What can we learn from the recent blood glucose lowering megatrials?

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ABSTRACT

In the past two decades, we have acquired an enormous amount of knowledge regarding the epidemiology, diagnosis, pathophysiology and treatment of type 2 diabetes and its comorbidities. In addition to the earlier landmark blood lipid and blood pressure lowering trials, the latest blood glucose lowering megatrials represent the zenith of this global effort to prevent and control diabetes, and its devastating consequences. Although many of these latter trials have yielded negative results and have shown the narrow risk-benefit ratio of intensive treatment in patients with advanced disease, the exceedingly low event rates in these high-risk patients who were carefully monitored and intensively managed made possible in these clinical trial settings have not been emphasized enough. The heterogeneity of the clinical outcomes in these studies further highlight the complexity of diabetes, which is more than managing a disease, but the multiple needs of a patient with multisystem dysfunction. In the final analysis, what transpires from these megatrials is the need to translate the key components of these studies, namely, protocol, team, documentation and monitoring, into our daily clinical practice to enable the care team to stratify risk, define needs, individualize therapy, monitor progress and reinforce compliance in order to achieve positive outcomes. (J Diabetes Invest, doi: 10.1111/j.2040-1124.2010.00063.x, 2010)

KEY WORDS: Randomized clinical trials, Disease management, Diabetes

DIABETES AND CARDIOVASCULAR DISEASE REVISITED

More than a decade ago, Haffner *et al*[1]. first reported the similar incidence of myocardial infarction (19% in 7 years) between type 2 diabetic patients without a history of myocardial infarction and non-diabetic patients with a history of myocardial infarction. This landmark study also confirmed the fourfold higher risk of coronary heart disease (CHD) in diabetic subjects compared with non-diabetic subjects (4% in 7 years) and their high risk of having recurrent events once they had CHD (45% in 7 years). Importantly, type 2 diabetic patients with myocardial infarction were more likely to die before hospitalization[2] and during the post-myocardial infarction period than non-diabetic subjects[3], thus emphasizing the importance of optimal control of CHD risk factors for both primary and secondary prevention in type 2 diabetes.

RESIDUAL CARDIOVASCULAR RISK IN TYPE 2 DIABETES

Due to their high absolute risk for CHD, for the same intervention, whether blood pressure or lipid lowering or blockade of renin angiotensin system, more events were prevented in type 2 diabetic patients than their non-diabetic counterparts in large randomized clinical trials[4–6]. However, despite control of these multiple risk factors, type 2 diabetic patients continue to have high residual risk with an annual CHD event rate of 3–5%. In the Steno 2 Study, although 30–80% of patients receiving multifaceted care attained lifestyle modification, blood pressure and lipid goals, less than 10% of patients achieved the predefined HbA_{1c} goal of 6.5%[7].

INTENSIVE BLOOD GLUCOSE LOWERING IN TYPE 2 DIABETES

In the United Kingdom Prospective Diabetes Study (UKPDS), which recruited newly diagnosed type 2 diabetic patients, a difference of 0.9% in HbA_{1c} (7% in the intensively-treated group *vs* 7.9% in the standard treatment group) over a 10-year period was translated to 13–24% reduction in all-cause death, cardiovascular events and microvascular complication rates in the 10-year post-trial period[8]. In the epidemiological analysis of the UKPDS, there was a linear relationship between HbA_{1c} and incidence of macrovascular complications beyond 7%, raising the possibility that the lower the HbA_{1c}, the better the clinical outcomes[9]. Three subsequent large scale randomized clinical trials, ACCORD[10], ADVANCE[11] and VADT[12] were carried out to address the question whether lowering HbA_{1c} to <7% conferred additional cardiovascular benefits. However, these studies have yielded heterogeneous results with many controversies rather than consensus[13].

Despite achieving a similar HbA_{1c} level of 6.5%, intensively-treated patients in the ACCORD study had a higher mortality rate than the standard treatment group[10], but not in the ADVANCE study[11]. In the latter study, there was a 21% risk

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Received 26 July 2010; accepted 28 July 2010

reduction in nephropathy, but not retinopathy[11]. In contrast, in the ACCORD study, intensive control of blood glucose and lipids was respectively associated with 33% and 44% risk reduction in retinopathy[14]. Apart from differences in baseline risk factors, patterns of drug use and rapidity in reaching target HbA_{1c}[15], it is noteworthy that 30% of patients in the ADVANCE study came from Asia, mainly from China, whereas participants in the ACCORD study were mainly Caucasians.

IMPORTANCE OF EARLY INTENSIVE TREATMENT TO ACHIEVE LONG-TERM BENEFITS

In the Asia-Pacific Collaborative Study Cohort, diabetes conferred 2–3-fold increased risk of CHD in both Asian and Caucasian populations. However, the effect size was considerably higher with an odds ratio of 4 in subjects younger than 60 years compared with 2 in those aged 60 years or older[16]. These findings are particularly pertinent to Asia, where the major increase in diabetes prevalence will occur in the young to middle-aged group[17,18]. In the subgroup analysis of the ACCORD study, intensive blood glucose lowering reduced CHD by 20% in patients with no previous history of CHD and HbA_{1c} <8%[10]. Given that type 2 diabetes is the predominant form of disease in young Asian subjects[18] and that disease duration is one of the most important determinants for CHD[19], together with findings from the ACCORD[10] and ADVANCE study[11], it can be inferred that early intensive glycemic control in young patients is likely to bring major reductions in cardiorenal event and mortality rates.

IMPORTANCE OF DETECTING RENAL DISEASE TO PREVENT CHD

The predilection of Asian type 2 diabetic patients to renal disease was first reported in the World Health Organization Multicenter Study for Vascular Disease in Diabetes (WHO-MSVDD)[20]. This was subsequently confirmed by the reported 60% prevalence of nephropathy in Asian type 2 diabetic patients[21] compared with 40% in their Caucasian counterparts[22]. In a subanalysis of the RENAAL study, Asian type 2 diabetic patients with moderate renal insufficiency had a higher rate of end-stage renal disease (35%) than Caucasian patients (30%) in the placebo group after receiving comparable treatments for 3.5 years[23,24]. Similarly, in the ADVANCE study, Asian patients (5%) had the highest incidence of new onset or progression of nephropathy compared with Caucasian (3%) and eastern European populations (4%) after 5 years of follow up[25].

IMPORTANCE IN STRATIFYING RISK AND PERSONALIZING THERAPY

Albuminuria, a marker of endothelial damage, predicts cardiovascular and renal disease in both diabetic and non-diabetic subjects[26]. In the Hong Kong Diabetes Registry, albuminuria and estimated glomerular filtration rate (eGFR) were the most consistent predictors for cardiorenal events and all-cause death[27,28]. These findings emphasize the importance of periodic monitoring of renal parameters to stratify risks and assess treatment effectiveness.

In the UKPDS[29] and Hong Kong Diabetes Registry[30], HbA_{1c} was a major determinant for progression of albuminuria and deterioration of renal function. With the onset of diabetic kidney disease (DKD), arbitrarily defined as eGFR <60 mL/min/1.72 m^2, the risk of CHD is increased by 4–5-fold compared with those without. This is mainly due to further changes in internal milieu associated with DKD, which include anemia, vascular calcification, oxidative stress and inflammation[24].

Of note, the onset of DKD increases the risk of hypoglycemia as a result of impaired pharmacokinetics and pharmacodynamics with drug–drug interactions, prolonged effects of blood glucose lowering drugs and reduced counterregulation[31]. In these high-risk subjects who often have autonomic neuropathy[32] and silent cardiac ischemia[33], hypoglycemia might precipitate cardiac events. Given the multiplicative effects of these risk factors and complications of clinical course, the need to phenotype and individualize treatment represents the first step to good clinical practice[34].

USING STRUCTURED CARE AND TEAM APPROACH TO IMPROVE CLINICAL OUTCOMES

In the ACCORD study, one or more hypoglycemic episodes requiring assistance was associated with an increased risk of death, although the effect size was considerably lower in the intensively-treated group with a hazard ratio of 1.4 compared with 2.3 in the standard treatment group[35]. Counter-intuitively, the risk of death in intensively-treated patients who had severe hypoglycemia requiring medical assistance had a lower hazard ratio of 0.55 for mortality compared with the standard treatment group. These seemingly paradoxical findings suggest that with intensive monitoring, the adverse effects of intensive treatment might be mitigated, resulting in clinical benefits.

CHANGING OUR CLINICAL PRACTICE AND HEALTH CARE SYSTEM

These observations led to a growing consensus on the need to use a team of trained health-care personnel to stratify risk and deliver care protocols in order to get these patients to treatment goals safely and effectively[36]. Indeed, using these disease management protocols with predefined procedures, targets and decision support, major event rates can be reduced by 50–70% compared with usual care, which often lacks integration, coordination, monitoring and feedback[37–40].

Despite the endorsement of the International Diabetes Federation on these principles[41], there is a general lack of resources or incentives to develop care systems that incorporate these components, except in a few areas or centers. Without these changes in practice environment to facilitate integrated care and self management[42], doctors managing patients with chronic diseases will not be able to fully utilize their expertise and knowledge to benefit their patients, just like a surgeon working without an

operating theatre or a cardiologist working without a catheterization laboratory.

In contrast to real-life practice, where fewer than 5% of patients attained three treatment goals (HbA_{1c} <7%, blood pressure <130/80 mmHg and LDL-cholesterol <2.6 mmol/L)[43], nearly all patients in these megatrials attained treatment targets and were put on life-saving drugs[15]. These changes in practice made possible by enrolment into a trial might explain the often negative results in these megatrials as a result of underestimation of these 'trial effects'. Thus, although there is a need to learn from these negative findings, we must not lose sight of the extremely low annual event rate in these megatrials.

IMPORTANCE OF PROTOCOL, TEAM, DOCUMENTATION AND MONITORING

Using the ACCORD Study as an example, despite the old age, long disease duration and high percentage of patients with prior history of CHD, the annual rate of cardiovascular event was only 1–1.5%[10]. This is in stark contrast to 2% per year in the younger and newly diagnosed patients in the UKPDS[44], 3–5% per year in patients with multiple risk factors, but no prior history of CHD in the Steno 2 study, and 3–8% per year in the East-West Study where treatment was less intensive in the early 1970–90s[1] (Figure 1). Thus, what really transpires from these megatrials is the need to incorporate the key components of clinical trials (protocols, team, monitoring and feedback) into our daily clinical practice with cost-effective analysis in order to persuade policy makers and payors to make these care systems accessible, affordable and sustainable (Figure 2).

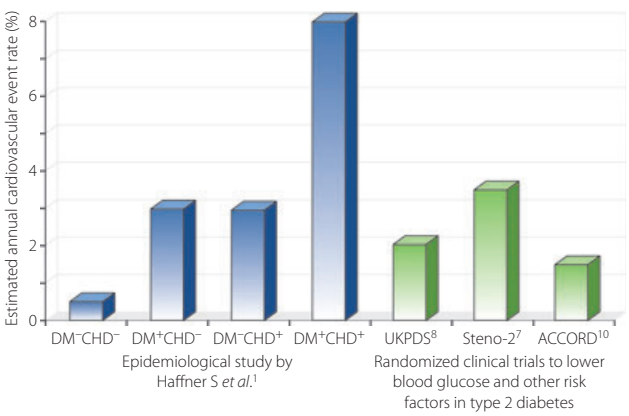

Figure 1 | Estimated annual cardiovascular event rates in large scale epidemiological studies and randomized clinical trials since 1990. Despite the high-risk nature of type 2 diabetic (DM) patients in the ACCORD study, more than 30% of whom had a history of coronary heart disease (CHD), intensive treatment and monitoring in a trial setting has given rise to event rates lower than the younger and newly diagnosed patients in the UKPDS, and patients with multiple risk factors without prior history of CHD in the Steno-2 study, who were managed less intensively.

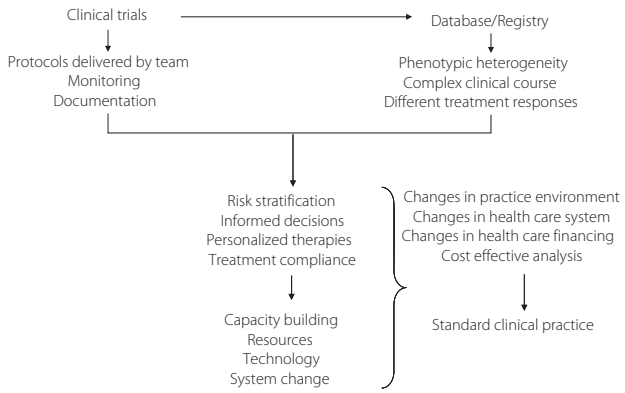

Figure 2 | Learning from recent megatrials. The key components of a clinical trial include baseline assessments and delivery of protocol by a team with frequent monitoring and documentation of processes and responses. This team-based approach enables risk stratification, informed decisions, individualized regimens, regular monitoring, improved compliance and better outcomes. In order to increase the accessibility of these care models, changes in clinical practice and health care system is needed to ensure its accessibility, affordability and sustainability.

CONCLUSION

During the past two decades, we have gained enormous insights into the epidemiology, pathophysiology and treatment of type 2 diabetes and its comorbidities. The heterogeneity of age, sex, ethnicity, disease duration, risk factors and complications interact in a multiplicative manner to increase the complexity of the clinical course and treatment responses. Thus, treating diabetes is more than treating a disease(s), but managing the multiple needs of an individual with multisystem dysfunction. By using a systematic approach to document these risk factors, complications, processes and outcomes, care providers will be in a better position to define their needs, make informed decisions and individualize treatment in order to maximize benefits and minimize harm. Although our ultimate goal is to discover a cure for diabetes and change our environment and lifestyle to prevent diabetes, given the compelling evidence from these megatrials, there is an urgent need to reform our health care system to ensure those who already have the disease receive proper education, care, monitoring and support using a team approach to reduce the societal and personal impacts of this devastating condition.

ACKNOWLEDGEMENTS

The author has received research grants, speakers' fees and consultancy fee from Astra-Zeneca, Bayer, Bristol-Myers-Squibbs, Daiichi-Sankyo, Lilly, MSD, Pfizer and sanofi-aventis, all of which have been donated to the Chinese University of Hong Kong to support ongoing research and education in the field of diabetes.

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