Risks, Benefits, and Current Management – Strategies of Statin Therapy

Statins Markedly Reduce Cardiovascular Risk

Methods We undertook meta-analyses of individual participant data from randomised trials involving at least 1000 participants and at least 2 years' treatment duration of more versus less intensive statin regimens (five trials; 39 612 individuals; median follow-up 5·1 years) and of statin versus control (21 trials; 129 526 individuals; median follow-up 4·8 years). For each type of trial, we calculated not only the average risk reduction, but also the average risk reduction per 1·0 mmol/L LDL cholesterol reduction at 1 year after randomisation.

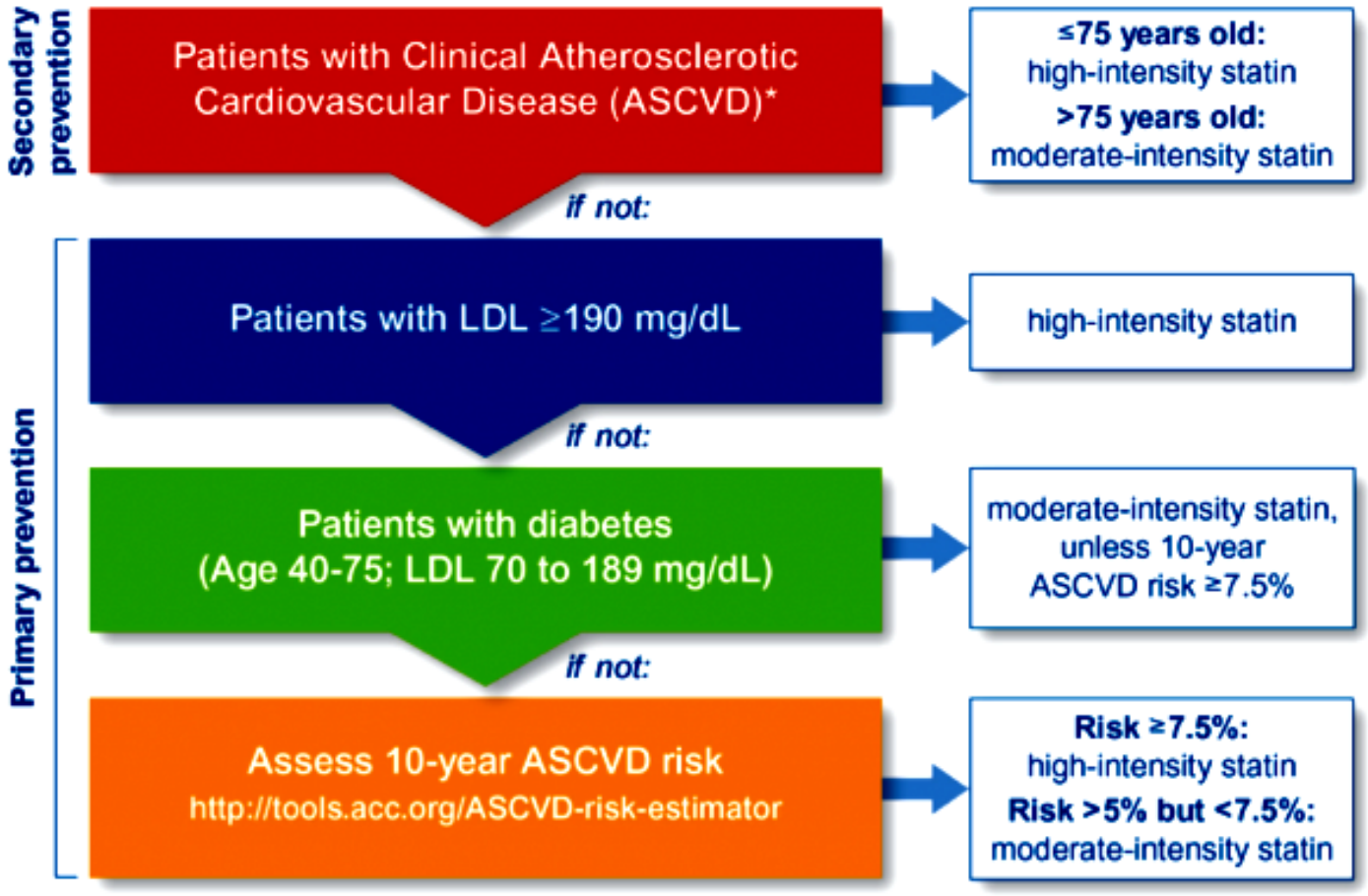
Findings In the trials of more versus less intensive statin therapy, the weighted mean further reduction in LDL cholesterol at 1 year was 0·51 mmol/L. Compared with less intensive regimens, more intensive regimens produced a highly significant 15% (95% CI 11–18; p<0·0001) further reduction in major vascular events, consisting of separately significant reductions in coronary death or non-fatal myocardial infarction of 13% (95% CI 7–19; p<0·0001), in coronary revascularisation of 19% (95% CI 15–24; p<0·0001), and in ischaemic stroke of 16% (95% CI 5–26; p=0·005). Per 1·0 mmol/L reduction in LDL cholesterol, these further reductions in risk were similar to the proportional reductions in the trials of statin versus control. When both types of trial were combined, similar proportional reductions in major vascular events per 1·0 mmol/L LDL cholesterol reduction were found in all types of patient studied (rate ratio [RR] 0·78, 95% CI 0·76–0·80; p<0·0001), including those with LDL cholesterol lower than 2 mmol/L on the less intensive or control regimen. Across all 26 trials, all-cause mortality was reduced by 10% per 1·0 mmol/L LDL reduction (RR 0·90, 95% CI 0·87–0·93; p<0·0001), largely reflecting significant reductions in deaths due to coronary heart disease (RR 0·80, 99% CI 0·74–0·87; p<0·0001) and other cardiac causes (RR 0·89, 99% CI 0·81–0·98; p=0·002), with no significant effect on deaths due to stroke (RR 0·96, 95% CI

每降低 1.0 mmol / L，主要血管事件的年發生率就會降低 20% 以上。

膽固醇範圍內沒有任何閾值的證據，LDLC降低 2-3mmol / L 將使風險降低約 40-50%

Interpretation Further reductions in LDL cholesterol safely produce definite further reductions in the incidence of heart attack, of revascularisation, and of ischaemic stroke, with each 1·0 mmol/L reduction reducing the annual rate of these major vascular events by just over a fifth. There was no evidence of any threshold within the cholesterol range studied, suggesting that reduction of LDL cholesterol by 2–3 mmol/L would reduce risk by about 40–50%.

The 2013 American College of Cardiology and American Heart Association (ACC/AHA) Guidelines define four risk groups for treatment.[1]



*Clinical ASCVD: acute coronary syndrome (ACS), myocardial infarction (MI), angina, revascularization, stroke, TIA, or peripheral arterial disease.

使用 Statin 降低心血管風險
(包含初級與次級預防)
所帶來的好處遠超出副作用
的 4 大族群

Table 5. High- Moderate- and Low-Intensity Statin Therapy (Used in the RCTs reviewed by the Expert Panel)*

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL–C on average, by approximately ≥50%	Daily dose lowers LDL–C on average, by approximately 30% to <50%	Daily dose lowers LDL–C on average, by <30%
Atorvastatin (40†)–80 mg **Rosuvastatin 20** *(40)* **mg**	**Atorvastatin 10** *(20)* **mg** **Rosuvastatin** (*5*) **10 mg** **Simvastatin 20–40 mg‡** **Pravastatin 40** *(80)* **mg** **Lovastatin 40 mg** *Fluvastatin XL 80 mg* **Fluvastatin 40 mg bid** *Pitavastatin 2–4 mg*	*Simvastatin 10 mg* **Pravastatin 10–20 mg** **Lovastatin 20 mg** *Fluvastatin 20–40 mg* *Pitavastatin 1 mg*

Am J Cardiovasc Drugs
https://doi.org/10.1007/s40256-017-0259-7

REVIEW ARTICLE

Management of Statin Intolerance in 2018: Still More Questions Than Answers

Abstract：Statin therapy is **generally well tolerated** and **very effective in the prevention and treatment of cardiovascular disease**, regardless of cholesterol levels; however, it can be **associated with various adverse events (myalgia, myopathy, rhabdomyolysis, and diabetes mellitus, among others)**. Patients **frequently discontinue statin therapy** without medical advice because of perceived side effects and consequently increase their risk for cardiovascular events. In patients with statin intolerance, it may be advisable to **change the dose, switch to a different statin, or try an alternate-day regimen**. If intolerance is associated with all statins—even at the lowest dose—non-statin drugs and certain nutraceuticals can be considered.

各種不良事件（肌痛，肌病變，横紋肌溶解症和糖尿病等）。患者經常停止 Statin 類藥物治療因為有明顯的副作用。 Statin intolerance 患者中，可能建議改變劑量，換不同的 Statin 類藥物

In Real-world Practice, As Opposed to Clinical Trials, Persistence Drops Off Rapidly

- Ir
- F
- E

2

真道理性 真愛台灣
中時電子報
chinatimes.com

2017年11月17日 04:10 中國時報 陳世宗 / 台中報導

台灣1年被丟掉藥品至少193噸、約5棟101大樓，被丟掉的藥至少超過5億顆，排起來可環島近8圈。台中市議員張雅旻16日質詢說，台中市的廢棄藥品回收成效不彰，市府應重視，當環保局編列1億做廚餘回收桶時，衛生局亦應處理「廢棄藥品」問題。

–674.

4–573.

5–752.

Drug Saf. 2012;21:61–69.

Aust Fam Physician. 2011 May;40(5):319-22.

Long term persistence with statin therapy -- experience in Australia 2006-2010.

Simons LA[1], Ortiz M, Calcino G.

43%的患者, 6 個月內停用 Statin ,
平均持續使用 11 個月

METHOD: We conducted a longitudinal assessment of Pharmaceutical Benefit Scheme claim records dating from April 2005 to March 2010. Main outcome measures were the proportion of patients who were not filling a first repeat prescription at 1 month, and median persistence time during follow up.

RESULTS: For 77,867 patients initiated to statin, 86% of prescriptions came from general practitioners. Forty-three percent of patients discontinued statin within 6 months, 23% failed to collect their first repeat at 1 month, and median persistence time was only 11 months. In those aged 65--74 years, median persistence time was 19 months but only 3--6 months for those less than 55 years.

DISCUSSION: Unsatisfactory long term persistence on statin therapy has changed little over the past 10 years. There may be an opportunity for early intervention within 3--4 weeks of initiation to improve persistence, as valuable resources are being wasted and an opportunity for disease prevention missed.

Table 1. Reasons for Discontinuation of Statins

Reasons for Discontinuation of Statins Among Patients With a Statin-Attributed Event	Percent of Patients
No longer necessary, ineffective, change requested by insurance	16
Inadequate coverage by insurance, too expensive, switch to another drug, rejected by patient	4.8
Adverse events attributed to statins	11.9
Myalgia or myopathy	4.71
Other musculoskeletal problems (cramps, arthralgia, extremity pain, other)	2.54
General medical (asthenia, pain fatigue, other)	2.31
Hepatobiliary	2.1
Gastrointestinal	1.6
Nervous system and psychiatric disorders (memory, other)	0.82
Immune, vascular, cardiac disorders	0.86
Injury, poisoning, skin, reproductive, respiratory, thoracic, mediastinal, ear/labyrinth	0.4
Blood/lymphatic, renal/urinary, eye, metabolism/nutrition	0.08

Based on data from 107 835 patients in routine care from Zhang et al.

Zhang et al. Ann Intern Med. 2013;158:526–534.

Patterns of Statin Use in a Real-World Population of Patients at High Cardiovascular Risk

ABSTRACT

BACKGROUND: Widespread use of statins has improved hypercholesterolemia management, yet a significant proportion of patients remain at risk for cardiovascular (CV) events. Analyses of treatment patterns reveal inadequate intensity and duration of statin therapy among patients with hypercholesterolemia, and little is known about real-world statin use, specifically in subgroups of patients at high risk for CV events.

OBJECTIVE: To examine patterns of statin use and outcomes among patients with high-risk features who newly initiated statin monotherapy.

METHODS: Adult patients (aged ≥18 years) at high CV risk who received ≥1 prescription for statin monotherapy and who had not received lipid-modifying therapy during the previous 12 months were identified from the Truven MarketScan Commercial and Medicare Supplemental databases (from January 2007 to June 2013). Patients with atherosclerotic cardiovascular disease (ASCVD) or diabetes were hierarchically classified into 5 mutually exclusive CV risk categories (listed here in order from highest to lowest risk): (1) recent CV event (subcategorized by hospitalization for acute coronary syndrome [ACS] or other non-ACS CV event within 90 days of index); (2) coronary heart disease (CHD); (3) history of ischemic stroke; (4) peripheral artery disease (PAD); and (5) diabetes. Outcomes of interest included changes in therapy, proportion of days covered (PDC), time to discontinuation, and proportion of patients with ASCVD-related inpatient visit during the follow-up period. Statin therapy was subdivided into high-intensity treatment (atorvastatin 40 mg or 80 mg, rosuvastatin 20 mg or 40 mg, or simvastatin 80 mg) or moderate- to low-intensity treatment (all other statins and statin dosing regimens). Follow-up data were obtained from the index date (statin initiation) until the end of continuous enrollment.

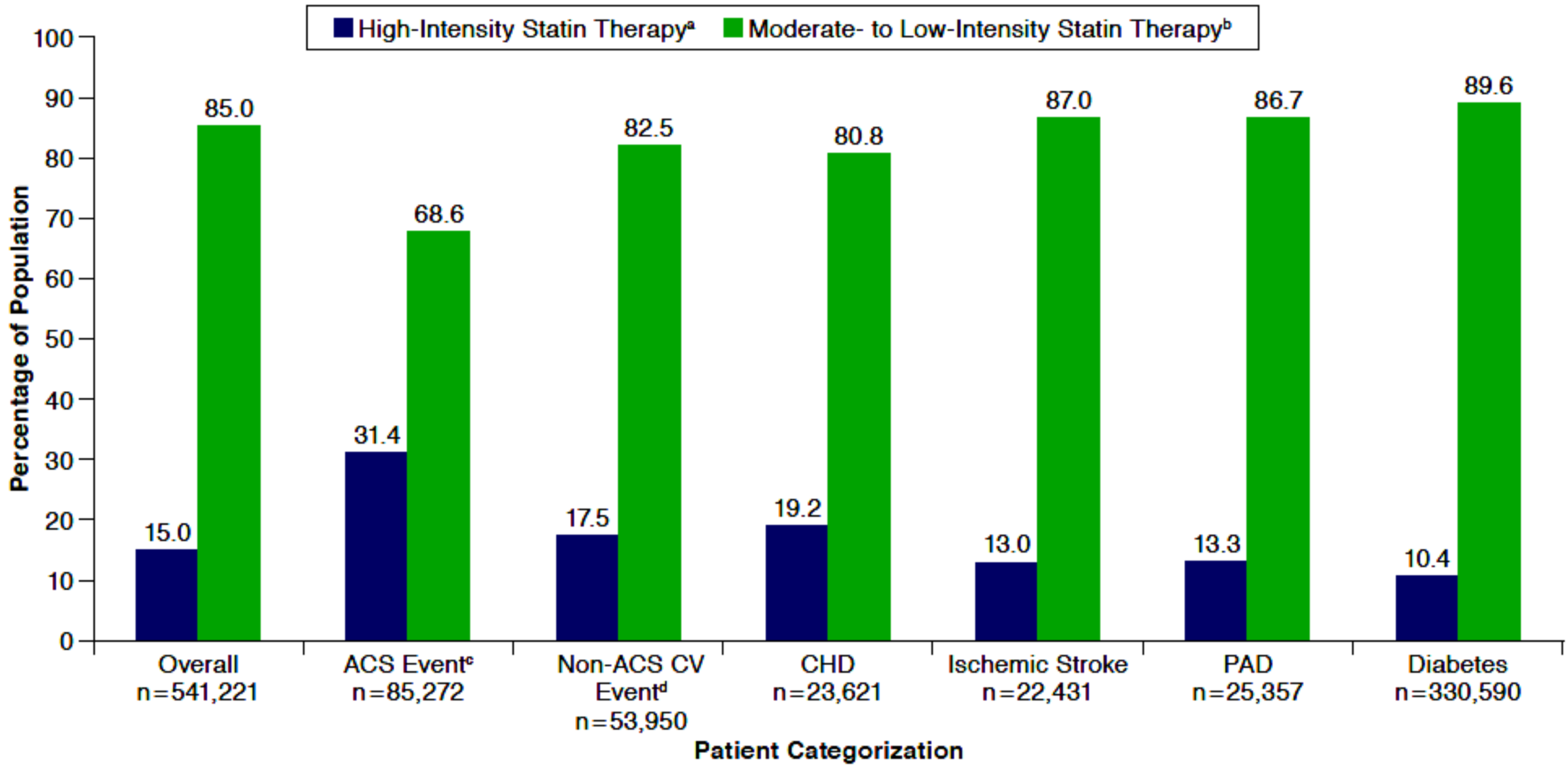
J Manag Care Spec Pharm. 2016;22(6):685-98

美國密西根州商業和醫療保險資料 2007~2013

Statin 廣泛使用,仍有相當部分患者處於心血管（CV）事件風險之中

分析真實臨床藥物治療高膽固醇血症的強度和持續時間治療模式，尤其 CV 事件高危患者

FIGURE 2 Intensity of Statin Therapy at Index



[a]*High-intensity statin treatment was defined as atorvastatin 40 mg or 80 mg, rosuvastatin 20 mg or 40 mg, or simvastatin 80 mg.*

[b]*Moderate- to low-intensity statin treatment included all other statins and statin dosing regimens.*

[c]*Includes acute myocardial infarction and unstable angina.*

[d]*Includes revascularization and ischemic stroke within 90 days pre-index.*

ACS = acute coronary syndrome; CHD = coronary heart disease; CV = cardiovascular; PAD = peripheral artery disease.

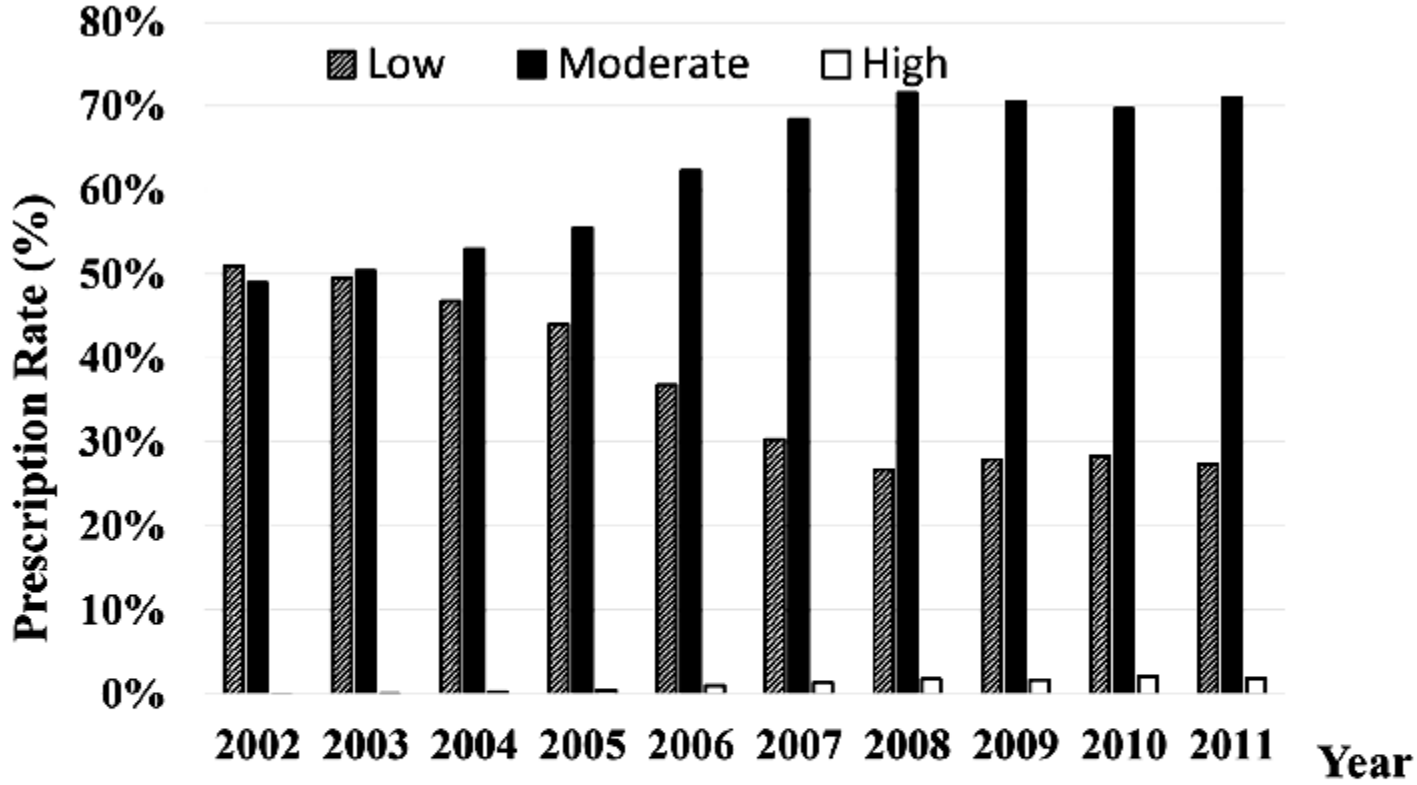
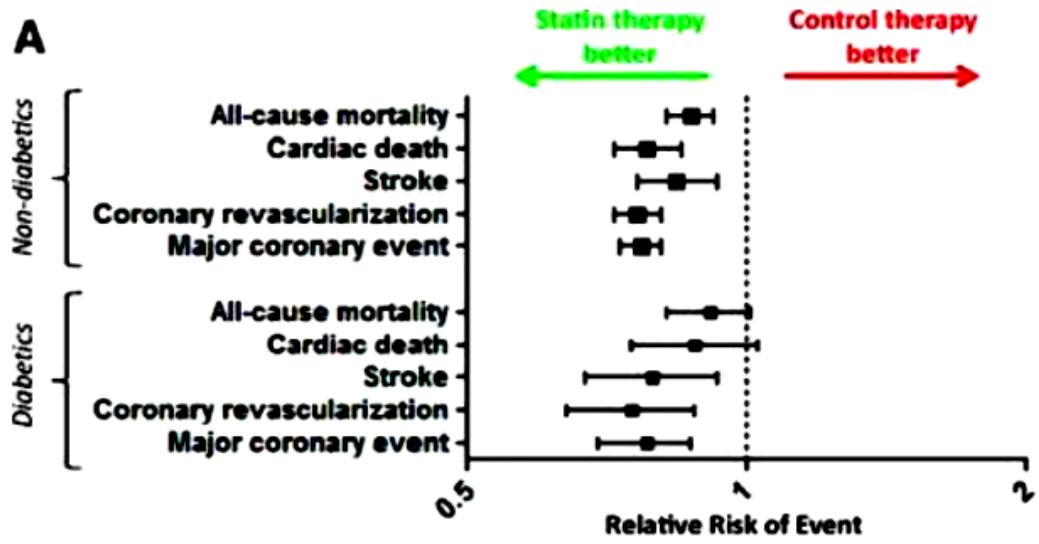


Figure 2 Prescribing rates of statins by intensity. All values were calculated in patient number. Yearly prescription rate = number of patients prescribed with the specific statin agent / total number of new statin users in the year. Statins were grouped into three levels of intensity according to their ability to lower LDL-C based on the 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol[7] and Rosenson *et al*[28]: (1) high-intensity statins: atorvastatin ≧40 mg/day, rosuvastatin ≧20 mg/day and simvastatin ≧80 mg/day; (2) moderate-intensity statins: 10 mg/day ≦ atorvastatin <40 mg/day, 5 mg/day ≦ rosuvastatin <20 mg/day, 20 mg/day ≦ simvastatin <80 mg/day, pravastatin ≧ 40 mg/day, lovastatin ≧40 mg/day and fluvastatin ≧80 mg/day; and

Use of moderate-intensity statins increased from 49.0% in 2002 to 71.0% in 2011, while high-intensity statins remained low. Prescribing of higher intensity statins was not greater among people with diabetes compared with those without during 2007–2011.

Statin Risk / Benefit Ratio



B

Benefits

- Reduction in cardiovascular risk (primary and secondary prevention in diabetics and non-diabetics)

Risks

- New-onset diabetes
- Liver and muscle toxicity
- Rare serious side effects (rhabdomyolysis, death)

Should I start a statin in my patient?

What is the underlying patient-specific risk of a cardiac event?
(by conventional risk algorithms, e.g., Framingham score; primary vs. secondary prevention)

Reducing LDL-C by 40 mg/dL with statins reduces ASCVD risk by 20%

Acta Cardiol Sin 2016;32:631–639
Review Article
doi: 10.6515/ACS20160611A
中華民國心臟學會

Background: Hydroxymethyl glutaryl coenzyme A reductase inhibitors, commonly called statins, are some of the most commonly prescribed medications worldwide. Evidence suggests that statin therapy has significant mortality and morbidity benefit for both primary and secondary prevention from cardiovascular disease. Nonetheless, concern has been expressed regarding the adverse effects of long term statin use. The purpose of this article was to review the current medical literature regarding the safety of statins.

Methods: Major trials and review articles on the safety of statins were identified in a search of the MEDLINE database from 1980 to 2016, which was limited to English articles.

Results: Myalgia is the most common side effect of statin use, with documented rates from 1-10%. Rhabdomyolysis is the most serious adverse effect from statin use, though it occurs quite rarely (less than 0.1%). The most common risk factors for statin-related myopathy include hypothyroidism, polypharmacy and alcohol abuse. Derangement in liver function tests is common, affecting up to 1% of patients; however, the clinical significance of this is unknown. Some statin drugs are potentially diabetogenic and the risk appears to increase in those patients on higher doses. Pitavastatin has not been associated with increased risk of diabetes. Statins have not been proven to increase the risk of malignancy, dementia, mood disorders or acute interstitial nephritis. However, statins do have multiple drug interactions, primarily those which interact with the cytochrome p450 enzyme group.

Conclusions: Overall, statin drugs appear to be safe for use in the vast majority of patients. However, patients with multiple medical co-morbidities are at increased risk of adverse effects from long-term statin use.

The FDA Safety Information and Adverse Event Reporting Program

Statin Drugs - Drug Safety Communication: Class Labeling Change

[Posted 02/28/2012]

最近美國食品藥物管理局於回顧statin 類藥品之上市後安全資訊及多個臨床試驗結果報告，作出以下建議(1)肝功能監測：病人於開始使用statin 前，需監測肝功能指數，服藥期間若出現疑似肝功能異常之臨床症狀時，需再次檢測肝功能指數；(2)於仿單中新增不良事件訊息：部分報告顯示，該類藥品可能導致非嚴重且停藥後可恢復之可逆性認知障礙（例如失憶、混亂），及些微增加血糖及糖化血色素(HbA1c)上升之風險；惟美國食品藥物管理局認為該類藥品對心血管之臨床效益仍高於些微血糖上升之風險 (3) lovastatin 藥物交互作用：lovastatin 併用CYP3A4 抑制劑藥品時會產生交互作用，而提高橫紋肌溶解症之不良反應風險。

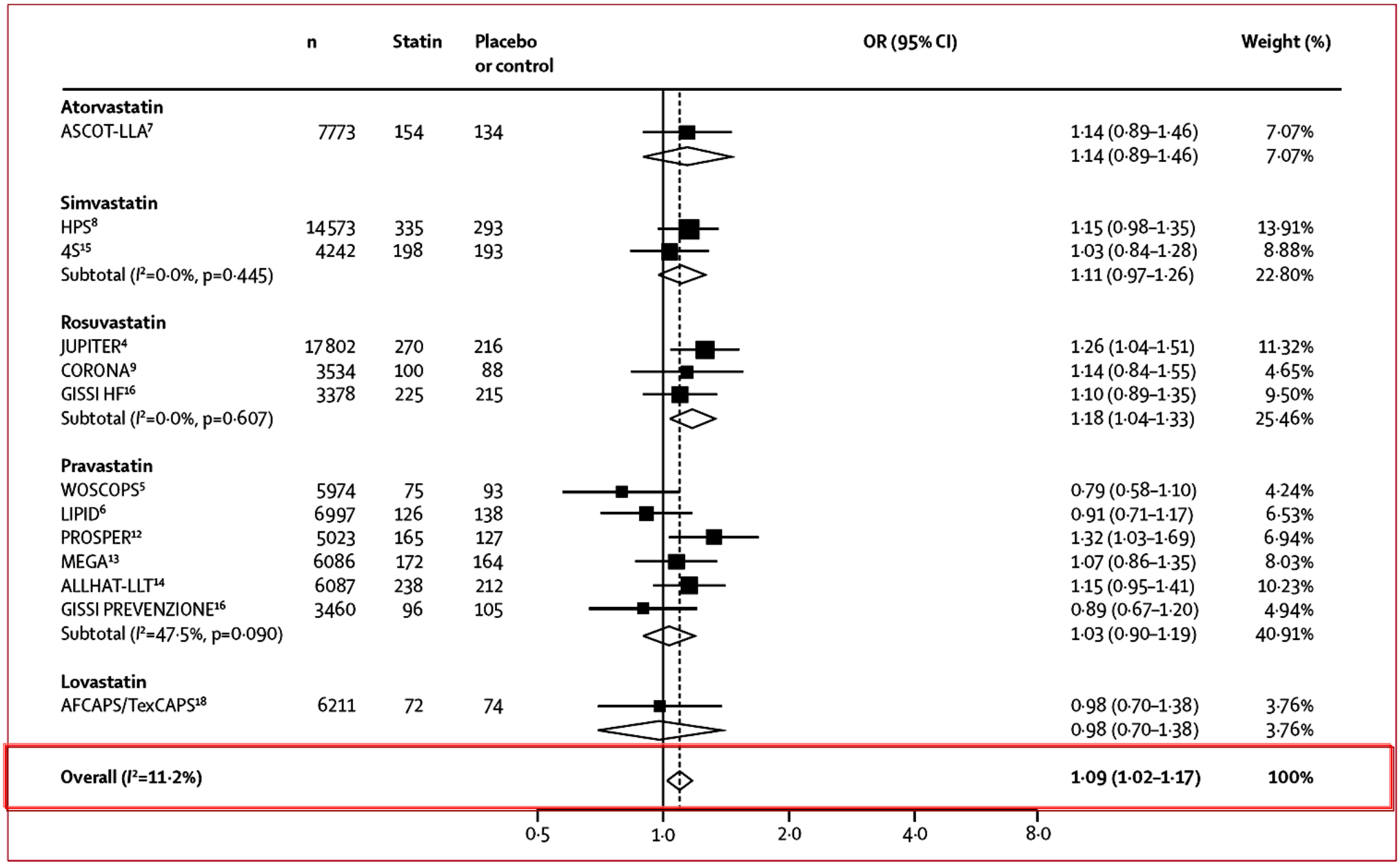


***Figure 3*: Association between different statins and development of diabetes**

Lancet 2010; 375.

Table 1—*Randomized controlled trials evaluating the effect of statin use risk of incident type 2 diabetes*

	Study population, follow-up time	Median follow-up	Intervention (sample size)	Diagnosis of incident diabetes	Results for primary outcome, RR (95%CI)	Results for diabetes: Incident diabetes cases (*n* in statin group/*n* in placebo group)	Results for diabetes: RR (95% CI) for diabetes comparing statin treatment with placebo
WOSCOPS (2001)[1]	Men aged 45–67 years (mean 55.2 years) from West of Scotland with moderately elevated cholesterol	4.9 years	Pravastatin 40 mg (*n* = 2,999) vs. placebo (*n* = 2,975)	Fasting glucose ≥126 mg/dl on two occasions, one of which must be ≥36 mg/dl above baseline or use of hypoglycemic agents	Nonfatal MI and cardiovascular death, 0.69 (0.57–0.83)	57/82	0.7 (0.50–0.99)
HPS (2003)[2]	Adults (78% men) aged 40–80 years (mean 62.1 years) with occlusive arterial disease	4.6 years	Simvastatin 40 mg (*n* = 7,291) vs. placebo (*n* = 7,282)	Initiation of pharmacotherapy for diabetes or a specific report of diabetes during follow-up	All-cause mortality, 0.87 (0.81–0.94)	335/293	1.14 (0.98–1.33)
ASCOT (2003)[3]	Adults aged 40–79 years (mean 63.2 years) with hypertension and at high-risk for CVD	3.3 years	Atorvastatin 10 mg (*n* = 3,910) vs. placebo (*n* =	Fasting glucose ≥126 mg/dl or 2-h OGTT glucose level ≥200 mg/dl	Nonfatal MI, cardiovascular death, 0.64 (0.50–0.83)	154/134	1.15 (0.91–1.44)

研究指出，使用Statin可能影響糖尿病發生以及糖尿病病人血糖控制。

WOSCOPS 研究發現使用 pravastatin 可減少 30% 的糖尿病發生，

而 HPS 和 ASCOT-LLA 團隊分別研究 simvastatin 和 atorvastatin，兩種藥物對糖尿病新生的影響並無統計意義。

JUPITOR 研究則指出使用 rosuvastatin 可能增加新診斷糖尿病之機會

JUPITER (2008)[6]	Multicenter trial with a median follow-up of 1.9 years. Apparently healthy men and women (median age 66 years) with LDL cholesterol <130 mg/dl and hsCRP ≥2.0 mg/l	1.9 years	Rosuvastatin, 20 mg (*n* = 8,901) vs. placebo (*n* = 8,901)	Physician-diagnosed diabetes	Nonfatal MI and stroke, unstable angina, arterial revascularization, and cardiovascular death, 0.56 (0.46–0.69)	270/216	1.13 (95% CI: 0.86, 1.50) 1.25 1.05–1.49)

hsCRP, high-sensitivity C-reactive protein; MI, myocardial infarction; OGTT, oral glucose tolerance test.

Diabetes Care 32:1924–1929, 2009

REVIEW

Statin-induced diabetes: incidence, mechanisms, and implications [version 1; referees: 2 approved]

Table 1. Meta-analyses of randomized controlled trials.

Authors	n	Age (years)	Duration of follow-up (years)	Adjusted odds ratio (95% confidence interval)	Comments
Sattar *et al.*[10] 13 trials, statin vs. placebo	91,140	Means: 55.0–76.0	Mean: 4.0	1.09 (1.02–1.17)	Highest risk in older patients; unrelated to % low-density lipoprotein cholesterol reduction
Preiss *et al.*[11] 5 trials, more- vs. less-intensive statin	32,752	Means: 58.0–64.0	Mean: 4.9	1.12 (1.04–1.22)	Odds ratio for incident cardiovascular disease 0.84 (95% confidence interval 0.75–0.94)
Navarese *et al.*[15] 17 trials, various statins and doses	113,394	Means: 55.0–65.0	2.0–6.0	Pravastatin 40 mg vs. placebo: 1.07 (0.89–1.30) Atorvastatin 80 mg vs. placebo: 1.15 (0.90–1.50) Rosuvastatin 20 mg vs. placebo: 1.25 (0.82–1.90)	Odds ratio unrelated to % low-density lipoprotein cholesterol reduction

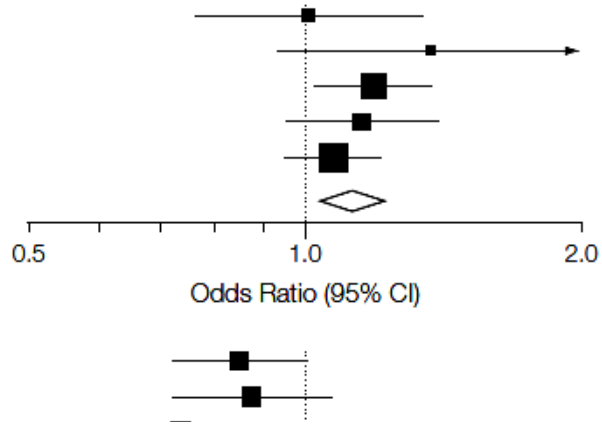
Risk of Incident Diabetes With Intensive-Dose Compared With Moderate-Dose Statin Therapy

A Meta-analysis

JAMA. 2011;305(24):2556-2564

Figure 2. Meta-analysis of New-Onset Diabetes and First Major Cardiovascular Events in 5 Large Trials Comparing Intensive-Dose to Moderate-Dose Statin Therapy

	Cases/Total, No. (%)		
	Intensive Dose	Moderate Dose	OR (95% CI)
Incident Diabetes			
PROVE IT–TIMI 22,[18] 2004	101/1707 (5.9)	99/1688 (5.9)	1.01 (0.76-1.34)
A to Z,[17] 2004	65/1768 (3.7)	47/1736 (2.7)	1.37 (0.94-2.01)
TNT,[15] 2005	418/3798 (11.0)	358/3797 (9.4)	1.19 (1.02-1.38)
IDEAL,[16] 2005	240/3737 (6.4)	209/3724 (5.6)	1.15 (0.95-1.40)
SEARCH,[5] 2010	625/5398 (11.6)	587/5399 (10.9)	1.07 (0.95-1.21)
Pooled odds ratio	**1449/16 408 (8.8)**	**1300/16 344 (8.0)**	**1.12 (1.04-1.22)**
Heterogeneity: $I^2 = 0\%$; $P = .60$			
Incident CVD			
PROVE IT–TIMI 22,[18] 2004	315/1707 (18.4)	355/1688 (21.0)	0.85 (0.72-1.01)
A to Z,[17] 2004	212/1768 (12.0)	234/1736 (13.5)	0.87 (0.72-1.07)



As compared with moderate-dose statin therapy, the number needed to harm per year for intensive-dose statin therapy was 498 for new-onset diabetes while the number needed to treat per year for intensive-dose statin therapy was 155 for cardiovascular events.

Data marker size indicates relative weight of the studies; OR, odds ratio; and CI, confidence interval.

BMJ

Participants 136 966 patients aged ≥40 years newly treated with statins between 1 January 1997 and 31 March 2011.

Methods Within each cohort of patients newly prescribed a statin after hospitalisation for a major cardiovascular event or procedure, we performed as-treated, nested case-control analyses to compare diabetes incidence in users of higher potency statins with incidence in users of lower potency statins. Rate ratios of new diabetes events were estimated

比較較高效力 Statin 使用者和低效力 Statin 使用者的糖尿病發生率

methods were used to estimate overall effects across sites.

Main outcome measures Hospitalisation for new onset diabetes, or a prescription for insulin or an oral antidiabetic drug.

Results In the first two years of regular statin use, we observed a significant increase in the risk of new onset diabetes with higher potency statins compared with lower potency agents (rate ratio 1.15, 95% confidence interval 1.05 to 1.26). The risk increase seemed to be highest in the first four months of use (rate ratio 1.26, 1.07 to 1.47).

高效力 Statin 比低效力 Statin 使用者的糖尿病發生率高 1.15 倍

尤其前 1 ~ 4 個月

Rosuvastatin ≥10 mg, atorvastatin ≥20 mg, and simvastatin ≥40 mg as higher potency statins, and all other statins were defined as lower potency statins.

SCIENTIFIC REPORTS

OPEN

Association between reductions in low-density lipoprotein cholesterol with statin therapy and the risk of new-onset diabetes: a meta-analysis

Received: 22 February 2016
Accepted: 30 November 2016
Published: 10 January 2017

以 Statin 減少低密度脂蛋白膽固醇和新發生糖尿病的風險之間的關聯

A recent meta-analysis demonstrated that statin therapy was associated with a risk of diabetes. The present study investigated whether the relative reduction in low-density lipoprotein cholesterol (LDL-c) was a good indicator of the risk of new-onset diabetes. We searched the PubMed, Embase, Cochrane Central Register, Lilacs, Food and Drug Administration, and European Medicines Agency databases for randomized controlled trials of statins. Fourteen trials were included in the study. Eight trials with target LDL-c levels $\leq$100 mg/dL (2.6 mmol/L) or LDL-c reductions of at least 30% were extracted separately. The results showed that the overall risk of incident diabetes increased by 11% (OR = 1.11; 95% CI 1.03–1.20). The group with intensive LDL-c-lowering statin had an 18% increase in the likelihood of developing diabetes (OR = 1.18; 95% CI, 1.10–1.28). Furthermore, the risks of incident diabetes were 13% (OR = 1.13; 95% CI 1.01–1.26) and 29% (OR = 1.29; 95% CI 1.13–1.47) in the subgroups with 30–40% and 40–50% reductions in LDL-c, respectively, suggesting that LDL-c reduction may provide a dynamic risk assessment parameter for new-onset diabetes. In conclusion, LDL-c reduction is positively related to the risk of new-onset diabetes. When LDL-c is reduced by more than 30% during lipid-lowering therapy, blood glucose monitoring is suggested to detect incident diabetes in high-risk populations.

LDL-C 降低為新發生糖尿病提供動態風險評估參數，LDL-C 減少與新發生糖尿病的風險正相關

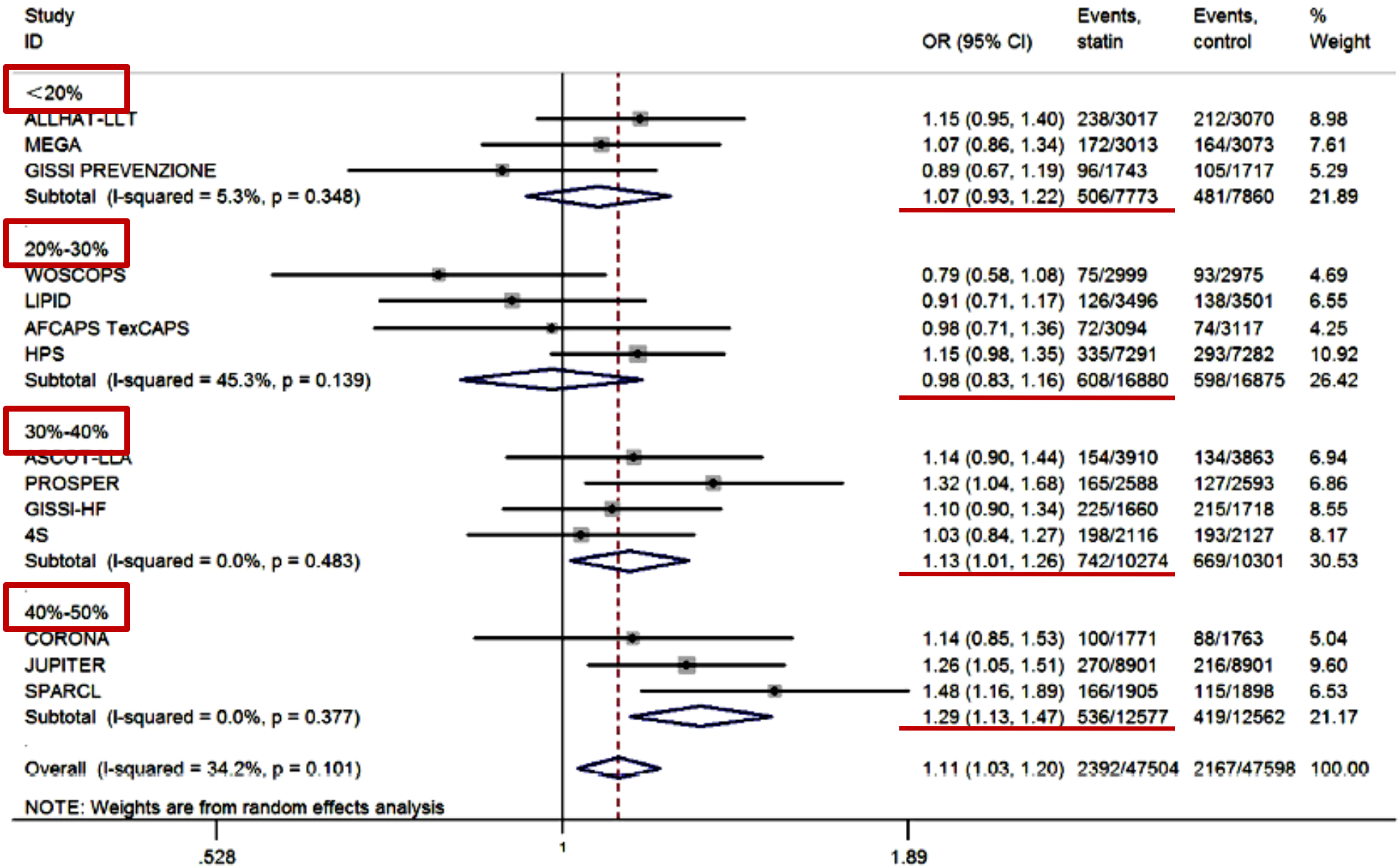


Figure 2. **Association between different LDL-c reduction and incident diabetes.**

Abstract: Statin therapy is beneficial in reducing cardiovascular events and mortalities in patients with atherosclerotic cardiovascular diseases. Yet, there have been concerns of increased risk of diabetes with statin use. This study was aimed to evaluate the association between statins and new onset diabetes mellitus (NODM) in patients with ischemic heart disease (IHD) utilizing the Korean Health Insurance Review and Assessment Service claims database. Among adult patients with preexisting IHD, new statin users and matched nonstatin users were identified on a 1:1 ratio using proportionate stratified random sampling by sex and age. They were subsequently propensity score matched further with age and comorbidities to reduce the selection bias. Overall incidence rates, cumulative rates and hazard ratios (HRs) between statin use and occurrence of NODM were estimated. The subgroup analyses were performed according to sex, age groups, and the individual agents and intensities of statins. A total of 156,360 patients (94,370 in the statin users and 61,990 in the nonstatin users) were included in the analysis. The incidence rates of NODM were 7.8% and 4.8% in the statin users and nonstatin users, respectively. The risk of NODM was higher among statin users (crude HR 2.01, 95% confidence interval [CI] 1.93–2.10; adjusted HR 1.84, 95% CI 1.63–2.09). Pravastatin had the lowest risk (adjusted HR 1.54, 95% CI 1.32–1.81) while those who were exposed to more than one statin were at the highest risk of NODM (adjusted HR 2.17, 95% CI 1.93–2.37). It has been concluded that all statins are associated with the risk of NODM in patients with IHD, and it is believed that our study would contribute to a better understanding of statin and NODM association by analyzing statin use in the real-world setting. Periodic screening and monitoring for diabetes are warranted during prolonged statin therapy in patients with IHD.

Table 1 Incidence rates and HRs for NODM among statin users versus nonstatin users according to the individual statin agents and intensities

Variables	Patients (A, n)	%	NODM (B, n)	Risk, $\frac{B}{A}$ (%)	Total PYs	Incidence rate/100 PYs	Crude HR (95% CI)	Adjusted HR[a] (95% CI)
Non-statin users	61,990	39.6	3,001	4.8	243,764	1.66	1.00 (reference)	1.00 (reference)
Statin users	94,370	60.4	7,383	7.8	195,042	3.79	2.01 (1.93–2.10)	1.84 (1.63–2.09)
Overall	156,360	100.0	10,384	6.6	438,806	2.61	–	–
Statin agents								
Atorvastatin	58,036	61.5	4,634	8.0	120,729	3.84	2.04 (1.95–2.14)	2.05 (1.96–2.16)
Rosuvastatin	11,851	12.6	957	8.1	25,400	3.77	2.00 (1.86–2.16)	2.00 (1.85–2.15)
Simvastatin	13,012	13.8	1,002	7.7	25,346	3.95	2.10 (1.96–2.26)	2.12 (1.97–2.28)
Pravastatin	2,733	2.9	163	6.0	5,652	2.88	1.53 (1.31–1.80)	1.54 (1.32–1.81)
Lovastatin	833	0.9	64	7.7	1,589	4.03	2.14 (1.67–2.74)	2.16 (1.68–2.77)
Fluvastatin	1,262	1.3	77	6.1	2,471	3.12	1.65 (1.32–2.07)	1.66 (1.32–2.08)
Pitavastatin	4,075	4.3	279	6.8	8,789	3.17	1.69 (1.49–1.91)	1.70 (1.50–1.92)
Complex	2,568	2.7	207	8.1	5,066	4.09	2.18 (1.89–2.51)	2.17 (1.93–2.37)
Statin users, total	94,370	100.0	7,383	7.8	195,042	3.79	2.01 (1.93–2.10)	1.84 (1.63–2.09)
Intensity								
Low	3,796	4.0	127	6.2	4,030	3.15	1.67 (1.40–2.00)	1.69 (1.41–2.01)
Moderate	88,529	93.8	6,961	7.9	183,077	3.80	2.02 (1.94–2.11)	2.03 (1.94–2.12)
High	2,045	2.2	295	7.8	7,935	3.72	1.98 (1.75–2.23)	1.97 (1.74–2.22)
Statin users, total	94,370	100.0	7,383	7.8	195,042	3.79	2.01 (1.93–2.10)	1.84 (1.63–2.09)

Notes: [a]Adjusted HR was calculated using the Cox proportional hazard model adjusting for the comorbidities. "–" Indicates not applicable.
Abbreviations: CI, confidence interval; HR, hazard ratio; NODM, new onset diabetes mellitus; PY, person-year.

Can J Diabetes. 2016 Jun;40(3):264-9. doi: 10.1016/j.jcjd.2015.12.006. Epub 2016 Mar 15.

Statin Use and the Risk for Incident Diabetes Mellitus in Patients with Acute Coronary Syndrome after Percutaneous Coronary Intervention: A Population-Based Retrospective Cohort Study in Taiwan.

Lin ZF[1], Wang CY[2], Shen LJ[1], Hsiao FY[3], Lin Wu FL[4].

⊕ **Author information** **School of Pharmacy, College of Medicine, National Taiwan University, Taipei, Taiwan**

Abstract

OBJECTIVES: The purpose of this study was to examine the association between statin use by individuals and the risk for incident diabetes mellitus in patients with acute coronary syndrome (ACS) following percutaneous coronary intervention (PCI).

METHODS: We conducted a retrospective cohort study of patients who were hospitalized for ACS between January 1, 2006, and December 31, 2010, and who had undergone PCI (n=30,665); the data were retrieved from the Taiwan National Health Insurance Research Database. A propensity score technique was used to establish a 1:1 matched cohort for statin users and non-statin users (n=9043 for each group). The risk for incident diabetes mellitus in statin users compared to non-statin users for patients with ACS after PCI was estimated by the multivariable Cox proportional hazards regression model.

RESULTS: Statin use was associated with a significant increase of 27% in the risk for new-onset diabetes mellitus (adjusted hazard ratio [HR] 1.27, 95% CI 1.14 to 1.41) compared to non-statin use in the matched cohort. The matched cohort analysis indicated that almost all individual statins were associated with a statistically significant increase in the risk for new-onset diabetes mellitus compared to those without statin use.

SCIENTIFIC REPORTS

OPEN

Received: 20 February 2017
Accepted: 14 August 2017
Published online: 19 September 2017

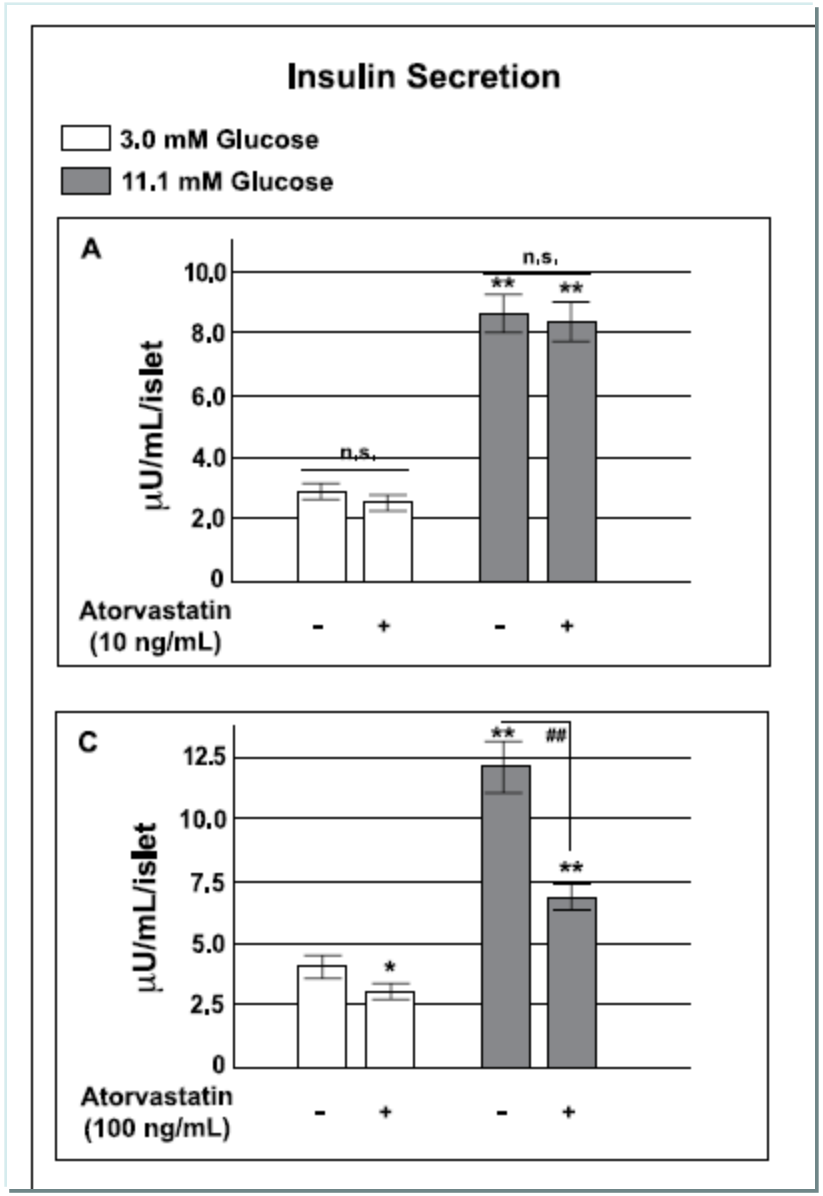
Atorvastatin but Not Pravastatin Impairs Mitochondrial Function in Human Pancreatic Islets and Rat β-Cells. Direct Effect of Oxidative Stress

使用人類胰島和大鼠分泌胰島素的 INS-1 細胞; 探討親脂性和親水性 statin 類藥物對 β 細胞功能的影響 focus 線粒體和氧化應激。

Statins are a class of drugs widely prescribed as frontline therapy for lowering plasma LDL-cholesterol in cardiovascular risk prevention. Several clinical reports have recently suggested an increased risk of type 2 diabetes associated with chronic use of these drugs. The pathophysiology of this effect remains to be fully elucidated but impaired β-cell function constitutes a potential mechanism. The aim of this study was to explore the effect of a chronic treatment with lipophilic and hydrophilic statins on β-cell function, using human pancreatic islets and rat insulin-secreting INS-1 cells; we particularly focused on the role of mitochondria and oxidative stress. The present study demonstrates, for the first time, that atorvastatin (lipophilic) but not pravastatin (hydrophilic) affected insulin release and mitochondrial metabolism due to the suppression of antioxidant defense system and induction of ROS production in pancreatic β-cell models. Mevalonate addition and treatment with a specific antioxidant (N-AcetylCysteine) effectively reversed the observed defects. These data demonstrate that mitochondrial oxidative stress is a key element in the pathogenesis of statin-related diabetes and may have clinical relevance to design strategies for prevention or reduction of statin induced β-cell dysfunction and diabetes in patients treated with lipophilic statins.

闡明β細胞功能受損的構成潛在的機制。

研究首次證實 Atorvastatin（親脂性）而不是 Pravastatin（親水性）抑制胰島β細胞抗氧化防禦系統和誘導 ROS 產生,影響胰島素釋放和由此引起的線粒體代謝



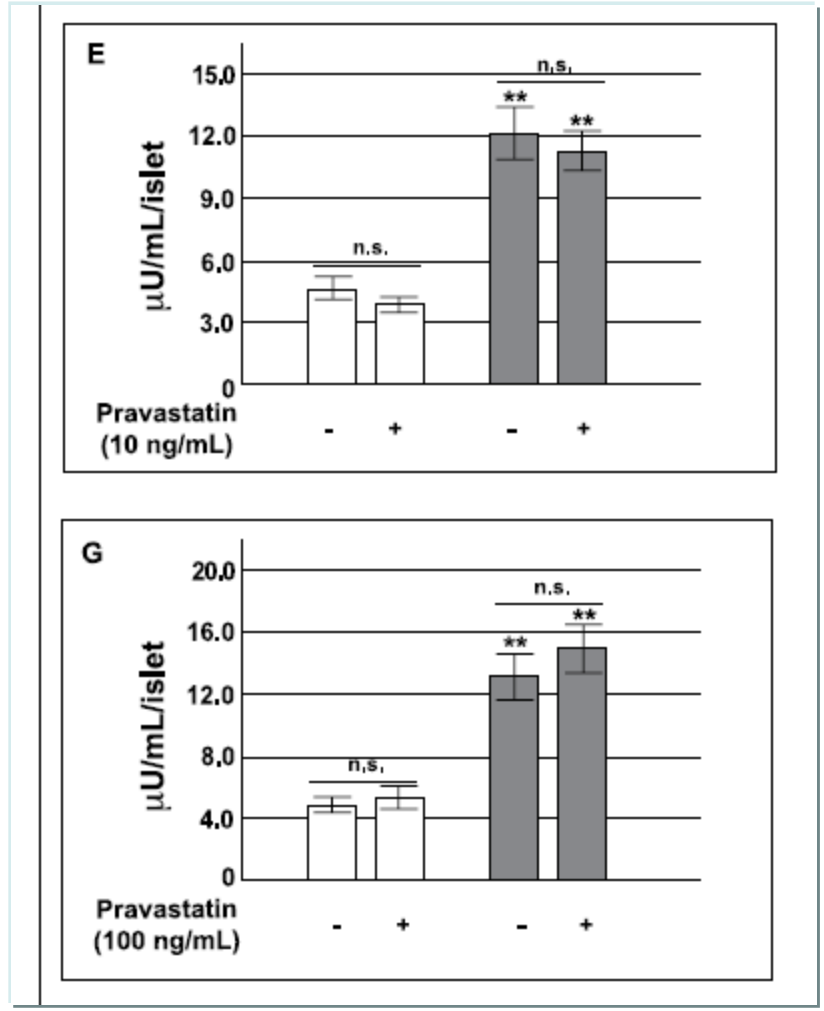


Figure 1. Effect of atorvastatin and pravastatin on glucose-induced insulin release in human pancreatic islets. Absolute glucose-induced insulin secretion

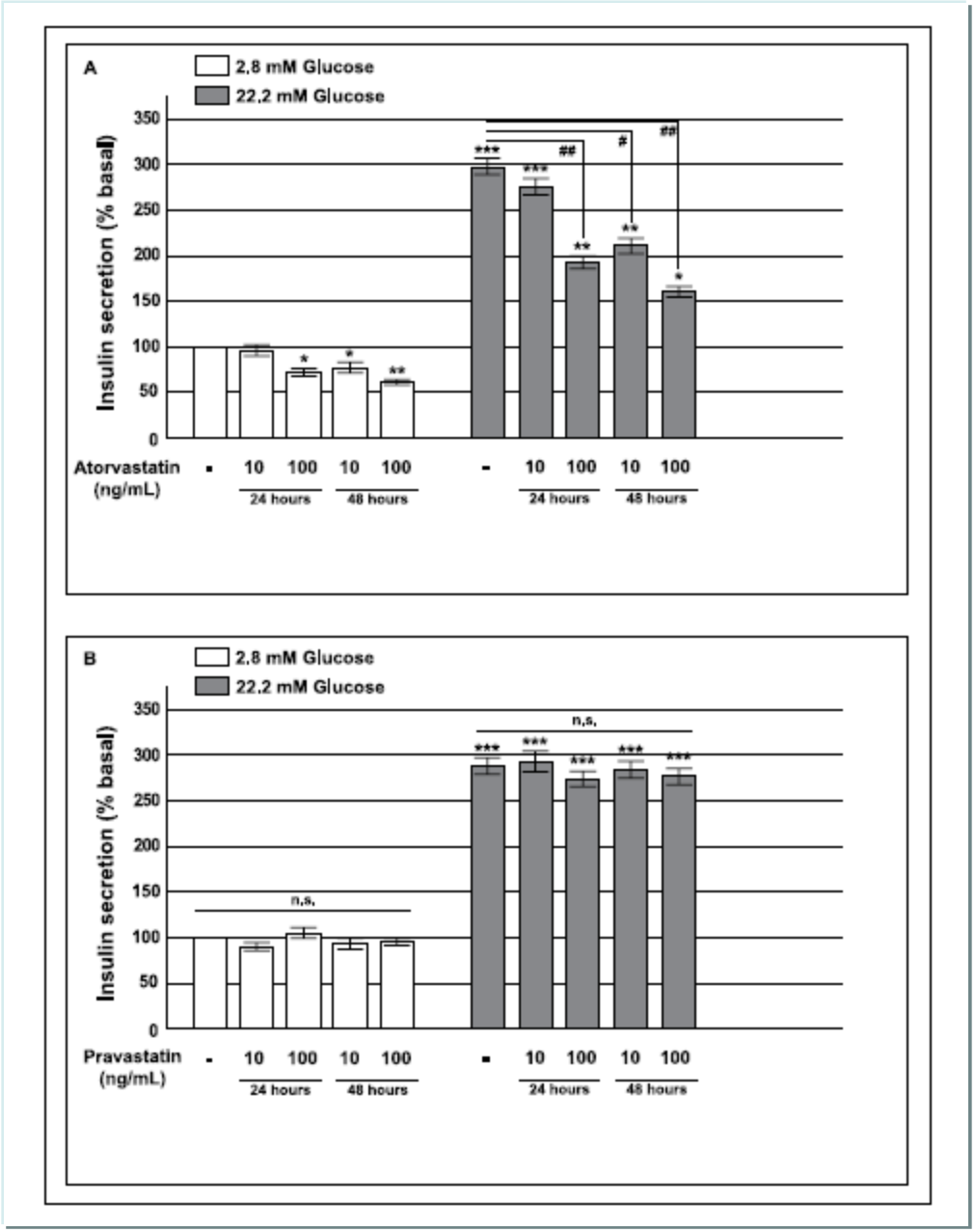


Figure 2. Effect of atorvastatin and pravastatin on glucose-induced insulin release in INS-1 cells.
Panel A: acute glucose-induced insulin secretion in control cells and in cells pre-exposed to 10 or 100 ng/mL of atorvastatin for 24 or 48 h (baseline secretory rate at 2.8 mM glucose: 32.3 ± 3.5 ng/mg of protein in 1 h); Panel B: acute insulin secretion in INS-1 cells pre-exposed to 10 or 100 ng/mL of pravastatin for 24 or 48 h (baseline secretory rate at 2.8 mM glucose: 37.1 ± 4.8 ng/mg of protein in 1 h). *P < 0.05, **P < 0.01, ***P < 0.001 vs. control at 2.8 mM glucose; #P < 0.05, ##P < 0.01 vs. control at 22.2 mM glucose; n.s. not significant (1-way ANOVA followed by Bonferroni test, n = 4).

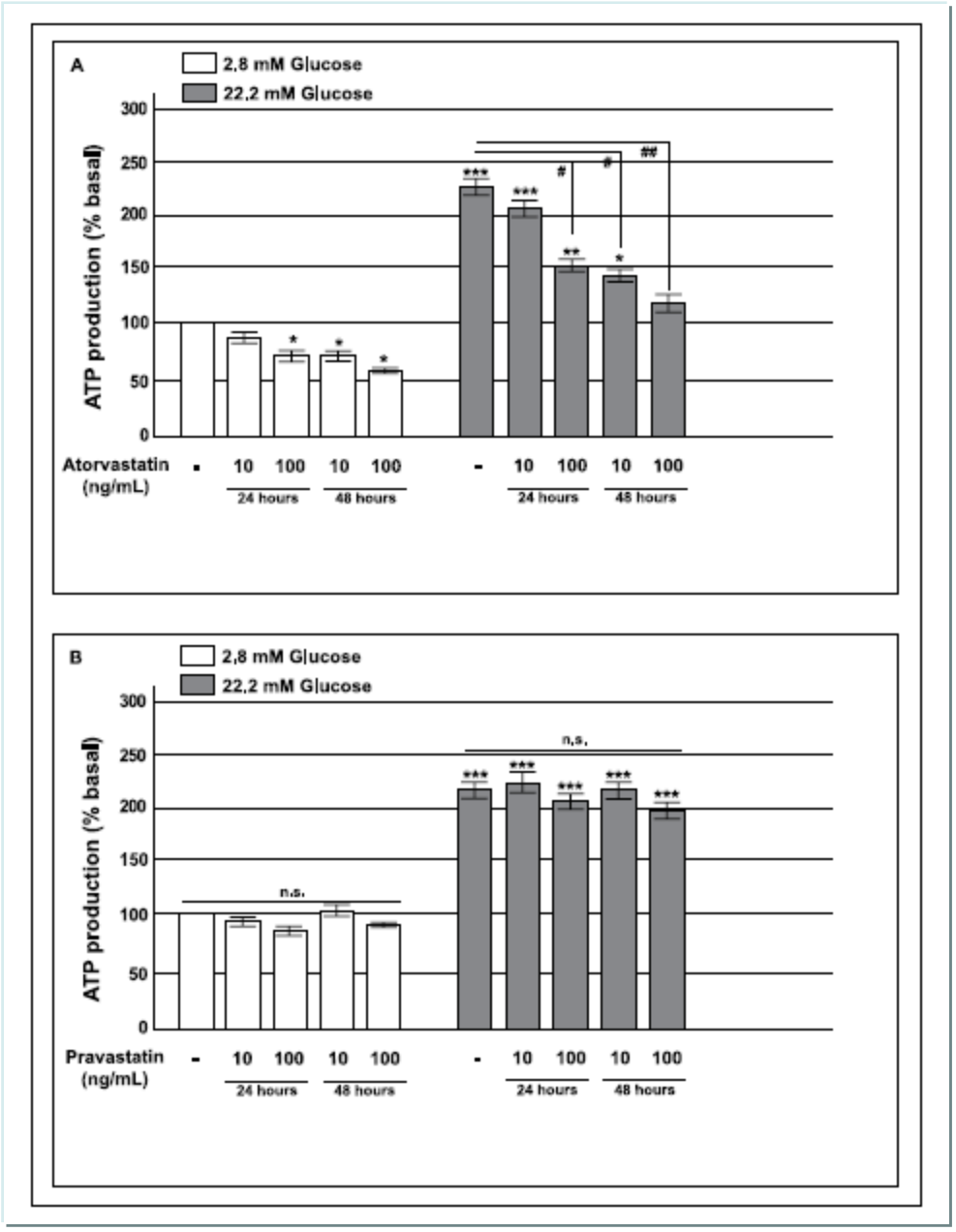


Figure 3. Effect of atorvastatin and pravastatin on glucose-induced ATP synthesis in INS-1 cells. Panel A: acute glucose-induced ATP production in control cells and in cells pre-exposed to 10 or 100 ng/mL of atorvastatin for 24 or 48 h; Panel B: acute glucose-induced ATP production in INS-1 cells pre-exposed to 10 or 100 ng/ mL of pravastatin for 24 or 48 h. *P < 0.05, **P < 0.01, ***P < 0.001 vs. control at 2.8 mM glucose; #P < 0.05, ##P < 0.01 vs. control at 22.2 mM glucose; n.s. not significant (1-way ANOVA followed by Bonferroni test, n = 4).

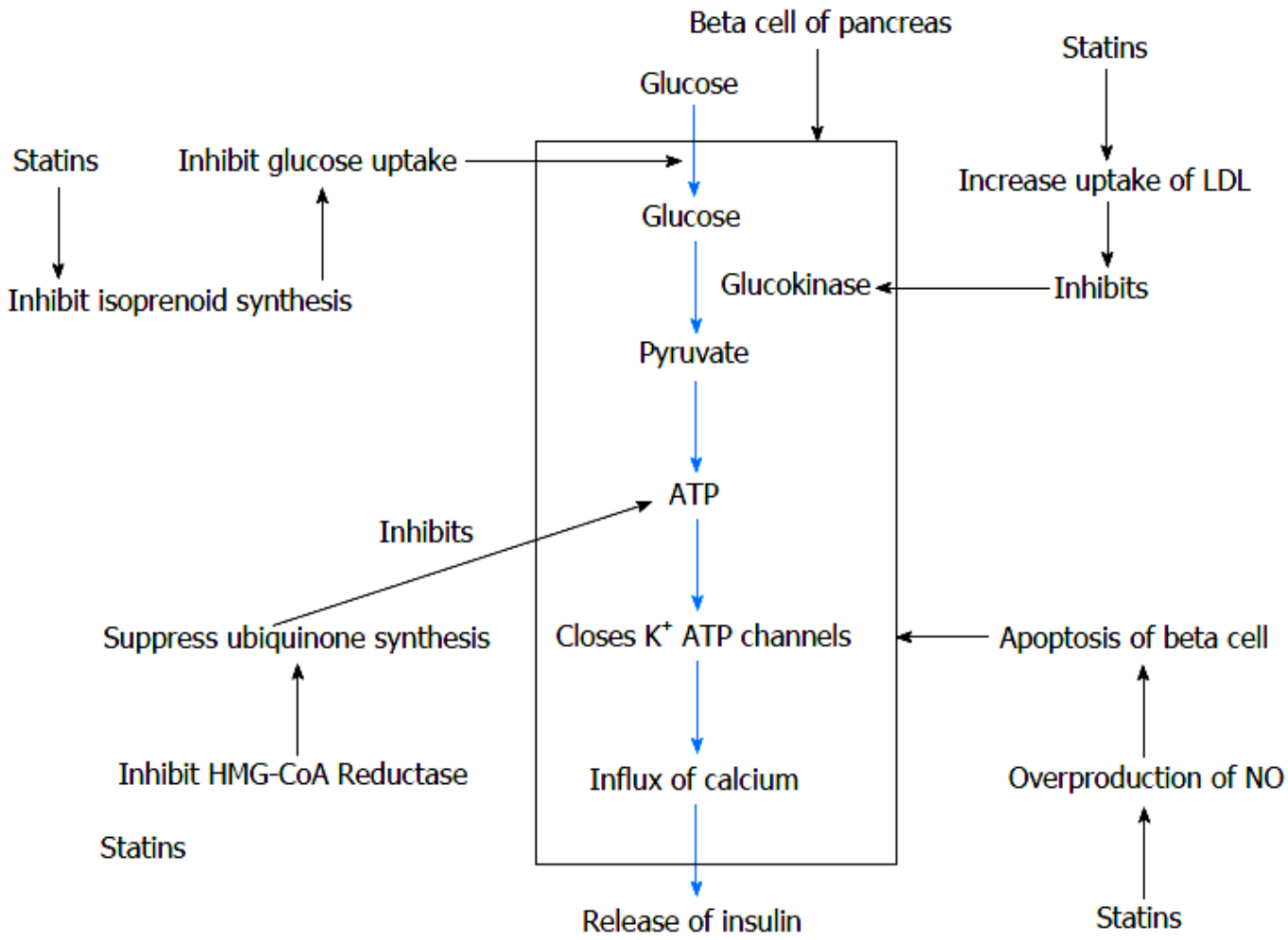


Figure 1 Actions of statins on beta cell of pancreas[43]. HMG-CoA: 3-hydroxy-methylglutaryl coenzyme A; NO: Nitric oxide; LDL: Low density lipoprotein.

Potential Mechanisms

Previously Examined with Inconsistent Results

β-cell dysfunction	▪ Decreased insulin secretion, due to reduced ubiquinone and delayed ATP production ▪ Apoptosis, islet inflammation
Insulin Resistance	▪ Statin-induced myopathy and ensuing peripheral insulin resistance, diminished glucose uptake ▪ Hepatic insulin resistance
Adipocyte Signaling and Function	▪ Isoprenoid depletion causing reduced glucose uptake in adipocytes ▪ Decreased adiponectin levels with some but not all statins
Change in Body Composition	▪ Increase total adiposity ▪ Increase in visceral fat

輔酶

Table 1
Statin use and risk of T2DM: individual risk factors assessment.

Score calculation (0–4) (*Water and coll.* [34,39])
Fasting plasma glucose >100 mg/dl
Plasma triglycerides >150 mg/dl
Body mass index >30 kg/m^2
Arterial hypertension
Additional features
Familial history of T2DM
Female gender
Older age (especially with high-dose statins)
Asian ethnicity
Duration of statin treatment
Concomitant diabetogenic medications
Polycystic ovary syndrome

HR for incident T2DM increased in parallel with the score

The FDA Safety Information and Adverse Event Reporting Program

Statin Drugs - Drug Safety Communication: Class Labeling Change

[Posted 02/28/2012]

最近美國食品藥物管理局於回顧statin 類藥品之上市後安全資訊及多個臨床試驗結果報告，作出以下建議(1)肝功能監測：病人於開始使用statin 前，需監測肝功能指數，服藥期間若出現疑似肝功能異常之臨床症狀時，需再次檢測肝功能指數；(2)於仿單中新增不良事件訊息：部分報告顯示，該類藥品可能導致非嚴重且停藥後可恢復之可逆性認知障礙（例如失憶、混亂），及些微增加血糖及糖化血色素(HbA1c)上升之風險；惟美國食品藥物管理局認為該類藥品對心血管之臨床效益仍高於些微血糖上升之風險 (3) lovastatin 藥物交互作用：lovastatin 併用CYP3A4 抑制劑藥品時會產生交互作用，而提高橫紋肌溶解症之不良反應風險。

Statin Myopathy

- The most common causally related adverse effect of statins is **myopathy.**

- Even without myopathic symptoms, simvastatin 40 mg daily **impaired adaptation to exercise training** and **muscle mitochondrial content** in participants with metabolic syndrome. **J Am Coll Cardiol.2013;62:709–714.**

  即使沒有肌病症狀， 適應運動訓練和肌肉線粒體含量受損

- In real-world practice, **myalgias and cramps** are more common than estimated from clinical trials; 肌痛和痙攣更常見

  - a cardiology clinic in the Netherlands, **one-third** of p’ts reported such problems. **Curr Med Res Opin. 2012;28:1247–1252.**

Discontinuation of statin therapy due to muscular side effects: A survey in real life

Nutrition, Metabolism & Cardiovascular Diseases (2012) xx, 1–5

Abstract *Backgrounds and aims:* To assess the burden of statin related muscular symptom in real life.

Methods and results: We conducted a wide survey on 10,409 French subjects. Among these, 2850 (27%) had hypercholesterolemia and 1074 were treated with statins. Muscular symptoms were reported by 104 (10%) statin treated patients and led to discontinuation in 30% of the symptomatic patients. The main prescribed statins were low doses rosuvastatin, atorvastatin and simvastatin. Pains were the most commonly described symptoms (87%) but many patients also reported stiffness (62%), cramps (67%), weakness or a loss of strength during exertion (55%). Pain was localized in 70% but mostly described as affecting several muscular groups. Approximately 38% of patients reported that their symptoms prevented even moderate exertion during everyday activities, while 42% of patients suffered major disruption to their everyday life.

Conclusion: Muscular symptoms associated with average dosage statin therapy are more frequent than in clinical trials and have a greater impact on patients' life than usually thought.

Muscular Symptoms are severer than expected…

A Survey of the FDA's AERS Database Regarding Muscle and Tendon Adverse Events Linked to the Statin Drug Class

Keith B. Hoffman et. al., PLOS ONE 7(8): e42866. doi:10.1371/journal.pone.0042866

Keith B. Hoffman[1], Christina Kraus[1], Mo Dimbil[1], Beatrice A. Golomb[2,3]*

1 AdverseEvents, Inc., Healdsburg, California, United States of America, 2 Department of Medicine, University of California San Diego, La Jolla, California, United States of America, 3 Department of Family and Preventive Medicine, University of California San Diego La Jolla, California, United States of America

Abstract

Background: Cholesterol management drugs known as statins are widely used and often well tolerated; however, a variety of muscle-related side effects can arise. These adverse events (AEs) can have serious impact, and form a significant barrier to therapy adherence. Surveillance of post-marketing AEs is of vital importance to understand real-world AEs and reporting differences between individual statin drugs. We conducted a review of post-approval muscle and tendon AE reports in association with statin use, to assess differences within the drug class.

Methods: We analyzed all case reports from the FDA AE Reporting System (AERS) database linking muscle-related AEs to statin use (07/01/2005–03/31/2011). Drugs examined were: atorvastatin, simvastatin, lovastatin, pravastatin, rosuvastatin, and fluvastatin.

Results: Relative risk rates for rosuvastatin were consistently higher than other statins. Atorvastatin and simvastatin showed intermediate risks, while pravastatin and lovastatin appeared to have the lowest risk rates. Relative risk of muscle-related AEs, therefore, approximately tracked with per milligram LDL-lowering potency, with fluvastatin an apparent exception. Incorporating all muscle categories, rates for atorvastatin, simvastatin, pravastatin, and lovastatin were, respectively, 55%, 26%, 17%, and 7.5% as high, as rosuvastatin, approximately tracking per milligram potency (Rosuvastatin>Atorvastatin>Simvastatin>Pravastatin≈Lovastatin) and comporting with findings of other studies. Relative potency, therefore, appears to be a fundamental predictor of muscle-related AE risk, with fluvastatin, the least potent statin, an apparent exception (risk 74% vs rosuvastatin).

Interpretation: AE reporting rates differed strikingly for drugs within the statin class, with relative reporting aligning substantially with potency. The data presented in this report offer important reference points for the selection of statins for cholesterol management in general and, especially, for the rechallenge of patients who have experienced muscle-related AEs (for whom agents of lower expected potency should be preferred).

TABLE 2

Factors that increase risk of statin-associated myopathy

- Age > 70 (women at higher risk than men)
- Frailty and small body frame
- Multisystem disease (eg, chronic renal insufficiency, heart failure)
- Solid organ transplant recipients
- Polypharmacy
- Perioperative period
- Specific concomitant medications
  - Fibrates (especially gemfibrozil)
  - Nicotinic acid (rarely)
  - Cyclosporine
  - Azole antifungals (itraconazole and ketoconazole)
  - Macrolide antibiotics (erythromycin and clarithromycin)
  - Protease inhibitors (for human immunodeficiency virus infection)
  - Nefazodone
  - Verapamil
  - Amiodarone
  - Large quantities of grapefruit juice (usually more than 1 quart per day)
  - Alcohol abuse

ADAPTED FROM DATA FROM PASTERNAK RC, SMITH SC JR, BAIREY-MERZ CN, GRUNDY SM, CLEEMAN JI, LENFANT C. ACC/AHA/NHLBI CLINICAL ADVISORY ON THE USE AND SAFETY OF STATINS. STROKE 2002; 33:2337–2341.

CLEVELAND CLINIC JOURNAL OF MEDICINE 2005.

Prevalence of potentially severe drug-drug interactions in ambulatory patients with dyslipidaemia receiving HMG-CoA reductase inhibitor therapy.

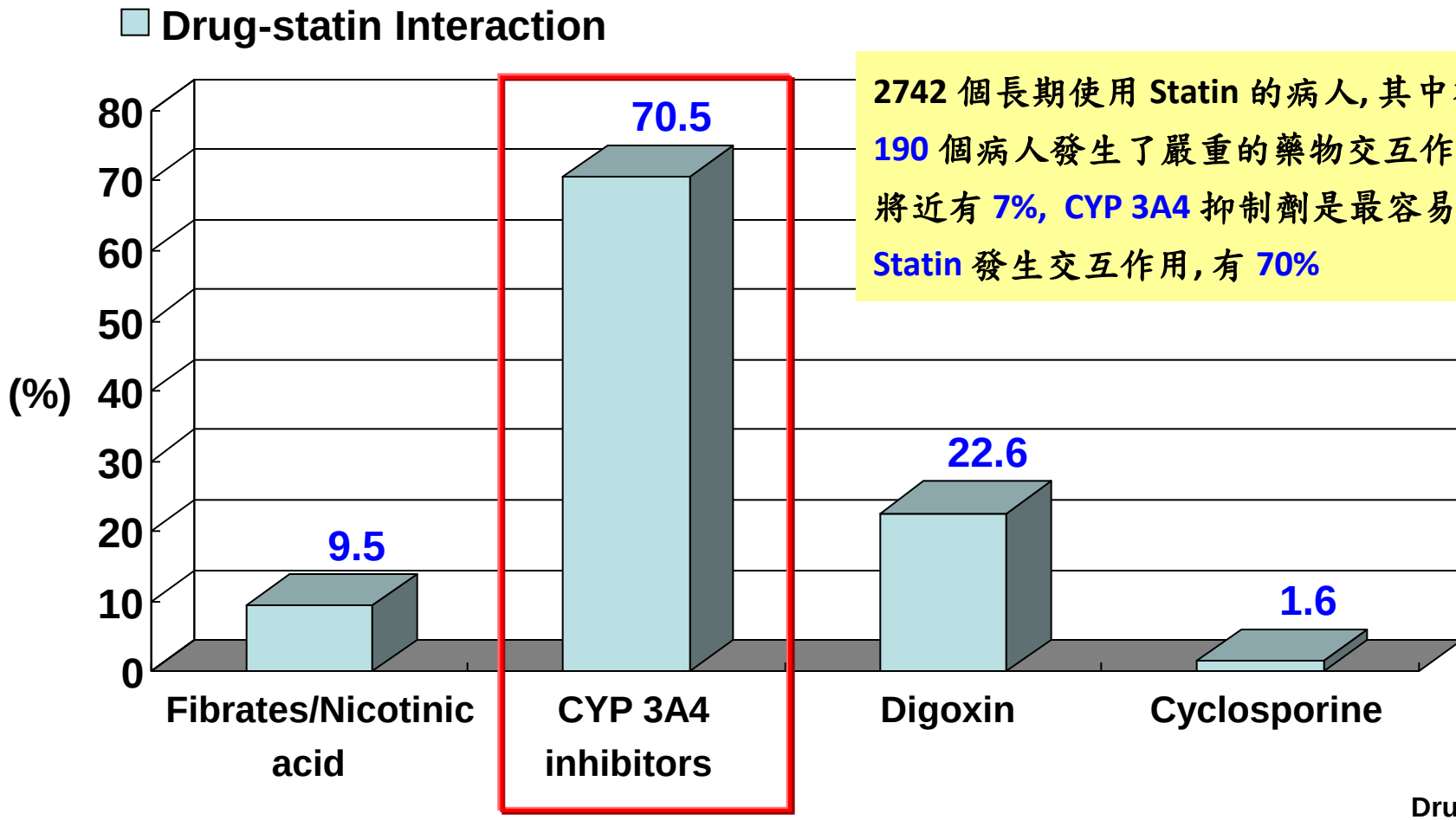
(Drug Saf. 2005;28(3):263-75.)

2005年 Drug Safety發表的一篇有關 Statin-Drug interaction的paper,

探討了市場上主要的 Statin 臨床上發生藥物交互作用的情形,

Result

190 p’ts **(6.9%)** had a total of 198 potentially harmful drug-statin interactions from **2742** ambulatory statin-treated patients



2742 個長期使用 Statin 的病人, 其中有 190 個病人發生了嚴重的藥物交互作用, 將近有 7%, CYP 3A4 抑制劑是最容易與 Statin 發生交互作用, 有 70%

Drug Saf. 2005.

Conclusion

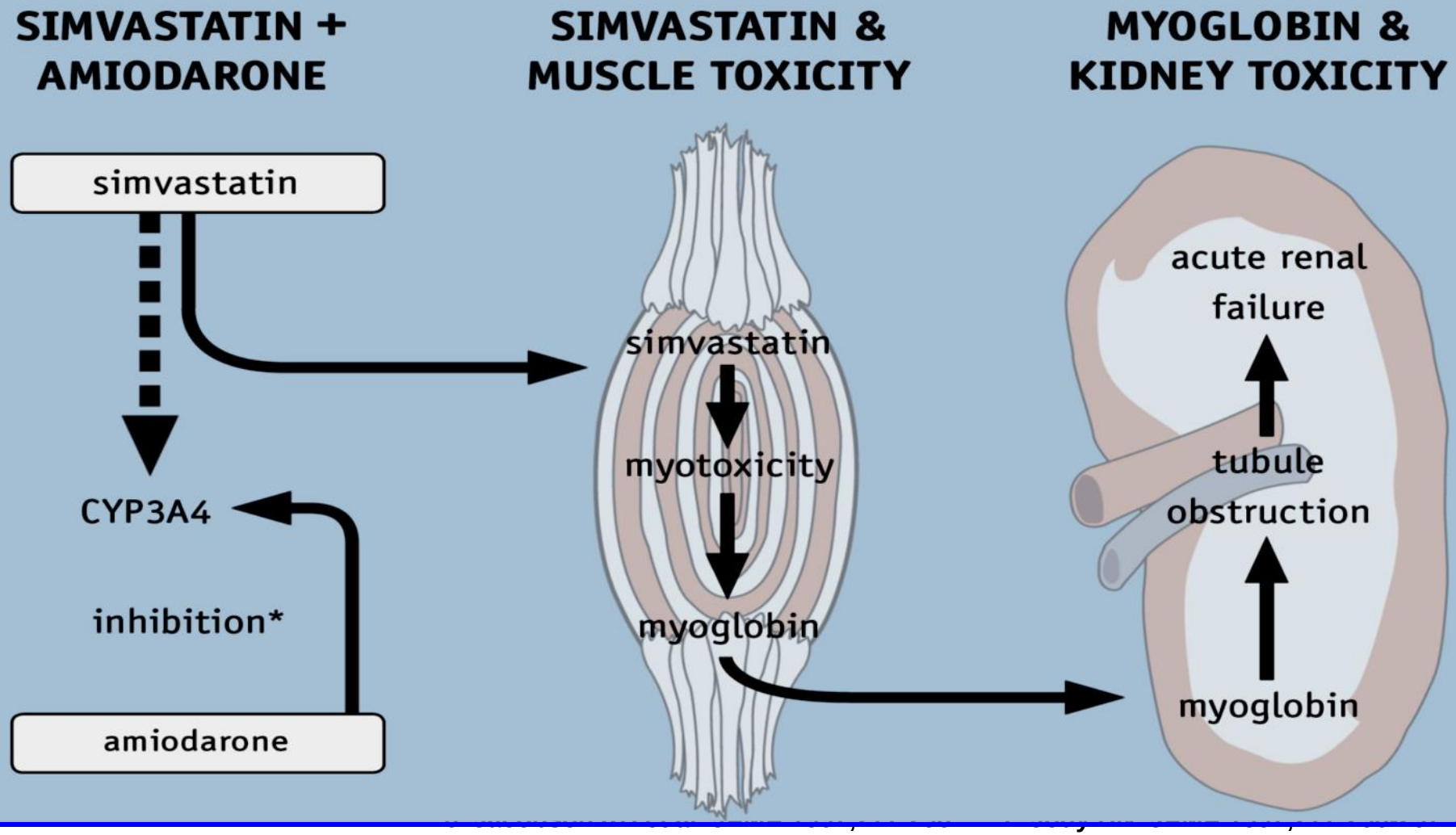
- As the risk for developing **rhabdomyolysis** is increased in patients with drug-statin interactions
- **CYP3A4 inhibitors** are the most frequent cause of potential drug interactions with statins.
- Clinicians should be aware of the most frequently observed drug-statin interactions and how these interactions can be avoided.

ILLUSTRATION 1

Amiodarone-Simvastatin Interaction

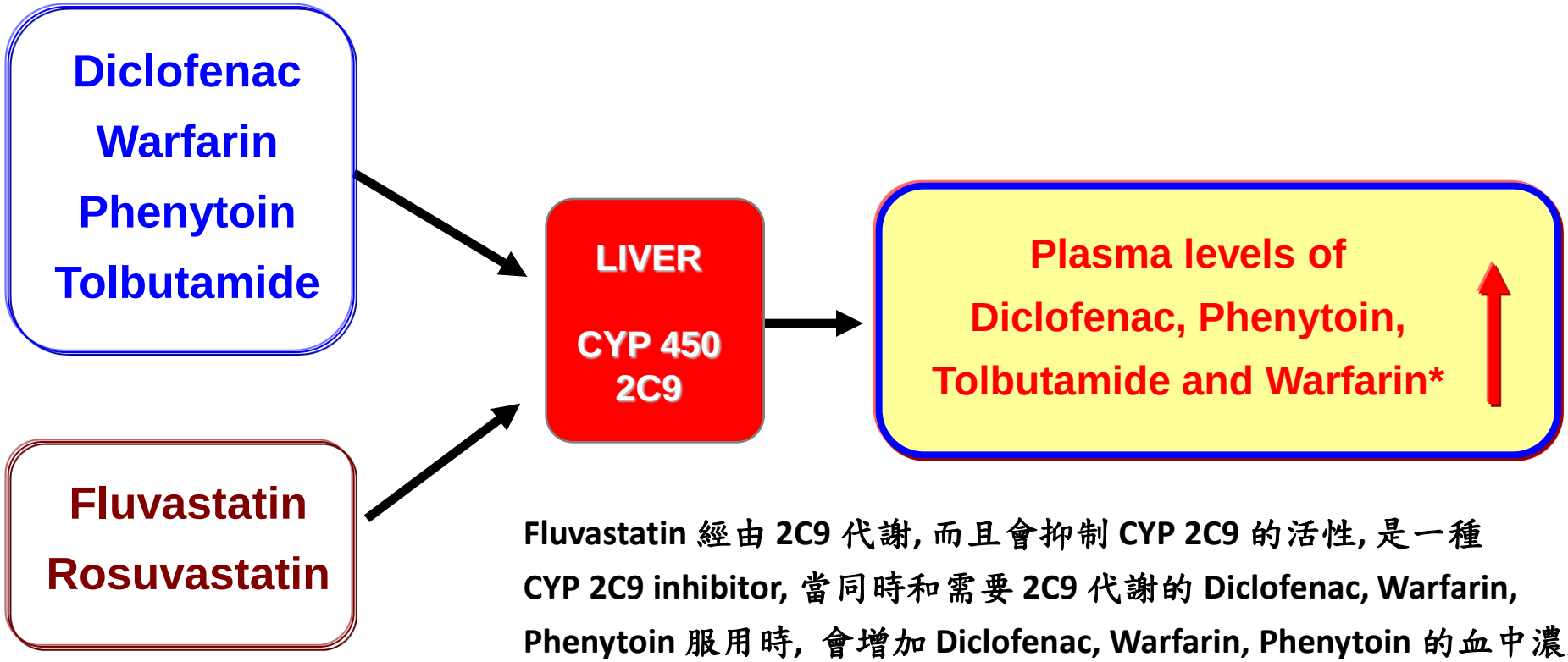
Postulated Mechanism

FDA Drug Safety News letter 2008.



Segaert MF et al. Reactions 1996;622:10-11. 9. FDA report 1997.

CYP2-C9 Mediated Drug Interactions



Fluvastatin 經由 2C9 代謝, 而且會抑制 CYP 2C9 的活性, 是一種 CYP 2C9 inhibitor, 當同時和需要 2C9 代謝的 Diclofenac, Warfarin, Phenytoin 服用時, 會增加 Diclofenac, Warfarin, Phenytoin 的血中濃度, 增加病人出血的危險

*Transon et al. Clin Pharmacol Ther 1995;58:412-7. *Transon et al. Eur J Clin Pharmacol 1996;50:209-15. *Rosuvasatin 仿單

Table 2. Pharmacokinetic properties of statins

	Pitavastatin	Atorvastatin	Rosuvastatin	Simvastatin	Pravastatin	Fluvastatin
Half life (hours)	12	15-30	19	2-3	1.3-2.8	0.5-2.3
Bioavilability (%)	60	12	20	5	18	19-29
Protein binding (%)	> 99	80-90	88	94-98	43-55	> 99
Solubility	Lipophilic	Lipophilic	Hydrophilic	Lipophilic	Hydrophilic	Lipophilic
Metabolism (cytochrome P450)	CYP2C9	CYP3A4	CYP2C9	CYP3A4, 3A5	-	CYP2C9
Urinary excretion (%)	< 2	2	10	13	20	6
Faecal excretion (%)	80	70	90	58	71	90
Common drug interactions (increase toxicity risk)	Diclofenac Amiodarone Azole antifungals Protease inhibitors Metroniadazole Gemfibrozil	Amiodarone Grapefruit Juice Protease inhibitors Azole antifungals Macrolide antibiotics Verapamil Cyclosporin Sildenafil Tacrolimus Colchicine	Diclofenac Amiodarone Azole antifungals Protease inhibitors Metroniadazole Gemfibrozil	Amiodarone Grapefruit Juice Protease inhibitors Azole antifungals Macrolide antibiotics Verapamil Cyclosporin Sildenafil Tacrolimus Colchicine	Colchicine Gemfibrozil	Diclofenac Amiodarone Azole antifungals Protease inhibitors Metroniadazole Gemfibrozil

Statin-Drug Interaction

- Pharmacokinetic properties vary among the statins
- **Medications that increase the likelihood of drug interactions are often co-prescribed during the course of statin therapy**
- **Pravastatin** has a low potential for drug interactions with commonly prescribed drugs
- As with other drug therapy decisions, the potential for clinically **significant drug interactions must be considered when selecting long-term statin therapy**

The FDA Safety Information and Adverse Event Reporting Program

Statin Drugs - Drug Safety Communication: Class Labeling Change

[Posted 02/28/2012]

最近美國食品藥物管理局於回顧statin 類藥品之上市後安全資訊及多個臨床試驗結果報告，作出以下建議(1)肝功能監測：病人於開始使用statin 前，需監測肝功能指數，服藥期間若出現疑似肝功能異常之臨床症狀時，需再次檢測肝功能指數；(2)於仿單中新增不良事件訊息：部分報告顯示，該類藥品可能導致非嚴重且停藥後可恢復之可逆性認知障礙（例如失憶、混亂），及些微增加血糖及糖化血色素(HbA1c)上升之風險；惟美國食品藥物管理局認為該類藥品對心血管之臨床效益仍高於些微血糖上升之風險 (3) lovastatin 藥物交互作用：lovastatin 併用CYP3A4 抑制劑藥品時會產生交互作用，而提高橫紋肌溶解症之不良反應風險。

Considerations for Safe Use of Statins: Liver Enzyme Abnormalities and Muscle Toxicity

R. CLARK GILLETT, JR., MD, and ANGELICA NORRELL, PharmD, *Columbus Regional Healthcare System, The Medical Center, Columbus, Georgia*

Am Fam Physician. 2011;83(6):711-716.

Statins play an important role in the care of patients with cardiovascular disease and have a good safety record in clinical practice. The risk of hepatic injury caused by statins is estimated to be about 1 percent, similar to that of patients taking a placebo. Patients with transaminase levels no more than three times the upper limit of normal can continue taking statins; often the elevations will resolve spontaneously. Coexisting elevations of transaminase levels from nonalcoholic fatty liver disease and stable hepatitis B and C viral infections are not contraindications to statin use. Although myalgias are common with statin use, myositis and rhabdomyolysis are rare. When prescribed at one-half the recommended maximal dosage or less, statins are associated with an incidence of myopathy similar to that of placebo; therefore, routine monitoring of creatine kinase levels in asymptomatic patients is not recommended. Myopathic symptoms usually resolve approximately two months after discontinuing the statin, and the same statin can be restarted at a lower dosage, or patients can try a different statin. Clinically important drugs that interact with statins and increase the risk of adverse effects include fibrates, diltiazem, verapamil, and amiodarone. (*Am Fam Physician.* 2011;83(6):711-716. Copyright © 2011 American Academy of Family Physicians.)

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

HEPATOLOGY 2014;60:679-686.

Spectrum of Statin Hepatotoxicity: Experience of the Drug-Induced Liver Injury Network

The HMG-CoA reductase inhibitors (statins) are widely prescribed for patients with hyperlipidemia and are generally well tolerated. Mild elevations in serum aminotransferases arise in up to 3% of treated patients, but clinically apparent drug-induced liver injury is rare. The aim of this study is to report the presenting features and outcomes of 22 patients with clinically apparent liver injury due to statins. Among 1,188 cases of drug-induced liver injury enrolled between 2004 and 2012 in a prospective registry by the U.S. Drug Induced Liver Injury Network, 22 were attributed to a statin. All patients were evaluated in a standard fashion and followed for at least 6 months after onset. The median age was 60 years (range 41-80), and 15 (68%) were female. The latency to onset of liver injury ranged from 34 days to 10 years (median = 155 days). Median peak levels were alanine aminotransferase 892 U/L, alkaline phosphatase 358 U/L, and total bilirubin 6.1 mg/dL. Nine patients presented with cholestatic hepatitis and 12 patients presented with hepatocellular injury, of which six had an autoimmune phenotype. Nine patients were hospitalized, four developed evidence of hepatic failure, and one died. All commonly used statins were implicated. Four patients developed chronic liver injury, of which three had an autoimmune phenotype of liver injury. *Conclusion:* Drug-induced liver injury from statins is rare and characterized by variable patterns of injury, a range of latencies to onset, autoimmune features in some cases, and persistent or chronic injury in 18% of patients, most of whom have an autoimmune phenotype. (HEPATOLOGY 2014;60:679-686)

The FDA Safety Information and Adverse Event Reporting Program

Statin Drugs - Drug Safety Communication: Class Labeling Change

[Posted 02/28/2012]

最近美國食品藥物管理局於回顧statin 類藥品之上市後安全資訊及多個臨床試驗結果報告，作出以下建議(1)肝功能監測：病人於開始使用statin 前，需監測肝功能指數，服藥期間若出現疑似肝功能異常之臨床症狀時，需再次檢測肝功能指數；(2)於仿單中新增不良事件訊息：部分報告顯示，該類藥品可能導致非嚴重且停藥後可恢復之可逆性認知障礙（例如失憶、混亂），及些微增加血糖及糖化血色素(HbA1c)上升之風險；惟美國食品藥物管理局認為該類藥品對心血管之臨床效益仍高於些微血糖上升之風險 (3) lovastatin 藥物交互作用：lovastatin 併用CYP3A4 抑制劑藥品時會產生交互作用，而提高橫紋肌溶解症之不良反應風險。

Remembering Statins: Do Statins Have Adverse Cognitive Effects?

Diabetes Care 2016;39(Suppl. 2):S253–S259 | DOI: 10.2337/dcS15-3022

The issue of statin-associated cognitive impairment has been a hot topic among both patients and health care providers, especially since the U.S. Food and Drug Administration (FDA) issued a statement regarding rare postmarketing reports of ill-defined cognitive impairment associated with statin use. This statement was based on case reports, and no objective measures of cognitive function were used. Nevertheless, many patients at high risk of cardiovascular disease have expressed concerns about possible cognitive decline and may have opted to forgo statin therapy. In this overview, the evidence leading to the statement by the FDA is reviewed. Potential mechanisms of the effect of LDL cholesterol reduction and statin therapy on cognition are discussed. Evidence from observational and prospective randomized trials is summarized, leading to the conclusion that as for now, there is no good evidence that statins cause cognitive impairment to a significant degree. Reported cases seem to be rare, and a causal relationship has not been established.

New Clinical Evidence
--Primary prevention in Asian

在亞洲所進行的大型 **Primary prevention, MEGA study,**
第一個針對亞洲人種所做的研究,

MEGA = Management of Elevated cholesterol in the primary prevention Group of Adult Japanese.

H. Nakamura, Lancet 2006 .

Entry Criteria

- **Inclusion Criteria:**

  TC **220-270 mg/dL**

  Age Men 40-70 yrs

  Women postmenopause - 70 yrs

  Weight ≥ 40 kg (88 pounds)

- **Major Exclusion Criteria:**

  Familial hypercholesterolemia

  History of **CHD, stroke, TIA and ASO**

  History of **cancer**

  History of serious liver or kidney disease

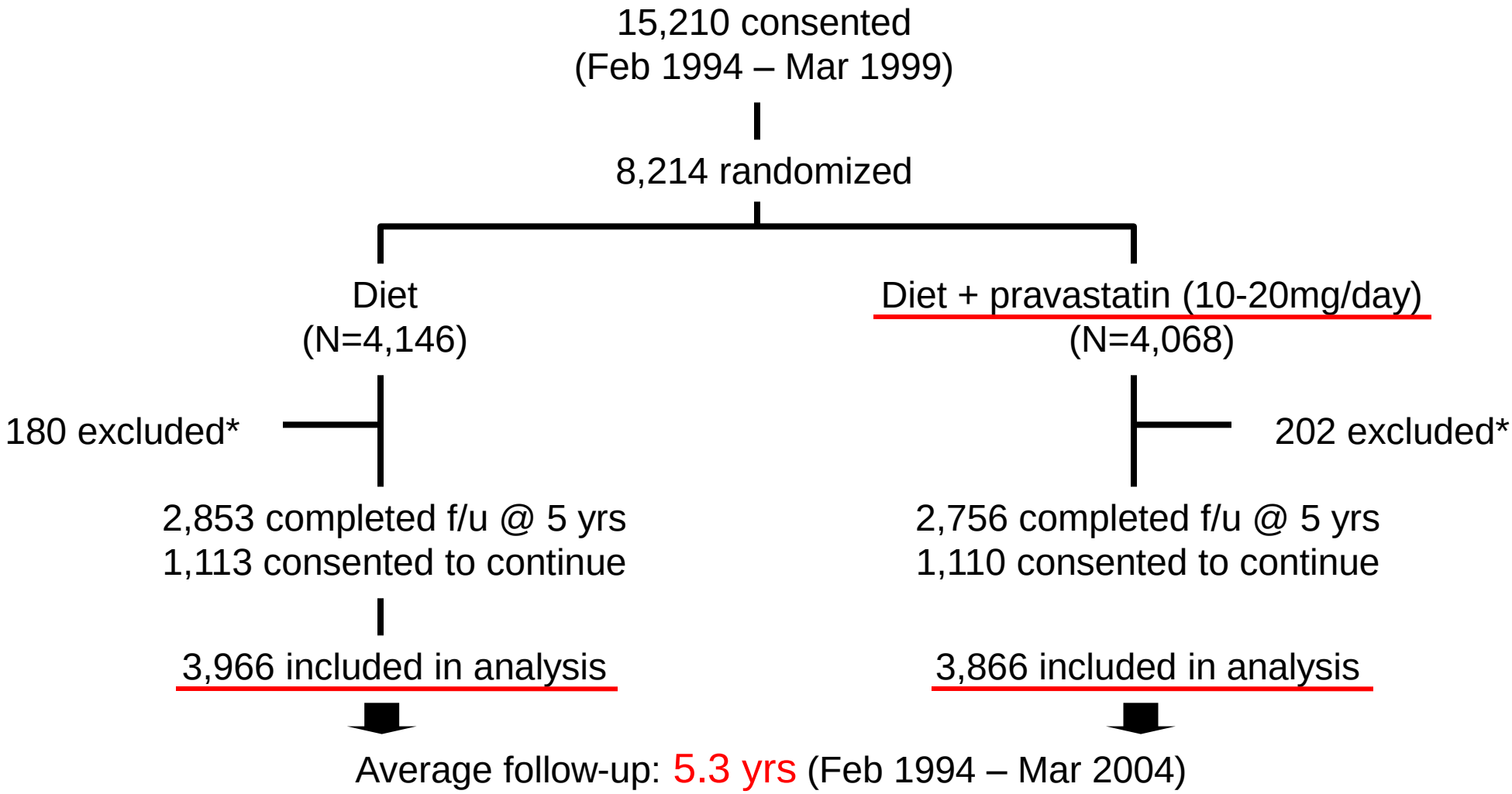
  Secondary hypercholesterolemia

對輕度升高膽固醇沒有動脈粥樣硬化的日本患者,
評估以 Pravastatin降低膽固醇對心血管疾病的發病率

MEGA study 收的病人血脂較低
primary prevention 的研究,
有任何心血管腦血管病史的病人也排除

H. Nakamura, Lancet 2006 .

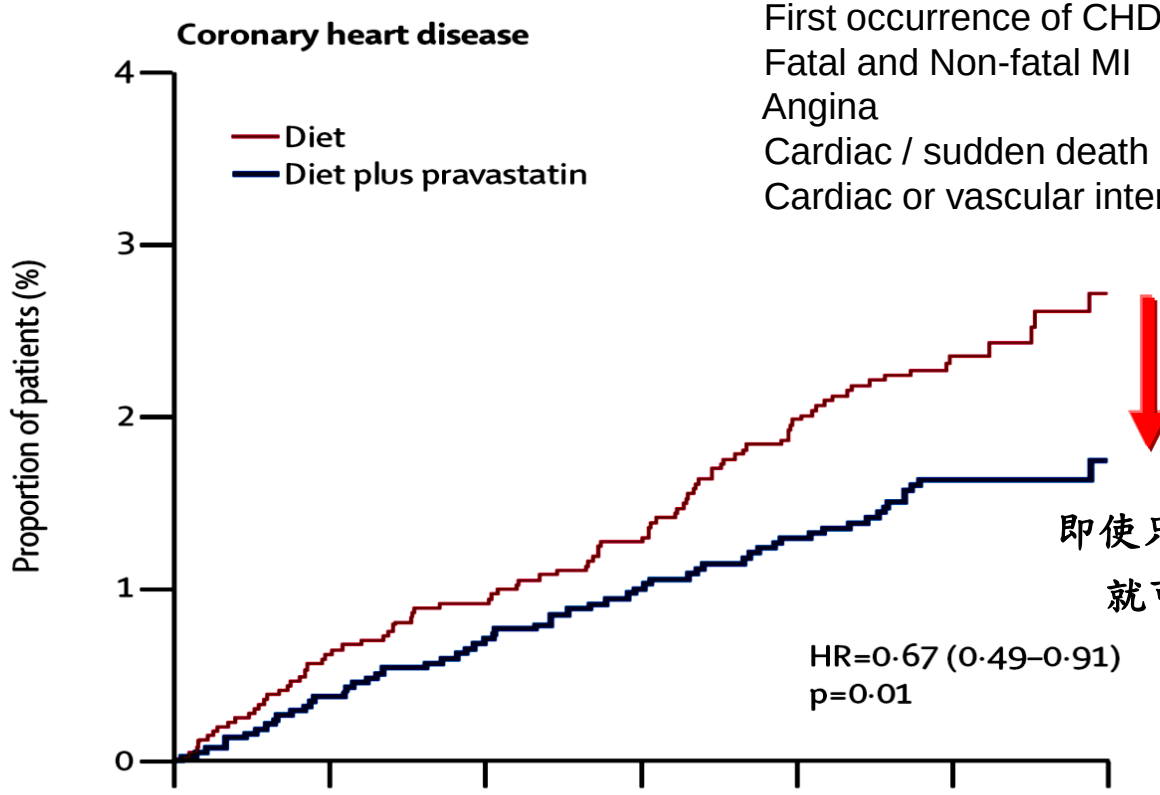
Flowchart



*Excluded patients were selected under blinding, based on information of pre-randomization by data reviewing committee before end of study.

H. Nakamura, Lancet 2006.

Primary Endpoint



First occurrence of CHD :
Fatal and Non-fatal MI
Angina
Cardiac / sudden death
Cardiac or vascular intervention

即使只使用 **10-20 mg** 的 **Mevalotin**
就可以降低 **33%** 的相對危險

Number at risk							
Diet	3966	3758	3648	3529	3430	2476	830
Diet plus pravastatin	3866	3642	3490	3385	3307	2434	859

H. Nakamura, Lancet 2006 .

Side Effects

	Diet (N=3,966)	Diet+ pravastatin (N=3,866)
	No. (%)	
Serious Adverse Events	395 (10.0)	404 (10.5)
ALT >100 IU	107 (2.8)	104 (2.8)
CK > 500 IU	98 (2.6)	111 (3.1)
Rhabdomyolysis	0	0

嚴重的副作用,肝功能,肌肉問題, Mevalotin 都呈現和安慰季一樣的安全,

在橫紋肌溶解症也完全沒有病例

H. Nakamura, Lancet 2006 .

Lipoproteins and CHD Risk in Primary Prevention Trials

Trials	LDL-C		HDL-C		CHD relative risk reduction (RRR)
	Pre	Post	Pre	Post	
	mg/dL, (% change)				
*WOSCOPS	192	142 (-26)	44	46 (+5)	-31
AFCAPS/TexCAPS	150	115 (-25)	36	39 (+6)	-37
†ASCOT-LLA	133	87 (-35)	51	50 (0)	-36
†CARDS	118	71 (-40)	54	55 (1)	-37
MEGA	157	128 (-18)	58	60 (+6)	-33

MEGA使用10-20mg 的 mevalotin, 大部分病人只有使用 10mg 的劑量,
降血脂的能力較低世, 但 33% 的 CV event 下降, 和其他的研究結果差不多,
降血脂的多寡, 和心血管事件的預防, 並不是呈現絕對正比的關係,

* Post /Pre LDL-C and HDL-C values was calculated by % change.

† To convert mmol/L into mg/dL , 38.7 was multiplied in LDL-C and HDL-C values.

H. Nakamura, Lancet 2006 .

Table 2. The change of LDL-C levels after 6 months of statin treatment

Variable	Atorvastatin		Rosuvastatin		Pitavastatin 2 mg	Pravastatin 40 mg	Total
	10 mg	20 mg	5 mg	10 mg			
LDL-C baseline, mg/dL	134.0±28.2	142.3±33.0	136.3±31.0	143.8±35.6	121.6±20.8	130.1±18.5	134.8±29.4
LDL-C after 6 months, mg/dL	84.0±26.9[a]	75.4±18.3[a]	71.7±17.3[a]	69.4±24.0[a]	74.7±16.0[a]	79.0±20.9[a]	75.9±21.3[a]
LDL-C change after 6 months, mg/dL	–61.5 (–77.0 to –37.8)	–67.0 (–94.0 to –37.0)	–73.0 (–90.5 to –50.0)	–84.0 (–97.5 to –65.0)	–51.0 (–64.0 to –35.0)	–56.0 (–67.0 to –38.0)	–63.0 (–83.0 to –40.0)
LDL-C change after 6 months, %	–44.1 (–52.6 to –36.6)	–48.2 (–56.6 to –35.5)	–51.6 (–59.5 to –37.3)	–56.0 (–62.5 to –45.2)	–41.7 (–49.1 to –29.2)	–42.4 (–50.7 to –31.0)	–47.4 (–56.6 to –34.1)
30%–50% LDL-C decreased	28 (46.7)	18 (31.0)	22 (36.7)	10 (16.7)	29 (50.9)	29 (48.3)	136 (38.3)
LDL-C decreased >50%	20 (33.3)	28 (48.3)	33 (55.0)	42 (70.0)	11 (19.3)	16 (26.7)	150 (42.3)
LDL-C <100 mg/dL	49 (81.7)	54 (93.1)	57 (95.0)	57 (95.0)	55 (96.5)	55 (91.7)	327 (92.1)

Values are presented as mean±standard deviation, median (interquartile range), or number (%).
LDL-C, low density lipoprotein cholesterol.
[a]For $P<0.05$ with paired t-test between data of baseline and after 6 months.

OPEN

Long-Term Safety and Efficacy of Lowering Low-Density Lipoprotein Cholesterol With Statin Therapy

20-Year Follow-Up of West of Scotland Coronary Prevention Study

Background—Extended follow-up of statin-based low-density lipoprotein cholesterol lowering trials improves the understanding of statin safety and efficacy. Examining cumulative cardiovascular events (total burden of disease) gives a better appreciation of the clinical value of statins. This article evaluates the long-term impact of therapy on mortality and cumulative morbidity in a high-risk cohort of men.

Methods and Results—The West of Scotland Coronary Prevention Study was a primary prevention trial in 45- to 64-year-old men with high low-density lipoprotein cholesterol. A total of 6595 men were randomized to receive pravastatin 40 mg once daily or placebo for an average of 4.9 years. Subsequent linkage to electronic health records permitted analysis of major incident events over 20 years. Post trial statin use was recorded for 5 years after the trial but not for the last 10 years. Men allocated to pravastatin had reduced all-cause mortality (hazard ratio, 0.87; 95% confidence interval, 0.80–0.94; P=0.0007), attributable mainly to a 21% decrease in cardiovascular death (hazard ratio, 0.79; 95% confidence interval, 0.69–0.90; P=0.0004). There was no difference in noncardiovascular or cancer death rates between groups. Cumulative hospitalization event rates were lower in the statin-treated arm: by 18% for any coronary event (P=0.002), by 24% for myocardial infarction (P=0.01), and by 35% for heart failure (P=0.002). There were no significant differences between groups in hospitalization for noncardiovascular causes.

Conclusion—Statin treatment for 5 years was associated with a legacy benefit, with improved survival and a substantial reduction in cardiovascular disease outcomes over a 20-year period, supporting the wider adoption of primary prevention strategies.

(***Circulation***. **2016;133:1073-1080. DOI: 10.1161/CIRCULATIONAHA.115.019014.**)

Table 1. Number of Events and HRs for Pravastatin Treatment Effect for Mortality Outcomes

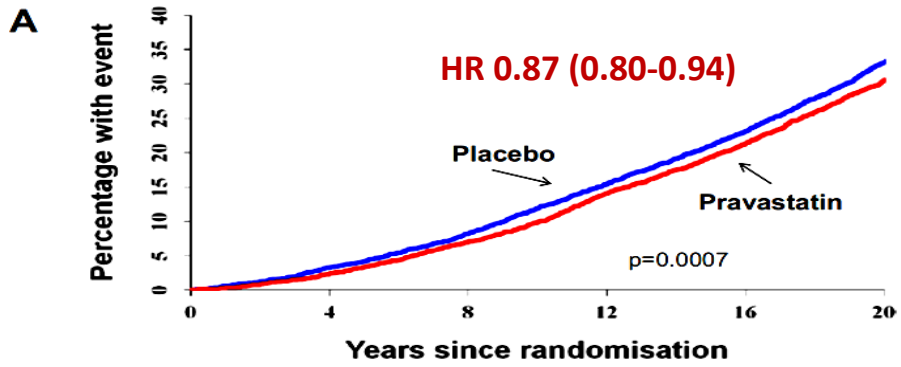
	Placebo (n=3293)	Pravastatin (n=3302)
All causes		
Deaths, n (%)	1253 (38.0)	1145 (34.7)
HR (95% CI)*		0.87 (0.80–0.94)
P value*		0.0007
All cardiovascular		
Deaths, n (%)	496 (15.1)	414 (12.5)
HR (95% CI)*		0.79 (0.69–0.90)
P value*		0.0004
CHD		
Deaths, n (%)	326 (9.9)	252 (7.6)
HR (95% CI)*		0.73 (0.62–0.86)
P value*		0.0002
Stroke		
Deaths, n (%)	86 (2.6)	103 (3.1)
HR (95% CI)*		1.15 (0.86–1.53)
P value*		0.35
All noncardiovascular		
Deaths, n (%)	757 (23.0)	731 (22.1)
HR (95% CI)*		0.92 (0.83–1.02)
P value*		0.12
Cancer		
Deaths, n (%)	469 (14.2)	468 (14.2)
HR (95% CI)†		0.96 (0.84–1.09)
P value†		0.49

CHD indicates coronary heart disease; CI, confidence interval; and HR, hazard ratio.

*Adjusted for age, body mass index, systolic and diastolic blood pressures, high- and low-density lipoprotein cholesterol, log triglycerides, nitrate use, history of angina, history of diabetes mellitus, history of hypertension, smoking status (current, ex-smoker, never), and deprivation (Carstairs category).

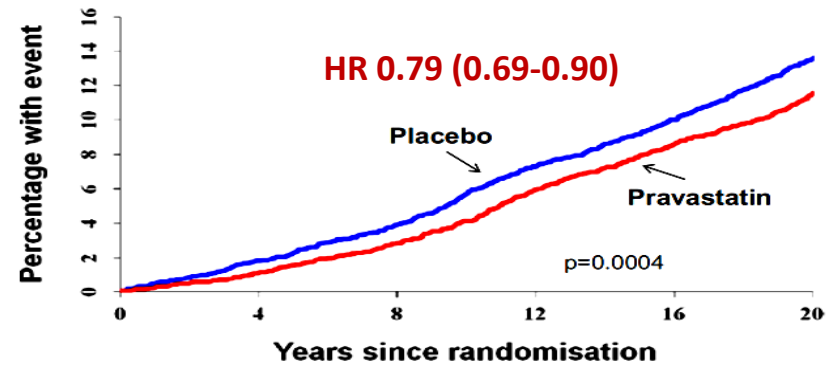
†Adjusted for age, body mass index, smoking status (current, ex-smoker, never), and deprivation (Carstairs category).

(A) all causes



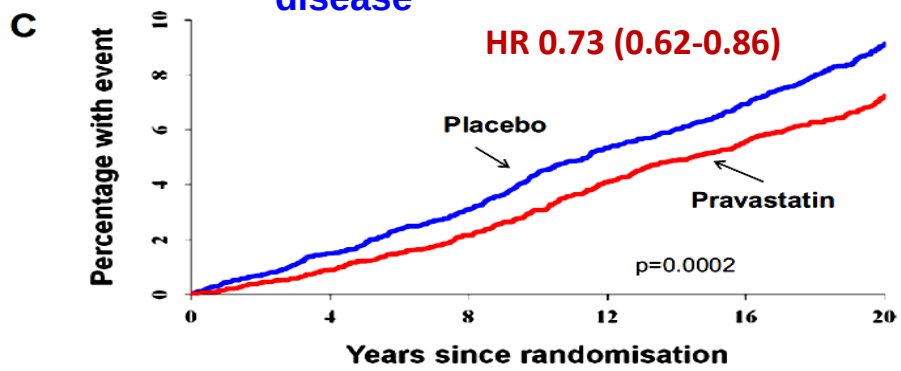
Numbers at risk:						
Placebo	3293	3185	3021	2785	2501	2203
Pravastatin	3302	3223	3069	2838	2598	2295

(B) cardiovascular disease



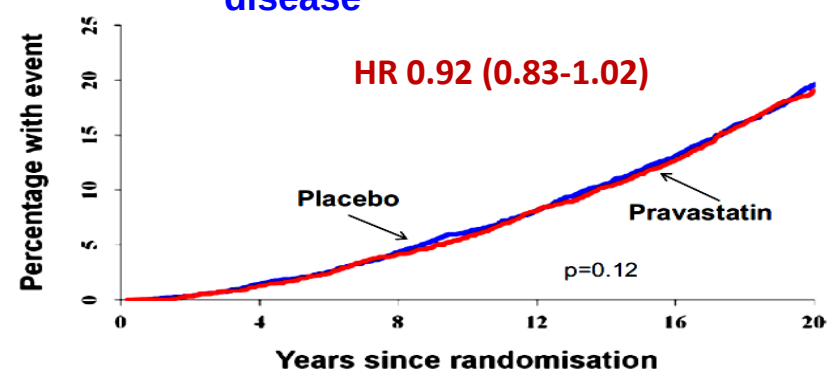
Numbers at risk:						
Placebo	3293	3185	3021	2785	2501	2203
Pravastatin	3302	3223	3069	2838	2598	2295

(C) coronary heart disease



Numbers at risk:						
Placebo	3293	3185	3021	2785	2501	2203
Pravastatin	3302	3223	3069	2838	2598	2295

(D) noncardiovascular disease



Numbers at risk:						
Placebo	3293	3185	3021	2785	2501	2203
Pravastatin	3302	3223	3069	2838	2598	2295

Figure 1. Cumulative events over the 20-year follow-up period. Cumulative incidence functions are provided for the outcomes of death resulting from (**A**) all causes, (**B**) cardiovascular disease, (**C**) coronary heart disease, and (**D**) noncardiovascular disease. *P* values were determined by Cox proportional hazards model.

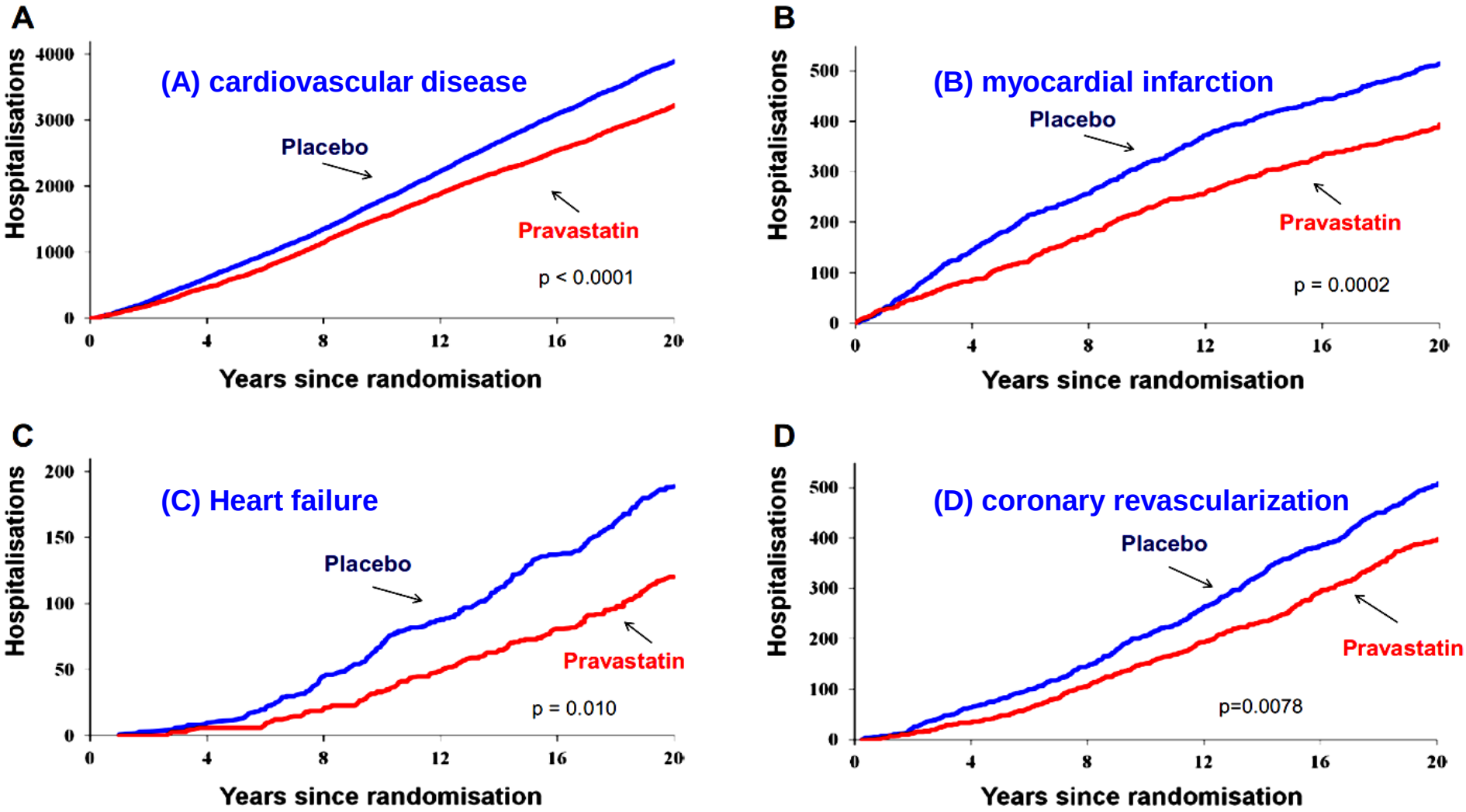


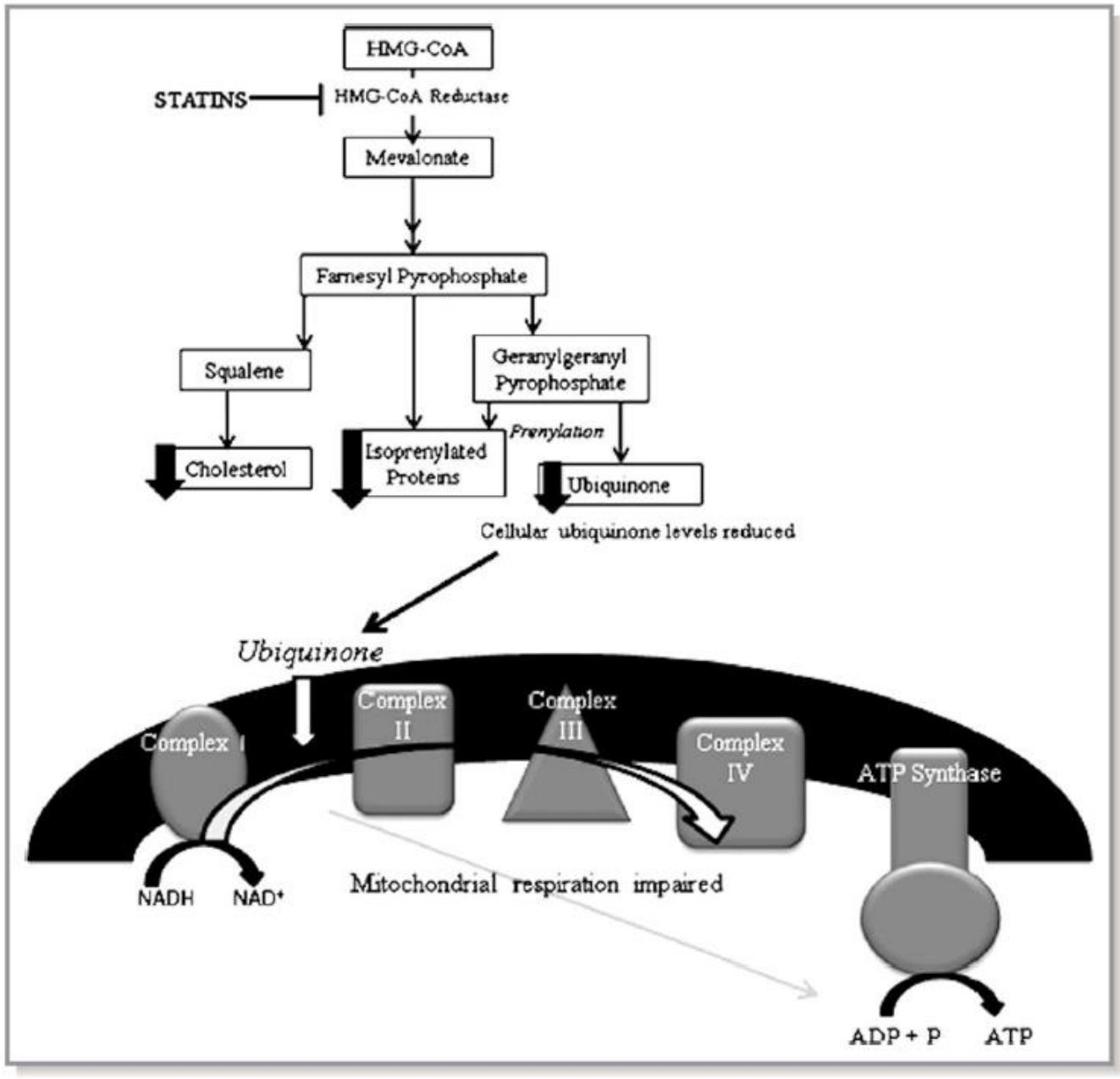
Figure 2. Cumulative numbers of hospital admissions for the outcomes of (**A**) cardiovascular disease, (**B**) myocardial infarction, (**C**) heart failure, and (**D**) coronary revascularization. *P* values were computed by rerandomization tests.

- Statins are the cornerstone of lipid-lowering therapy with beneficial effects for both primary and secondary cardiovascular (CV) disease prevention
- Although statin treatment is essential for CV event prevention, statin intolerance remains a problem in clinical practice
- MEGA study: even in this lower risk population, primary prevention with low-dose statin therapy can be effective in reducing cardiac events, with a modest reduction in lipid parameters

- Considering statin adherence of p’ts is inversely correlated with the intensity of statins , and “high intensity-like” effect of namely moderate intensity statins among Koreans, to resettle the evidence-based Korean dyslipidemia treatment guidelines for patients with diabetes.

- If a patient reports adverse effects when taking high intensity statin, can consider to change to a moderate intensity statin or consider a water soluble statin


VEEQI
Спасибо
RUSSIAN
Gracias
SPANISH
ありがとう
ございました。
JAPANESE
CÁM ƠN
VIETNAMESE
Thank
You!
ENGLISH
Merci
FRENCH
Ευχαριστώ
GREEK
شكرًا
ARABIC
고맙습니다
KOREAN
谢谢
CHINESE



Statins inhibit hydroxy-methylglutaryl-coenzyme A (HMG-CoA) reductase, leading to reduced production of **mevalonate** pathway metabolites, including **ubiquinone or CoQ10.** Ubiquinone is an essential **coenzyme in the process of mitochondrial respiration, facilitating the transfer of electrons between complex I and II of the respiratory chain.** Consequently, **depletion of ubiquinone may impair mitochondrial respiration and cellular energy production within skeletal muscle.** ADP indicates adenosine diphosphate; ATP, adenosine triphosphate; NAD1, nicotinamide adenine dinucleotide (reduced form); NADH, nicotinamide adenine dinucleotide (oxidized form); P, phosphate. Reproduced by permission of the publisher from Parker et al.