

EDITORIAL COMMENT

Lifestyle and CV Risk in Patients With Diabetes

Time to Get “Back to Basics”*

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Type 2 diabetes mellitus (T2DM) has emerged as the major worldwide epidemic of the 21st century, driven in part by a combination of societal changes leading to excessive caloric intake, altered dietary patterns, increased sedentary behaviors, and the mechanization of many manual labors, which previously led to significant daily energy expenditure. Within the United States, the prevalence of T2DM is expected to reach >54 million people by 2030, with total costs estimated at >\$600 billion U.S. dollars (1). Furthermore, there are approximately 84 million Americans age >18 years with “pre-diabetes,” of whom 5% to 10% will go onto to develop frank T2DM each year (2).

The health impact from T2DM remains significant, and the costs associated with diabetes complications are enormous. Importantly, cardiovascular disease, including stroke, myocardial infarction, peripheral arterial disease, and heart failure, remains a substantial contributor to T2DM-associated mortality and morbidity. Significantly, data from the National Registry in Sweden over a 2-decade time frame support the concept that multifactorial risk factor reduction results in modest, but significant declines in cardiovascular morbidity and mortality in patients with T2DM (3). This temporal trend may be attributed to

multifaceted interventions with improvements in chronic care models and health care delivery systems. Multifactorial risk factor reduction, including healthy lifestyle behaviors and pharmacological therapy, has played a key role in successfully reducing both microvascular and macrovascular complications in patients with T2DM (4). To date, most of the benefit has been attributed to pharmacological therapy (5), with the impact of adherence to healthy lifestyle behaviors being neutral or difficult to quantify. Furthermore, the impact of new pharmacological therapies with proven cardiovascular efficacy, such as the sodium glucose cotransporter 2 inhibitors (e.g., empagliflozin and canagliflozin) as well as glucagon-like peptide receptor agonists (e.g., liraglutide), will take some time to quantify.

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Within this complex landscape, in this issue of the *Journal*, Liu et al. (6) present pooled cohort data from the NHS (Nurses’ Health Study) and the HPFS (Health Professionals Follow-up Study) that enrolled health care professionals with a new diagnosis of T2DM. A total of 11,527 patients were included with approximately 13 years of follow-up, with the main goal being the assessment of cardiovascular outcomes in relation to *low-risk lifestyle factors*. Specifically, low-risk lifestyle factors included a high-quality diet (top two-fifths of Alternative Healthy Eating Index), nonsmoking, moderate to vigorous physical activity (≥ 150 min/week), and moderate alcohol consumption (5 to 15 g/day for women and 5 to 30 g/day for men). Data was collected through validated questionnaires at baseline and every 2 to 4 years. After multivariable adjustment, individuals with ≥ 3 low-risk lifestyle factors compared with those with 0 low-risk lifestyle factors had a decreased risk of incident

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cardiovascular disease (hazard ratio [HR]: 0.48; 95% confidence interval [CI]: 0.40 to 0.59), coronary heart disease (HR: 0.53; 95% CI: 0.42 to 0.66) and stroke (HR 0.33; 95% CI: 0.21 to 0.51). The reduction in cardiovascular events remained significant after adjustment for several variables, such as body mass index, hypertension, hypercholesterolemia, use of antihypertensive agents, cholesterol lowering drugs, diabetes medication, and HbA1c. Encouragingly, patients who increased the number of low-risk lifestyle factors from the time of initial diagnosis were also shown to have a lower incidence of cardiovascular disease (HR: 0.79; 95% CI: 0.70 to 0.89), coronary heart disease (HR: 0.82; 95% CI: 0.72 to 0.94), stroke (HR: 0.68; 95% CI: 0.52 to 0.89), and cardiovascular mortality (HR: 0.80; 95% CI: 0.66 to 0.96). The authors acknowledge key limitations affecting the generalization of their study. The population studied in the NHS and HPFS pooled cohort studies was comprised of nearly all-Caucasian health care professionals of high socioeconomic status, and participation in these cohorts was voluntary.

Liu *et al.* (6) provide an important addition to the published data for the benefit of healthy life style behavior for the prevention of cardiovascular disease in patients with T2DM. Although each low-risk lifestyle factor provided incremental benefit for cardiovascular risk reduction, there was a clear synergistic effect of combined multiple healthy lifestyle behaviors, consistent with previous observational studies in patients with T2DM (7-9). These positive findings are in contrast to the Look AHEAD (Action for Health in Diabetes) (10) randomized control trial, which did not show a reduction in cardiovascular events in overweight or obese patients with T2DM randomized to the intervention of targeted weight loss based upon increasing physical activity and reducing caloric intake over a 9-year follow-up period. How do we reconcile these disparate results? First, as acknowledged by the authors, the population was comprised of Caucasian, professional persons of high socioeconomic class who had a formal diagnosis of T2DM. Although this homogeneity in socioeconomic class and ethnicity does not neutralize the suggested benefit of low-risk lifestyle factors, the response of different ethnic groups or socioeconomic classes to such interventions may be variable, particularly when the impact may only be seen after a decade! As such, to generalize these findings, they need to be corroborated in more diverse multiethnic populations with variable socioeconomic status to better understand the true magnitude of the benefits observed. Second,

participation was voluntary, and it cannot be ruled out that health care professionals who agreed to participate are more likely to adhere to guideline-recommended therapies as well as to other positive health-related behaviors that are not included in the low-risk lifestyle factors studied in this paper. The impact of such a bias would be an overestimate of the benefit seen in the general population. Finally, the current study used questionnaires and self-reported findings, with inherent limitations of validity and reproducibility—which is vastly different from prospective, formally measured outcomes as observed in a randomized control clinical trial such as Look AHEAD. That being said, the findings of this study by Liu *et al.* (6) will help guide future clinical trials in this area, by focusing upon a package of healthy lifestyle behaviors to maximize the cumulative benefit as opposed to intensive targeting of an individual lifestyle factor in patients with T2DM. A further novel finding of this study is that despite the duration of T2DM or the number of unhealthy lifestyle behaviors at the time of diagnosis, patients with T2DM who were able to increase their number of low-risk lifestyle factors showed a significant reduction in incident cardiovascular events including cardiovascular mortality. This supports current recommendations that health care practitioners managing patients with T2DM should continue to promote adherence to healthy lifestyle behaviors, as benefits persist after diagnosis.

As we pursue the exploration of antihyperglycemic agents for the prevention of cardiovascular disease and even further aggressive low-density lipoprotein lowering, what new insights are we left with? The authors highlight through their analysis that despite further pharmacological advances in diabetes, the cornerstone of cardiovascular risk reduction will commence with lifestyle interventions. Lifestyle intervention in patients with T2DM remains low risk, cost effective, and relatively easy to integrate into health care delivery models. Despite this, important questions remain unanswered: which diet(s) are best? What quantity of alcohol is safe in this cohort? Is there a “minimum” or “maximum” amount of exercise and is the type of exercise important? How do we monitor compliance? Who should write the diet and exercise prescription—physicians or other health care professionals? How generalizable are these findings to other groups of different ethnicity and/or socioeconomic status? As practitioners managing patients with T2DM, we need to send a clear message that health care promotion, advocacy, and research should continue to focus

on these healthy lifestyle factors not only to improve glycemic control, but to reduce overall cardiovascular risk. As society continues to evolve and becomes increasingly complex, it is important that we do not overlook the so-called simple and fundamental aspects of patient care and always return “back to basics.”

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