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Review article

Cardiovascular risk changes after lipid lowering medications: are they predictable?

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Abstract

Changes in cardiovascular risk after lipid lowering medications are generally expressed as relative risk reduction (RRR). Comparison of the eight major studies published in this last decade indicates that the RRRs ranged from a minimum (19%) for the LRC Study with cholestyramine, to maximal values of 34–37% for studies such as the HHS, 4S and AFCAPS/TexCAPS. These RRRs were barely related to the drugs' effects on major lipid parameters, e.g. LDL cholesterol. Instead, by using the absolute risk reduction (ARRs), easily calculated by subtracting the percentage end points for the drug treated from these values of the placebo group in all studies, a wide range of values was found, also adding to the series a non pharmacological study such as the Program on the Surgical Control of the Hyperlipidemias (POSCH) trial. Calculated ARRs were directly correlated to the baseline cardiovascular (CV) risk in all studies, thus allowing an easy prediction of a drug's effect in the selected population. Drugs with different mechanisms (statins, fibrates and resins) all fitted into this correlation nomogram. These findings clearly indicate that the CV effects of lipid changes, such as LDL cholesterol and triglyceride reduction or HDL rises, are in the same direction, and can be well predicted. The similar, almost identical behavior of drugs affecting LDL cholesterolemia to a different degree or not at all, indicates that novel approaches should be sought to improve risk reduction and that individual therapy should be ideally pursued, rather than a 'one drug' approach. © 2000 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Cardiovascular risk; Absolute risk; Relative risk reduction; Absolute risk reduction; Cholesterol lowering; HDL raising; Risk prediction

1. Introduction

A large number of studies, both of primary and secondary prevention have consistently shown a cardiovascular benefit from lipid lowering treatments. Most of these studies have been carried out with the novel HMG-CoA reductase inhibitors or statins [1–5], but studies with drugs with different modes of actions, i.e. fibrates and non absorbable resins, have also provided positive findings [6–8].

Cardiovascular (CV) prevention studies with lipid lowering agents have generally resulted in a dispute mainly over two issues:

1. the safety and efficacy of one drug versus another, also raising the possibility that some, in particular fibrates and resins, may exert untoward effects [9];
2. the apparent relation, or lack of relation, derived from the outcome analysis of large studies, between the extent of LDL cholesterol reduction and cardiovascular prevention [10,11].

Conclusions on these issues have generally proven difficult, when considering that all studies have come up with essentially identical reductions in risk. The so-called relative risk reduction (RRR) has, in fact, generally ranged around 30% in the majority of studies, independent of drug choice. Minimal values of RRR were reported in the LRC study with cholestyramine (-19%) and maximal (based on the major selected end points) in the HHS Study with gemfibrozil (-34%),

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the 4S Study with simvastatin (-35%), and the AF-CAPS/TexCAPS Study with lovastatin (-37%). The issue of cholesterol reduction vs. cardiovascular benefit has been examined in a number of other trials, in the past (e.g. the WHO Trial with clofibrate) and in more recent years. A meta-analysis of the data from most of these trials, many of them of the angiographic type, is given in reference [12].

Analysis of the clinical results of treatment is generally focused on the reduction of events occurring in treated vs. control patients. By this strategy, percent differences in events, be they death or major CV events, e.g. myocardial infarction, coronary bypass, angioplasty or others, have been used to support the efficacy of treatment. Percent reduction of risk obviously provides a 'relative' difference: a 30% reduction may be interpreted as approximately one less event out of 100, if the event in the control group occurs in 3% of the patients, or ten events out of 100 if the control incidence is 30%. The RRR, generally used to report final

results may, therefore, provide at times misleading information. In this review we reevaluated the major lipid-lowering trials focusing our attention on changes in absolute risk as a potential predictor of risk changes induced by drug therapy.

2. Evidence based medicine, absolute risk reduction and number needed to treat

Evidence based medicine (EBM) dictates strict criteria for the evaluation of clinical studies [13]. By EBM criteria, in fact, not only are clinical results evaluated in terms of proper clinical design (controlled investigation and clinical significance of findings), but also on the clinical 'weight' that decisions to treat may have on therapy [14]. Results of a clinical study, apparently successful in terms of RRR may thus provide indication of an extremely costly and demanding therapy, either because of a relatively small overall change in clinical outcome, e.g., for rare diseases, or for infrequent consequences of disease (e.g. stroke in hyperlipidemic patients) [15]. For this reason, EBM criteria prefer not to use the RRR as the major parameter of evaluation, but rather the absolute risk reduction (ARR).

Isles and Norrie were the first to propose that the RRR in the incidence of coronary death and non fatal MI in statin trials should be replaced by the ARR [16]. In Fig. 1, taken from their work, it is clear that the RRR is essentially identical in all, at the time, statin trials. These had, however, widely divergent absolute CV risk, ranging from 22.6% in the placebo arm over 5 years in the 4S trial, to 7.9% in the WOSCOPS Study. Participants of this latter study could be, however, divided into two subgroups, a 'low risk' group with isolated hypercholesterolemia, and a 'high risk' one, i.e. older patients with pre-existing vascular disease [17]. Interestingly, these two subgroups had an identical RRR, i.e. 31%.

Furthermore, in order to evaluate, by a single figure, whether a treatment is of significant value, a parameter selected by investigators working in the field of EBM is the 'number needed to treat' (NNT) [18]. This is given by 100/ARR, and reflects the number of patients needing active treatment to have one additional patient alive (or avoiding morbidity) versus the case if all patients were given a placebo. NNT may range between $100/100 = 1$ (treatment always effective vs. a placebo) to $100/0 = \infty$ (treatment never effective). NNTs for major studies are given in Table 1.

The absolute risk (AR) for CV events varies widely among the different hypolipidemic drug studies [17], in such a way as to obtain considerable overlap in the ARs between studies of primary and secondary prevention. Subjects with a high baseline risk profile in the WOSCOPS trial had an AR very similar to the post-in-
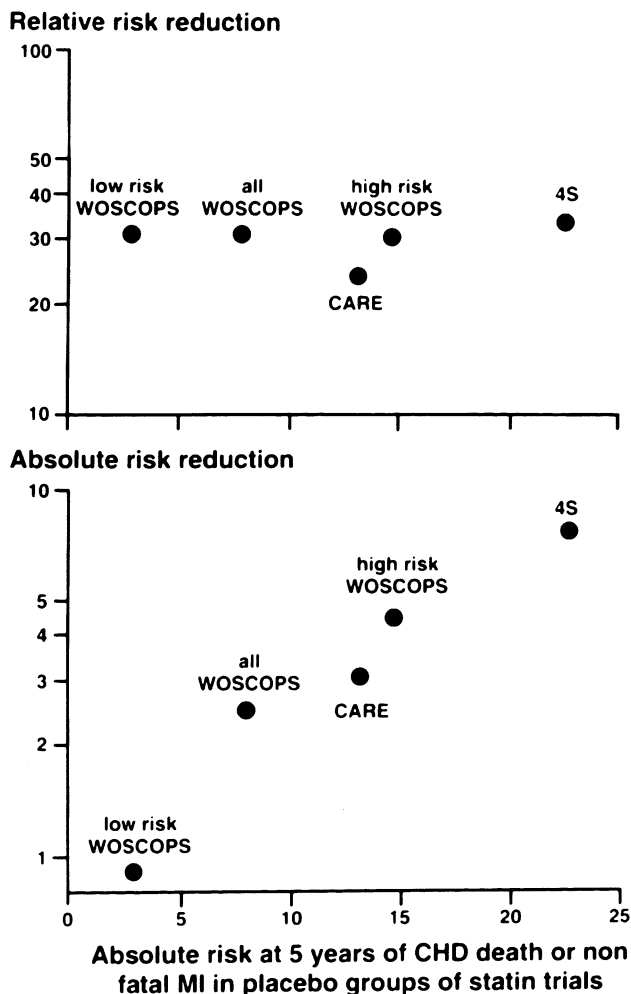

Fig. 1. Relative and absolute benefit from reduction in CV events in 4S, WOSCOPS and CARE studies, including high and low risk WOSCOPS subgroups (from reference [16]).

Table 1
Comparison of coronary risks and benefit in primary and secondary prevention trials on plasma lipids

	LRC	HHS	WOSCOPS	CAPS	POSCH	4S	CARE	LIPID	HIT
Prevention	Primary	Primary	Primary	Primary	Secondary	Secondary	Secondary	Secondary	Secondary
Number	3806	4081	6595	6605	838	4444	4159	9014	2531
Average cholesterol (mg/dl)	292	289	272	221	237	262	209	218	175
CR	−8%	−11%	−20%	−18%	−23%	−28%	−20%	−18%	−4%
AR (CHD death, MI)	8.6	4.1	7.9	5.5	18.0	22.6	13.2	15.9	21.7
RRR	19	34	31	37	35	34	24	24	22
ARR	1.63	1.31	2.45	2.03	6.10	7.68	3.17	3.54	4.40
NNT (100/ARR)	61	76	41	50	16	13	32	28	23

farction patients in the 4S Study [17]. The RRRs in all studies on lipid reduction being around 30%, it was of interest to evaluate what were the effects of individual drugs.

3. Determinants of absolute risk reduction in lipid lowering therapy

Numerous epidemiological studies have linked serum cholesterol, and in particular LDL-cholesterol levels to the risk of coronary heart disease (CHD). In addition, a growing number of studies indicates that low HDL cholesterol levels are a major risk factor and that raising HDL may be an important therapeutic target [19].

In view of the possibility that baseline CV risk could be a more important determinant of CV benefit as compared to lipid/lipoprotein changes (i.e. that lipid/lipoprotein changes per se might not be responsible for the CV risk benefit and this might be regulated by the baseline CV risk), we inserted into the original graph in Fig. 1 the results of the HHS with gemfibrozil, of the LRC study with cholestyramine and also of a non pharmacological intervention study to treat hypercholesterolemia, i.e. the Program on the Surgical Control of the Hyperlipidemias (POSCH) [20]. It may be noted (Fig. 2, upper panel) that the slope of the regression line and the correlation coefficient essentially did not change versus Fig. 1.

The HHS and LRC study are of primary prevention, i.e. similar to the WOSCOPS Study, but, as it is clearly evident, both show a very low absolute CV risk, of 4.1 and 8.6%, respectively. The ARRs can be easily obtained from the difference between end points in the placebo and drug treated groups, i.e. respectively, 1.31 and 1.63%.

It became, therefore, clear, that the major difference in e.g. the HHS and 4S Studies was that in the former only one patient out of 20 in the placebo group had an end point, versus more than 1 out of 5 in the 4S. The

respective NNTs can be thus calculated as 100: 1.31 = 76 for the HHS and 100: 22.6 = 13 for the 4S. A very high correlation ($r = 0.972$, $P = 0.0012$) was thus apparent between absolute CV risk and ARR in 5 years in all lipid lowering studies, including a non pharmacological intervention.

By adding the results of the LIPID Study [4], a very large secondary prevention study in patients with a wide range of cholesterolemia, treated with pravastatin or a placebo, the identity line was not modified (Fig. 2, middle panel), i.e. the LIPID endpoint results (absolute CV risk vs. ARR) gave little further information compared to what was already available in terms of benefit of lipoprotein modifications versus absolute CV risk. In the AFCAPS/TexCAPS Study [5], carried out in 6605 individuals with low HDL cholesterolemia (< 50 mg/
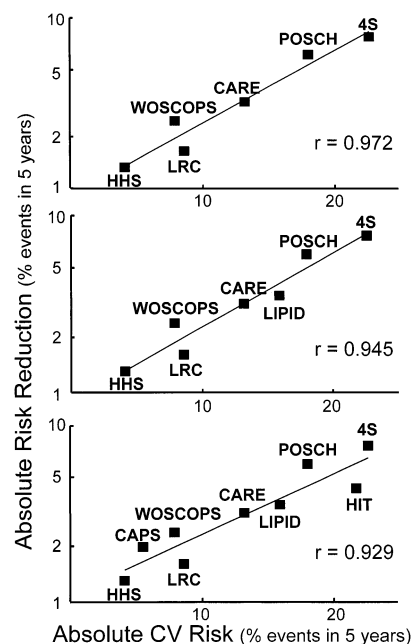
Fig. 2. Relation of absolute benefit, i.e. absolute risk reduction in CV events, versus absolute risk in the earlier lipid-lowering trials (upper panel), plus the LIPID trial (middle panel), and plus the LIPID, AFCAPS/TexCAPS and VA-HIT trials (lower panel).

Table 2
Meta-regression analysis on the none trials considered[a]

Model	Intercept	lnAR	TC baseline	LDL-C baseline	TC reduction	LDL-C reduction	R^2
1	−1.361236	1.035149	–	–	–	–	0.8192
	(0.0002)	(0.0008)					(0.0008)
2	−0.444737		0.000375		–	–	0.0005
	(0.7659)	–	(0.9257)				(0.9527)
3	−1.159272	–	–	–	−0.042929	–	0.3555
	(0.0336)				(0.0902)		(0.0902)
4	−1.620554	0.899532	−0.000435	–	−0.02634	–	0.9294
	(0.0314)	(0.0023)	(0.8682)		(0.0703)		(0.0026)
5	−1.859487	1.019624	–	0.001333	–	0.11272	0.899
	(0.0260)	(0.0032)		(0.7302)		(0.2586)	(0.0064)

[a] Each row shows the results of a multiple regression model including logarithm of absolute risk reduction as outcome and one or more of the various explanatory variables. Numbers indicate coefficients of the mathematical equations. P values are given in brackets. The R^2 statistics indicate the amount of variance of results explained by the explanatory variables.

dl) the AR in the placebo group was slightly higher than in the HHS study (5.5 vs. 4.1%) and the ARR was 2% with a consequent NNT of 50. Interestingly, also in this low risk study, similar to the case of the LRC and HHS studies, there appeared to be excess total mortality (non-statistically significant) in the drug treated group.

Finally, the last reported study, the VA-HIT of secondary prevention [8] with gemfibrozil, was carried out in 2531 men < 74 years of age, selected based on a low HDL cholesterol level (below 40 mg/dl) with normal LDL cholesterolemia (< 140 mg/dl) and triglyceridemia. In this study the primary event occurred in 21.7% of the placebo patients (not different from the 4S Study) and the ARR was 4.4%. In spite of the differences in the selection criteria in this last study, addition of the final results does not modify to a significant extent the regression line between AR and ARR (Fig. 2, lower panel).

Fig. 2 also allows to evaluate some similarities/differences among studies. Comparison of the two low risk primary prevention trials with either a statin (AF-CAPS/TexCAPS) or a fibrate (HHS) suggests that the reduction in end point risk in the statin trial (2%) may be somewhat better than that in the fibrate trial (1.3%), both having a rather similar baseline risks (respectively 5.5 and 4.3%); this may be due to a different selection of the primary end points (cardiac death and myocardial infarction in the HHS, and these two plus unstable angina in the CAPS). A similar case may be provided by comparing the ARRs in the two trials with a very high CV risk (one event out of five in the placebo group, i.e. the 4S and VA-HIT Studies). However, in view of the entirely different lipid profile in the selected population and wide confidence intervals in the mean results, such conclusions would be unwarranted and would possibly need future direct comparative trials.

Taken together, the primary and secondary prevention trials confirm that the RRRs for CHD are similar in all studies (Table 1), independent of the type of intervention. In the LRC study the RRR was clearly lower, most likely possibly due to poor patient compliance; the subset of patients who took correctly the medication reportedly had an RRR of 50% [21]. Benefit of treatment is strongly dependent upon the AR in the examined populations. The higher the AR for coronary events, the more an individual has to gain by treatment [22]. ARRs, when calculated as the NNT, consequently vary widely among studies. In secondary prevention it is sufficient to treat 10–32 patients to prevent a CV event, whereas in primary prevention 41–76 patients need to be treated, in order to have the same benefit (Table 1).

4. Development of linear models for predicting cardiovascular risk changes

A series of linear models on the nine trails were also fitted by weighing them according to their informative content, by adjusting AR and ARR for study duration, and by using a logarithm transformation for AR and ARR [12] (Table 2). From Table 2 it is evident that AR has definitely the major impact on the degree of ARR obtained in the trials considered in the analysis. Total cholesterol reduction and LDL reduction are also important and barely not statistically significant. Baseline total and LDL cholesterol levels appear to be less important. It was not possible to fit baseline HDL cholesterol and HDL cholesterol changes in the models, due to the paucity of available data. Such is also the case of triglycerides.

The results of this meta-regression analysis indicate that AR was undoubtedly the best predictor of absolute risk reduction and models 4 and 5 provide an indication that reductions of total and LDL cholesterol could be well fit into the prediction model. The data used to develop model 1 are given graphically in Fig. 3. Control

of blood lipid level remains a major factor in pharmacological reduction of clinical events. The present results, however, suggest that level of background CV risk is likely to be the most important determinant of the benefit achievable with lipoprotein modifying drugs in clinical practice.

5. Discussion

The analysis according to EBM criteria of the major lipid lowering trials comes to the conclusion that the patient characteristics, rather than the selected drug, is the major factor in eliciting a differential benefit. This finding is to a large extent superimposable to that derived from trials with antihypertensive therapy in populations with a different stroke risk; in these trials, in the face of similar relative benefits as expressed in the percent reduction of stroke, absolute benefit varied widely and was directly correlated with the stroke event rate in the placebo group over a defined time period (figure 5 in [23]). This conclusion is obviously at variance with that from some recently published reviews, suggesting that the percent decrease in LDL cholesterol levels is the major predictor of CV outcome, both as assessed from coronary stenosis changes and reduction in CV end points [24].

Evaluation of CV risk becomes thus an important issue in the selection of treatment and, more importantly, in the decision as to whether a drug should or should not be given [25]. Such conclusion has been supported recently by a reanalysis of the CAPS trial, carried out according to the Framingham Risk equation [26]. By this method, it becomes apparent that men in the five highest deciles had 90% of the events and clearly benefited from treatment. In contrast, men in the five lowest deciles had very few events and, if anything, had an increased risk following drug treatment.

Recently, particularly in Europe, there has been considerable emphasis on the CV risk level at which an individual should be prescribed drug treatment, particularly of the lipid lowering type. In the EAS guidelines, with considerable technical flaws (in particular in the evaluation of HDL levels as a risk factor) and a limited diffusion, a CV risk of 2% per year was indicated as the threshold for drug intervention [27]. With this threshold most drug studies, including essentially all primary prevention studies quoted in Fig. 2, would not have been ethically justified. Other technically more up to date methods for risk evaluation, ie the CERCA Program based on the Münster Prospective Heart Study [28] and the British Heart Association Program [29], the latter based on the Framingham equation, do not suggest any specific threshold. Interestingly, with a novel computer program based on the Framingham risk equation, it was recently possible to predict with reasonable accuracy the event rates in the WOSCOPS Study [30]. Other guidelines, e.g. the Sheffield Tables, based on dichotomous variables (e.g. hypertension present or absent), again assume an average concentration of HDL cholesterol and grossly over-evaluate risk for some individuals [31].

The major issues today are thus twofold, one that of selecting the most appropriate drug therapy candidates (possibly based on available computerized risk programs), and second that of possibly increasing the ARR, eventually achieving a RRR of 50% or higher.
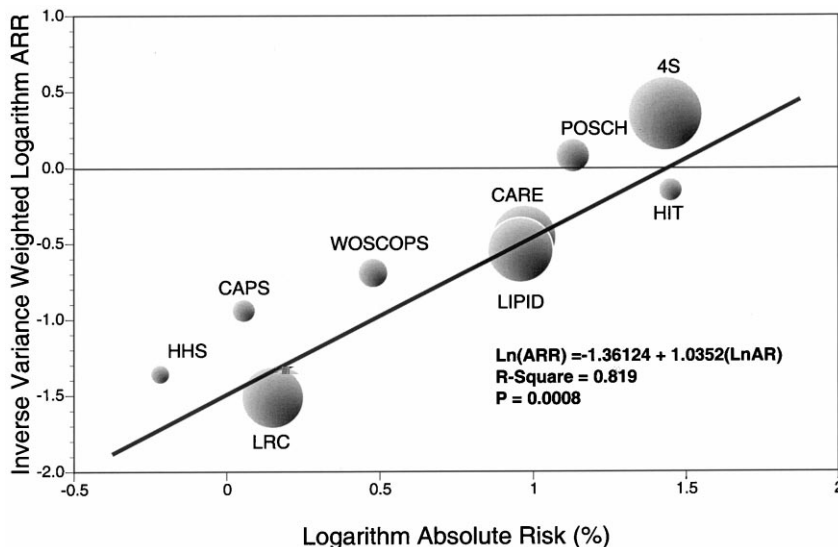

Fig. 3. Meta-regression analysis of absolute benefit, i.e. absolute risk reduction in CV events. The graph represents the inverse-variance weighted linear regression of the logarithmic ARR against the logarithmic AR, according to the equation: ln (ARR) = 1.35124 + 1.0352 (ln AR). Size of circle is proportional to the weight of the trial.

By the proposed approach, the reduction in CV risk appears to be virtually identical for drugs widely different in their LDL-cholesterol lowering potential. A number of studies are now investigating whether, in secondary prevention, higher drug doses of, e.g. atorvastatin and simvastatin (respectively in the TNT and SEARCH Studies) may reduce CV risk to a greater extent vs. ordinary doses. Skepticism on such an approach has been expressed in a recent overview [32] suggesting that the slope of the regression line: cholesterol (or LDL cholesterol)/CV risk is definitely lower in the statin trials vs. that in a control population of coronary patients. From this analysis, it would appear that lowering total cholesterol to 180 mg/dl (or LDL cholesterol to 120 mg/dl) would still leave the coronary patient at a 6-fold excess risk versus a normal individual [32]. While aggressive lipid lowering therapy may indeed rapidly affect arterial disease, thus leading to a similar benefit as coronary angioplasty [33], this may not necessarily translate into clinical benefit in a large population at risk. Indeed, the coronary angiographic studies have not clearly supported a high correlation between extent of LDL lowering and coronary diameter improvement [34,35]. If anything, the CABG study [36] did show a benefit in terms of coronary diameter by more extensive LDL-cholesterol reduction, but this was not accompanied by any decrease in CV events. Novel methodologies, e.g. the IVUS technology, may provide more reliable information on the effect of drugs on unstable plaque structure and composition [37]; the ongoing ALERT Study may allow to better select which patients do benefit from lipid lowering treatment, thus potentially improving the choice of those to be treated [38].

Recently, a number of investigators have suggested that LDL cholesterol levels may not be the most appropriate target of lipid modifying therapy. Groves et al. [39] suggest that CV risk calculation, e.g. in the Framingham, but also in the majority of lipid lowering studies, is best predicted by changes in the LDL/HDL cholesterol ratio. In a recent evaluation of the WO-SCOPS findings [40] it appears that the best predictors of events were not LDL cholesterol changes (in a narrow range in the selected population) but rather high triglycerides and low HDL levels, thus suggesting that an 'atherogenic phenotype' does occur in moderate to severe hypercholesterolemia [41]. Low HDL levels are a clearly established risk factor both for progression of coronary heart disease and for reduction of events following treatment [19]; an overview of available lipid lowering trials with statin and other drugs clearly indicates that subjects with high HDL levels are rather insensitive to treatment, both in terms of event reduction and also of coronary regression [42]. Alterations in the cholesterol ester transfer protein system may possibly be responsible for the apparent insensitivity [43].

Interestingly also in terms of the so called pleiotropic effects of statins [44], a number of studies indicate that low HDL [19] and even high triglycerides do lead to endothelial dysfunction [45]. The presence of high triglycerides has also been suggested to have an important impact on CV risk, reduction in triglyceride leading to a doubling in statistical terms of the effect of concomitant cholesterol reduction on changes in CV incidence [46]. It is however still to be properly evaluated whether not-lipid related pleiotropic effects of statins play a quantitatively significant role [47].

While the importance of AR and ARR seems to be well clarified by the present analysis, thus not requiring inclusion of more trials, the role of lipid levels and of their reduction in CV prevention may need more points/trials in order to confirm the importance of all three major risk factors (LDL cholesterol, HDL cholesterol, triglycerides) in predicting effect of lipid lowering medications in clinical practice. The decision whether to treat aggressively (i.e. with a drug) should in any case depend mostly on an assessment of the patient's baseline CV risk through the use of any of the variety of risk assessment tools presently available.

Once a decision to treat has been made based on the assessment that the patient has a high baseline CV risk, the choice of which drug to use should be dictated by the lipid profile. Patients with a high LDL (> 130 mg/dl for people with established CHD or high risk of CHD and > 160 mg/dl for patients at moderate risk) should receive a statin because there is stronger clinical trial evidence for the benefit of statins. If patients cannot tolerate a statin, there is at least clinical trial evidence for gemfibrozil, bile acid binding resins, and niacin, which can be used as second line therapy. There have been no head to head comparisons of statins in a clinical end point trial, so, while waiting for the results of secondary prevention trials such as the PROVE IT (pravastatin vs. atorvastatin) it is impossible to say that any one statin is better than another. The degree of LDL lowering achievable with any given statin is probably irrelevant as long as there is at least a 25% reduction [48]. Patients without a high LDL (i.e. < 130) but with a low HDL-C, who have established heart disease (and probably those without established heart disease but at high risk) should be given gemfibrozil based on the results of VA-HIT. No statin trial has demonstrated benefit for patients who start out with low LDL-C and the subgroup analyses of CARE and LIPID suggest that statins do not benefit patients with LDL-C < 125 mg/dl. Patients without a high LDL but with a low HDL-C who are at moderate or low risk of heart disease should probably not be treated with drugs. At any rate, it seems now as mandatory to evaluate the global CV risk of selected patients prior to starting any clinical trials with drugs.

The present overview, based on a simple analysis of the effect of drugs with different lipid lowering mechanisms, fully adheres to the EBM criteria for the evaluation of the impact of drug treatment on major diseases [12,13]. It is obviously limited by the relative dyshomogeneity of the trials, carried out in different populations, possibly with different drug compliance and with at times diverging end points (see the AFACPS/Tex-CAPS). At present, the best suggestion is that the 'one pill for all' approach, particularly in secondary prevention, is ill founded, particularly in the case of patients with low cholesterolemia. The presence on the market of a significant number of drugs for lipid control suggests that choice should be based on the drug's clinical and pharmacological properties (kinetics, interactions, etc.), but also on the patient's lipoprotein profile.

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