

Intensive Diabetes Management for High-Risk Patients: How Best to Deliver?

Type 2 diabetic patients with microalbuminuria or more advanced chronic kidney disease are at extremely high risk of cardiovascular disease (CVD) and end-stage renal disease (ESRD), with the risk of both increasing as kidney disease progresses. CVD and renal disease share many risk factors. The Steno-2 study demonstrated that intensive structured care, targeting these risk factors aggressively, slowed progression of nephropathy and retinopathy and reduced cardiovascular death in type 2 diabetic patients with microalbuminuria by 40–60% (1–3).

In this issue of *Diabetes Care*, Chan et al. (4), for the Structured Versus Usual Care on Renal Endpoint in Type 2 Diabetes (SURE) Study Group, provide further evidence of the benefits of intensive target-driven care and raise questions as to how best to deliver such care. They compared structured care, including a predefined protocol and tight treatment targets delivered by a diabetologist-led specialist team, with usual care, delivered by specialists or nonspecialists. The study was conducted in nine hospitals; 205 type 2 diabetic patients, aged 35–75 years with plasma creatinine 150–350 $\mu\text{mol/l}$, were randomized, and 167 completed the 2-year study. The main reasons for withdrawal included death ($n = 19$) and referral to nephrology for dialysis ($n = 14$). The number of patients reaching the primary end point (death or ESRD, defined as a need for dialysis or having plasma creatinine $\geq 500 \mu\text{mol/l}$) was similar in the two groups, as was the number of clinical events, hospital admissions, and emergency room visits. However, after 2 years, the structured care group had lower diastolic blood pressure and A1C and was more likely to attain ≥ 3 treatment goals than was the usual care group (61% [$n = 63$] vs. 28% [$n = 28$], respectively). In a per-protocol analysis, there was a 60% risk reduction in reaching the primary end point for patients who achieved ≥ 3 treatment goals compared with those who did not (14 vs. 34; relative risk 0.43 [95% CI 0.21–0.86]).

The major strengths of this study are the inclusion of type 2 diabetic patients at

extremely high risk of CVD and ESRD and the design of the structured care arm. Structured care, delivered by a multidisciplinary team of diabetes specialists, encompassed prespecified care plans, tight treatment targets, frequent visits, ongoing education and counseling, and a pre-printed case-report book to prompt clinician action. The study demonstrates clearly that those receiving structured care were more likely to achieve ≥ 3 treatment targets and showed a strong relationship between the number of targets achieved and outcome. However, the study was underpowered: the observed primary outcome rate was approximately half that expected from the Asian subgroup of the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study (5) and another small local pilot study (6). Thus, diabetes care generally in Hong Kong SAR, China, may have improved. Usual care was provided by diabetes specialists or nonspecialists according to the individual clinic's usual practice rather than being prescribed. Clearly, in at least some of these usual care clinics, particularly those run by diabetes specialists, management was aggressive and many tight targets were reached. This contamination contributed to the failure to establish a clear superiority of structured care in improving outcome. However, this is real-life; it would be virtually impossible, and perhaps now even unethical, to randomize high-risk individuals to less active care.

What implications does this report have for the management of high-risk type 2 diabetic patients? First, there is now a wealth of evidence that type 2 diabetes management is no longer simply about glucose. The UK Prospective Diabetes Study showed the independent and additive effects of glucose and blood pressure on the development of microvascular and macrovascular complications (7). A similar 5-year observational study demonstrated that the more treatment targets reached at baseline, the less likely the risk of new-onset CHD (8). The Steno-2 study (1–3) and the SURE study attest to the vital importance of addressing many factors simultaneously. The higher the num-

ber of targets reached, the better the outcome: patients achieving ≥ 3 targets fared better than those achieving ≤ 2 . Second, what is good for the macrovascular system also seems good for the microvasculature: in the Steno-2 study, the risk reduction for CVD end points was similar to the reduction for progression of nephropathy and retinopathy (2,3). Third, even in a clinical trial setting, it is difficult to achieve these tight targets. In the Steno-2 study, 16–75% of patients in the intensively managed arm achieved individual targets (2). In the SURE study, only 61% of patients in the structured care arm reached ≥ 3 targets. This should not discourage us from striving to meet the targets but, rather, spur us on to find new and better ways of delivering care.

What do these studies tell us about care delivery? The intensively treated arm of the Steno-2 study included care provided by a multidisciplinary, secondary care team of diabetes specialists in a dedicated diabetes center, delivering target-driven, prespecified, multiple risk factor interventions (1). The conventionally managed arm was treated in a primary care setting, following the recommendations of the Danish Medical Association. The SURE study compared specialist care and usual general care, both within the secondary care service. Whether care is provided as primary or secondary care is probably not important. What is vital is that care is delivered by a multidisciplinary team of diabetes specialists that is fully trained and has appropriate skills to provide all aspects of diabetes management. Prespecified guidelines and protocols, agreed on by all and followed by all team members, are undoubtedly important. Specification of treatment targets, agreed on by patients and professionals on an individual basis, is essential. A decision not to aim for a recognized tight treatment target must not happen by default but must be openly discussed and justified. However, even with these measures, targets are not met uniformly in everyone. Clinical inertia, patient and professional reluctance to intensify management, and, on occasion, lack of appropriate tools and knowledge all contribute

to failure. In the SURE study, a preprinted case-report book was used that was similar to those in a research study. This may have helped to prompt change, overcome clinical inertia, and thus improve the achievement of targets. A similar, computer-based interactive system might be worthwhile. Efforts to keep health care professionals up to date, enthusiastic, and involved are crucial; regular audits, benchmarking of services, and feedback are essential. In the U.K., modest financial incentives in primary care have improved process and outcome care measures (9), although the qualifying targets have not yet been as strict as those required for high-risk patients. Intensive management is onerous for the person with diabetes. Measures to improve concordance with therapy and to empower patients—such as regular telephone calls (10), text messaging (11), and structured education (12)—are also needed.

Is provision of such high-intensity care cost-effective? In Europe, hospital admissions account for 55% of health care costs associated with type 2 diabetes (13), and in patients with both microvascular and macrovascular complications, the total cost of management is increased by up to 250% compared with those without complications (14). In the U.S., an estimated 58 billion USD, (half of the total annual cost of diabetes care) is spent on managing diabetes-related chronic complications (15). One model suggests that myocardial infarction, heart failure, and renal disease (all of which can be reduced by multifactorial intervention) have the greatest fiscal impact (16). Economic analysis of the Steno-2 study suggests that in the Danish health care system, intensive therapy was more cost-effective than conventional therapy, with an incremental cost-effectiveness ratio of 2,538 Euro/quality-adjusted life-year gained (17). The increased costs of intensive care were due to increased pharmacy and consultation costs. Pharmacy costs can be minimized by prescribing generic drugs. When both intensive and conventional care were delivered in primary care, then intensive therapy became cost saving and lifesaving.

Of type 2 diabetic patients, 25–50% have microalbuminuria or more severe chronic kidney disease and are therefore at extremely high risk for CVD and ESRD. We now have irrefutable evidence that their prognosis can be greatly improved

by intensive structured care targeting multiple risk factors and delivered by multidisciplinary, specialist diabetes teams. Such care is cost-effective. The challenge to all health care providers, now, is to develop systems of care whereby all high-risk patients can access such high-quality care.

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