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Where to draw the line using statins: Lessons from 4S to AFCAPS/TexCAPS

EVENTUALLY, physicians will have to draw a line in prescribing lipid-lowering therapy. A splendid assortment of studies performed in the past 10 years has demonstrated that treatment with HMG-CoA reductase inhibitors (ie, "statins") can reduce the rates of morbidity and mortality from coronary artery disease in a variety of populations by a statistically significant amount—approximately one third as a matter of fact. But for patients at low risk, a treatment that is beneficial statistically may not be practical or economical: it may involve treating too many patients to prevent too few events.

But how should this question be decided? And *who* should decide: patients, physicians, or health maintenance organizations?

Two recent studies illustrate the quandary: The Scandinavian Simvastatin Survival Study (4S)[1] and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS).[2]

4S: TREATMENT REDUCES MORTALITY IN PATIENTS AT HIGH RISK

The 4S[1] was designed to determine if treatment with simvastatin would decrease the mortality rate in patients at high risk. All 4,444 patients in this study had either survived a previous myocardial infarction or suffered from angina, indicating they already had coronary artery disease.

Another criterion for entry: all patients had to have a serum cholesterol level of at least 213 mg/dL while on a low-fat diet. The mean cholesterol level at baseline was 261 mg/dL. The mean level of low-density lipoprotein (LDL) was also high at 188 mg/dL.

4S study results

At the end of 5.4 years, the 4S investigators noted statistically significant differences between the groups in the following measures.

Lipid levels. Cholesterol levels decreased by 25% in patients receiving simvastatin but increased by 1% in those receiving placebo. LDL levels decreased by 35% in simvastatin patients but increased by 1% in placebo patients.

Mortality. Of the 2,221 patients in the simvastatin group, 182 (8%) died, compared with 256 (12%) of those receiving placebo ($P = .0003$).

Major coronary events (ie, coronary death, nonfatal definite or probable myocardial infarction [MI], silent MI, or resuscitated cardiac arrest) occurred in 431 (19%) of the patients in the simvastatin group vs 622 (28%) in the placebo group ($P < .00001$).

Should low-risk patients receive statins? Who should decide?

AFCAPS/TexCAPS: TREATMENT REDUCES RISK IN HEALTHY PERSONS

In contrast, patients in the recently-published AFCAPS/TexCAPS[2] occupied the other end of the spectrum of risk. None of the 6,605 patients had evidence of coronary artery disease at baseline. Baseline lipid levels were also lower than in the 4S study: the mean cholesterol level was 221 mg/dL, and the mean LDL level was 150 mg/dL. In fact, only 17% of the patients would have met the National Cholesterol Education Program (NCEP) criteria for drug therapy.[3]

AFCAPS/TexCAPS study results

At the end of 5.2 years, the investigators noted the following differences in patients

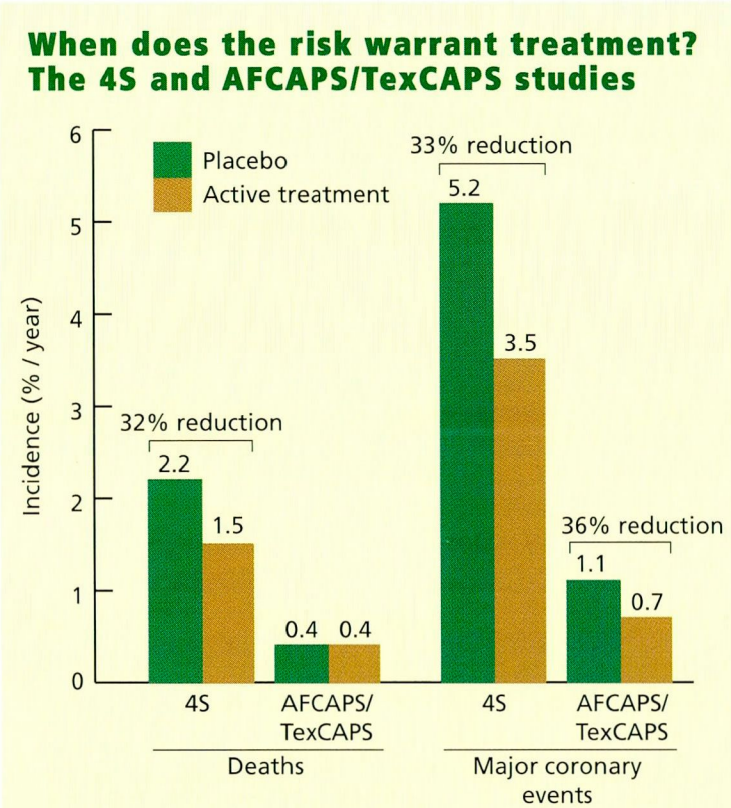

FIGURE 1. Effect of lipid-lowering drugs on the incidence of death and major coronary events in the Scandinavian Simvastatin Survival Study (4S)[1] and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS).[2] Although treatment reduced risk by approximately one third in both studies (except for deaths in AFCAPS/TexCAPS), the patients in AFCAPS/TexCAPS were at less risk than those in 4S to begin with and had a much smaller reduction in absolute risk.

randomized to receive lovastatin compared with those receiving placebo.

Lipid levels. Total cholesterol levels decreased by 18% and LDL levels decreased by 25% in the lovastatin group, but did not change in the placebo group.

Mortality. Only 2% of patients in each group died, reflecting the healthy status of the cohort. In any event, the AFCAPS/TexCAPS study was not designed to detect a difference in mortality rates with treatment.

Major coronary events (ie, fatal or nonfatal MI, unstable angina, or sudden cardiac death) occurred in 116 (3.5%) of the patients receiving lovastatin, compared with 183 (5.5%) of those receiving placebo ($P < .001$).

SOCIETAL CHALLENGES FOR PREVENTIVE STRATEGIES

The 4S,[1] published in 1994, was a landmark study, as it established that therapy could substantially reduce lipid levels, coronary heart disease events, and mortality in patients with heart disease. As a result, a statin is now recommended as part of the standard regimen for patients who have had an MI or who have angina. (Fewer than 40% of these high-risk patients actually receive a statin, however, and only 25% achieve goal LDL levels.[4])

AFCAPS/TexCAPS,[2] published in 1998, was no less a landmark study, as it demonstrated that lipid-lowering therapy could reduce the risk of coronary events in "average" adults. It has further strengthened the position of lipid-lowering strategies in clinical medicine.

Yet, another look at the numbers might temper our enthusiasm. Although the risk of a major coronary event was reduced by 36% in AFCAPS/TexCAPS, the risk was only 1.1% per year to begin with (FIGURE 1). Thus, the absolute risk reduction was only 0.4% per year.

As reviewed in an editorial by Pearson,[5] these realities pose intriguing societal challenges for preventive strategies, as outlined below.

Is lipid-lowering cost-effective?

Lipid-lowering drugs are expensive, as is the ancillary health care required to prescribe them. Managed care organizations have viewed a risk of coronary heart disease events of 1.5% to 2% per year as the floor at which preventive strategies become cost-effective. Haq et al,[6] in a document called the Sheffield table, originally also placed this number at 1.5%, but later revised it to 3.0%.[7]

Patients may view the economic equation differently. Many would far prefer to take a lipid-lowering drug now than possibly undergo coronary bypass surgery later, however remote the possibility. Some theories do posit the patient as being the final arbiter as to whether a particular strategy is worth the cost. This is complex with third-party payers.

Is the benefit of treatment greater than the risk?

Another issue is the medical risk associated with drug use in light of a benefit that becomes progressively narrow. Suppose, for example, that 0.5% of persons who take a preventive drug for a year suffer a side effect, but only 0.4% per year actually benefit by avoiding a coronary event. Is the drug worth it? This would depend on whether the side effect is worse than a coronary event.

Need to calculate the individual patient's risk

A major shortcoming of both the 4S and AFCAPS/TexCAPS was that they did not truly take into account the absolute risk of the individual patient. The main entry criterion in the 4S was that the patient have known coronary artery disease, and in AFCAPS/TexCAPS that the patient *not* have known coronary artery disease. And indeed, a person with known coronary artery disease is at greater risk of a coronary event than a person without known coronary artery disease—but only if all other factors are equivalent. In reality, a person without known coronary artery disease who has multiple risk factors can be at as much risk as a person who already has coronary disease, as demonstrated by Framingham data[8] and data from the West of Scotland Coronary Prevention Study.[9]

For this reason, the current NCEP guidelines base the decision of whether to treat on the patient's LDL level, whether the patient has known coronary heart disease, and whether the patient has two or more risk factors (eg, cigarette smoking, diabetes, hypertension, obesity).

The AFCAPS/TexCAPS investigators will most assuredly publish data in the near future in which they stratify the subjects according to risk. This information might be helpful in deciding when a very healthy patient may appropriately be offered a preventive therapy.

Women and African-Americans remain under-represented

Some subpopulations remain seriously underrepresented in clinical trials. Only 19% of the patients in 4S were women, and only 15% of the patients in AFCAPS/TexCAPS. In addition, few studies have included large numbers of persons of African descent.

This under-representation makes it even more difficult to make recommendations about primary prevention in these subgroups.

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Many would rather take a statin now than possibly undergo CABG later