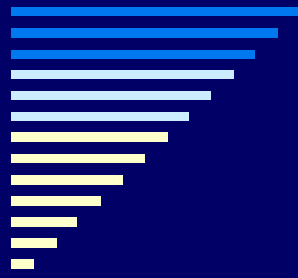


5 Congres AFLC

**PLACE DES STATINES DANS
LE TRAITEMENT DU
DIABÈTE**

Dr. Elie GHARIOS

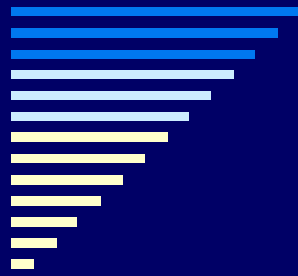
Novembre 2005



The New England Journal of Medicine

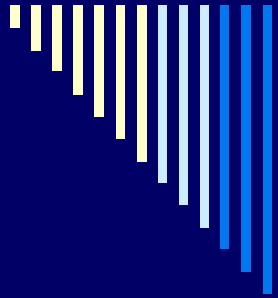
AGGRESSIVE LIPID-LOWERING THERAPY COMPARED WITH ANGIOPLASTY
IN STABLE CORONARY ARTERY DISEASE

BERTRAM PITT, M.D., DAVID WATERS, M.D., WILLIAM VIRGIL BROWN, M.D., AD J. VAN BOVEN, M.D., PH.D.,
LEONARD SCHWARTZ, M.D., LAWRENCE M. TITLE, M.D., DANIEL EISENBERG, M.D., LINDA SHURZINSKE, M.S.,
AND LISA S. MCCORMICK, PHARM.D., FOR THE ATORVASTATIN VERSUS REVASCULARIZATION TREATMENT INVESTIGATORS*



Conclusions In low-risk patients with stable coronary artery disease, aggressive lipid-lowering therapy is at least as effective as angioplasty and usual care in reducing the incidence of ischemic events. (N Engl J Med 1999;341:70-6.)

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DIABÈTE & STATINES

- ❑ Le diabète par sa fréquence et sa morbi-mortalité devient un sujet de préoccupation mondiale.
- ❑ On prévoit d'ici 2036 un accroissement de 20% du nombre des diabétiques dans le monde soit environ 100 millions de nouveaux diabétiques par an.
- ❑ Le risque des complications cardio-vasculaires est 2 à 8 fois plus élevé chez le diabétique par rapport au non diabétique et 80% des diabétiques meurent de complications cardio-vasculaires.
- ❑ On conçoit le danger que représente cette maladie et le souci de la traiter et prévenir.

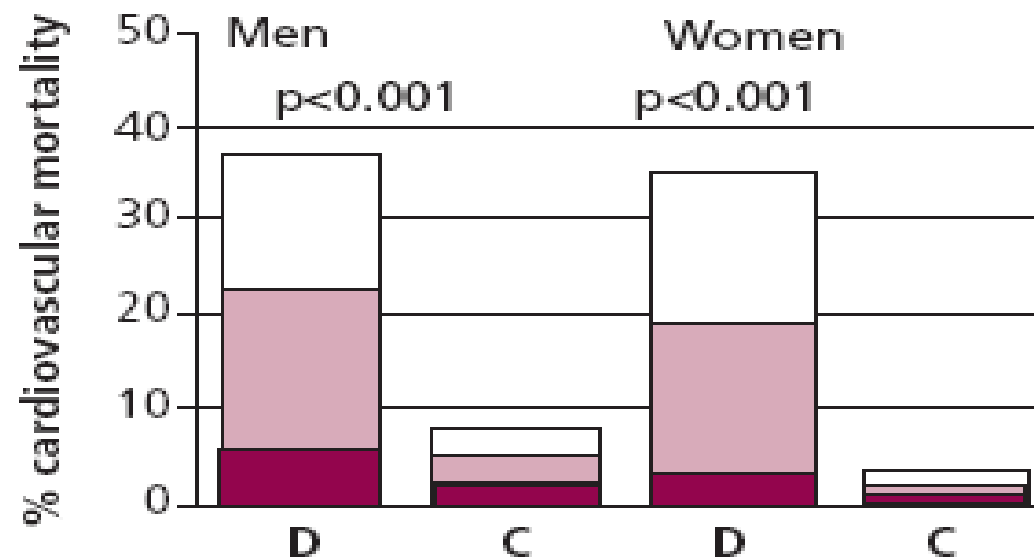
DIABETE & STATINES

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Key: ■ = 5-year ■ + ■ = 10-year

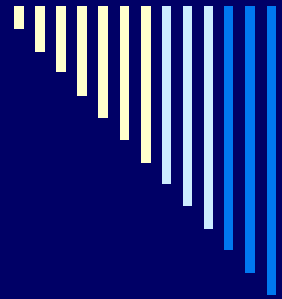
Total height of the bar = 15-year follow-up



Copyright © 1998 American Diabetes Association. From *Diabetes Care* 1998;21:1861-9.

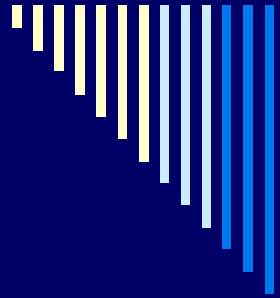
Reprinted with permission from *The American Diabetes Association*

Source: Br J Diabetes Vasc Dis © 2005 Sherbourne Gibbs, Ltd.



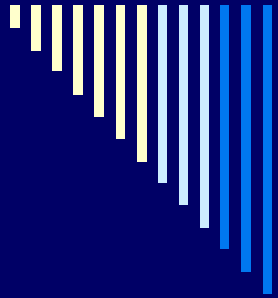
UNITED KINGDOM PROSPECTIVE DIBETES STUDY (UKPDS)

- 6000 diabétiques type II. soumis a un **contrôle glycémique strict**
- Réduction de 25% des complications micro-vasculaires. (***p 0,010***)
- Réduction du risque relatif de l'infarctus du myocarde de 16% (***p 0,052***)
- Résultats décevants sur la macro-circulation.



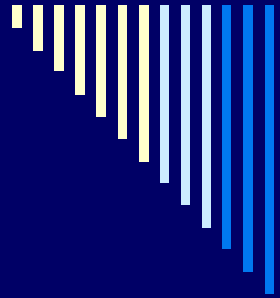
FACTEURS DE RISQUE CHEZ LE DIABETIQUE

- ❑ Dyslipidémie
- ❑ Hypertension artérielle
- ❑ Micro-albuminurie & Atteinte Rénale.
- ❑ Augmentation du stress vasculaire oxydatif
- ❑ Perturbations de la fonction endothéliale vaso-dilatatrice.
- ❑ Tabac
- ❑ Sédentarité.



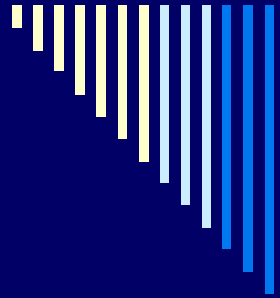
ALTERATIONS DES PLAQUETTES

- ❑ **Augmentation de la sensibilité à l'agrégation par :**
 - Epinephrine
 - Thrombine
 - Adenosine diphosphate
 - Acide arachidonique
- ❑ **Augmentation des recepteurs des glyco-proteines IIb IIIa**
- ❑ **Diminution de la concentration de l'adenosine monophosphate (AMP)**
- ❑ **Augmentation de la synthèse du thromboxane A2 et B2**
- ❑ **Diminution de l'activité du gualynate cyclase.**



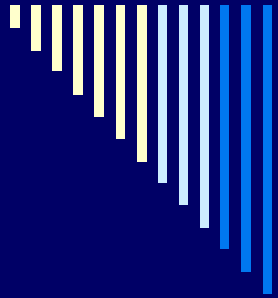
ANOMALIES DE LA FONCTION PLAQUETTAIRE

- ❑ Augmentation de l'adhésivité plaquettaire
- ❑ Diminution de la survie plaquettaire
- ❑ Augmentation de la génération des vaso constricteurs prostanoids
- ❑ Reduction de la génération des prostacyclines et autres vaso-dilatateurs prostanoids
- ❑ Altération de la bivalence ctionique homéostasique ($\uparrow\text{Ca}^{2+}$ et $\downarrow\text{Mg}^{2+}$)
- ❑ $\uparrow$ de la glycolysation non enzymatique des protéines plaquettaires.
- ❑ - $\downarrow$ de la concentration en phosphoinositide
- ❑ $\downarrow$ de la production de nitirite d'oxyde.
- ❑ $\uparrow$ de la phosphorylation des chaînes légères de myosine



ANOMALIES DE LA COAGULATION

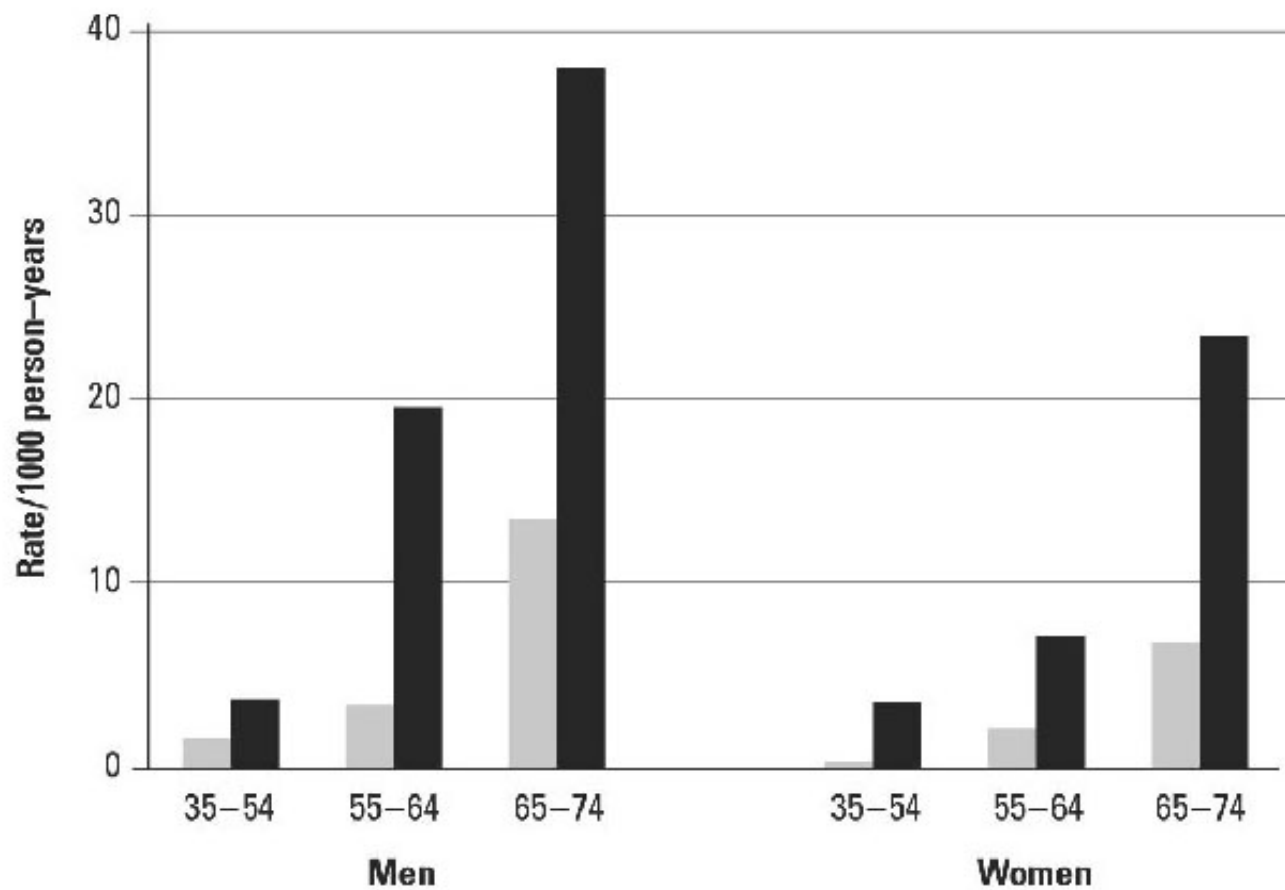
- ❑ Elévation des taux plasmatiques de facteur VII et VII
- ❑ Elévation du taux de fibrinogène et de l'inhibiteur du plasminogen-activator
- ❑ Elévation du complexe thrombine-antithrombine
- ❑ Diminution de l'anti thrombine III, et des taux de protéine C et S
- ❑ Diminution de l'activité fibrinolytique.



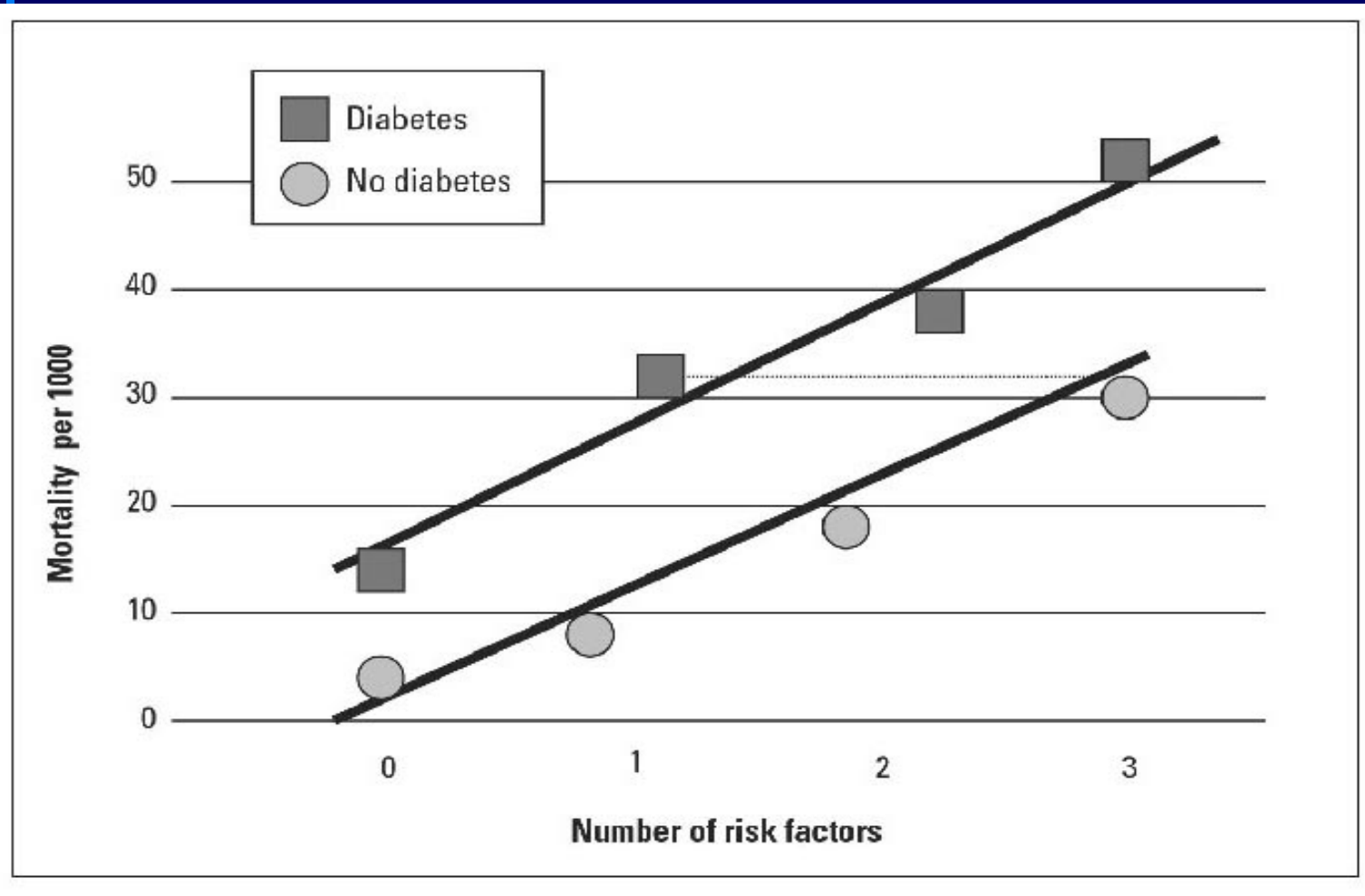
DYSLIPIDEMIE ET DIABETE

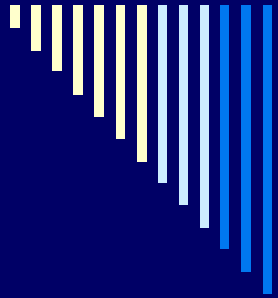
- Les troubles lipidiques observés chez le diabétique consistent en :
 - une augmentation du taux des triglycérides
 - une diminution du taux des HDL
 - Si l'augmentation des LDL est moins constante, il est à noter que les particules de LDL sont plus petites et plus denses, donc plus athérogènes que chez les non diabétiques.
- ***Ces anomalies sont retrouvées non seulement chez les diabétiques de type II mais aussi chez les sujets présentant une tolérance glucidique perturbée ou une insulino-résistance.***

DYSLIPIDEMIE ET DIABETE



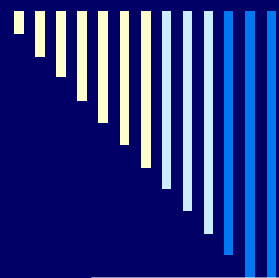
DIABETE & FACTEURS DE RISQUE





HIERARCHIE DES FACTEURS DE RISQUE

1. Taux de LDL
2. Taux de HDL
3. Hémoglobine A1C
4. Chiffres de pression artérielle
5. Tabagisme
6. Anomalies de la coagulation sanguine et insulino-résistance
7. Hyper adhésivité plaquettaire
8. Augmentation de la CRP
9. Taux élevé d'homocystéine



Primary Prevention Trials of Lipid-Altering Therapy Including Patients with Diabetes

Trial	Diabetic,* n	Total N in Study	Lipid-Altering Drug, mg/d	CHD* Risk vs Placebo in Diabetic Patients, %
ASCOT	2,532	10,305	Atorvastatin 10	-16 (NS)
CARDS †	2,838	2,838	Atorvastatin 10	-37 (p=.001)
HPS §	2,912	7,150	Simvastatin 40	-33 (p=.0003)
PROSPER	623	5,804	Pravastatin 40	+27 (NS)
AFCAPS	155	6,605	Lovastatin 20-40 ‡	-44 (NS)

* By history

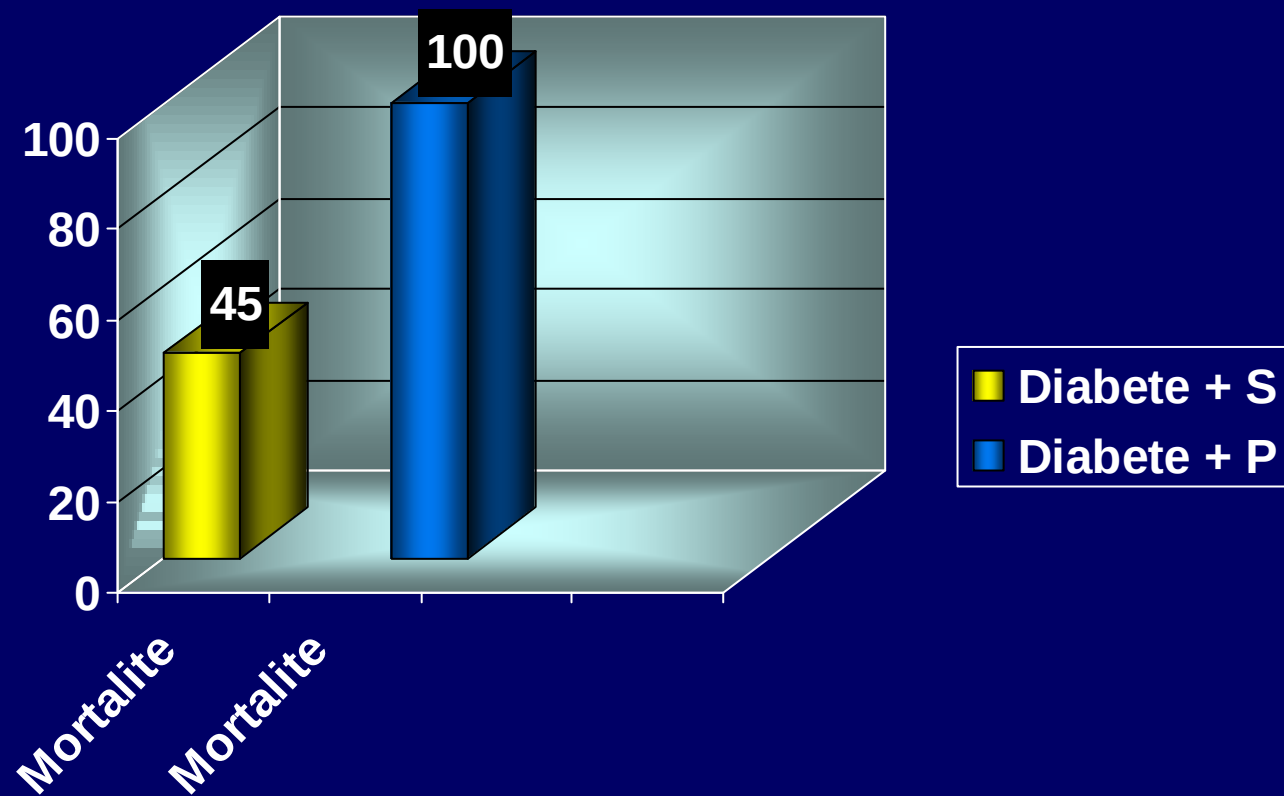
† Prospective trial in diabetic subjects; others are subgroup analyses

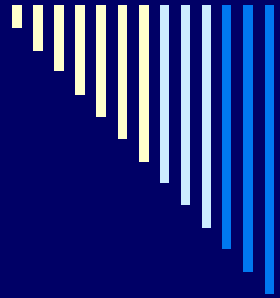
‡ Mean 30 mg/d

§ Type 1 or 2 diabetes

Bays H et al. *Future Cardiology* 2005;1:39-59. | Colhoun HM et al. *Lancet* 2004;364:685-696. |
Downs JR et al. *JAMA* 1998;279:1615-1622. | HPS Collaborative Group. *Lancet* 2003;361:2005-
2016. | Sever PS et al. *Lancet* 2003;361:1149-1158. | Shepherd J et al. *Lancet* 2002;360:1623-
1630. | Koskinen P et al. *Diabetes Care* 1992;15:820-825.

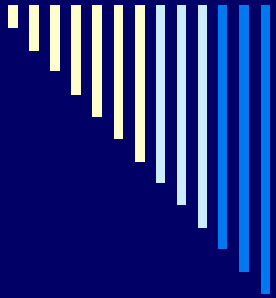
SCANDINAVIAN SIMVASTATIN SURVIVAL STUDY]





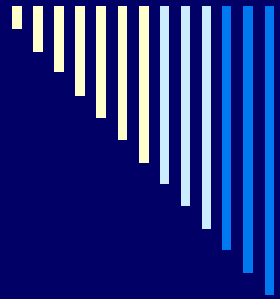
STATINES ET PREVENTION DIABETIQUE

- Dans un autre ordre d'idées l'étude WOSCOP suggère que 30% de diminution dans le développement d'un diabète ou le retard de son apparition ont été obtenus avec la PRAVASTATIN.
- Ces résultats semblent confirmer avec la LOVASTATIN
- De possibles explications de ces effets incluent le rôle anti-inflammatoire des statines [diminution de la CRP, de l'Interleukine 6 et de la P-Selectine ainsi que leur effet sur l'endothélium vasculaire.
- Ce rôle apparaît indépendant de l'abaissement des lipides.



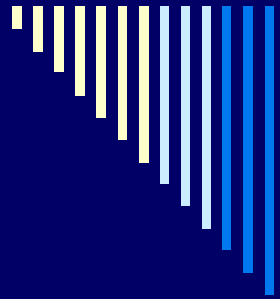
CONCLUSION

le traitement par les statines
chez le diabétique
dyslipidémique semble apporter
un bénéfice réel.



PLACE DES AUTRES HYPOLIPIDEMIANTS CHEZ LE DIABETIQUE

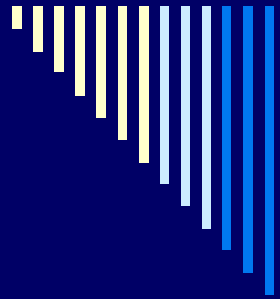
- ❑ L'abaissement des taux lipidiques chez le diabétique, par d'autres médicaments, est-il aussi efficace ?
- ❑ L'étude DAIS [Diabetes Atherosclerosis Intervention Study] a évalué la progression des lésions coronariennes par coronarographie, chez les diabétiques traités par 200 mgs de FENOFIBRATE, par rapport à un autre groupe recevant un placebo :



PLACE DES AUTRES HYPOLILIDEMIANTS CHEZ LE DIABETIQUE

- ❑ Les résultats enregistrés ont montré :
- ❑ Une diminution de 29% des triglycérides
- ❑ Une augmentation de 7% des HDL
- ❑ Une diminution de 6% des LDL
- ❑ Une moindre progression des lésions coronariennes [40% en moyenne de moindre réduction du diamètre des artères coronaires]
- ❑ 38 accidents coronariens enregistré versus 50 dans le groupe placebo.

- ❑ **Les résultats évalués sur les artères coronaires n'ont pas été jugés formellement significatifs.**

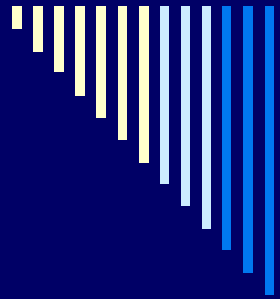


PLACE DES AUTRES HYPOLILIDEMIANTS CHEZ LE DIABETIQUE

La Helsinki Heart Study a utilisé le Gemfibrozil chez les diabétiques de type II.

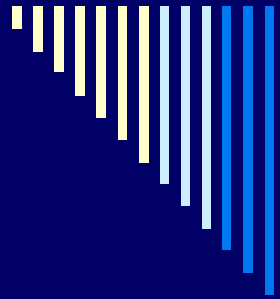
Il est à noter que :

- ❑ Les LDL n'ont pas diminués
- ❑ Les HDL ont augmenté de 6%
- ❑ Les Triglycérides ont diminué de 31%
- ❑ Il n'y a pas eu de différence significative dans la survenue d'accidents coronariens par rapport au groupe placebo



FAUT-IL ASSOCIER AUX STATINES D'AUTRES HYPOLIPEMIANTS ?

- ❑ L'essentiel est un abaissement des lipides.
- ❑ La cible clé est le taux de LDL qui doit être **inférieur à 100mgs/l** chez le diabétique ayant déjà une lésion vasculaire
- ❑ **L'ADA 2005 suggère fortement un taux de LDL cholesterol a 70mg/l**
- ❑ Un taux de 1,30 est acceptable chez un diabétique indemne de lésion vasculaire apparente,
- ❑ Parallèlement le taux de cholesterol doit être inférieur à 1,35mg/l
- ❑ L'association de fibrates ou de Niacin (HATS Study) peut être utile pour atteindre ces chiffres.

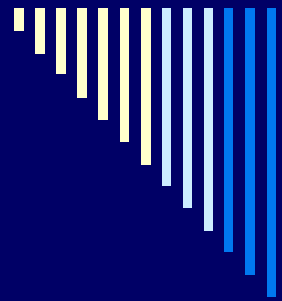


FAUT-IL PRESCRIRE DES STATINES A UN DIABETIQUE NONDYSLIPIDEMIQUE ?

- La CARDS Trial [Collaborative Atrovastatine Diabetes Study] a porté sur des diabétiques de type II avec des taux de LDL oscillant entre 2,6 à 4,14mmol, mais associés à un autre facteur de risque (HTA) à qui une dose quotidienne de 10mgs d'ATROVASTATIN fut prescrite.

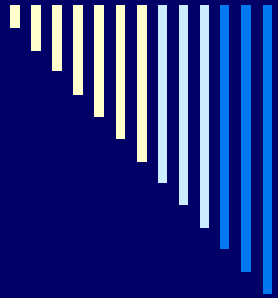
Résultats par rapport au groupe placebo :

- 36% de réduction des événements coronariens
 - 31% de réduction de revascularisation coronaire
 - 48% de réduction d'accidents cérébraux
 - 27% de réduction de mortalité
-



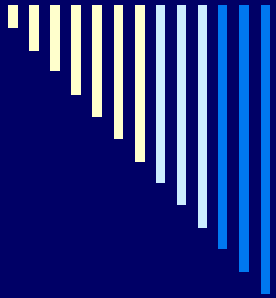
FAUT-IL PRESCRIRE DES STATINES A UN DIABETIQUE NONDYSLIPIDEMIQUE ?

- ❑ Les auteurs concluent que **les statines doivent être systématiquement prescrits chez tout diabétique de type II (surtout après 50 ans) indépendamment de son taux lipidique** à cause vraisemblablement d'effets pleiotropiques.
- ❑ Cette opinion est toutefois sujet a discussion.

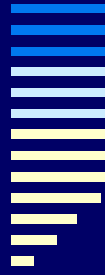


EFFETS PLEIOTROPIQUES DES STATINES

- Les statines ont un effet stabilisant sur la plaque, préventif de sa rupture grâce à un effet direct sur les métallo-protéinases qui contribuent à cette rupture
- Les statines inhibent la synthèse des myocytes artériels, des cellules musculaires lisses et des facteurs de croissance en inhibant la synthèse des isoprénoïds
- Les statines ont un effet anti athéro-thrombique.
- Les statines peuvent moduler l'activité du facteur tissulaire ainsi que l'activité fibrinolytique, la croissance des macrophages induite par l'oxydation des LDL et des T cellules.
- Elles inhibent la sécrétion des lipoprotéines, des récepteurs des « scavengers » des cellules adhésives, de la synthèse de l'oxyde nitrique et de l'endothéline I et son expression.
- Ces effets ne sont pas en rapport avec l'abaissement du taux de cholestérol.
- L'effet de protection renale de la Simvastatin a été démontré récemment.



- Quelle statine ?
- Quelle dose de statine ?
- IDEAL STUDY
- TNT STUDY



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Intensive Lipid Lowering with Atorvastatin in Patients with Stable Coronary Disease

John C. LaRosa, M.D., Scott M. Grundy, M.D., Ph.D.,
David D. Waters, M.D., Charles Shear, Ph.D., Philip Barter, M.D., Ph.D.,
Jean-Charles Fruchart, Pharm.D., Ph.D., Antonio M. Gotto, M.D., D.Phil.,
Heiner Greten, M.D., John J.P. Kastelein, M.D., James Shepherd, M.D.,
and Nanette K. Wenger, M.D., for the Treating to New Targets (TNT) Investigators*

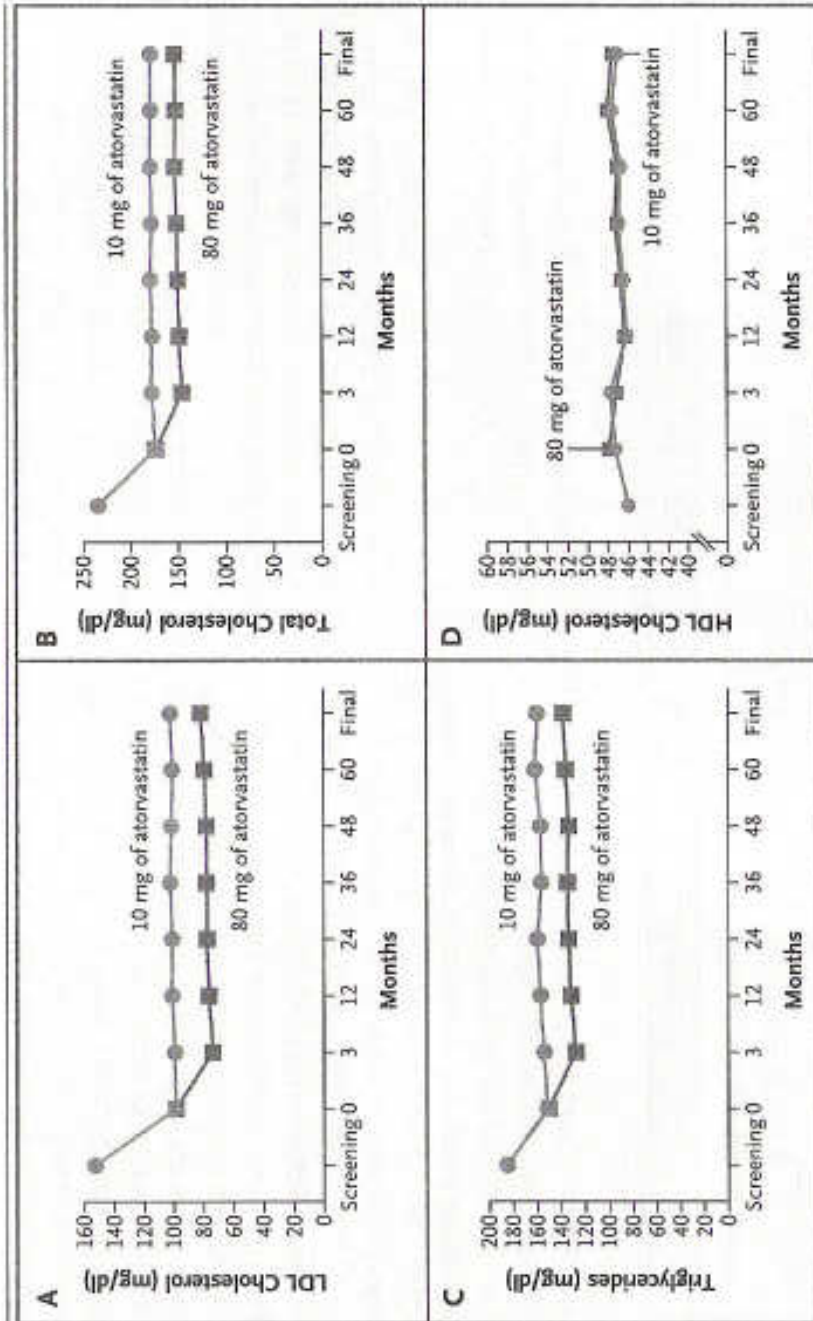


Figure 2. Mean Lipid Levels during the Study.

To convert values for cholesterol to millimoles per liter, multiply by 0.02586; to convert values for triglycerides to millimoles per liter, multiply by 0.0113.

INTENSIVE ATORVASTATIN THERAPY FOR STABLE CORONARY DISEASE

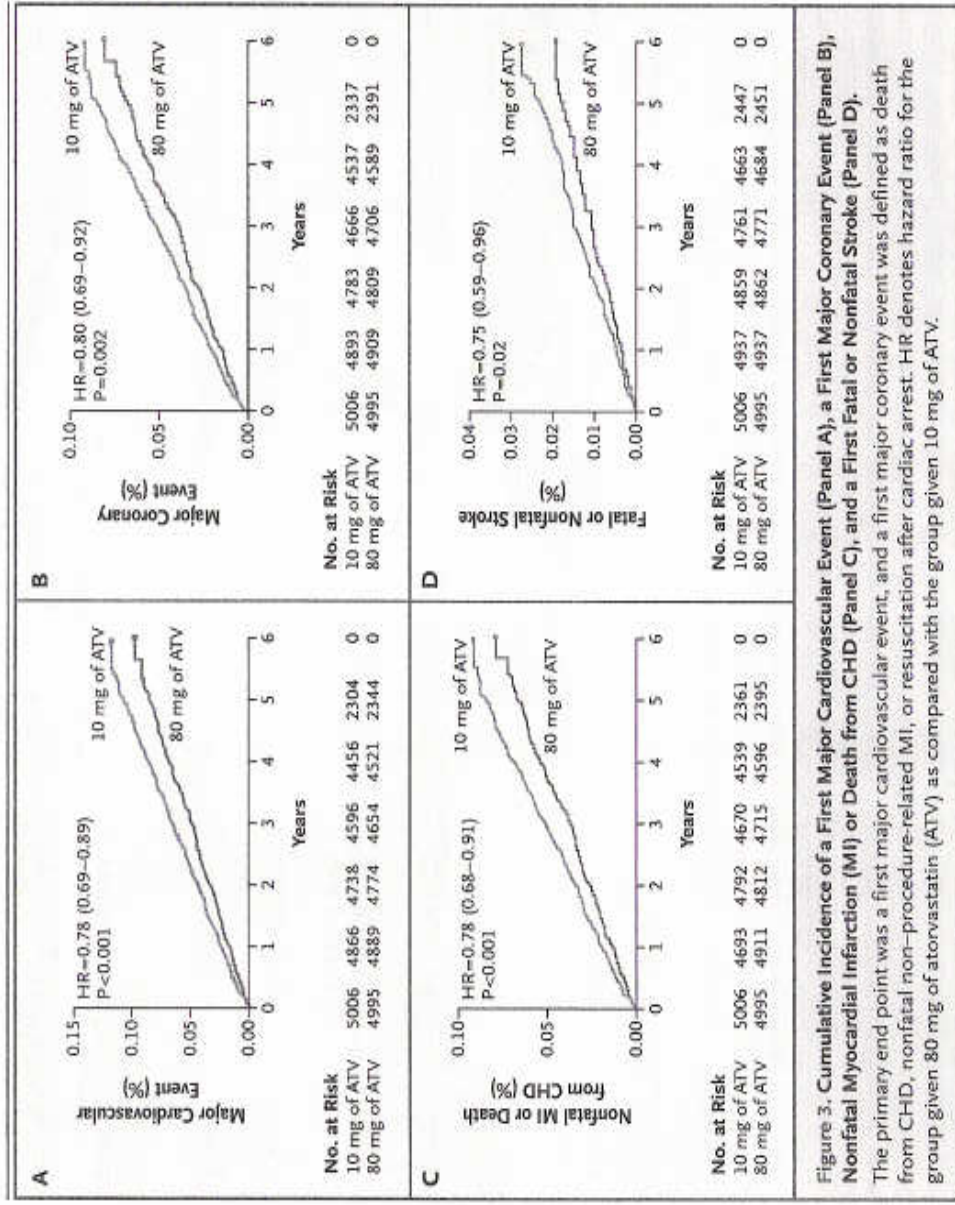


Figure 3. Cumulative Incidence of a First Major Cardiovascular Event (Panel A), a First Major Coronary Event (Panel B), Nonfatal Myocardial Infarction (MI) or Death from CHD (Panel C), and a First Fatal or Nonfatal Stroke (Panel D). The primary end point was a first major cardiovascular event, and a first major coronary event was defined as death from CHD, nonfatal non-procedure-related MI, or resuscitation after cardiac arrest. HR denotes hazard ratio for the group given 80 mg of atorvastatin (ATV) as compared with the group given 10 mg of ATV.

Table 2. Estimated Hazard Ratio for Individual Components of the Primary and Secondary Efficacy Outcomes.*

Outcome	10 mg of Atorvastatin (N=5006)	80 mg of Atorvastatin (N=4995)	Hazard Ratio (95% CI)	P Value
<i>no. with first event (%)</i>				
Primary outcome				
Total major cardiovascular events	548 (10.9)	434 (8.7)	0.78 (0.69–0.89)	<0.001
Death from CHD	127 (2.5)	101 (2.0)	0.80 (0.61–1.03)	0.09
Nonfatal, non-procedure-related myocardial infarction	308 (6.2)	243 (4.9)	0.78 (0.66–0.93)	0.004
Resuscitation after cardiac arrest	26 (0.5)	25 (0.5)	0.96 (0.56–1.67)	0.89
Fatal or nonfatal stroke	155 (3.1)	117 (2.3)	0.75 (0.59–0.96)	0.02
Secondary outcomes				
Major coronary event†	418 (8.3)	334 (6.7)	0.80 (0.69–0.92)	0.002
Cerebrovascular event‡	250 (5.0)	196 (3.9)	0.77 (0.64–0.93)	0.007
Hospitalization for congestive heart failure	164 (3.3)	122 (2.4)	0.74 (0.59–0.94)	0.01
Peripheral-artery disease§	282 (5.6)	275 (5.5)	0.97 (0.83–1.15)	0.76
Death from any cause	282 (5.6)	284 (5.7)	1.01 (0.85–1.19)	0.92
Any cardiovascular event	1677 (33.5)	1405 (28.1)	0.81 (0.75–0.87)	<0.001
Any coronary event¶	1326 (26.5)	1078 (21.6)	0.79 (0.73–0.86)	<0.001

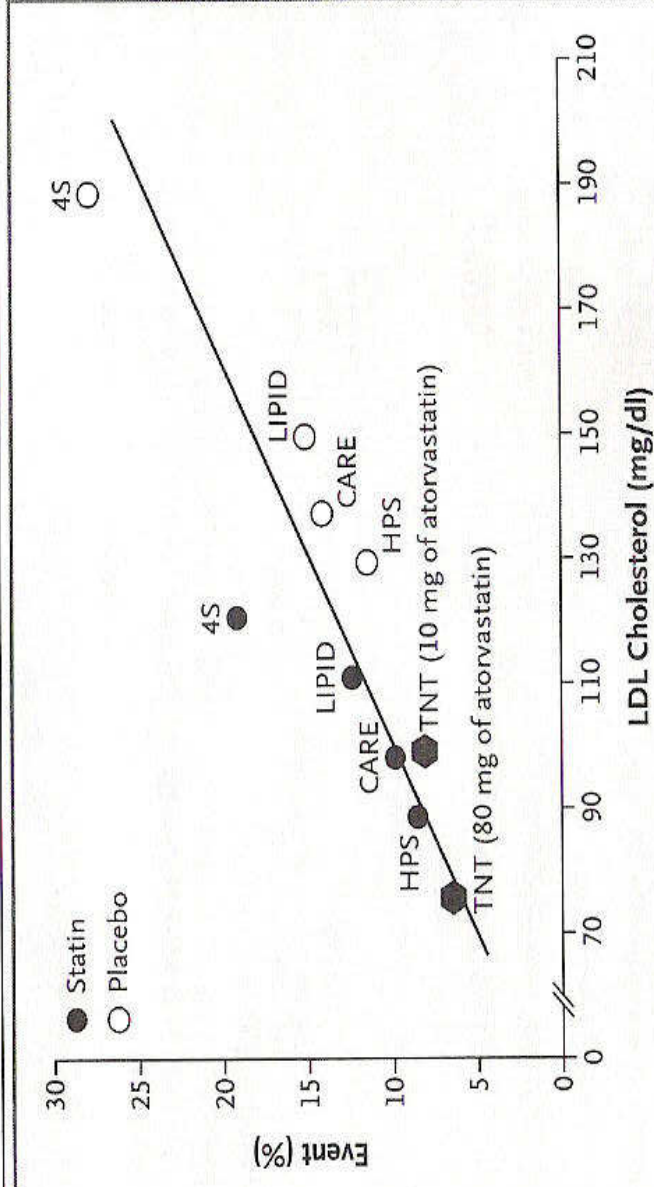
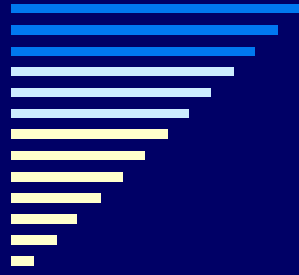
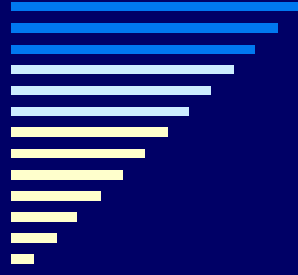


Figure 4. Event Rates Plotted against LDL Cholesterol Levels during Statin Therapy in Secondary-Prevention Studies.

HPS denotes Heart Protection Study,¹ CARE Cholesterol and Recurrent Events Trial,¹⁰ LIPID Long-term Intervention with Pravastatin in Ischaemic Disease,¹¹ and 4S Scandinavian Simvastatin Survival Study.¹² Event rates for HPS, CARE, and LIPID are for death from CHD and nonfatal myocardial infarction. Event rates for 4S and the TNT Study also include resuscitation after cardiac arrest. To convert values for LDL cholesterol to millimoles per liter, multiply by 0.02586.



CONCLUSIONS

Intensive lipid-lowering therapy with 80 mg of atorvastatin per day in patients with stable CHD provides significant clinical benefit beyond that afforded by treatment with 10 mg of atorvastatin per day. This occurred with a greater incidence of elevated aminotransferase levels.

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Lipid-lowering Medications and Effects on HDL-C Levels.

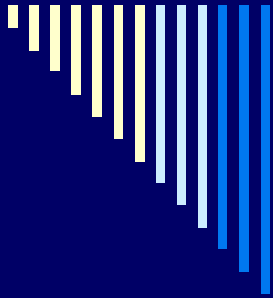
Medication	HDL Increase†	Mechanism	Specific Agents	Contraindications by Class	Common and Serious Side Effects by Class
Niacin	20–35%	Inhibits hepatic uptake of apolipoprotein A-I and enhances plasma pre- β HDL cholesterol; improves endothelial function and enhances endothelial nitric oxide synthase activity	Extended-release niacin (Niaspan), 1000–2000 mg orally nightly Niacin (nicotinic acid), 1–2 g orally two or three times daily Sustained-release niacin (Slo-Niacin), 250–750 mg orally once or twice daily	Hypersensitivity, hepatic dysfunction, active peptic ulcer, unexplained elevations of liver-function tests, alcoholism	Common: flushing,‡ pruritus, nausea, vomiting, rash, dyspepsia, elevated liver aminotransferase levels, hypotension, paresthesias, abdominal pain, hyperglycemia,§ elevated lactate dehydrogenase levels, hyperuricemia Serious: hepatotoxicity, arrhythmias, severe hypotension or hemorrhage (rare reports with nicotinic acid and Slo-Niacin)
Fibrates	10–25%	Activates PPAR α , which stimulates apolipoprotein A-I expression ³⁶	Fenofibrate, micronized (Antara), 43–130 mg orally once daily Fenofibrate, micronized (Lofibra), 67–200 mg orally once daily Fenofibrate (Tricor), 48–145 mg orally once daily Gemfibrozil (Lopid), 600 mg orally twice daily	Hypersensitivity, gallbladder disease, hepatic dysfunction, severe renal dysfunction, unexplained elevations of liver-function tests, primary biliary cirrhosis	Common: elevated liver aminotransferase levels, abnormal liver-function tests, abdominal pain, elevated creatine kinase levels, nausea, respiratory disorders, back pain, headache, rhinitis, constipation Serious: myositis, myopathy, cholelithiasis, hepatitis, pancreatitis
Statins	5–15%	Increases apolipoprotein A-I synthesis	Rosuvastatin (Crestor), 5–40 mg orally once daily Fluvastatin (Lescol), 20–40 mg orally nightly Fluvastatin (Lescol XL), 80 mg orally nightly Simvastatin (Zocor), 5–80 mg orally every evening	Hypersensitivity, active liver disease, unexplained elevations of liver-function tests, pregnancy, breast-feeding	Common: myalgia, elevated creatine kinase levels, elevated liver aminotransferase levels, dyspepsia, abdominal pain, diarrhea, nausea, headache, back pain, flu-like syndrome, urinary tract infection, rhinitis or sinusitis, constipation, arthralgia or arthritis, rash, paresthesias, peripheral edema, pharyngitis, asthenia Serious: myopathy, hepatotoxicity, pancreatitis, angioedema, leukopenia, thrombocytopenia, vesiculobullous rash, photosensitivity, rhabdomyolysis (rare)
	2–12%		Pravastatin (Pravachol), 10–80 mg orally once daily		
	2–10%		Atorvastatin (Lipitor), 10–80 mg orally once daily		
	2–8%		Lovastatin (Altoprev), 10–60 mg orally nightly		
Combination: statin and niacin	21–26%		Lovastatin–niacin (Advicor), 20–500 mg to 20–1000 mg orally nightly	Hypersensitivity, active liver disease, unexplained elevations of liver-function tests, active peptic ulcer, arterial bleeding, pregnancy, breast-feeding	Common: flushing, warm sensation, redness of skin, pruritus, tingling, nausea or vomiting, diarrhea, dyspepsia, flatulence, constipation, paresthesias, rash, asthenia, myalgia, hyperglycemia, elevated creatine kinase levels, elevated liver aminotransferase levels, hyperuricemia, hypotension Serious: hepatotoxicity, fulminant hepatic necrosis, thrombocytopenia, peptic ulcer, arrhythmias, myopathy, pancreatitis

* The agents included have been approved by the Food and Drug Administration for the management of dyslipidemia. Trials involving agents to increase HDL cholesterol levels include the Coronary Drug Project (niacin),³⁵ the Helsinki Heart Study³⁸ and the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA HLT) (fibrates),³⁹ the Air Force–Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) (statins),⁴⁰ and the HDL Atherosclerosis Treatment Study (HATS)⁴¹ and the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2 trial (combination therapy).⁴² PPAR α denotes peroxisome-proliferator-activated receptor α .

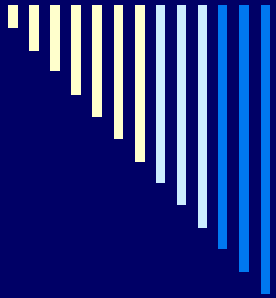
† LDL cholesterol and triglyceride changes by class are as follows: niacin — LDL cholesterol, –5 to –25 percent and triglycerides, –20 to –50 percent; statins — LDL cholesterol, –15 to –55 percent and triglycerides, –7 to –30 percent.

‡ Flushing can be minimized by using extended-release niacin, starting with a low dose (500 mg nightly) and increasing slowly (e.g., by 500-mg increments per month) to a target dose (1000 to 2000 mg nightly) and by taking the medication 30 minutes after taking an aspirin, with a low-fat snack.

§ High-dose niacin should be used with caution in patients with diabetes.

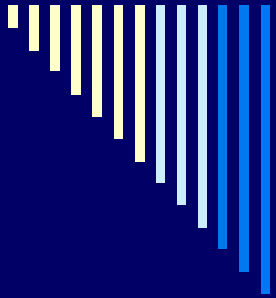


- **New Drugs Ezetimibe**
- **Effect of ezetimibe Coadministered With Atorvastatin in 628 patients With Primary Hypercholesterolemia: A Prospective, Randomized, Double-Blind Trial**
- Ballantyne CM, for the Ezetimibe study Group (Baylor College of Medicine, Houston; et al)
- Circulation 107:2409-2415,2003
- Conclusion. – The combination of ezetimibe with atorvastatin was found to be safe and well tolerated. Ezetimibe coadministered with atorvastatin provided significant incremental reductions in LDL – Cholesterol and triglycerides and increases in HDL – Cholesterol. Coadministration of ezetimibe and atorvastatin is a well-tolerated and efficacious new option for the treatment of patients with hypercholesterolemia.
- NB: LDL reduction may reach 50 to 60%

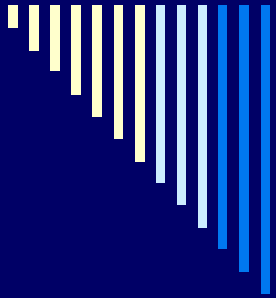


- **New Drugs** (Continued)
- TORCETRABIP
- Increases HDL by 25 to 30%

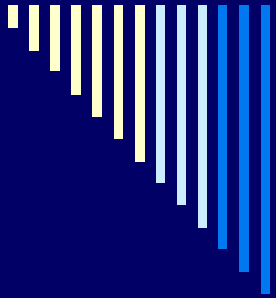
- A problem for Medical Research.



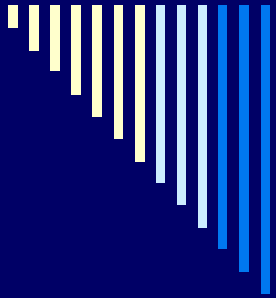
- Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and treatment of high blood Cholesterol in Adult (Adult Treatment Panel III)
- Jama 285:2486-2497, 2001
- It focuses on multiple coronary artery disease (CAD) risk factors, declares diabetes mellitus as a CAD equivalent, uses the Framingham equations to estimate absolute CAD risk, and identifies individuals with the metabolic syndrome (insulin resistance) for extensive lifestyle changes.



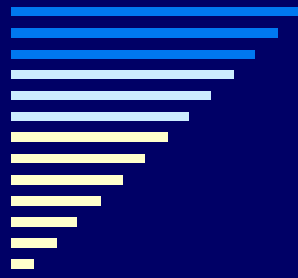
- 2 It identifies LDL Cholesterol levels less than 100 mg/dl as optimal (...), changes the definition of low HDL cholesterol levels from less than 35mg/dl to less than 40 mg/dl and defines normal triglyceride levels as less than 150 mg/dl, and 150 mg/dl to 199mg/dl as borderline.
- It recommends use of the non-HDL cholesterol as a target for therapy once LDL cholesterol has reached the target.
- It recognizes the importance of life-habit risk factors and emerging risk factors such as Lp (a), homocysteine, C-reactive protein, procoagulant factors, and LDL size as contributing to CAD risk and guiding the intensity of risk-reduction therapy.



- It simplifies the therapeutic life-style diet: less than 7% of total calories from saturated fat, 10% from polyunsaturated fat, 20% from monounsaturated fat, and a cholesterol intake of less than 200mg/d; it also features use of plant stanol / sterol margarines, weight reduction, and increased physical activity.
- It identifies individuals with a projected event rate of greater than 20% over 10 years or 10% to 20% over 10 years and more than 2 risk factors as being at high risk.
- It recommends a complete lipoprotein profile as the preferred initial test. It is estimated that only 30% of patients eligible under ATP II were being appropriately treated and that now 36 million US adults would qualify for pharmacologic therapy under ATP III.



- It recommends that lipid-lowering drug therapy be initiated at hospital **discharge**.
- ATP III also provides important information on the goals of lipid-lowering therapy in patients after ACS. The challenge for the specialist is to establish a predischARGE plan that includes maximal dosing to achieve aggressive target goals and to work with the patient's primary care provider to maintain these goals long-term.



THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Comparison of Intensive and Moderate Lipid Lowering with Statins after Acute Coronary Syndromes

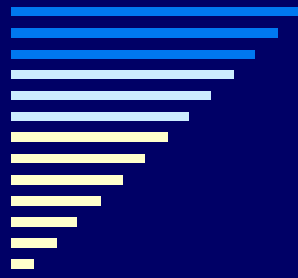
Christopher P. Cannon, M.D., Eugene Braunwald, M.D., Carolyn H. McCabe, B.S.,

Daniel J. Rader, M.D., Jean L. Rouleau, M.D., Rene Belder, M.D.,

Steven V. Joyal, M.D., Karen A. Hill, B.A., Marc A. Pfeffer, M.D., Ph.D.,

and Allan M. Skene, Ph.D., for the Pravastatin or Atorvastatin Evaluation

and Infection Therapy – Thrombolysis in Myocardial Infarction 22 Investigators*

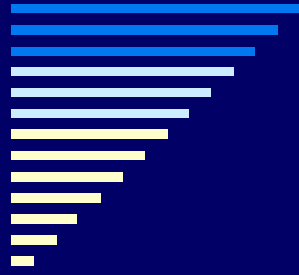


BACKGROUND

Lipid-lowering therapy with statins reduces the risk of cardiovascular events, but the optimal level of low-density lipoprotein (LDL) cholesterol is unclear.

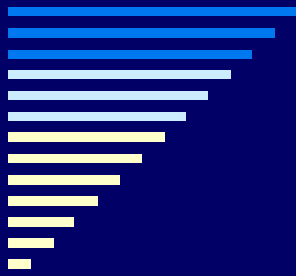
METHODS

We enrolled 4162 patients who had been hospitalized for an acute coronary syndrome within the preceding 10 days and compared 40 mg of pravastatin daily (standard therapy) with 80 mg of atorvastatin daily (intensive therapy). The primary end point was a composite of death from any cause, myocardial infarction, documented unstable angina requiring rehospitalization, revascularization (performed at least 30 days after randomization), and stroke. The study was designed to establish the noninferiority of pravastatin as compared with atorvastatin with respect to the time to an end-point event. Follow-up lasted 18 to 36 months (mean, 24).



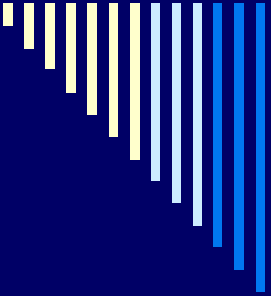
RESULTS

The median LDL cholesterol level achieved during treatment was 95 mg per deciliter (2.46 mmol per liter) in the standard-dose pravastatin group and 62 mg per deciliter (1.60 mmol per liter) in the high-dose atorvastatin group ($P < 0.001$). Kaplan–Meier estimates of the rates of the primary end point at two years were 26.3 percent in the pravastatin group and 22.4 percent in the atorvastatin group, reflecting a 16 percent reduction in the hazard ratio in favor of atorvastatin ($P = 0.005$; 95 percent confidence interval, 5 to 26 percent). The study did not meet the prespecified criterion for equivalence but did identify the superiority of the more intensive regimen.



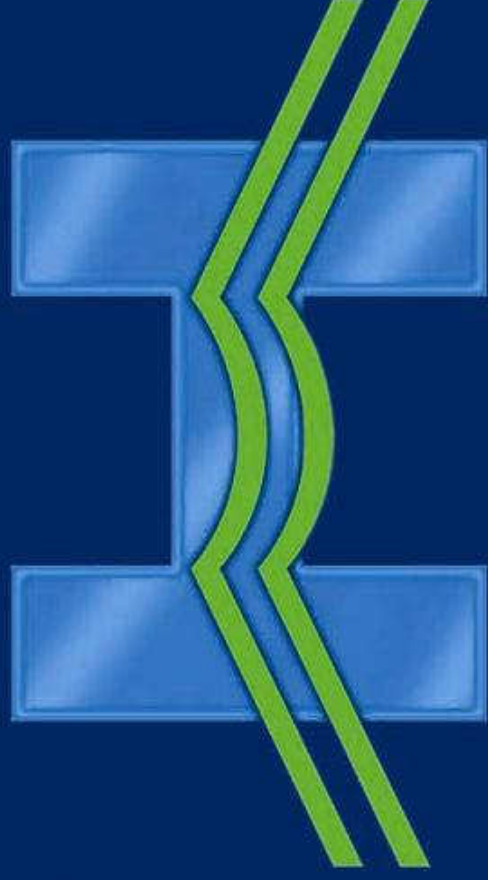
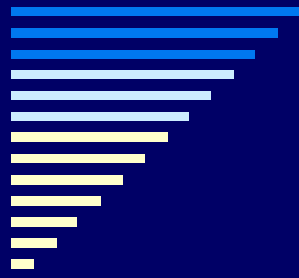
CONCLUSIONS

Among patients who have recently had an acute coronary syndrome, an intensive lipid-lowering statin regimen provides greater protection against death or major cardiovascular events than does a standard regimen. These findings indicate that such patients benefit from early and continued lowering of LDL cholesterol to levels substantially below current target levels.



Take home message:

- The lower the better
- Le traitement est aussi efficace que le traitement chirurgical ou les procédures interventionnelles.
- Le traitement medical est necessaire apres toute procedure chirurgicale ou interventionnelle.



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