AMCARE is a membership-based program that aims to meet the daily necessities of diabetes patients through a call center model. The popularity of the AMCARE pilot has encouraged the Diabetic Association of Bangladesh to continue collaborating with TRCL to scale up the project to reach total 6 million diabetic patients in Bangladesh by 2013.

Key program components:

AMCARE is a subscription-based membership program that aims to encourage patient at-home compliance with diabetes care protocol and build stronger relationships between the patient and provider. The program’s main feature is a diabetes call center staffed by licensed physicians and nurses that is reachable by a hotline number. The basic membership is open to all diabetic patients through a monthly fee starting from US$ 0.60 to US$ 20.00. The hotline has decreased the cost of seeking health care by eliminating the cost of transportation to a hospital and consultation fees for services for a significant number of patients.

Technical Platform:

AMCARE’s technical platform is based on cloud computing and uses Oracle CCA and Siebel CRM On Demand. The telephone system acts as the core networking component between patients, providers and partners, and uses unified communication tools for adherence and monitoring. The TRCL Medical Portal is the clinical process warehouse and maintains a record of all processes, (e.g. algorithms and protocols). The smart phone applications connect patients, doctors, and field staff (clinical, sales, and administrative) in real-time.

A total of 1,920 patients participated in the pilot phase of this project: (1) 77% of diabetic patients had mobile phones; (2) all patients under the pilot had java enabled mobile handsets; (3) 11% were irregular; (4) among the irregular patients, 62% improved their compliance to treatment following home monitoring and education; (5) most importantly, 61.2% reduced doctor/hospital visits from 5-6 to 1-2 per year.

Source: http://healthmarketinnovations.org/program/amcare-diabetes-management-bangladesh
Type 1 Diabetes Linked to Lower Fertility

Significantly fewer children are born to couples when 1 partner has type 1 diabetes, according to results from a cross-sectional study conducted in Germany.

The researchers studied 697 individuals with type 1 diabetes (364 women, 333 men) who were part of a background regional German population of 350,000 people. The investigators assessed the number of children born to families, the sex of the children, and whether the family had a prior history of diabetes. They then compared those findings with 2009 government statistics for the overall region.

More men with type 1 diabetes were childless compared with their female counterparts. The ratio of male to female offspring was nearly equal, the researchers say.

The authors say the presence of diabetes in fathers did not appear to have a significant effect on development of the disease in offspring, but that was not the case in mothers with diabetes. They found that maternal type 2 diabetes delayed the onset of type 1 diabetes in children by 7.25 years on average. Maternal type 1 diabetes delayed the onset of type 1 disease in their children by 5.8 years. Irrespective of the type of diabetes, there may be a protective effect of maternal diabetes per se.

The authors emphasize that decreased fecundability may not be the only reason for lower birth rates among people with type 1 diabetes. Although there have been significant improvements in maternal and fetal care in recent years, they note, pregnancies with type 1 diabetes are still associated with more complications and poorer outcomes than normal pregnancies.

*Diabetic Med. Published online February 23, 2012.*

Selenium Supplements May Increase Risk for Type 2 Diabetes

One study of more than 1,200 Americans found that those who took 200 micrograms of selenium daily for an average of nearly eight years had a higher risk of developing type 2 diabetes compared to those taking a placebo.

And those who started the study with the highest selenium levels — 122 micrograms or higher — saw a nearly three-fold jump in diabetes risk compared to those taking a placebo.

One limitation of that study, however, was that doctors didn’t set out to study type 2 diabetes as an outcome. People were recruited to see if selenium could cut their risk for non-melanoma skin cancer.

Researchers concede that looking at outcomes that weren’t part of the design of the study can muddy the results.

Still, other studies have also suggested an association between selenium and diabetes.

Having a higher selenium level was linked to an increased prevalence of diabetes in adults tracked by the CDC’s National Health and Nutrition Examination Surveys.

In the same vein, a French study found that higher selenium levels were associated with having higher blood sugar levels.

Researchers note that selenium might have an effect on type 2 diabetes because at high levels, it can interfere with the body’s ability to effectively use insulin.

Impaired glycemia (IG) is not a risk factor for typical or atypical diabetic polyneuropathy, according to the findings of a population-matched prospective study. The authors note that the findings regarding associations between IG and both typical and atypical diabetic polyneuropathy have been inconsistent.

The authors conducted a survey in Olmsted County in Minnesota to identify patients without IG, with IG, and with new diabetes in local population-based medical and laboratory registries. Among the 542 age- and sex-matched volunteers (150 with non-IG, 174 with IG, and 218 with new diabetes) the incidence of diabetic neuropathy was not significantly different between individuals with IG and those without IG for both narrow.

However, the frequency of diabetic neuropathy was higher among individuals with new diabetes, particularly when diabetic neuropathy was defined narrowly.

The incidence of retinopathy and nephropathy was higher in the group with new diabetes (9.4% and 10.7%), which was higher than that in the non-IG (3.4% and 4.1%) and IG (4.7% and 4.7%) groups. No differences in the incidence of retinopathy and nephropathy were observed between the IG and non-IG groups.

Findings might have several implications. By showing that IG alone does not cause diabetic microvessel complications, results support present ADA criteria for the diagnosis of diabetes, based on the idea that the lowest level of chronic hyperglycemia that induces microvessel complications should be the minimal criteria for the diagnosis of diabetes.


A novel investigational drug called TAK-875 (Takeda), the first in its class to be tested in diabetes, provides glycemic control in patients with type 2 diabetes with less risk for hypoglycemia compared with standard treatment.

TAK-875 targets the free fatty acid receptor (FFAR1), which results in increased insulin secretion when the receptor is activated in the presence of rising glucose levels.

Treatment with TAK-875 for 12 weeks resulted in dose-dependent improvement in glycemic control of patients with type 2 diabetes who were not adequately treated with metformin or diet and exercise alone.

In the phase 2 randomized, double-blind, placebo-controlled trial, 426 patients with type 2 diabetes were randomly assigned to receive 1 of 5 doses of TAK-875 (n = 303), glimepiride (n = 62), or placebo (n = 61). At 12 weeks, compared with placebo (18%), almost twice as many patients (range, 33%-48%) receiving TAK-875 doses of 25 mg or higher achieved the ADA target of glycosylated hemoglobin (HbA1c) levels less than 7%.

The percentage of patients who achieved target HbA1c levels while receiving glimepiride (40%) was similar to the rate seen among patients taking TAK-875 doses of 25 mg or more.

The incidence of hypoglycemia was significantly lower in patients receiving TAK-875 (2%) than in those taking glimepiride (19%) and no significant weight gain.

The rate of adverse events in TAK-875 patients was similar to that in the placebo group (49% vs 48%), and significantly lower than in the glimepiride groups (61%).

However, 3 patients (1%) treated with TAK-875 had serious adverse events that led to discontinuation.

Lancet. Published online February 27, 2012.
1. Introduction
The International Diabetes Federation (IDF) projects that without effective preventive action, the number of individuals with diabetes will increase from 285 million in 2010 to 439 million in 2030, of whom T2DM accounts for approximately 85–95% of cases in high-income countries and possibly a higher proportion in less affluent populations. The largest increase is expected in low- and middle-income countries, which already bear some 70% of the total global burden of diabetes. In Asia, as elsewhere, healthy lifestyle modifications are the keystone of effective T2DM prevention and management. Despite great progress in the pharmacological management of T2DM in past decades, the side effects of all current conventional therapies limit their uses and although they yield short-term improvements, none effectively arrest or reverse the inexorable worsening of the disease.

In this context, a pan-Asian panel of experts from China, India, Hong Kong, Indonesia, Malaysia, Philippines, Singapore, South Korea, Taiwan, Thailand and Vietnam, convened to review current standards and challenges in the management of T2DM. They discussed diverse aspects of T2DM care including the epidemiological burden and challenges in preventing complications; gaps between guidelines and ‘real-world’ clinical practice; diagnosis and management of patients with or at risk of renal impairment; and the current and future role of new therapeutic modalities in clinical practice, in particular the use of dipeptidyl peptidase-IV (DPP-IV) inhibitors to enhance the action of incretin hormones.

2. Epidemiology and burden of type 2 diabetes in Asia
Numbers of Asians with T2DM are increasing due to population growth and aging, urbanisation, increasing obesity, and more sedentary lifestyles. Latest national figures are probably underestimates and the substantial increase in prevalence predicted in future decades (Fig. 1) will increase the number of Asians with diabetes by 58%, from 135.4 million today to 213.7 million by 2030.

Although T2DM is becoming increasingly prevalent throughout Asia, it is not homogenously distributed. Unlike Caucasians, where T2DM affects mostly the older population, the rising burden of T2DM in Asia is disproportionately high in young and middle-aged adults. Compared to other races, Asians tend to develop T2DM at younger ages and a lesser degree of obesity, suffer longer from its complications and die earlier.

3. Complications and comorbid conditions of diabetes
The most prevalent T2DM comorbidities are hypertension, dyslipidaemia, and obesity. Complications arising from inadequately managed T2DM include macrovascular and microvascular sequelae. The leading causes of death in patients with diabetes were stroke and kidney failure in the Chinese and Japanese, but coronary heart disease (CHD) in Caucasians. The Asia Pacific Cohort Studies Collaboration (APCSC) reported the leading cardiovascular (CV) causes of death among patients with diabetes, as stroke (42%) in Asia and CHD (59%) in Australia and New Zealand; however, there were marked differences within Asia, with China and Japan having higher rates of stroke than CHD, while in Hong Kong and Singapore, the rate of stroke was similar to, or even lower than, that of CHD. Based on prevalence data from 12 countries in the Asia Pacific region, the APCSC has estimated population attributable fractions for the contribution of diabetes to CV mortality to be 2–12% for CHD, 1–6% for haemorrhagic stroke, and 2–11% for ischaemic stroke.

Asians with diabetes are at particularly high risk of renal complications. In an international study, 55% of Asian T2DM patients had increased albuminuria, compared to 40% of Caucasians. The Thailand Diabetes Registry has reported rates as high as 42–44%. Others have reported microalbuminuria in 26.9% of Indian diabetics, 31.6% of Japanese T2DM patients, and 26.3% of T2DM patients in Hong Kong. In a Japanese study, approximately 80% of patients diagnosed with T2DM before age 30 developed endstage renal failure by mean age of 50 years. A retrospective review at a Malaysian hospital indicated that diabetic nephropathy accounted for 55% of new dialysis cases.

Meta-analyses have associated diabetes with a 30–40% increased risk of cancer. A combination of factors, including changing disease patterns and advances in medical care, are altering the major causes of death among Asian patients with diabetes. In Hong Kong, for example, until the

![Prevalence chart](chart.png)

**Fig.1**– Estimated prevalence of diabetes among adults aged 20–79 years in 11 Asian countries (%). Age-adjusted to world population, except Taiwan.
early 1990s most Chinese patients with T2DM died from stroke and end-stage renal disease. A prospective diabetes registry established in 1995 recruited more than 7000 patients; 10 years after diagnosis, almost 30% had died or had a major adverse clinical event, with cancer (~20%), CHD (~20%), endstage renal disease (~10%), and stroke (~10%) emerging as the leading causes of death. Recent data from this registry suggest that metformin antidiabetic therapy may reduce cancer risk in T2DM patients, particularly those with low levels of high-density lipoprotein cholesterol.

4. Current type 2 diabetes management practice in Asia

Asian countries are very heterogeneous in terms of genetic predisposition, diet, urbanisation, relative affluence, clinical practices and healthcare and reimbursement systems; nevertheless there are commonalities in T2DM management. Most countries have their own formal clinical practice guidelines for T2DM and/or follow international guidelines such as those of the American Diabetes Association (ADA), joint consensus recommendations from ADA and European Association for the Study of Diabetes (EASD), or the IDF global guideline. Cost is a universal consideration and consequently, well validated non-pharmacologic interventions such as lifestyle modification, and inexpensive, reimbursable oral antidiabetic agents (OADs), notably biguanides (metformin) and sulphonylureas, predominate as routine treatments, especially in the public sector. Prevention studies in both Caucasians and Asians populations have shown consistently that compared to no-treatment or standard lifestyle advice, intensive lifestyle modification can significantly reduce the risk of progression from impaired glucose tolerance to diabetes by up to 40–50% or more, and if assiduously applied, can be equally or even more effective than standard lifestyle advice plus first-line pharmacotherapy with metformin. The early addition of metformin to intensive lifestyle modification may be particularly beneficial in younger and obese patients, and both interventions, particularly metformin, have proven very cost effective for long-term management of at-risk patients.

Sulphonylureas are still used as first-line therapy, particularly in some resource-limited settings, because they yield rapid and substantial blood glucose reductions and are inexpensive. However, as in Caucasians, currently available treatment modalities in Asia are limited by deteriorating glycaemic control with increasing duration of disease, and combination therapy is often required to achieve glycosylated haemoglobin (HbA1c) goals (Fig. 2). An initial combination of metformin and sulphonylurea or other OADs is generally used in patients with high HbA1c levels, with insulin plus an OAD the most common second-line combination therapy. In a survey of specialist diabetes centres in Taiwan, the most commonly used OADs were metformin (64.5%), sulphonylureas (60.5%), thiazolidinedione (17.0%), alpha-glucosidase inhibitor (13.1%) and glinide (9.5%). About half of patients requiring insulin (16.9%) used it in combination with OADs.

Diebetologists are witnessing a rising trend in the use of DPP-IV inhibitors, especially as a patient-paid item for private patients in cities. The latest guidelines by the United Kingdom National Institute for Health and Clinical Excellence (NICE) and the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE), specifically recommend DPP-IV inhibitors as a second-line option, in combination with metformin and sulphonylureas.

While not yet included in the ADA algorithm, the latest ADA/ EASD consensus statement suggests that DPP-4 inhibitors may be appropriate in certain patients by virtue of their relatively low likelihood of incurring weight gain or hypoglycaemia. In practice, DPP-IV inhibitors are used mainly as a second-line add-on to metformin; however, some providers use them as first-line therapy, for example, in non-obese patients, those who cannot tolerate metformin or are reluctant to risk its side effects, or combined with metformin in patients with high HbA1c levels.

5. Challenges of type 2 diabetes management in Asia

Several key issues and challenges concerning current management of T2DM in Asia have been identified. These include lack of access to specialist care facilities, especially in rural areas; insufficient clinical evaluation and delayed diagnosis; inadequate educational supports and resources; difficulty in preventing progressively declining β-cell function...
and rising HbA1c levels; side effects of currently available OADs; cost of non-reimbursable therapies; and limited choice of drugs suitable for high-risk patients, for example, those with diabetic nephropathy. There are major gaps between published guidelines for the management of T2DM and associated complications, and actual clinical practice in Asia, particularly with respect to vulnerable patient groups, who are often under-represented in the clinical trials underlying evidence based guidelines. Most physicians know how to manage common T2DM comorbidities in theory and follow guidelines that recommend controlling not only blood glucose, but also blood pressure and cholesterol; however, in practice, more intensive monitoring and management of risk factors is required to prevent complications. Many physicians are ‘glucocentric’ and not all patients, even in major urban hospitals, have comprehensive annual evaluations of blood glucose, HbA1c, blood pressure, and lipid profile. Although nephropathy is common, many physicians lack awareness of this problem and the importance of early diagnosis. For example, microalbuminuria is much cheaper to measure than HbA1c, yet may not be assessed routinely, even by specialists. Not all physicians consider the renal burden of OADs when treating T2DM patients and HbA1c goals for patients with moderate/severe kidney disease are uncertain, especially for new OADs, due to a lack of outcomes data. In cases where insulin is not the only option (i.e., HbA1c <9%) or a patient refuses insulin therapy, lack of clear guidelines engenders uncertainty among primary care physicians about the appropriate OADs to use, and at which creatinine levels.

Because sulphonylureas can be started quickly and are potent in restoring short-term glycaemic control, they may be used to initiate treatment, but not subsequently switched for a more appropriate therapy. Even specialist diabetologists and nephrologists with extensive experience in treating T2DM differ in their approaches to managing T2DM in the context of renal impairment.

6. Managing hyperglycaemia in high-risk patient groups
The presence of comorbidities is associated with poorer outcomes and increased CV risk in T2DM patients. For example, untreated or poorly-controlled hypertension can significantly accelerate the development and progression of both micro- and macrovascular complications. Aggressive blood pressure control is therefore required to improve patient outcomes. Angiotensin receptor blockers and angiotensin converting enzyme inhibitors, which slow the progressive decline in glomerular filtration rate (GFR) and are equally effective in long-term renoprotection in T2DM patients, are preferred in patients with, or at risk of developing, diabetic nephropathy.

In T2DM patients with dyslipidaemia, aggressive lipid lowering therapy, as recommended by agencies including the United States National Institutes of Health National Cholesterol Education Program, AACE, American College of Physicians, and ADA, is required to reduce the risk of CV disease.

Achieving and sustaining weight control among obese patients with T2DM is also important. Even modest weight loss can yield significant health benefits. Unlike sulphonylureas, metformin does not stimulate insulin secretion or cause hypoglycaemia and weight gain; therefore, metformin should be used for overweight patients and sulphonylureas avoided.

Elderly patients are vulnerable to hypoglycaemia and agents that increase this risk, for example long-acting sulphonylureas, should therefore be avoided. Thiazolidinediones increase the risk of congestive heart failure, particularly in patients aged above 50 years, and should also be avoided in elderly patients. GFR below 60 mL/min is not unusual in septuagenarian women and fulfils the criteria for chronic kidney disease – GFR below 60 mL/min/1.73 m² for 3 months or more; physicians treating female T2DM patients in this age group would therefore be prudent to take similar precautions to those that apply for renal impairment.

Many believe that treating T2DM patients before they develop overt renal disease is a very important aspect of clinical practice. Asians are more susceptible than Caucasians to diabetic nephropathy and exhibit faster progression from microalbuminuria to macroalbuminuria and renal failure. Microalbuminuria or albuminuria resulting from increased intraglomerular pressure is an important predictor of CV risk and is the principal marker of renal disease risk in diabetes. Post-hoc analysis of the Action in Diabetes and Vascular Disease: Preterax and DiaMicron MR Controlled Evaluation (ADVANCE) study – the largest ever clinical trial in T2DM – shows that both albuminuria and kidney function are independent risk factors for CV and renal events among T2DM patients. Research in Hong Kong, Japan and Taiwan, has positively correlated declining GFR with increased mortality in T2DM patients. Therefore, in addition to assessing markers of renal impairment, it is necessary to precisely measure functional parameters and consider the implications for treatment choice. Hypertension is the most important risk factor associated with renal disease in diabetic patients. Family history of renal disease, which is another important risk factor for diabetic nephropathy, is often overlooked in clinical practice. Other ‘covert’ risk factors include hyperuricaemia, excessive use of non-steroidal anti-inflammatory drugs, and retinopathy.

OADs are not contraindicated in T2DM patients with normal creatinine clearance, but impaired renal function limits their therapeutic application, the main concerns being the risks of overdose and hypoglycaemia, rather than nephrotoxicity.
Hypoglycaemia is the leading cause of hospitalisation in T2DM patients with renal impairment. Therefore, short-acting OADs with a low risk of hypoglycaemia and non-renal excretion are preferable and it is prudent to avoid agents with greater likelihood of overdose, or to reduce the dose accordingly. Although contraindicated, metformin is still sometimes used in Asian patients with moderate renal impairment (serum creatinine >150 mmol/L). We suggest that long-acting sulphonylureas should be avoided and sulphonylurea dose reduced if creatinine clearance is significantly impaired. Thiazolidinediones should be avoided in the presence of fluid retention or oedema, for example in patients with severe renal disease.

Pioglitazone exacerbates oedema and should be used with caution, particularly in patients with macular oedema or diabetic retinopathy. Most patients with significant proteinuria or severe or end-stage renal disease have multiple comorbidities and complications, and should ideally be managed in specialist rather than primary care settings. In practice, OADs suitable for use in such patients are very unlikely to reduce HbA1c of 8–9% or more to the predetermined goal, and insulin is the only realistic option. The ADA algorithm advocates early use of insulin in patients who do not achieve HbA1c goals, because adequate doses can rapidly bring any level of HbA1c close to the therapeutic target, with no limiting dose above which this therapeutic effect is lost.

However, relatively large insulin doses may be required in T2DM, and it is also important to avoid hypoglycaemia. In this context, particular caution is necessary in T2DM patients with diabetic nephropathy, who are at increased risk of hypoglycaemia because of impaired renal insulin clearance and decreased renal gluconeogenesis. For this reason, it is imperative to monitor glucose levels intensively and reduce the doses of insulin and OADs as necessary to avoid hypoglycaemia; however, this is not straightforward, because there are very few data on which to base monitoring of glycaemic control in T2DM patients with chronic kidney disease. Possible add-on drugs in such cases include nonsulphonylurea insulin secretagogues or pioglitazone, depending on the circumstances.

7. Current and future role of DPP-IV inhibitors

DPP-IV inhibitors are a new therapeutic class for T2DM that may have some advantages over existing OADs, particularly for certain high-risk groups. DPP-IV inhibitors allow effective glycaemic control (Fig. 3), with low risk of hypoglycaemia (e.g. elderly), neutral effect on body weight (e.g. in obese patients), and the convenience of once-daily oral dosing, which may help to improve patient adherence to therapy. DPP-IV inhibitors suppress glucagon and appear to be effective at all stages of T2DM, even with diminished b-cell function; therefore, combining DPP-IV inhibitors with insulin is feasible and may enable the insulin dose to be reduced, due to their capacity to suppress glucagon despite b-cell failure. In pre-clinical models, DPP-IV inhibitors alter several substrates with putative cardioprotective effects. However, the clinical implications of these preliminary findings in humans remain unclear.

Data on DPP-IV inhibition in Asians are limited; nevertheless, efficacy comparable to that in Caucasians has been demonstrated in Japanese, Chinese, Indian and Korean T2DM patients. In general, DPP-IV inhibitors appear to be well-tolerated in Asian patients, with a similar safety profile to that seen in Caucasians; the most common adverse events are gastrointestinal in nature. Other new incretin-basedantidiabetic agents, for example GLP1 analogues, have also demonstrated anti-hyperglycaemic efficacy and safety in clinical trials with Asian subjects.

Current recommendations on DPP-IV inhibitors, position these as a second-line alternative to sulphonylureas in patients who have inadequate glucose control on metformin, either if sulphonylureas are contraindicated (e.g. impaired renal function) or they are at increased risk of hypoglycaemia or its consequences (e.g. elderly). Patients with mild renal impairment who still experience hypoglycaemia during treatment with low-dose short-acting sulphonylureas would therefore be potential candidates for switching to a DPP-IV inhibitor. However, current DPP-IV inhibitors including sitagliptin, vildagliptin and saxagliptin, either require dose adjustment according to creatinine clearance or are not recommended for patients with
There have been postmarketing reports of worsening renal function, including acute renal failure, in patients treated with sitagliptin, some of whom were prescribed inappropriate doses. Linagliptin is a new DPP-IV inhibitor with a unique xanthine-based structure that, unlike other DPP-IV inhibitors, is primarily excreted via bile and gut. These characteristics mean that linagliptin could be used in treating early-stage or newly-diagnosed T2DM, without the need to first assess renal function, and potentially be continued without dose modification in mild, moderate, or severe renal disease. The United States Food and Drug Administration and the European Medicines Agency have approved linagliptin for treating T2DM, with no dose adjustment recommended for patients with renal impairment. Such agents may play a significant future role in the management of T2DM; however, until evidence from long-term studies on mortality, CV disease and renal outcomes with DPP-IV inhibitors becomes available, it remains to be seen whether their promising therapeutic profile is borne out by long-term efficacy and safety.

8. Conclusions and recommendations
To curb the epidemic of T2DM in Asia, an integrated strategy employing a risk-based, holistic and, where necessary, multidisciplinary approach is needed. Preventing complications of diabetes becomes an increasing priority as a higher proportion of the population lives on into old age. We believe that there is an unmet need for pharmacological agents that are efficacious, safe, cost-effective and convenient to use, both short- and long-term, for treating different stages of T2DM and preventing micro- and macrovascular complications.