STATINS IN PRIMARY PREVENTION
Who can benefit from them?

High blood cholesterol is one of the main risk factors for Cardiovascular disease, but it must be considered in a whole framework including others, both those that **can be modified** (smoking habit, high blood pressure, diabetes mellitus and high blood cholesterol itself) and those that **cannot be modified** (age, sex, family, genetic and environmental factors).

Global Cardiovascular Risk (GCVR), that takes the multifactor origin of cardiovascular disease into account, permits a better assessment of the probability of cardiovascular events developing in a given population.

In order to calculate the specific GCVR for the Italian population, Istituto Superiore di Sanità has prepared the Italian Cardiovascular Risk Charts and the Calculator of individual risk.

The Italian Cardiovascular Risk Charts have been used in the latest version of AIFA note no. 13 that has been the subject of more or less extensive interpretations in the various regions of Italy.

In this respect, this **Information Package** gives more details of:

- the results of the studies on the effectiveness of statins in primary prevention of cardiovascular disease;
- the clinical importance of cholesterol lowering treatments in the elderly, women and patients with diabetes mellitus.

The Information Package also comes with a special **Insert** (in Italian) for the Italian risk Charts and for the individual risk Calculator and their use in clinical practice.

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Insert. Global CardioVascular Risk (GCVR) calculation

Cholesterolemia and Cardiovascular Risk

In the 50s, the Framingham study had shown a correlation between the levels of cholesterolemia and the risk of heart disease.[1]

Currently, the desirable levels of cholesterolemia are considered to be those of the United States National Cholesterol Education Program for healthy subjects[2], that is:

- cholesterolemia < 200 mg/dL,
- LDL cholesterol < 130 mg/dL.

These values are those shown in the blood chemistry reports of most analysis laboratories.

Studies after Framingham, among which is the Seven Countries Study (that refers to a 25-year observation),[3] have shown that (figure 1):

1. there is no threshold level of cholesterolemia below which the risk cancels out;
2. in a population, the risk varies as cholesterolemia varies and increases strongly for high cholesterol levels;
3. in the various populations with equal cholesterolemia, the risk can be very different.

As can be seen (figure 1), **in Mediterranean populations the probability of coronary death, cholesterolemia being equal, is clearly lower** than that of the North American or Northern European populations.

Framingham data and those of other observational studies had also made it possible to estimate the impact of individual risk factors (high blood cholesterol, hypertension, smoking, age, sex) and their interaction on the probability of cardiovascular events occurring.[4]

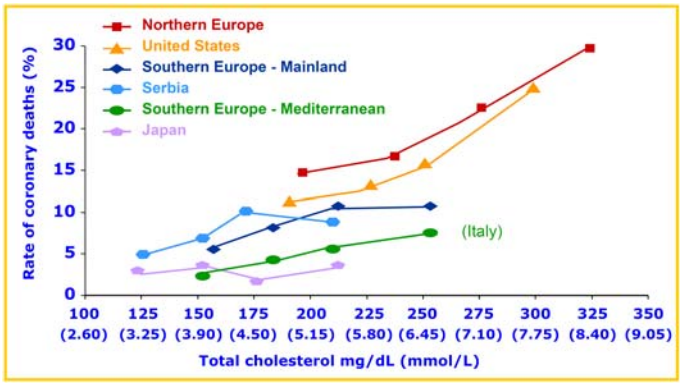


Figure 1. *As for cholesterolemia (horizontal axis), the extent of coronary risk (vertical axis - coronary mortality at 25 years of age) varies in the different geographical areas. Data adjusted according to age, sex, smoking, systolic pressure.*

The Framingham study provided data for developing the first risk chart; others followed from this that were specific for each population studied, including the Italian one[5] (see insert).

On all the charts, it is clear that, **in the absence of other risk factors, the increase of cholesterolemia alone could have a relatively small effect on the overall risk.**

SEE INSERT ON CARDIOVASCULAR RISK

ITALIAN CHARTS: THE WEIGHT OF THE MAIN CARDIOVASCULAR RISK FACTORS

By applying the risk function of the Italian Charts to some clinical scenarios (figure 2) it can be seen that:

- the **oldest** patients and those treated for **hypertension** have a higher cardiovascular risk, with similar blood pressure and cholesterolemia levels;
- compared to men, **women** have a clearly lower cardiovascular risk, with similar risk factors;
- in **men**, giving up smoking or lowering total cholesterolemia by 30% have a similar effect on reducing the cardiovascular risk;
- in **women**, giving up smoking reduces the risk more than lowering cholesterol by 30 mg/dL.

It is important to remember that the charts do not take into consideration all the clinically important cardiovascular risk factors, such as genetic factors, lifestyles and overweight.
The charts are, therefore, useful instruments for the doctor to assess the patient's risk, but they do not replace his overall clinical judgement.

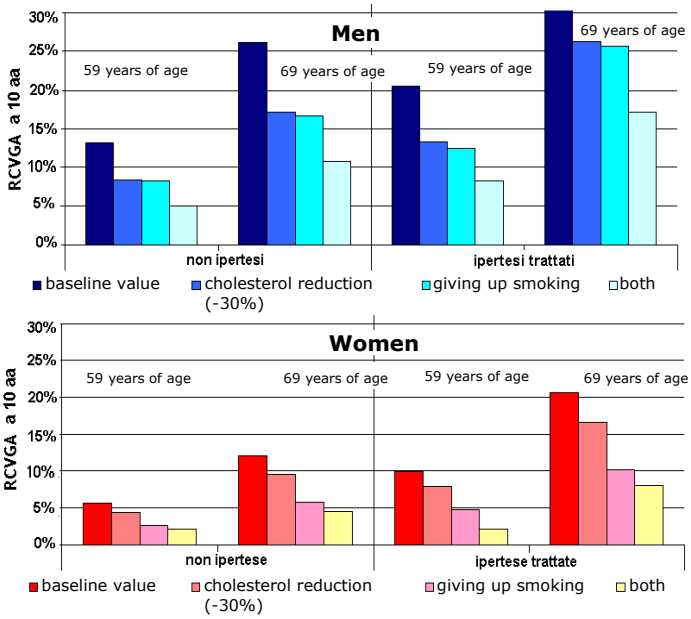


Figure 2. *How the baseline cardiovascular risk changes by modifying smoking and cholesterolemia, in men and women of different age ranges (59 and 69 years of age) with SBP of 140 mmHg (treated normal or hypertensive patients) and cholesterolemia of 250 mg/d*

Statins in primary prevention

The features of the main studies

KEY MESSAGES

- The RCTs on the effectiveness of statins in primary prevention were conducted on subjects with a high baseline cardiovascular risk.
- In the populations under study, women for the most part are underrepresented.
- There are no RCTs on Mediterranean populations.

Table 1. *Features of the 6 double-blind randomized trials - with at least 1500 patients and lasting over 3 years - that provide data on the effectiveness of statins in PRIMARY PREVENTION.*[6-11]

Trial, year of publication and population	Molecule and dose	No. of patients Average age Sex (M)	Length (years)	Average total cholest. mg/dL,	Estimate of GCVR at 10 years
WOSCOPS, 1995[6] cholesterolemia > 252 Hypertensives 15%	Pravastatin 40 mg	6565 55 years of age M=100%	4.9	**272**	***> 24 %***
AFCAPS/TEX, 1998[7] hypertensives 220%, diabetics 6%	Lovastatin 20-40 mg	6605 58 years of age M=85%	5.2	**221**	***> 20 %***
PROSPER, 2002[8] elderly population primary prev. 56%	Pravastatin 40 mg	5804 75.3 years of age M=48%	3.2	**218**	***> 37,8 %***
ASCOT-LLA, 2003[9] hypertensives 100% + 3.7 risk factors for CHD	Atorvastatin 10 mg	10.305 63 years of age M=81%	3.3	**213**	***> 30,6 %***
Primary prevention in diabetes					
HPS diabetes, 2003[10] diabetics 100% hypertensives on treatment 40%	Simvastatin 40 mg	2912 62 years of age M=70%	5.0	**221**	***> 27 %***
CARDS, 2004[11] diabetics 100% hypertensives on treatment 67%	Atorvastatin 10 mg	2838 62 years of age M=68%	3.9	**210**	***> 24,6 %***

It is a **rough estimate**, obtained by taking into consideration the frequency of events in the placebo group of each trial and projecting this number at 10 years (with a simple proportion).

Where possible, the events used on the Italian risk chart were taken into consideration.

It is an **underestimation** because it takes into consideration a constant risk increase over time (in fact the events are more frequent as the years go by).

There are no RCTs available to assess **ROSUVASTATIN** on cardiovascular clinical events

TRANSFERABILITY OF THE RESULTS:

- All these trials were conducted in Northern Europe or in the United States, in populations with a baseline risk higher than in Italy.
- Mainly male populations were enrolled in the trials.
- The cardiovascular risk of these populations is estimated to be over 20% at 10 years.
- There are no data on effectiveness for populations with a cardiovascular risk below 20%.

HPS AND ALLHAT-LLT: WHY THEY HAVE NOT BEEN CONSIDERED IN THIS INFORMATION PACKAGE

HPS: is the largest of the randomized trial on statins (20,536 patients), with a 5 year follow-up.[12]

It included patients with at least one previous cardiovascular and/or diabetic event. In these populations the trial clearly demonstrated the effectiveness of simvastatin, justifying its use in secondary prevention as a "new aspirin".[13]

According to the HPS data, it is necessary to treat on average 19 of these patients for 5 years to have one less case of myocardial infarction, stroke or revascularization, and 56 patients to prevent one death

Taking into account the objectives of this **Information Package (that does not take secondary prevention into consideration)**, an assessment was made only of the part of the trial relating to diabetic patients without CV disease (page 10)[10]

ALLHAT-LLT: this is a part of the ALLHAT trial that assesses the effectiveness of pravastatin in 10,355 patients. Since this subtrial was not "double-blind", around 30% of the patients who had been randomized for placebo in fact also took a statin of their own accord, thus weakening the trial results.[14]

ASCOT Study (statin part)

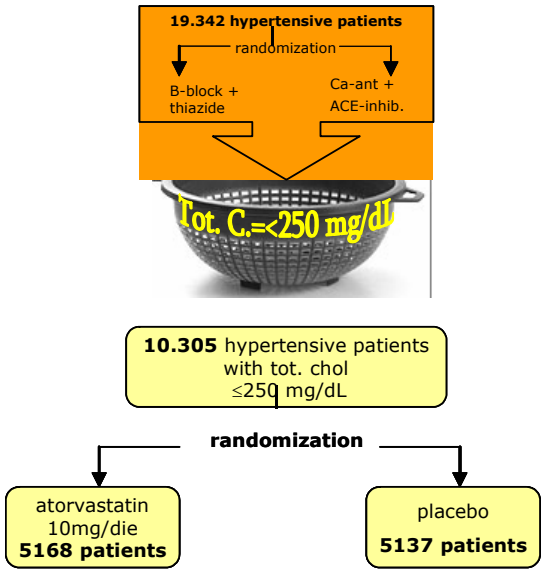
Effectiveness of statins in high-risk patients

KEY MESSAGES

- In a very high-risk male population, atorvastatin reduces the probability of a first cardiovascular event.
- The absolute impact of the treatment is moderate: it is necessary to treat an average of 94 patients for 3 years to prevent one of them having a non-fatal myocardial infarction or a fatal cardiovascular event.

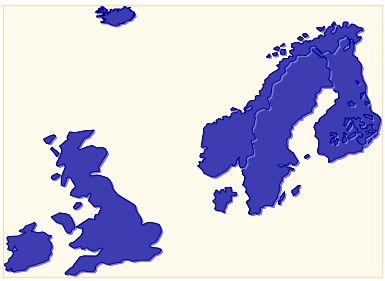
The ASCOT study recruited a total of 19,342 hypertensive patients without previous coronary events, with two objectives:

1. to assess the effectiveness of two different antihypertensive methods;[15] the results of this assessment will be the subject of a further information pack.
2. to assess the effectiveness of atorvastatin in reducing cardiovascular events in a population of hypertensive patients with cholesterolemia below the average.[9] Only 10,305 patients with total cholesterolemia ≤ 250 mg/dl, whose GP decided a hypolipemizing treatment was not strictly necessary, were therefore randomized for atorvastatin or placebo.



In this Information Package we deal only with the part of the ASCOT study relating to the hypolipemizing treatment (ASCOT-LLA)[9]

The trial on atorvastatin, initially programmed to last for 5 years, was stopped after 3.3 years, after an intermediate statistical analysis had shown a significant difference between drug and placebo in reducing the main indicator.



A HIGH-RISK POPULATION

It is a northern European population with a higher baseline cardiovascular risk than the Italian population, cholesterolemia and the main risk factors being equal.

In this population, with an average cholesterol of 213 mg/dL, the frequency of cardiovascular events, which is 3% a year in the placebo group, is at least 30% if projected at 10 years (with a simple proportion).

All the risk charts (both the Italian one and the others) consider a risk of this size as **very high**.

POPULATION AND METHOD	
GEOGRAPHICAL AREA	**United Kingdom and Scandinavia**
POPULATION (10.305 patients)	**Patients with no previous coronary events, with:** • **total cholesterol ≤** 250 mg/dL; mean 213 mg/dL • **systolic BP** > 160 mm Hg (>140 mm Hg if treated); mean: 164 mm Hg or **diastolic BP** > 100 mm Hg (>90 mm Hg if treated); mean: 95 mm Hg • and with **at least three of the** following risk factors:
	Frequency observed
Male sex	81% men (8363 patients)
Age > 55 years	mean: 63 years of age (64% > 60 years of age)
Smokers	33% (3374 patients)
Diabetes	~ 25% (2532 patients)
Previous stroke or TIA	~ 10% (1001 patients)
	Others: ECG abnormalities, left ventricular hypertrophy, peripheral vasculopathy, occurrence of early CV events, microalbuminuria/proteinuria, tot cholesterol/HDL ratio > 6
INTERVENTION	atorvastatin 10 mg
CONTROL	placebo
OUTCOMES	• **non-fatal and/or silent myocardial infarction (MI) + coronary mortality (main outcome)** • fatal and non-fatal MI (excluding silent MI) • fatal and non-fatal stroke • cardiovascular mortality • overall mortality
FOLLOW UP TIME	**3.3 years** (suspended before the planned 5 years)

ASCOT Study (statin part)
The results and their transferability

Treatment with atorvastatin was shown to be more effective than placebo in reducing non-fatal myocardial infarction, both silent and non-silent, and coronary mortality (main outcome), fatal and non-fatal stroke and all cardiovascular events including revascularization procedures.
It was not more effective than placebo in reducing cardiovascular and total mortality.

Table 2. *Main results of the ASCOT-LLA study.*

	Atorvastatin 10 mg (5168 patients)	**Placebo** (5137 patients)	**Absolute risk reduction**	**NNT***
Non-fatal AMI (silent and non-silent) + coronary mortality (main outcome)	1.9 %	3.0%	1.1%	91
Fatal and non-fatal AMI (excluding silent AMI)	1.7 %	2.7%	1.0%	100
Stroke (fatal and non-fatal)	1.7 %	2.4 %	0.7%	143
Cardiovascular mortality	1.4 %	1.6 %	NS	--
All cardiovascular events + revascularization procedures ^	7.5%	9.5%	2.0%	50
Total mortality	3.6%	4.1%	NS	--

NS = statistically not significant
**NNT = number of people to be treated for 3.3 years with atorvastatin rather than placebo to prevent an event; it is not stated whether the absolute risk reduction is not significant.*

TREATMENT FOR MANY, BENEFITS FOR FEW

In order to prevent a myocardial infarction, it is necessary to treat an average of 94 patients with very high cardiovascular risk for 3.3 years.

Statin also reduces the risk of stroke.

In order to prevent a major cardiovascular event (including revascularization procedures), it is necessary to treat an average of 53 patients with very high cardiovascular risk for 3.3 years.

CONSIDERATIONS ON THE TRANSFERABILITY OF RESULTS

- The trial was carried out in the United Kingdom and Scandinavia; the results could therefore overestimate the impact of statin in the Italian population (figure 1 on page 2)
- Results of this trial can be transferred to a population that the charts consider "very high-risk" (table 1 on page 3)
- The main guidelines agree on treating these cases with lipid lowering drugs.

FEW DATA ON SIDE EFFECTS

The trial reports that the most frequent side effects of statins (myalgia, variations of muscle and liver enzymes, etc.) are similar in the two treatment groups (atorvastatin or placebo), but without showing numerical data.

A single case of rhabdomyolysis with atorvastatin, attributed to concomitant alcohol abuse, is reported.[16,17]

SUBGROUP ANALYSIS: POTENTIALLY USEFUL, TO BE USED WITH CAUTION

- Besides assessing the outcomes in the whole population enrolled, the authors also planned to carry out analyses on some subgroups.
- Subgroup analyses in the ASCOT-LLA study are not conclusive on the effectiveness of statins in women, in patients under 60 years of age and in diabetics.
- No analysis was planned to assess whether there are benefits in patients with cholesterolemia of between 180 and 240 mg/dL.
- It is necessary to take care not to assign a final value to the results of the subgroups, because they are obtained on samples with small numbers (compared to the starting population) and which are often insufficient to record differences that may be real and not merely casual.[16,17]
- These analyses can, however, provide useful information and/or suggest the need to carry out further in-depth ad hoc studies. For this reason they are also defined 'hypostheses generating analyses' .

Statins and elderly patients

How effective in primary prevention

KEY MESSAGES

In the over-seventies:

- the correlation between cholesterolemia and CV risk is weaker than in those between 40 and 70 years of age.
- There are no conclusive data on the effectiveness of statins in *primary* prevention of CV events.

ELDERLY PATIENTS AND CHOLESTEROLEMIA: THE LOWER THE BETTER?

- **At present, the main risk charts, including the Italian one, do not permit an assessment of the probability of CV events of people over 70 years of age**
- It emerges from observational studies that the cholesterolemia-CV risk correlation is more evident between 40 and 70 years of age, even if the importance of cholesterol levels tend to diminish with age.[18]
- Over 70, the few data available do not confirm that the reduction in cholesterolemia produces the same benefits as in the 40-70 year old age range.[19-20]
- The usefulness of a hypocholesterolemizing treatment in the elderly, in particular in those with no previous CV events, is therefore an open question.

PROSPER STUDY: PRIMARY AND SECONDARY PREVENTION IN THE OVER-SEVENTIES[8]

The PROSPER study is the only RCT to have included only people over 70 years of age, half of whom had no previous cardio-cerebrovascular events.

Northern European population with or without previous events

The patients are high-risk patients. The frequency of major CV events in untreated patients (placebo group) is 12.1% after 3.2 years. By making a rough estimate through a simple proportion, the risk at 10 years would be above 37%.

GEOGRAPHICAL AREA	Northern Europe (Scotland, Ireland and the Netherlands)
POPULATION (5804 patients)	• **3239 without previous CV events** (56% of the total) • 2565 with previous CV events The features of the overall population are: • average **age**: 75 years (range: 70 – 82) • **52% women** • Total **colesterolemia**:mean 220 (range: 154-347 mg/dl) • 62% hypertensives (average BP 155/84 mm Hg); 27% smokers; • 11% diabetics
INTERVENTION	Pravastatin 40 mg (2891 individuals, of whom 1585 have no previous CV events)
CONTROL	Placebo (2913 individuals, of whom 1654 have no previous CV events)
OUTCOMES	• **Coronary disease and stroke (fatal and non-fatal, main outcome)** • fatal and non-fatal infarction • fatal and non-fatal stroke • coronary mortality
FOLLOW UP TIME	Average 3.2 years

IN PRIMARY PREVENTION, INCONCLUSIVE INFORMATION

- The main objective of the study was to show the effectiveness of statins in patients with and without previous events.
- In the whole **population studied**, statin reduced the main indicator by 2.1% compared with placebo (14.1 vs 16.2%) after three years of treatment.
- Analysis of only **patients without previous events** showed no statistically significant differences between pravastatin and placebo in reducing a first cardiovascular event (from 12.1% to 11.4%). However, the small size of this subgroup could have hindered any small differences from being shown.
- It is stressed that in the subgroup of patients in **secondary prevention** (for whom the baseline frequency of new events is almost double that of patients in primary prevention) it was possible to show the efficacy of statin, with a frequency of cardiovascular events of 17.4% compared to 21.7% of placebo.

In practice, in the over-seventies, without strong evidence and the help of risk charts, the doctor will assess each case on the basis of the patient's general medical history.

Statins in women

Little data available

KEY MESSAGES

- The cardiovascular risk in women is lower than in men.
- In women, high blood pressure and smoking have more weight than high cholesterolemia.
- The number of women enrolled in the trials is insufficient to assess whether statins are effective in this group in reducing CV events.

It is well-known that **cardiovascular risk** is **lower in women than in men**, when the other risk factors are equivalent [1-4]

If the conventional value of 1 (baseline risk: BR) is attributed to the starting risk for each of the sexes, it can be seen that with the increase in **cholesterolemia** the risk increases much more in men than in women. For example, going from total cholesterol values lower than 200 mg/dL to values higher than 240 mg/dL, for men the risk increases to almost double - compared to their baseline risk - while for women it increases by less than half (figure 3)

In women, other modifiable factors such as hypertension and **smoking** have a greater impact than cholesterolemia in determining GCVR (figure 3).

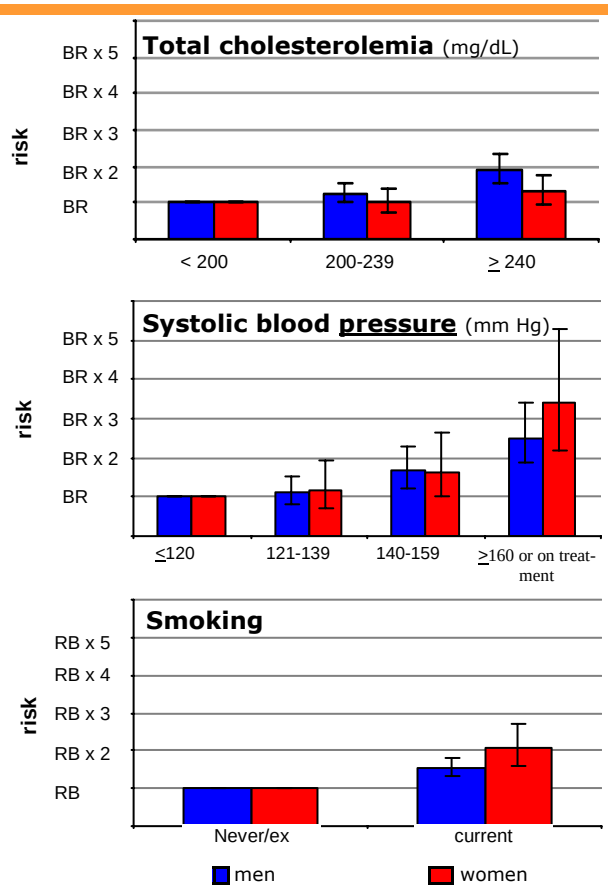


Figure 3. *How GCVR varies in women and men according to some risk factors (BR = baseline risk) Modified by Panico et al.*[21]

WOMEN AND STATINS: TRIAL LIMITS

- With equivalent risk factors, women have a lower incidence of CV events compared with men. This means that it is necessary to include in the trials a very large number of women (around double the number of men) in order to have conclusive information on the effectiveness of statins.
- On the other hand, women are poorly represented in the RCTs on statins (some RCTs have included only men).[22]

THE DATA AVAILABLE

Among the studies with over 1000 people, only 3 RCTs provide data on the efficacy of statins in primary CV prevention in women.

- The ASCOT-LLA[9] study (pages 4-5) included around 2000 women out of a total of 10,305 hypertensive patients, amounting to 19% of the sample. The effectiveness of the treatment with atorvastatin was not shown for women (absolute risk of myocardial infarctions of 1.9% vs 1.8% of the placebo group in 3.3 years), whereas it was shown in men (1.9% vs 3% respectively).
- The PROSPER[8] study (page 6) included 3000 women over seventy years of age, out of a total of 5804 elderly patients. In women, the effectiveness of pravastatin was not shown (absolute risk of CV events of 12.4% with pravastatin vs 12.9% with placebo) despite the presence of patients with previous events (around half).
- The AFCAPS[7] study included around 1000 women out of a total of 6605 patients. In this subgroup it is difficult to assess the effectiveness of statins because in the 5 years the study lasted few events occurred (20 in women, against 279 in men).

At present there are no metanalyses to assess the effectiveness of statins exclusively in primary prevention in women.[22,23]

AD HOC STUDIES ON WOMEN WOULD BE USEFUL

Ad hoc studies on female populations could permit an assessment to be made of what risk levels may benefit from preventive treatment with statins.

For the choice of therapeutic strategy in women, it is important to bear in mind that:

- lowering blood pressure and giving up smoking have a greater weight than lowering cholesterolemia;
- in the case where calculation of the GCVR gives a value < 20%, it is important to consider the presence of risk factors not included on the charts, such as early CV events occurring, obesity, etc.

Rosuvastatin and ezetimibe/simvastatin

There are no data on cardiovascular outcomes

KEY MESSAGES

With regard to prevention of cardiovascular events, at present there are no studies available showing:

- the effectiveness of rosuvastatin;
- the greater effectiveness of the ezetimibe/ simvastatin association compared to simvastatin alone

STATINS AND LDL CHOLESTEROL: THE EFFECT OF THE DIFFERENT DOSES

For rosuvastatin, the reduction of LDL cholesterol is over 30% even at lower doses (5-10 mg), as can be seen in table 3. A small-scale study shows that rosuvastatin reduces LDL cholesterol by around 30% even at 1 mg.[25]
The side effects are, however, dose-dependent.[26]

ROSUVASTATIN: REDUCES CHOLESTEROLEMIA BUT THERE ARE NO DATA ON CV EVENTS

- Rosuvastatin has been available in Italy since 2004 at doses of 10, 20 and 40 mg
- The studies that are recorded show the efficacy of this drug in reducing total cholesterolemia and LDL. At the same doses, the **hypolipemizing** efficacy of rosuvastatin is greater than that of the other statins (table 3).[24]
- **Studies are not available (they are currently in progress) to show the reduction of clinical cardiovascular outcomes** with this drug.

Table 3: *lowering of LDL cholesterol with the various statins at progressive doses [modified by Law et al[24]]*

Statin	5 mg	10 mg	20 mg	40 mg
rosuvastatin	-38%	-43%	-48%	-53%
atorvastatin	-31%	-37%	-43%	-49%
pravastatin	-15%	-20%	-24%	-29%
simvastatin	-23%	-27%	-32%	-37%
fluvastatin	-10%	-15%	-21%	-27%

ROSUVASTATIN: SAFETY INFORMATION

- Preliminary studies had shown, at dose of 80 mg, an increase in myopathy (including rhabdomyolysis) and adverse kidney events (proteinuria, hematuria, increase in creatininemia). This dose has not been registered. [26-27]
- As stated on the technical sheet, the dose of 40 mg is contraindicated in patients with a predisposition to myopathy/rhabdomiolysis, such as those of Asian race, and moderate renal failure (creatinine clearance < 60 ml/min). The technical sheet also recommends the use of the dose of 40 mg/day under specialist supervision.
- In the United States rare cases have been reported (less than one in 10,000 prescriptions) of adverse muscle events (myopathy, rhabdomiolysis), adverse kidney events (renal failure, proteinuria) and adverse liver events. [28] It is, however, difficult to make a comparison with other statins, because the little data available are based on spontaneous reports.

EZETIMIBE + SIMVASTATIN

INDICATIONS

Ezetimibe is an inhibitor of the intestinal absorption of cholesterol, available at the dose of 10 mg both as an individual product (but only in the USA) and in association with 10, 20, 40 mg of simvastatin.
The association ezetimible/simvastatin was authorised in Italy in August, 2005 for the following indications:

- hypercholesterolemia: as treatment added to the diet in patients with primary hypercholesterolemia (family or non-family heterozygote) or with mixed hyperlipidemia **where the use of an association product is indicated**;
- homozygous family hypercholesterolemia: indicated as treatment added to the diet.

WHAT IS KNOWN OF THE EFFECTIVENESS

- Treatment with ezetimibe can reduce the levels of serum LDL by 20% compared to placebo. The association with simvastatin reduces the LDLs by a further 20% compared to the group treated with statin + placebo [29]
- As shown in the registered indications, **studies** to show the efficacy of the association ezetimibe + simvastatin **in the prevention of clinical CV outcomes have not been completed.**

Diabetes

Is it an 'ischemic equivalent'?

KEY MESSAGES

- Since 2001 the most authoritative guidelines consider diabetes as an "ischemic equivalent" and, as with post-infarction, recommend aggressive treatment with statins to reduce LDL cholesterol under 100 mg/dl.
- More recent studies seem to weaken this theory.
- In diabetic patients, other risk factors being equal, the reduction of blood pressure has a greater impact than the reduction of cholesterolemia on lowering the CV risk.

In the '90s, observational studies showed that:

- diabetics have a greater risk of a first cardiovascular event than non-diabetics (2 to 4 times more);
- this risk in diabetics is similar to that of non-diabetic patients with coronary disease.[30]

Already since 2001, these observations have led the most authoritative guidelines to consider diabetes as an "ischemic equivalent" and to recommend the use of aggressive treatment with statins to reduce LDL cholesterol below 100 mg/dL.[3,31] Since 2004, this concept has been taken into account in AIFA Note 13.

More recent studies seem to weaken the theory that diabetes is an "ischemic equivalent".

One study, published in 2004, observed the cardiovascular events in two groups of men between 35 and 57 years of age for 25 years[32]: compared to non-diabetic patients with previous episodes of myocardial infarction (4625 patients), diabetics without myocardial infarction (4809 patients) had a lower frequency of coronary events and a higher frequency of stroke (table 4).
In the HPS study (see pages 3 and 10), the risk of diabetic patients without CV disease is half that of non-diabetics with CV disease (13% vs 25% at 5 years).

Caution is necessary in interpreting all the data mentioned: in fact, it is not certain that the two groups can be compared for all the possible risk factors.

Table 4: *CV and non-CV mortality in patients with diabetes or previous myocardial infarction.*

Mortality from	**Non-diabetics with previous infarction** (no. of events x 10,000/year)	**Diabetics without previous CV events** (no. of events x 10,000/year)
Coronary disease	159.4	104.0
Stroke	8.1	14.2
Total CV diseases	193.7	144.2
Non-CV diseases	81.6	131.5

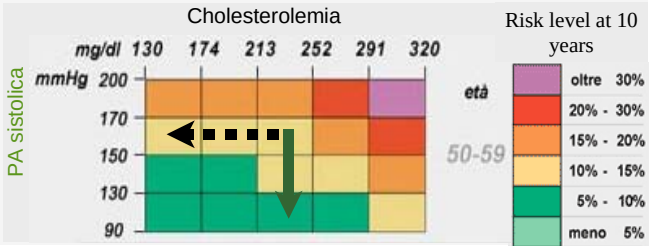
IN THE DIABETIC, THE CV RISK IS REDUCED FURTHER BY LOWERING BLOOD PRESSURE

As emerges also from the cardiovascular risk charts, **in diabetic patients**, other risk factors being equal, **the reduction of blood pressure has a greater impact than the reduction of cholesterolemia on lowering GCVR**.

For example, a 55-year-old diabetic, non-smoker, with a cholesterolemia level of 232mmg/dl and systolic pressure of 160 mmHg, will have an GCVR at 10 years of 10-15%.

As can be seen in the risk chart below, just the reduction of cholesterolemia (black dotted arrow) will not change the GCVR, whereas the reduction of blood pressure will reduce the GCVR to a value of 5-10% (green arrow).

(this will be dealt with in more detail in a subsequent Information Package on the treatment of hypertension)



DIABETES: TOTAL OR LDL CHOLESTEROL

Uncontrolled hyperglycemia is responsible for a change in the composition of the lipoproteic fractions. In particular, LDLs of smaller dimensions, greater density and atherogenic effect are present in diabetics.
Even if a direct dosage of LDL cholesterol is possible, in most laboratories it is still calculated with Friedwald's formula :

C-LDL = C-total — C-HDL — (TG/5)

It is therefore an important objective to monitor in the diabetic patient not only total cholesterolemia but also the concentration of LDLs.

Statins in diabetics without CV disease

The studies available

KEY MESSAGES

- Statins are effective in diabetic patients without previous cardiovascular events, but with high CV risk (> 20% in 10 years).
- There are no studies on the effectiveness of statins in diabetics with a CV risk that is not high.
- In diabetics also, the charts can help to decide whether or not to administer treatment depending on the risk level.

In diabetes, the effectiveness of statins in primary CV prevention was assessed in subgroups of large trials (HPS and ASCOT) and only recently in a specific trial (CARDS).

HPS STUDY and DIABETICS

HPS, which involved a total of 20,536 patients over 5 years, assessed the effectiveness of simvastatin in patients with previous CV disease or with diabetes (with or without CV disease). [12]

Presented here are the results relating to the subgroup of **2912 diabetic patients without cardiovascular disease.** [10] The authors do not provide detailed information on this specific subpopulation.

RESULTS after 5 years of treatment	Simvastatin 40 mg 1457 pat.	Placebo 1455 pat.	Absolute risk reduction	NNT*
Fatal and non-fatal CV events (including revascularizations)	9,3%	13,5%	**-4,2%**	**24**

The patients are high-risk patients. The frequency of first CV events (AMI, stroke, revascularization procedures) in untreated patients (placebo group) is 13.5% after 5 years. By making a rough estimate through a simple proportion, the risk at 10 years would be 27%.

Simvastatin reduces the risk of CV events by 4.2% in 5 years. In this population of diabetics, it is necessary to treat 24 patients for 5 years in order to prevent one of them having a first CV event (NNT=24).

ASCOT-LLA STUDY (statin part) and DIABETICS

The ASCOT study (statin part, dealt with on page 4-5)[9] assessed the effectiveness of 10 mg of atorvastatin in hypertensive patients, predominantly (90%) without previous CV events.
Presented here are the results relating to the subgroup of **2532 diabetic patients without cardiovascular disease** [33]

The patients are high-risk patients. The frequency of first CV events in untreated patients (placebo group) is 11.9% after 3.3 years. By making a rough estimate through a simple proportion, the risk at 10 years would be around 38%.

Atorvastatin reduces the risk of CV events by 2.7% in 3.3 years. In this population of diabetics, it is necessary to treat 37 patients for 3.3 years in order to prevent one of them having a first CV event (NNT=37).

RESULTS after **3.3 years** of treatment	Atorvastatin 10 mg 1258 pat.	Placebo 1274 pat.	Absolute risk reduction	NNT
Non-fatal and/or silent AMI + coronary mortality	3.0%	3.6%	-0,6% (NS)	-
Total CV events	9.2%	11.9%	**-2.7%**	**37**

NS = not statistically significant

Statins in diabetics without CV disease

The CARDS study

The **CARDS**[11] study is an RCT that specifically assesses the effectiveness of atorvastatin in diabetic patients without medically evident CV disease, but with high CV risk (see table).

The study had initially been programmed to last for 5 years, but was suspended early after 3.9 years because an intermediate statistical analysis had shown the effectiveness of atorvastatin in reducing the main indicator.

IT IS A HIGH-RISK POPULATION

As for the other studies described, this one also assessed northern European patients with high CV risk.

In this population, with a mean LDL cholesterol of 117 mg/dL, the frequency of cardiovascular events (of 2.5% a year in the placebo group) is around 25% if projected at 10 years (with a simple proportion).

All the risk charts (both the Italian one and the others) consider a risk of this size as **high**.

POPULATION AND METHOD	
GEOGRAPHICAL AREA	**United Kingdom + Ireland**
POPULATION (2838 patients)	• type-2 diabetics diagnosed since at least 6 months (mean: 7.8 years; 85% on treatment) • without previous CV events • age: 40-75 years (50% between 60 and 70 years of age) • 68% men • LDL cholesterolemia<160 mg/dL (mean 117 mg/dL) • triglycerides < 600 mg/dL With at least one of the following risk factors: • history of hypertension (84%) • retinopathy or albuminuria (47%) • smoking habit (23%)
INTERVENTION	atorvastatin 10 mg (1428 patients)
CONTROL	placebo (1410 patients)
OUTCOMES	• **main outcome:** non-fatal and silent infarction + unstable angina + coronary mortality + fatal and non-fatal stroke + revascularization • **secondary outcome**: overall mortality
FOLLOW UP TIME	3.9 years (suspended before the planned 5 years)

OUTCOMES after 3.9 years	Atorvastatin 10 mg (1428 pat.)	Placebo (1410 pat.)	**Absolute risk reduction**	NNT
Non-fatal and/or silent myoc. infarction + coronary mortality + unstable angina + stroke + revascularizations	5.8%	9.0%	**-3.2%**	**31**
Total mortality	4.3	5.8	-1.5 % (NS)	-

NS = not statistically significant

Atorvastatin reduces the risk of CV events by 3.2% in around 4 years.

In this population, it is necessary to treat 31 patients for 4 years in order to prevent one of them having a first CV event (NNT=31)

AND IN A LOWER-RISK POPULATION?

- There are no studies available that have assessed the effectiveness of statins in diabetics without previous CV events with a risk <20% at 10 years.
- In these patients, it is not entirely clear whether lowering cholesterolemia gives rise to added benefits.
- **Calculation of the overall risk with the Charts / Calculator can provide useful support in the decision on whether or not to treat these pa-**

Final considerations

IN GENERAL …

- The RCTs on the effectiveness of statins in preventing a first major CV event have been conducted in populations where cholesterol is a particularly important risk factor: anglosaxon men with baseline GCVR > 20-30%.
- In these populations, statins have been shown to be effective.
- There are no RCTs available on Mediterranean populations.

… FOR THE ELDERLY AND WOMEN …

- For the **over-seventies**, there are no conclusive data on the effectiveness of statins in *primary* prevention of CV events.
- The number of **women** included in the RCTs available does not allow conclusive assessments on the preventive effectiveness of statins in this group.

Also, in women high blood pressure and smoking have more weight (on CV risk) than high cholesterolemia.

… FOR DIABETICS

- Statins have been shown to be effective in diabetic patients with no previous cardiovascular events, but with high CV risk (> 20% at 10 years). There are no studies on the effectiveness of statins in diabetics with a lower risk.
- Other risk factors being equal, the reduction of blood pressure has a greater impact than the reduction of cholesterolemia on lowering the GCVR.
- In diabetics with no previous CV events, the charts can help the doctor decide on a hypocholesterolemizing treatment, within the sphere of an overall therapeutic strategy.

A glance at local prescription data : Modena

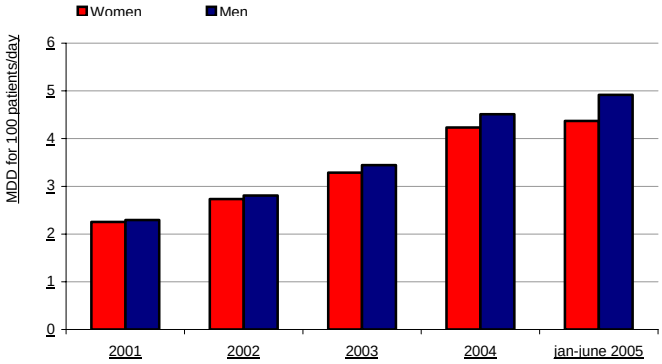


Figure 4: *Trend of the prescription of statins (DDD for 100 inhabitants/day)* ***in women and men****, from January, 2001 to June, 2005, at the Modena Local Health Care Trust*

Comparison between women and men

The percentage of mean daily doses (DDD, figure 4) prescribed for patients is

- similar for men and women
- constantly on the increase over the years.

Prescription per age range

In proportion, statins are mostly prescribed in the 60-69 year-old age range and (even more) in the 70-79 year-old age range (figure 5).

The prescription of statins in the 50-59 year-old age range is similar to that in the >80 year-old range.

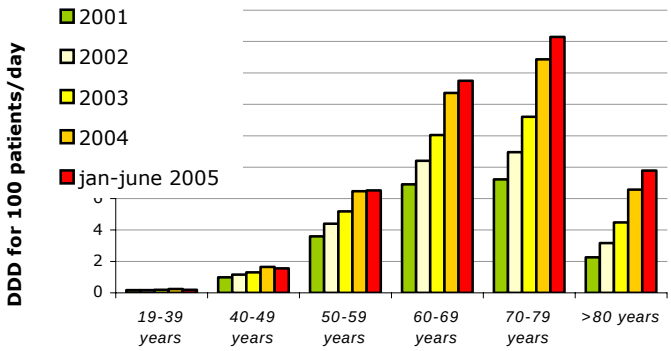


Figure 5: *Trend of the prescription of statins (DDD for 100 inhabitants/day)* ***for each age range****, from January, 2001 to June, 2005, at the Modena Local Health Care Trust.*

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