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Perspective

Strategies in Coronary Artery Disease Management - Therapies Applied Too Little, Too Late

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Over the past 25 years, coronary artery disease treatment has evolved and mortality has been reduced. Yet, cardiovascular (CV) disease is still the leading cause of mortality in the Western World. We continue to spend hundreds of millions of dollars in development and testing of large randomized trials for new treatment strategies mainly targeting secondary prevention. However, most trials only marginally reduce hard CV end points, such as myocardial infarction and CV death, and still the residual event rate is large. Can we do better?

It is well known that the onset of atherosclerosis generally occurs decades prior to any CV event. Children, teenagers and young adults, whether based on autopsy findings or intravascular ultrasound data, often have intimal thickening or fatty streaks [1,2]. While by themselves, these cannot cause complications, it sets into motion a cascade of events that in some cases progress to myocardial infarction or sudden death as the first clinical manifestation of coronary artery disease.

Who gets adverse events? Although somewhat counter intuitive, Geoffrey Rose proposed in 1981 that most CV events do not occur in the high risk group, as determined by conventional scoring algorithms, since this group represents only a small proportion of the population [3]. Thus, most events originate from the lower risk groups, and for prevention to be truly successful, one must treat the many to prevent the few - the so called "Rose Prevention Paradox". There are several examples in the literature, subsequent to this article, which support the concept that most events (about two-thirds) originate from the less than high risk populations [4].

Can we then identify these lower risk individuals in primary or primordial prevention? While we as cardiologist utilize risk scores to guide therapy, these are insufficient to identify these lower risk individuals. Furthermore, risk scores do not consider therapy in primary/primordial prevention for asymptomatic individuals < 40 years of age. Non-invasive imaging such as calcium scoring or inflammatory markers such as C-RP can reassign individuals to a higher risk category, but this has not been sufficient to routinely capture those who will ultimately develop hard CV endpoints.

Options for therapeutic interventions in primary or primordial prevention

The basis of any prevention strategy is, of course, a healthy lifestyle with the proper diet, weight, exercise, and the avoidance of unhealthy habits. If we consider the four leading risk factors for coronary artery disease, which include hypertension, diabetes, elevated cholesterol and smoking, what else can be done to further reduce events? According to Framingham, control of these risk factors over a lifetime will result in less than a 10% incidence of CV death [5]. As expected, it follows that a combination of these risk factors will exponentially increase risk for a first myocardial infarction as demonstrated in the INTERHEART Study [6].

Hypertension

As the most common population based risk factor, one would think that this would be appropriately managed by all physicians. Unfortunately, it is very often undiagnosed and undertreated, particularly in teenagers and young adults. In an effort to reduce under treatment, our recent guidelines have lowered the definition of high blood pressure to 130/80 [7].

Diabetes

Very few diabetics are free from other associated risk factors for coronary artery disease. Why do we not mandate a more aggressive strategy for diabetics < 40 years of age? This younger population is typically managed with lifestyle alone and is not routinely prescribed statin therapy.

Cholesterol

The 2013 ACC and AHA guidelines on cholesterol advocated statins in all those 40 to 75 years of age with a 10 year risk of ≥ 7.5 percent by the Pooled Cohort Equation and an LDL of 70 - 189 mgs/dl [8]. This guideline did not advocate a specific LDL target but instead recommended moderate to high intensity statins along with lifestyle intervention. More recently, in 2017, guidelines from the endocrine societies reinstituted LDL goals for those at the highest risk [9]. Again, what about therapy in those with one or more risk factors < 40 years of age? While there are not enough randomized data here, it makes intuitive sense to consider statins along with lifestyle change. It is not that the guidelines suggest otherwise, but it is left up to the individual physician to discuss medical therapy with the patient. New studies are ongoing in younger populations.

Cigarette smoking

Over 450,000 deaths annually in the USA are caused by tobacco and at least 1/3 are related to coronary artery disease. Why do we allow this to continue? Quitting is often unsuccessful in those addicted to nicotine even with counseling, medication etcetera. We have favored a more draconian method to reduce smoking. Our solution would best work with federal rather than individual state legislation. It is based on the cigarette tax. Between the 1980`s and 2011, cigarette prices in the USA have increased 283%, which has contributed to reducing sales by more than 50% to 14 million packs sold in 2011. Making cigarettes economically unaffordable over time through higher taxes, and banning e-cigarettes to those < 21 years of age, should persuade many - including the adult who smokes but is not addicted and the adolescent/young adult - from continuing or embarking on such a habit [3].

Alternatively, the Food and Drug Administration (FDA) has recently come up with their own innovative strategy. Their proposal involves reducing nicotine content of cigarettes to an extent that makes them non-addictive. However, the FDA proposal is opposed by much of the public health community as it still leaves individuals unprotected from the toxic effects of cigarettes who are actively or passively exposed [10] and does not address the psychological addiction associated with smoking.

Conclusions

The emphasis in the mega trials alluded to in the introduction reflect an attempt to modify the disease process too late in its natural history to be, in most cases, of significant clinical benefit. While the ultimate solution in the future to prevent most adverse coronary events could be an atherosclerosis vaccine or some other yet to be developed methodology, one must deal in the present with a more aggressive, earlier multi-pronged attack on known CV risk factors. No medical health professional would argue with the earlier detection/treatment of hypertension, efforts to eliminate cigarettes, and lifestyle modification for all, particularly in pre-diabetics, aimed to reduce overt diabetes. Controversial would be how to eliminate tobacco, the increased use of cholesterol lowering agents, consideration for antiplatelet drugs in patients not presently included in the guidelines, and the age of onset of therapy. While long term studies are needed with multiple interventions (lifestyle and medications), the results may take years before the answers are known and the guidelines modified. In the meantime, our patients will continue to be at risk. We owe it to the patient to do better. Analogous to this discussion, aren`t vaccines such as those against influenza or pneumonia a preferable preventive strategy to one of treating the actual disease?

In proposing this new strategy however, it is not yet possible to accurately identify the appropriate candidates for the aforementioned interventions. Perhaps, taking a lead from the Eliminate Coronary Artery Disease trial [11] one should consider, with great concern, a more aggressive management in adults as young as 35 years of age with at least one major risk factor and an even earlier age for treat-

ment if multiple risk factors are present. This should include better control of hypertension, low dose or intermittent dosing of statins in addition to aggressive lifestyle modifications. Eliminating tobacco for good must be a goal for all physicians and health care providers. This will require a universal strategy that should be a top priority for the future.

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