studies were repeated.

**Laboratory Assays**

Two fasting blood samples were obtained at baseline 7 days apart and at the end of the 8-week drug-therapy phase (weeks 7.5 and 8). Venous blood samples were placed into tubes containing EDTA. Samples were centrifuged within 30 minutes at 2000 rpm for 10 minutes. The plasma was separated and stored at -70°C until analysis. Levels of total cholesterol, total triglycerides, LDL-C and HDL-C were assayed by routine laboratory techniques with the use of methodology of the Lipid Research Clinics, as reported previously. If plasma triglycerides were =400 mg/dL, LDL-C was assessed by a direct method. Plasma concentrations of IL-1β, IL-6, CD40, and sCD40L were determined in duplicate using commercially available immunosorbent kits (IL-1β and IL-6, R&D Systems; CD40 and sCD40L, Bender MedSystems). High-sensitivity CRP was assayed by rate nephelometry (Dade Behring, Newark, Del.). Routine chemical clinical analyses were performed by standard methods subjects to strict quality control. The coefficients of variation were <5% for every type of measurement.

**Vascular Studies**

Endothelium-dependent flow-mediated vasodilation in response to reactive hyperemia and endothelium-independent nitroglycerin-induced vasodilation were evaluated in the right brachial artery 1 week before randomization and after 8 weeks of active treatment. Ultrasound measurements were performed using a high-resolution ultrasound machine (Hewlett Packards, 5500) equipped with an L11-3 linear array transducer, as previously described by us. Arterial diameters were measured at rest, during reactive hyperemia, again at rest (after vessel recovery), and after administration of 0.6 mg sublingual nitroglycerin. The condition of reactive hyperemia was induced by inflation of a pneumatic cuff on the upper arm to suprasystolic pressure, followed by cuff deflation after 4.5 minutes. The brachial artery was scanned in longitudinal section 2 to 8 cm above the elbow, and the arterial diameter was measured on B-mode images with the use of ultrasonic calipers. The end-diastolic arterial diameter was measured from one media-adventitia interface to the other at the clearest section 3 times at baseline, every 30 seconds after reactive hyperemia, and after administration of nitroglycerin. The maximum vessel diameter is taken as the average of the 3 consecutive

maximum diameter measurements after hyperemia and nitroglycerin, respectively. Vasodilation will then be calculated as the percent change in diameter compared with baseline. In our laboratory, the measurements were performed by a single experienced operator in a temperature-controlled room (21 to 24°C) at the same time of day on patients fasted overnight. The intraobserver variation was 1.5%. Medications were omitted on the morning of the visit, and nitrates were withheld for 24 hours before studies.

**Genetic Studies**

Genomic DNA was prepared from samples of whole blood by standard methods. The first polymorphism of the eNOS gene studied in this study is a G-T substitution in exon 7 (at position 894) in codon 298 which alters the amino acid at this residue from Glu to Asp ($Glu_{298}Asp$). Genotyping of this polymorphism was performed by polymerase chain reaction (PCR) amplification of exon 7 with the flanking intronic primers 5'-CATGAGGCTCAGCCCCAGAAC-3' (sense) and 5'-AGTCAATCCCTTTGGTGCTCAC-3' (antisense) followed by *Mbo*I restriction endonuclease digestion for 16 hours at 37°C and resolution by electrophoresis on a 2.5% agarose gel. The 206 bp PCR product was cleaved into 119 bp and 87 bp fragments in the presence of a T at nucleotide 894 (which corresponds to $Asp^{298}$ but not in its absence. The second polymorphism (4a/b) studied was using the oligonucleotide primers (sense, 59-AGGCCCTATGGTAGTGCCTTT-39; antisense, 59-TCTCTTAGTGCTGTG-GTCAT-39) that flank the region of the 27-bp direct repeat in intron 4. Reactions were performed in a total volume of 50 µl containing 1 µg of genomic DNA, 40 pmol of each primer, 0.2 mmol/L of each deoxynucleoside triphosphate, 1.25 U of *Taq* DNA polymerase, 50 mmol/L KCl, 1.5 mmol/L $MgCl_2$, and 10 mmol/L Tris-HCl (pH 8.3). The thermocycling procedure was performed with a Gene Amp PCR System 9600-R (Perkin Elmer, Norwalk, Connecticut) and consisted of initial denaturation at 94°C for 4 minutes, 35 cycles of denaturation at 94°C for 1 minute, annealing at 56°C for 1 minute, extension at 72°C for 2 minutes, and a final extension at 74°C for 7 minutes. The PCR products were analyzed by 2% agarose gel electrophoresis and visualized by ethidium bromide staining. The large allele, eNOS4*b*, contains 5 tandem 27-bp repeats of the consensus sequence previously reported [GAAGTCTAGACCTGCTGC(A/G)GGGGTGAG]; the first 3 repeats contain A and the last 2 contain G as the 19th base of the 27-bp repeat. The smaller allele, eNOS4*a*, contains 4 repeats; the first 2 repeats have A and the last 2 have G as the 19th base of the repeat. PCR analysis of genomic DNA generates fragments of 393 or 420 bp, corresponding to the eNOS4*a* and eNOS4*b* alleles, respectively.

**Statistical Analysis**

Data analyses were performed with the SAS statistical software package, version 6.11 (SAS Institute, Cary, North Carolina, USA). The results for continuous variables are given as means

(±SD) or percentages. The differences among the groups were assessed by chi-square analysis (for categorical data) or ANOVA (for continuous data) for independent samples, when appropriate. Univariate and multivariate regression models were used to investigate the association of various lipoprotein and inflammatory parameters with FMD changes. All *P* values are two-sided.

**結果與討論：**

Parts of the results of this study were published in two articles.[24,25] In brief, we demonstrated that treatment with simvastatin was associated with significantly greater reduction of total cholesterol and low-density lipoprotein cholesterol (LDL-C), while the decrease in triglycerides was significantly greater in patients receiving fenofibrate. Both fenofibrate and simvastatin markedly reduced plasma levels of high-sensitivity CRP, IL-1, and sCD40L, and improved endothelium-dependent FMD without mutual differences. The changes in plasma inflammatory markers did not correlate with baseline clinical characteristics in both groups. However, the improvement in FMD with fenofibrate treatment correlated inversely with baseline high-density lipoprotein cholesterol (HDL-C) levels, whereas the improvement in FMD with simvastatin treatment was positively related to HDL-C levels. Accordingly, in the subgroup with a baseline HDL-C of ≤ 40 mg/dl, only fenofibrate significantly improved the endothelium-dependent FMD. On the other hand, in the subgroup with HDL-C > 40 mg/dl, only treatment with simvastatin achieved significant improvement in FMD. The data here indicate that, in patients with combined hyperlipidemia, both fenofibrate and simvastatin have comparative beneficial effects on various inflammatory markers and differential beneficial effects on endothelial function according to baseline HDL-C levels. These findings should be validated by additional prospective studies, in which patients are stratified by baseline HDL-C prior to randomization.

At the end of 8-week treatment, patients in the rosiglitazone group achieved significant reductions in fasting plasma insulin levels (-40%), homeostasis model assessment (HOMA) indexes (-45%), systolic and diastolic blood pressures, and high-sensitivity CRP levels (-31%), whereas no significant changes were observed in those receiving placebo. There was no significant change in body-mass index, waist circumference, or fasting plasma glucose levels with either treatment. Although rosiglitazone treatment markedly increased plasma levels of total cholesterol (10%), low-density lipoprotein cholesterol (18%), high-density lipoprotein cholesterol (HDL-C) (8%) and non-HDL-C (12%), it significantly improved both endothelium-dependent flow-mediated vasodilation ($p < 0.001$) and endothelium-independent nitroglycerin-induced vasodilation ($p = 0.01$) of the right brachial artery. To conclude, we demonstrated the safety and benefits of rosiglitazone use in ameliorating endothelial dysfunction and inflammation, reversing insulin resistance, and lowering blood pressures in non-diabetic patients with the metabolic syndrome. Given that treatment with rosiglitazone is associated with a worsening of the lipid profile, combination therapy with rosiglitazone plus

statins may be an ideal therapeutic option for non-diabetic patients with the metabolic syndrome.

There was no significant association between the two eNOS gene polymorphisms and pharmacological effects of all three study drugs on flow-mediated vasodilatation.

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## 計畫成果自評：

Results of this study, for the first time, answered the clinically important question of how to treat patients with combined hyperlipidemia in a more effective way. We found out that the

baseline HDL-C levels could be used as a guide to determine which lipid-lowering agent is more effective for patients with combined hyperlipidemia. Furthermore, our study is the first to demonstrate the safety and efficacy of glitazones in treating non-diabetic insulin resistant patients. The clinical significance of this study is also reflected in the fact that results of this study have already been published in two separate articles in high-ranking medical journals.