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The Evolving Paradigm for Statins

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Our paradigm for medicine and health care remains largely population-based (also known as "mass medicalization") rather than patient-centric. Further, notwithstanding the current dogma on "evidence-based" medicine, meaning that the health care provided is based on solid scientific evidence of utility, a large proportion of tests and prescriptions used frequently have little or no such supportive evidence. Another flaw of today's "*evidence-based*" medicine is what has been termed "eminence-based" medicine wherein experts make recommendations or "guidelines" for a large proportion of decisions for which no or minimal data exists. These guidelines have a pronounced impact, as they are believed to represent the standard of care, even though they are based on opinion with a paucity of facts. Actually, even the prestigious U.S. Institute of Medicine concluded that "*any valid evidence supports* "*well below half*" *of the practice of medicine (!)*" (Exclamation symbol and quotation marks added). While examples abound, I will concentrate here on statins and statin combinations.

Statins work by inhibiting the liver enzyme reductase (HMG CoA), an enzyme the body needs to produce cholesterol. As a result, low density lipoprotein (LDL or "bad" cholesterol) levels in the blood go down, thereby lowering total blood cholesterol levels. Statins may also be combined with other cholesterol medicines (such as fibric acid derivatives, bile acid sequestrants, or nicotinic acid) into one pill.

The main reason stated for the widespread prescription of statins is "to reduce the likelihood of a heart attack, stroke, or death". However, in place of this primary goal (or "real end point"), the pharmaceutical industry and the medical establishment use an intermediate measurement thought to correlate well with it. That is, lowering blood cholesterol, a "surrogate end point" and a proxy for improving patient outcomes. The thesis is that for each percentage point that LDL is lowered, there would be about 1 percent reduction of heart attacks. So these two end points (blood cholesterol level and heart attack) should track very closely. Unfortunately, that is not the case!

Not less than seven statins and four statin combinations (a total of no less than eleven drugs) in different doses, are dispensed. This makes up for a large variety of prescription pills which are heavily (albeit not always candidly) marketed so much so as to represent in the U.S. an annual market of $ 26 billion and climbing. The corresponding names are:

For statins:

Generic name	Brand name
1. Atorvastatin	Lipitor
2. Fluvastatin	Lescol
3. Lovastatin	Altoprev, Mevacor
4. Pitavastatin	Livalo
5. Pravastatin	Pravachol
6. Rosuvastatin	Crestor
7. Simvastatin	Zocor

For statin combinations:

Generic name	Brand name
1. Atorvastatin + Amlodipine (a calcium channel blocker)	Caduet
2. Lovastatin + Niacin (nicotinic acid)	Advicor
3. Simavastatin + Ezetimibe (a cholesterol absorption inhibitor)	Vytorin
4. Simvastatin + Niacin (nicotinic acid)	Simcot

Like with many medicines, the use of statins or statin combinations is accompanied by a number of side effects. Patients can either not feel or tolerate minor side effects: muscle aches (not severe pain), upset stomach, a feeling of tiredness, headache,. If these symptoms persist for an extended period of time, the patient is advised to consult the treating physician. However, in case of serious side effects: trouble breathing, swelling of the face, lips, tongue, or throat, hives, liver problems, diabetes, symptoms of *rhabdomyolysis* (a rare muscle problem), severe muscle pain, tenderness, or weakness, dark-colored urine, temporary memory problems, ...the patient is strongly advised to call 911 or other emergency services right away, or even to report to the emergency room of the nearest hospital. The side effects of statin medicines are more likely when higher doses are used.

In line with the current dogma for the use of statins, the leaflets accompanying the dispensed statin medicines systematically emphasize that: (a) the patient should take the medicine as the doctor prescribed to improve health and prevent future problems. Otherwise, health (and perhaps life) is placed at risk; (b) Women are advised not to take the medicine if they are pregnant or plan to get pregnant, or else are breast-feeding; and (c) Follow-up care is a key part of the treatment and safety.

In most patients, LDL levels can be substantially lowered (apparently by 18%-55%), high density lipoprotein (HDL or "good" cholesterol) levels can be increased (apparently by 5%-15%), and triglycerides can be reduced (apparently by 7%-30%). Such results provide great satisfaction to doctors and patients alike and give them a false sense of safety. If doctors do not prescribe statins in cases of elevated cholesterol levels, they may be given demerits by their hospital of affiliation or even be accused of medical malpractice for not adhering to "standards of care".

So, while most patients medicated with statins will have great blood test results, only one percent of them will actually benefit (those who have no history of heart disease but may, according to prevailing conventional norms, be at risk for developing such a condition). In other words, the predominant benefit is a cosmetic one (normalizing a blood test that is out of a conventional range) at the risk of entailing side effects and adding to the current annual burden for prescription drugs ($300 billion in the U.S.). The statin benefit will be greater in those individuals who have already manifested heart disease and could be justified in that situation.

Nonetheless, beyond its premise of an overwhelming regard for a surrogate end point, the wholesale use of statins for primary prevention is the outgrowth of clinical trials. The holy grail of evidence-based medicine is the large-scale randomized, double-blind, placebo-controlled clinical trial performed under the most rigorous conditions. Here, typically, 10,000 or more patients are randomly assigned to take a drug or placebo without the patients or their doctors knowing what they actually received, with extended follow-up to see if major adverse events were diminished with the drug. In such a trial with Crestor (enrolled cohort of 17,800 patients), the reduction was 4% for the placebo group and 2% for the Crestor population, a statistically significant result. But is helping 2 out of every 100 patients who take lifelong Crestor worth it? How about the 98 other patients who do not derive a benefit but undergo the side effects of that drug? Further, is the risk of developing diabetes in 1 out of every 400 patients justified? Lastly, a meta-analysis by the Cochrane Collaboration of all the data from 14 randomized trials and over 34,000 patients concluded that "*there was no net overall benefit of statins for patients without preexisting heart disease*". As just illustrated with statins, what is considered evidence-based medicine today is what is good for a large population, not for any particular individual.

The wide and prevailing prescription of statins illustrates "population medicine" at its best. This is to be opposed to "personalized medicine" that is directed at and for an individual patient. Should we not develop and implement the means and expertise for identifying the 1 or 2 persons out of every 100 who would benefit rather than considering the whole population as treatable?

In 2013, the American College of Cardiology (ACC) and the American Heart Association (AHA) jointly issued a new calculator of cardiovascular risk with associated new guidelines (see New *England Journal of Medicine*, issue of November 2013). These guidelines would add nearly 13 million people to those already receiving or eligible for statin drugs. The number includes: about half of all people under age 40-75; among people aged 60-75: 87% of men (up from 30% now) and 53% of women (up from 21% now).

The new guidelines prompted the following comments that generally support our contention that we should depart from the current population medicine and evolve to a new paradigm of patient-centric medicine.

"*If our goal is to help people feel better, live longer and have less heart disease, putting millions more on statins is not going to do that. Healthier lifestyles will do that, citing diet, exercise and smoking cessation. I think that's what our guidelines should be focusing on*." (Rita Redberg, cardiologist at the University of California-San Francisco).

"*Those who wrote the guidelines got carried away with a very minor benefit*." (Eric Topol, cardiologist at Scripps Health in San Diego).

"*The guidelines focus too much on an older population, without trying to prevent the development of heart disease in men and women ages 40-60*" (Steve Nissen, cardiologist at the Cleveland Clinic).

"*We think medicine should be more personalized based on evidence and the person's characteristics*." (Neil Stone, cardiologist at Northwestern University's Feinberg School of Medicine in Chicago). Dr. Stone further added that the new guidelines "*were intended to spark discussion between doctors and people older than 40 at risk for heart attack and stroke – not to set a cutoff for prescriptions*".

In summary, in the case of statins and statin combinations, I opined that:

1. In place of the primary goal (or "real end point"), namely reducing the likelihood of a heart attack, stroke, or death, the pharmaceutical industry and the medical establishment use the intermediate measurement of lowering blood cholesterol (a "surrogate end point") as a proxy for improving patient outcomes. The thesis is that for each percentage point that LDL is lowered, there would be about 1 percent reduction of heart attacks. Unfortunately, these two end points (blood cholesterol level and heart attack) do not track very closely.
2. While reducing LDL levels (apparently by 18%-55%), increasing HDL levels (apparently by 5%-15%), and reducing triglycerides (apparently by 7%-30%) provide great satisfaction to doctors and patients alike, it gives them a false sense of safety.

3. While most patients medicated with statins will have great blood test results, only one percent of them will actually benefit - those who have no history of heart disease but may, according to prevailing conventional norms, be at risk for developing such a condition. In other words, the predominant benefit is a cosmetic one (normalizing a blood test that is out of a conventional range) at the risk of entailing side effects and adding to the current annual burden for prescription drugs ($ 300 billion in the U.S. The statin benefit will be greater in those individuals who have already manifested heart disease and, according to the pharmaco-medical establishment, could be justified in that situation. Indeed, some physicians even consider in this case that statins are no less than "miraculous drugs"!
4. What about those patients for which statins have virtually no effect in lowering their LDL, raising their HDL, and lowering their triglycerides? The answer is apparently another surrogate end point of vague benefits in other unspecified health aspects.
5. The holy grail of evidence-based medicine is the large-scale randomized, double-blind, placebo-controlled clinical trial performed under the most rigorous conditions. In the trial with Crestor (enrolled cohort of 17,800 patients), the reduction was 4% for the placebo group and 2% for the Crestor population, a statistically significant result. I raised the questions: If placebo has the greater benefit, who needs the statin with lifetime use and side effects? Is helping 2 out of every 100 patients who take lifelong Crestor worth it? How about the 98 other patients who do not derive a benefit but undergo the lifelong side effects of that drug? Further, is the risk of developing diabetes in 1 out of every 400 patients justified?
6. Next, a meta-analysis by the Cochrane Collaboration of all the data from 14 randomized trials and over 34,000 patients concluded that "there was no net overall benefit of statins for patients without preexisting heart disease". Thus, what is considered evidence-based medicine today is what is good for a large population, not for any particular individual.
7. Lastly, if doctors do not prescribe statins in cases of elevated cholesterol levels, they may be given demerits by their hospital of affiliation or even be accused of medical malpractice for not adhering to "standards of care".

Much more could be said about statins and statin combinations. In particular, the long awaited new blood pressure guidelines by the American College of Cardiology/American Heart Association (ACC/AHA) have been issued in November 2017. They lowered again the guidelines setting a low threshold for diagnosis of hypertension from 140/90 mm Hg to 130/80 mm Hg, effectively elevating the prevalence of hypertension by roughly 14% and correspondingly the number of people "needing" statins. According to the authors of the guidelines, this will only increase the number of people requiring drug therapy by about 1.9% or 31 million more Americans with hypertension, but most of those will not be put on drug therapy because these guidelines take into account other cardiovascular risk factors such as lipid profile when recommending drug therapy. Fortunately, the update emphasizes lifestyle changes leaving hypertensive medications for the higher-risk stage 1 (130-139/80-89 mm Hg) and stage 2 (140-159/90-99) hypertensive patients.