Should We Be More Aggressive in the Therapy Against Cardiovascular Risk Factors?

Should we prescribe statin and aspirin for every diabetic patient, or is it time for a polypill?

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The reality of primary and secondary prevention of cardiovascular complications in people with diabetes is alarming, even in developed countries with a well-structured medical system. Even though therapeutic targets have been more clearly defined during the last decades, their implementation is still suboptimal. Financial and structural reasons, insufficient information of physicians and patients, along with a low compliance of the latter are only a few reasons that have been incriminated. To eliminate some of these inconveniences, attempts to standardize and simplify therapies have been made. Treatment with aspirin and statin for every patient with diabetes has been postulated. Some went even further, developing the concept of a "polypill," an integrated pharmacological agent with up to six different compounds meant to prevent cardiovascular disease in the broad population. Likewise, the idea of a "polymeal" tries to implement healthy nutrients into the populations' lifestyle in a standardized fashion. Our article highlights some of the advantages and pitfalls of these concepts and reflects our point of view with regard to some treatment aspects in people with diabetes. As part of a pro and contra discussion, our article is arguing against the use of statins in *all* patients with diabetes and especially against the indiscriminate use of a polypill.

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There is no longer doubt that people with diabetes constitute a population at high risk (1,2) and require special intervention. Guidelines for treatment of this patient group are available (3), but the reality of guideline implementation is disappointing. Only 13–37% of people with diabetes are treated with aspirin in the U.S. (4), and only around 27% of dyslipidemic individuals receive lipid-lowering treatment (5). LDL cholesterol of <100 mg/dl is achieved in 6.2–8.0% of patients for primary prevention and 17.3–21.3% for secondary prevention after 9 months of therapy (6). Vice versa, overtreatment in low-risk patients often occurs (6). Moreover, an A1C below 7% is found only in 35.8% of people with diabetes (7).

The Steno-2 study convincingly showed that beyond guideline-oriented treatment, continuous lifestyle education and motivation, together with a goal-oriented pharmacological treatment, further confers a cardiovascular risk reduction of ~50% (8). So, on one hand, guideline-based treatment does not provide the maximum benefit; on the other hand, in reality, not even guideline goals are achieved in a satisfactory amount of patients. This leads to the conclusion that a more aggressive treatment is required.

Beyond blood glucose optimization, antiplatelet and cholesterol-lowering therapies are two of the most powerful tools of diabetologists when aiming at reducing diabetes complications.

Several studies have proven beneficial effects of treatment with aspirin in people with diabetes (9). This evidence has emerged into the recommendations of the American Diabetes Association for treatment with aspirin in any diabetes patient over 30 years (10). Still, the aspirin treatment in these patients is under-optimal as highlighted above (4,11). Regular treatment was documented at the lowest rate in 13% of people with diabetes free of cardiovascular disease (4).

Dyslipidemia in diabetes is characterized by high LDL cholesterol and triglycerides and low HDL cholesterol. Statins proved risk reduction for major coronary events in the primary and secondary prevention in people with diabetes (12). The latter group had a higher therapeutic benefit than nondiabetic subjects. But statins mainly reduce LDL cholesterol (−18 to −55%) and exert a modest effect on HDL cholesterol (+5 to +15%) and triglycerides (−7 to −30%) (13). Still, low HDL cholesterol is a major risk factor for cardiovascular disease (14,15), and the reduced effect of statins on HDL could explain why statins prevent only about one-third of cardiovascular complications. Increasing HDL cholesterol (e.g., with niacin [16]) and decreasing triglycerides (e.g., with fibrates [17]) might further mitigate cardiovascular risk. Guidelines for the treatment with statins have been published (13) underlining also the importance of lifestyle changes. While the need for treating high-risk patients was emphasized, no specific pharmaceutical recommendations have been made in lower-risk categories.

We therefore do not consider that statin treatment should be initiated in every diabetic patient and advocate the careful assessment of the lipid profile in each individual patient before starting dyslipidemia treatment.

In a controversial article released in 2003, Wald and Law (18) introduced the term "polypill" (containing a statin; three blood pressure–lowering drugs, e.g., thiazide, β-blocker, and ACE inhibitor, each

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at half dose; folic acid, 0.8 mg; and aspirin, 75 mg). The polypill was suggested to reduce ischemic heart disease by 88% and stroke by 80% if taken by everyone over 55 years of age. One of the main arguments was that adherence to therapy decreases with the increase in number of medications (19). Advantages and pitfalls of the polypill were reviewed in detail elsewhere (18,20,21), and we will resume presenting our point of view.

Our patients present with a puzzle of clinical features (e.g., dyslipidemia, hypercoagulability, hypertension, insulin resistance, and/or glucose dysmetabolism), but only few of these conditions are leading causes for the development and progression of complications. To address the main disturbances, variable doses of the specific medication is required. The polypill provides fix combination of substances, possibly resulting in undertreatment of the main condition(s) and overtreatment of secondary conditions. The polypill also neglects differences in metabolism between younger and older people and racial and sex differences.

The cost-effectiveness of the polypill was highlighted in several articles (18,22), but questioned by others (21). A broad therapy with the polypill has to prove first its efficacy in terms of reducing end points and costs and increasing compliance. This can be ensured only by large-scale, financial consuming studies, which will considerably increase the production costs, making first enthusiastic calculations questionable.

A "polypill mark two" for preventing age-related complications has already been mentioned (23) and another composition of a "polypill" for people with diabetes has been proposed (metformin, aspirin, statin, and an ACE inhibitor [22]). We are no longer talking about "the polypill" but about a polypill for different pathological conditions. Modern medicine was often criticized for concentrating on an organ or a parameter and loosing sight of the entire patient. The polypill will eliminate this problem but will draw us into the other extreme: we will not further treat individuals, we will treat populations. This resembles an indiscriminative "globalization" of medicine, neglecting the fact that best results are achieved by individualized lifestyle changes and motivation together with a goal-oriented pharmacological treatment (8).

Wald (24) proposed that the polypill be used without medical examination or blood test, suggesting even an over-the-counter availability. In our opinion, this would open the door to uncontrolled side effects.

The "polypill" chapter is certainly still open. This concept could prove effective in carefully selected populations with poor compliance or at high risk or in old and/or plurimorbid patients taking numerous medications. A large indiscriminative population-based therapy is in our opinion not suitable.

Lifestyle interventions seem to be the most meaningful approach to the reduction of cardiovascular complications, with an impressive power of reducing events. Therefore, the concept of "polymeal" containing wine, fish, dark chocolate, fruits, vegetables, garlic, and almonds was proposed as a more natural, safer, and probably tastier alternative to the polypill. The polymeal was suggested to reduce cardiovascular disease by over 75% in people ≥50 years of age (25). The polymeal will certainly not be available in a package at the pharmacy around the corner, but it constitutes a concept that might help us change our way of thinking. Instead of taking a "wonder pill" that cures almost everyone, we should realize that our unhealthy lifestyle mainly contributes to the development of complications and that this is the place where we should start from when making a change.

Summarizing the discussions that followed the presentation, we recommend that aspirin treatment should be considered in all people with diabetes ≥21 years of age, depending on the comorbidity status. Statin therapy is not generalizable to all diabetes patients and the indiscriminate large-scale treatment with a "polypill" and especially its availability over the counter should be avoided.

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