

ASSESSING THE VALUE OF TREATMENT FOR DIABETES TO PATIENTS, THE HEALTHCARE SYSTEM, AND WIDER SOCIETY – A CASE STUDY ON CHINA

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THE INTERNATIONAL FEDERATION OF PHARMACEUTICAL MANUFACTURERS AND ASSOCIATIONS (IFPMA) ASKED CHARLES RIVER ASSOCIATES (CRA) TO UPDATE THE ASSESSMENT OF THE VALUE OF INNOVATION IN MIDDLE-INCOME COUNTRIES (MICS) FOR DIFFERENT THERAPY AREAS. THE AIM WAS TO TEST THE EXTENT TO WHICH THE VALUE OF INNOVATIVE TREATMENTS FOR TYPE 2 DIABETES (T2D) IN MIDDLE INCOME COUNTRIES IS ALIGNED WITH THE VALUE OBSERVED IN HIGH-INCOME COUNTRIES (HICS).¹

1 The original report was published in November 2013. "Assessing the value of radical and incremental innovation in key therapy areas in middle-income countries". http://www.ifpma.org/fileadmin/content/Publication/2014/value_of_innovation.pdf

EXECUTIVE SUMMARY

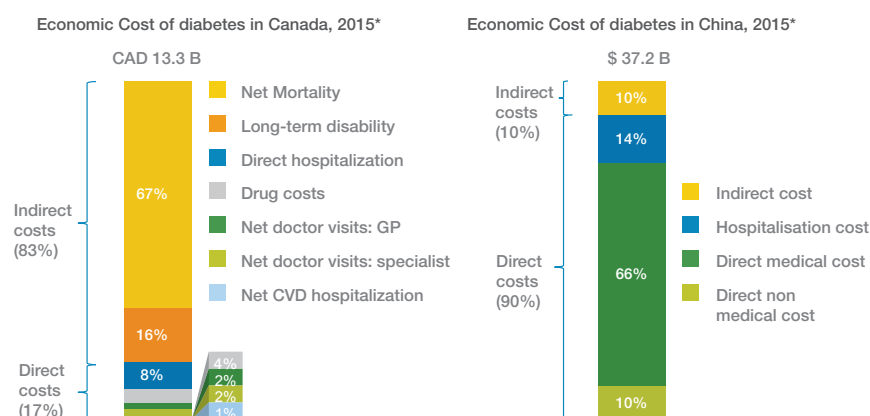
Diabetes is one of the most common non-communicable diseases (NCDs) in the world, with similar prevalence rates in HICs (high income countries) and MICs (middle income countries). However, the number of individuals suffering from diabetes is significantly larger in MICs (around 100 million in China alone) compared to HICs (52 million in Europe) simply due to relative size of populations.² The number of patients with diabetes in MICs is also growing rapidly. It is a chronic condition associated with long-term complications resulting in a high cost to patients, the health care system and the economy in affected countries. The purpose of this report is to compare the value of innovation in treatments for diabetes in MICs compared to that found in HICs. We chose China to illustrate the situation in MICs (as it is the MIC with the largest diabetes population and where diabetes has been recognised as an escalating problem) and we looked at a number of HICs – Australia, Canada, the United Kingdom, and the United States.

From a methodological perspective, the evidence base consists of a large number of studies publically available up to October 2015 including academic international comparisons, reports by organisations such as the WHO, reports derived from clinical research, and analysis undertaken as part of the clinical or economic assessment of these medicines.

THE COST ASSOCIATED TO DIABETES AND INNOVATION IN THE MANAGEMENT OF DIABETES

The improved economic status and the adoption of western life styles across society in MICs, notably poor diets and lack of exercise, is driving the incidence and prevalence of diabetes, to unprecedentedly high levels, creating a massive health challenge. Diabetes is a lifelong disease that requires a complex and delicate management of glycaemic control and the prevention of acute long-term complications to manage the significant economic burden that would otherwise fall on HICs and MICs. The cost burden and its composition for a HIC (Canada) and a MIC (China) have been estimated in a number of studies and are compared in Figure 1. In Canada, indirect costs make up a large proportion of total costs (>80%). However, in China, estimated indirect costs make up a much smaller percentage of total costs (10%).

Figure 1: Burden of Diabetes in HICs and MICs



Notes: + CAD 2010 dollars \$12.2 billion inflated to CAD 2015 dollars using Bank of Canada inflation data; * 2007 USD dollars \$32.3 billion inflated to USD 2015 dollars using Congressional Budget Office and Office of Management and Budget inflation rates. Source: CRA analysis using Canadian Diabetes Association (2009), 'An economic tsunami the cost of diabetes in Canada'. Note: CAD –

2 International Diabetes Federation. Title of subordinate document. In: Diabetes Atlas 6th ed. 2014 Update. http://www.idf.org/sites/default/files/Atlas-poster-2014_EN.pdf. [Accessed on 02.11.2015].

There has been considerable advance in the development of medicines available for treating diabetes. Diabetes is normally treated by using insulin therapy as a replacement therapy and/or by controlling blood glucose levels with oral anti-diabetic drugs (OAD). The International Diabetes Federation (IDF) recommends metformin as a first-line treatment, and other glucose control agents such as sulfonylurea as a second-line treatment. OADs such as Alpha-glucosidase inhibitor (AGI), meglitinides and thiazolidinediones were introduced in the early 1990s, and further innovative agents such as Glucagon-like peptide-1 (GLP-1) agonists and Dipeptidyl-Peptidase 4 (DPP-4) inhibitors were launched in the mid-2000s.

Diagnosis, treatment and management of diabetes are very well defined in HICs. The access to treatment in MICs appears significantly less complete. Diabetes care in China has limited infrastructure, and the delivery of healthcare varies considerably by location. Furthermore, access to monitoring is also limited. The Diabcare-China study of type 2 diabetes (T2D), which aimed to describe diabetes control, management and complication status, had over 2,700 participants and showed the challenges with screening and diagnosis:^{3,4}

- More than half of the people with diabetes had poor blood glucose control (glycaemic control).
- Half of the people had their glycated hemoglobin (HbA1c – an indicator of long-term blood glucose levels) measured in the last 12 months.
- About three in five people with diabetes had poor metabolic control, showing above-average levels of triglycerides and LDL cholesterol (so-called 'bad' cholesterol).

However, insulin and oral hypoglycaemic drugs are included on the Chinese Essential Drugs List (EDL), meaning that some treatments are available. The Chinese government recently launched the Chinese National Plan for Non-Communicable Diseases Prevention and Treatment 2012-2015, which aims to develop a plan for NCDs including diabetes and plans to develop a further 5 year plan for addressing NCDs.⁵

Studies have shown that appropriate treatment, close monitoring and behavioural changes can delay or prevent the progression of diabetes.⁶ We found evidence that diabetes therapies have brought value to HICs in terms of clinical benefits and reduction of healthcare costs, as well as wider socio-economic benefits such as the avoidance of disability adjusted life years (DALYs) lost. Diabetes treatments also yielded clinical benefits in China when they were used, and there is evidence that effective treatment results in savings to the health system. Treatment has also been shown to reduce lost productivity among diabetics in China, although since indirect costs were a smaller

3 The Diabcare-China study collected data between 1998 and 2006 from people with diabetes at 30 specialist centres across China. Available at: <http://professional.diabetes.org/Content/Posters/2008/p922-P.pdf>.

4 Pan (2005), 'Diabetes care in China: meeting the challenge', Diabetes Voice, 50,2.

5 Wang (2015). "2015第六届慢病管理大会6月9日开幕". Available at: <http://www.ncd.org.cn/Article/index/id/4439>. [Accessed on 04.11.2015].

6 Wang (2011), 'Diabetes care in China. Impacts of Traditional Chinese Medicine (TCM) and insurance on quality and utilization', dissertation for doctoral degree at the Pardee RAND Graduate School.

portion of the societal cost of diabetes in China compared to HICs (illustrated in Figure 1), the savings per person is not as large. Table 1 summarises these results.

Table 1: Evidence on the value of treatment for diabetes: HIC vs. China

	HICS	CHINA
Therapeutic/clinical value	✓	✓
Controlling costs	✓	✓
Wider benefits	✓	Limited

Source: CRA analysis

POLICY IMPLICATIONS

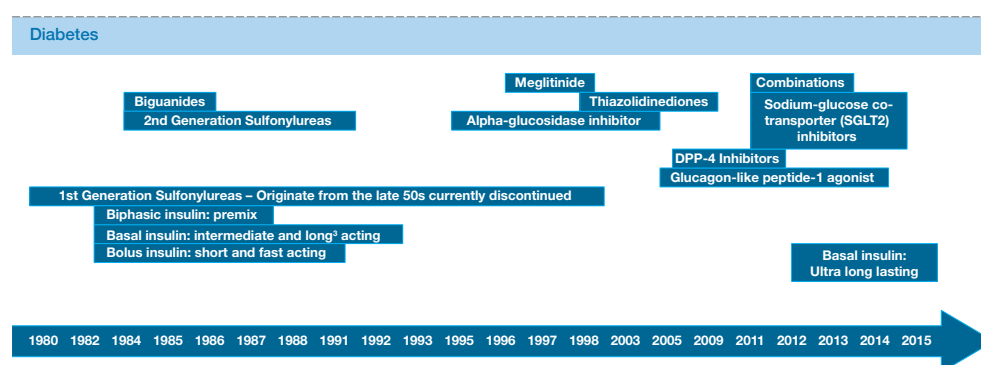
Drawing on the evidence regarding the value of innovation in T2D, a comparison of the policies adopted in MICs and HICs, we identified a number of policy implications:

1. **A national disease awareness programme is critical to ensuring that the widest population benefits from the value of innovative medicines** – The treatment of diabetes requires early diagnosis and care management, and the lack of infrastructure in MICs is clearly a barrier to benefiting from diabetes treatments. Only in recent years have we seen more attention paid to diabetes with the establishment of the CDS Chinese National Diabetes Management Programme (2003-2010), the Chinese National Plan for Non-Communicable Diseases Prevention and Treatment which includes diabetes (2012-2015) and the periodic update of diabetes treatment guidelines.^{7,8,9} In parallel, we have seen the awareness of recommended diabetes treatment amongst physicians rise to over 80%.¹⁰ As the government develops another 5 year national initiative for NCDs (2016-2020), we expect to see improvements in access to anti-diabetic treatment and management.¹¹
2. **The system needs to incorporate both patented and off-patent product delivering value to patients, the healthcare system and society** – There are both patented and off-patent anti-diabetic medications and both provide value.^{12,13} Indeed, the IDF guideline and published literature recognise that people with diabetes often need multiple anti-diabetic medicines to adequately control blood glucose. In this report, all major diabetes treatments are available in the selected HICs,

- 7 World Diabetes Foundation (2015). "National diabetes programme WDF02-036". Available at: <http://www.world-diabetesfoundation.org/projects/china-wdf02-036>. [Accessed 28.10.2015].
- 8 Wang (2011), 'Diabetes Care in China Impacts of Traditional Chinese Medicine (TCM) and Insurance on Quality and Utilization', Pardee Rand Graduate School dissertation.
- 9 中华医学会糖尿病学分会 (2014). "中国 2 型糖尿病防治指南(2013 年版)". Chin J Endocrinol Metab, October 2014, Vol. 30, No. 10. Available at: <http://www.endocrmetab.com/fileup/PDF/2014-10-893.pdf>. [Accessed on 26.10.2015].
- 10 Ji L, Newman, J., Lu, JM, and Cai XL. (2014). "Understanding the standard of care in the treatment of type 2 diabetes in China: results from a national survey." Chinese Medical Journal 127 (20): 3524-3529. Available at: http://124.205.33.103:81/ch/reader/view_abstract.aspx?file_no=20140826&flag=1. [Accessed 26.10.2015].
- 11 Wang (2015). "2015第六届慢病管理大会6月9日开幕". Available at: <http://www.ncd.org.cn/Article/index/id/4439>. [Accessed on 04.11.2015].
- 12 Leichter S & Thomas S (2003). "Combination medicine in diabetes care; an opportunity that merits more attention." Clinical Diabetes. Vol. 21 No. 4 pp 175-178.
- 13 International Diabetes Federation (2012) 'Global Guideline for Type 2 Diabetes', IDF, 2012 Clinical Guidelines Task Force.

with some differences in uptake for the latest anti-diabetic medicines.¹⁴ However, we also find evidence suggesting that the uptake of newer anti-diabetic innovations such as GLP-1s, DPP4s, and SGLT-2s (Figure 2) is low in China.¹⁵ Indeed, only older OADs and insulin are included in the 2012 Chinese EDL.¹⁶ While older off-patented medicines might be less costly, innovative patented medications can provide additional therapeutic benefit (for example, new SGLT-2s could lower risks for certain complications in diabetic patients but are more costly than older anti-diabetic medicines like sulfonylureas). Given the benefits of diabetes medicines on health outcomes, much more benefit could be achieved if both patented and off-patent medicines are accessible.

Figure 2: Therapy areas by class



3. **Appropriate healthcare infrastructure and integrated programmes that ensure diagnosis, testing, access to medicines and keeping patients on a course of treatment are necessary for medicines to fully deliver value.** – We find evidence of therapeutic benefits in HICs and China but there is scope for further clinical benefits from anti-diabetic treatment in China. In both HICs and China, we find that effective treatment, composed of treatment access, management and monitoring reduces diabetes related complications like heart attacks (by 50% in one UK study)¹⁷, and diabetic retinopathy (significantly lower progression rates in patients well controlled HbA1c levels).¹⁸ However, in China we also observe that diabetes care and management remains wanting as 3 in 5 people with diabetes have poor glucose control and only about half of all people with diabetes have had a blood glucose test in the last year.^{19,20} Diabetes is a therapy area that

14 For example, in the UK there is access to all major classes of anti-diabetic treatment. Available at: <https://www.medicinescomplete.com/about/>

15 Lu, C., et al (2015). "Uptake of new antidiabetic medications in three emerging markets: a comparisons between Brazil, China and Thailand." J. Pharm. Policy Pract. Vol 8, Issue (1). Available at: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4343056/>. [Accessed on 26.10.2015]

16 Chinese National Essential Drug List, 2012. Available at <http://trade.gov.il/china-en/2013/04/23/national-essential-medicine-list-2012-edition-released/>. [Accessed on 23.10.2015].

17 The diabetes control and complications trial research group (1993), "The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus", New England Journal of Medicine, 329; Nathan et al (2005), 'Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes', New England Journal of Medicine, 353; UKPDS group (1998), 'Intensive blood-glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes IKPDS33', The Lancet, 352.

18 Jin PY et al. (2015). "A five-year prospective study of diabetic retinopathy progression in Chinese Type 2 Diabetes patients with "well-controlled" blood glucose". PLoS ONE 10(4) Available at: <http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0123449>. [Accessed on 26.10.2015].

19 The Diabcare-China study collected data between 1998 and 2006 from people with diabetes at 30 specialist centres across China. Available at: <http://professional.diabetes.org/Content/Posters/2008/p922-P.pdf>.

20 Pan (2005), 'Diabetes care in China: meeting the challenge', Diabetes Voice, 50,2.

requires the availability of specialists or sophisticated technology and in China, the primary care infrastructure to properly manage diabetes is still a barrier to care.²¹ The benefits of innovative anti-diabetic medication is in part due to access but also depends on supporting healthcare infrastructure. Without patients being tested and appropriately managed, it is not possible to increase the appropriate use of medicine and, unsurprisingly, we are then unlikely to observe benefits from innovative medicines in MICs.

4. **In both HICs and MICs, medicines should be assessed according to the value they deliver directly to patients, to the healthcare system, and to the wider society** – Treatment of diabetes has brought a wide range of benefits within HICs. As diabetes drugs have reduced diabetes-related mortality rates within HICs, they have helped to reduce direct healthcare costs associated with the disease. For HICs, there was only indirect evidence (from Type 1 diabetes) suggesting that intensive glucose control would save an average of 10 deaths per year, and provide an annual value of £10 million to the British economy.²² To some extent, the same is true in China, where we have seen therapeutic benefits from anti-diabetic medicines and evidence that this has provided savings to the healthcare system. The evidence for wider benefits to society is admittedly weaker. For China, there are estimates of cost-savings per patient for particular types of management – care from pharmacies,²³ or specific types of insulin.²⁴ We have yet to see any aggregate evidence of societal benefits of diabetes in China. Thus, there remains considerable scope over the long term for HIC and MIC health authorities to refine their approaches to assessing the value of modern medicines from a national perspective. We would recommend therefore a modest investment of central resources in building better epidemiological and cost data bases to support the development of modern methods of evaluating the relative value of alternative therapies.

CONCLUSIONS

The purpose of this paper was to set out the evidence that innovative medicines deliver value in MICs and to compare this to evidence from HICs. For diabetes, there is evidence of value delivered by diabetes treatments but it is clear that the quality of the available evidence is weaker than in HICs. In terms of therapeutic benefit to patients and the potential for cost savings to the healthcare system there is robust evidence in China, however, the evidence on wider societal benefits is relatively weak.

However, the value that medicines deliver is linked to the extent medicines are accessible to patients. The availability of medicines depends on a range of factors but a

21 Novo Nordisk. "Improving the quality of diabetes care in China." Available at: http://www.changingdiabetesbarometer.com/docs/CDB_CHINA_GP_FINAL.pdf. [Accessed 04.11.2015].

22 Airolidi, et al (2006). "Estimating health and productivity gains in England from intensive glucose control in Type 1 diabetes." LSE Working Paper, 2046-4614.

23 Xin, C, Ge, X, Yang, X, Lin M, Jiang C, and Xia Z. (2014) "The impact of pharmaceutical care on improving outcomes in patients with type 2 diabetes mellitus from China: a pre – and post-intervention study." International Journal of Clinical Pharmacology 36 (5) pp. 936-938. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24993458> [Accessed on 26.10.2015].

24 Yang et al (2012), 'Cost-effectiveness of switching patients with type 2 diabetes from insulin glargine to insulin detemir in Chinese setting: a health economic model based on the PREDICTIVE study', Value in Health 15: S56-S59.

significant difference between HICs and MICs is that the government in China has only recently prioritised diabetes, along with other NCDs, and the availability of the appropriate infrastructure to diagnose and manage patients with these conditions is still developing. The value delivered by these medicines will therefore increase substantially in the future.

Diabetes treatment has developed rapidly with new classes being introduced over time. We have shown how anti-diabetic treatment has transformed diabetes into a disease that patients can comfortably live with, having reduced side effects and long term complications, and having expanded the choice of treatments for the patient population. This illustrates the significant value that incremental innovation delivers to MICs, just as they do in HICs.

1

INTRODUCTION

The International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) asked Charles River Associates (CRA) to review the evidence on the value of innovation for diabetes in middle-income countries (MICs) and to test the extent to which the experience of these countries is aligned with the experience of high-income countries (HICs).

1.1. BACKGROUND

Over the last ten years, the industry and academia have collated a range of evidence on the value that medicines bring to society. There have been papers setting out the different components of innovation,²⁵ studies attempting to quantify aggregate benefits that new medicines bring²⁶ and studies looking at the range of case studies illustrating the value that medicines deliver during the patented period.²⁷ In each of these areas, there is now a body of evidence in the United States and increasingly in European markets regarding the value of innovation in terms of case studies and empirical evidence. However, there is relatively little evidence on the value of innovation to emerging markets.²⁸ This report is intended to complement and build upon the existing IFPMA-commissioned research publications on innovation and access.²⁹

This report looks at the case of diabetes and specifically Type 2 Diabetes. Diabetes has become one of the most common NCDs in the world, representing one of the most challenging public health problems of the 21st century. There are two main types of diabetes:

- **Type 1 diabetes (T1D)** results from the autoimmune destruction of the pancreatic beta cells, the producers of insulin. T1D can occur at any age, although most cases develop amongst children, teenagers and young adults. There is currently no means of preventing or curing T1D.
- **Type 2 diabetes (T2D)** is characterised by insulin resistance, impaired insulin secretion, or both. It is the most common form of diabetes. This type of diabetes is typically diagnosed after the age of 40, though recently T2D has also been diagnosed in younger adults, and occasionally among adolescents. T2D has a strong genetic (familial) predisposition, which is exacerbated by lifestyle factors including obesity and lack of exercise. Thus it is potentially preventable in a substantial proportion of the population. Most people diagnosed with T2D will eventually require medication, which may include insulin therapy.

25 'The Many Faces of Innovation' by OHE Consulting for the European Federation of Pharmaceutical Industries and Associations (EFPIA), 18 February 2005.

26 Lichtenberg, 2010, 'The Contribution of Pharmaceutical Innovation to Longevity Growth in Germany and France' CESifo Working Paper Series No. 3095 or Lichtenberg, 2003, 'The Impact of New Drug Launches of Longevity: Evidence from Longitudinal, Disease-level Data from 52 Countries, 1982-2001', NBER Working Paper Series.

27 PhRMA 'Pharmaceutical Industry profile'.

28 The exceptions to this are the IFPMA report 'Incremental Innovation: Adapting to patient needs', February 2013, and the recent project undertaken by Charles River Associates on behalf of PhRMA. This takes a different approach by cataloguing examples of incremental innovation that have been aimed at addressing specific challenges in emerging markets.

29 This includes IFPMA report 'Policies that encourage innovation in middle-income countries'.

1.2. OUR APPROACH

There exists a large amount of evidence on the impact and value of T2D medication across HICs and MICs. For our purposes, we chose Australia, Canada, the United Kingdom and the United States as representatives of HICs. We focused on China as a representative of MICs.

In order to better understand the impact of diabetes medication on populations in HICs and MICs, we drew on existing academic and policymaker literature. The literature review is based on a combination of the following key search terms: “impact, value, cost, cost savings, cost-effectiveness, hospitalisations, burden” and “diabetes / anti-diabetic treatment” and “China, Australia, Canada, the United Kingdom or the United States”. The literature search was conducted on PubMed and Google Scholar. We updated the previous analysis to take into account literature published from 2013 to October 2015.

1.3. THE STRUCTURE OF THE REPORT

The remainder of the report examines the following in turn:

- First, we look at the evolution of the treatment options for diabetes and how these relate to the International Diabetes Federation (IDF) recommendations.
- Second, we review the extent to which diabetes treatments are actually available and accessible within the selected markets.
- Third, we present the evidence available of the added value that anti-diabetic treatments have brought MICs.

In the final chapter, we draw lessons and policy implications.

2

DIABETES

Diabetes receives a lot of attention from HICs, mostly due to the high number and costliness of its co-morbidities.³⁰ As an example, the risk for Coronary Heart Disease (CHD) increases fivefold for diabetics, and about 65% of diabetics die from heart disease and stroke.³¹ In addition to cardiovascular complications, there is an increased risk of eye and kidney diseases and limb amputations. Given this, it is not surprising that developed countries—where people tend to have more sedentary lifestyles and a greater risk of diabetes—have invested in addressing the disease.

However, the need to address diabetes is not restricted just to developed countries. For example, within one MIC, China, diabetes was responsible for 1.2 million deaths, making up 2% of total deaths in 2014.^{32,33} Diabetes is clearly a significant concern for all countries.

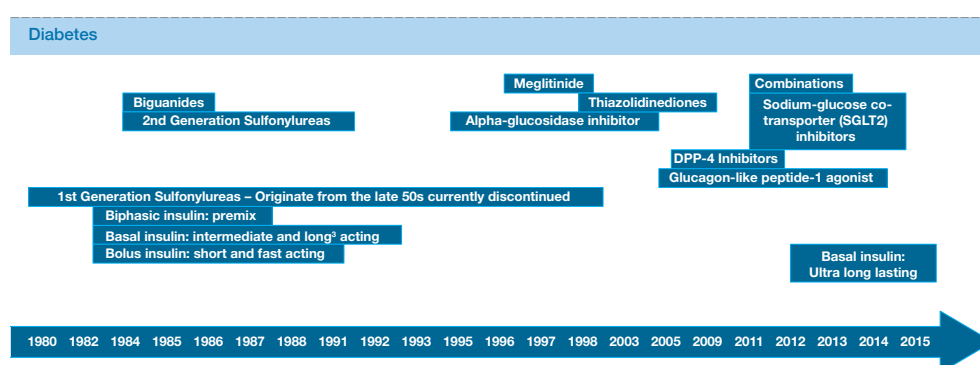
In this report, we provide a brief overview of treatment options for T2D within HICs and MICs. China was selected as the representative of MICs as it has the largest number of people with diabetes of any country in the world and has identified diabetes as a significant challenge, and we looked at a number of HICs – Australia, Canada, the United Kingdom, and the United States.

EVOLUTION OF TREATMENT OPTIONS FOR DIABETES

Medication for diabetes has been available since the 1920s, and the anti-diabetic effect of sulfonylurea was discovered in the early 1940s.^{34,35} These older treatments have either been discontinued due to poor safety profiles or replaced by newer, more efficacious products.³⁶

As Figure 3 shows by anti-diabetic therapy class, there have been a plethora of incremental innovations since the early 1980s.

Figure 3: Therapy areas by class



Source: CRA analysis

- 30 See, for example, IDF, 'What is diabetes?', <http://www.idf.org/node/23928>
- 31 Diabetes.UK, 'Cardiovascular disease', http://www.diabetes.org.uk/Guide-to-diabetes/Complications/Cardiovascular_disease/; National Diabetes Education Program, http://ndep.nih.gov/media/CVD_FactSheet.pdf
- 32 International Diabetes Federation. Title of subordinate document. In: Diabetes Atlas 6th ed. 2014 Update. http://www.idf.org/sites/default/files/Atlas-poster-2014_EN.pdf. [Accessed on 02.11.2015].
- 33 WHO. (2014). "China". Available at: http://www.who.int/nmh/countries/chn_en.pdf. [Accessed on 02.11.2015].
- 34 Diabetes UK (2010), 'First use of insulin in treatment of diabetes 88 years ago this week', Diabetes UK article.
- 35 Henquin (1992), 'The fiftieth anniversary of hypoglycaemic sulphonamides. How did the mother compound work?' Diabetologia, vol. 35, 907-912.
- 36 All classes include input from Diabetes UK, 'Diabetes Drugs'.

It must be noted that treatment is dependent on the type of diabetes the patient has. The main categories of treatment include insulin therapy and oral medication.

- **T1D** patients are treated with insulin therapy (also known as insulin replacement therapy).³⁷
- **T2D** patients are recommended oral hypoglycaemic agents ('oral anti-diabetic drugs') and insulin, in addition to lifestyle changes (e.g. regular exercise, dietary improvements, tobacco cessation).³⁸

THERAPY OPTIONS FOR THE TREATMENT OF T2D

Oral anti-diabetic drugs (OADs)

As seen in Figure 4, there was a phase of innovation starting in the early 1990s with the introduction of three new classes (alpha-glucosidase inhibitors, meglitinides and thiazolidinediones). Another round of innovation occurred from the mid-2000s with an additional three new classes (GLP-1 agonists, DPP-4 inhibitors, and SGLT2 inhibitors).³⁹

- **Sulfonylurea** is an insulin secretagogue⁴⁰ that increases the efficacy and production rate of insulin by the pancreas.⁴¹ Almost all first-generation sulfonylureas have been discontinued. Examples of second-generation sulfonylureas include glipizide (Glucotrol) and glimepiride (Amaryl).
- **Biguanides** is the class name for metformin and contains no other products. Metformin has been the universal first line therapy for T2D.⁴²
- **Alpha-glucosidase inhibitors (AGI)** slow down the digestion of starch in the intestinal tract, which subsequently reduces sugar levels after meals. Examples include miglitol and acarbose.
- **Meglitinide**, also known as glinides, similarly to sulfonylureas, are secretagogues. Examples include repaglinide and nateglinide.
- **Thiazolidinediones**, like biguanides, are insulin sensitisers. Examples include pioglitazone and rosiglitazone.
- **Glucagon-like peptide-1 (GLP-1) agonist** engages a specific G-protein receptor. Continuous activation of this receptor (GLP-1 receptor) also increases insulin synthesis.⁴³ Examples of GLP-1 agonists include exenatide and liraglutide.

37 WHO (2013), 'Diabetes', WHO fact sheet, 312.

38 NHS, 'Causes of type 2 diabetes', NHS online information guide.

39 All classes include input from Diabetes UK, 'Diabetes Drugs'.

40 Term given to a substance that causes the secretion of another substance.

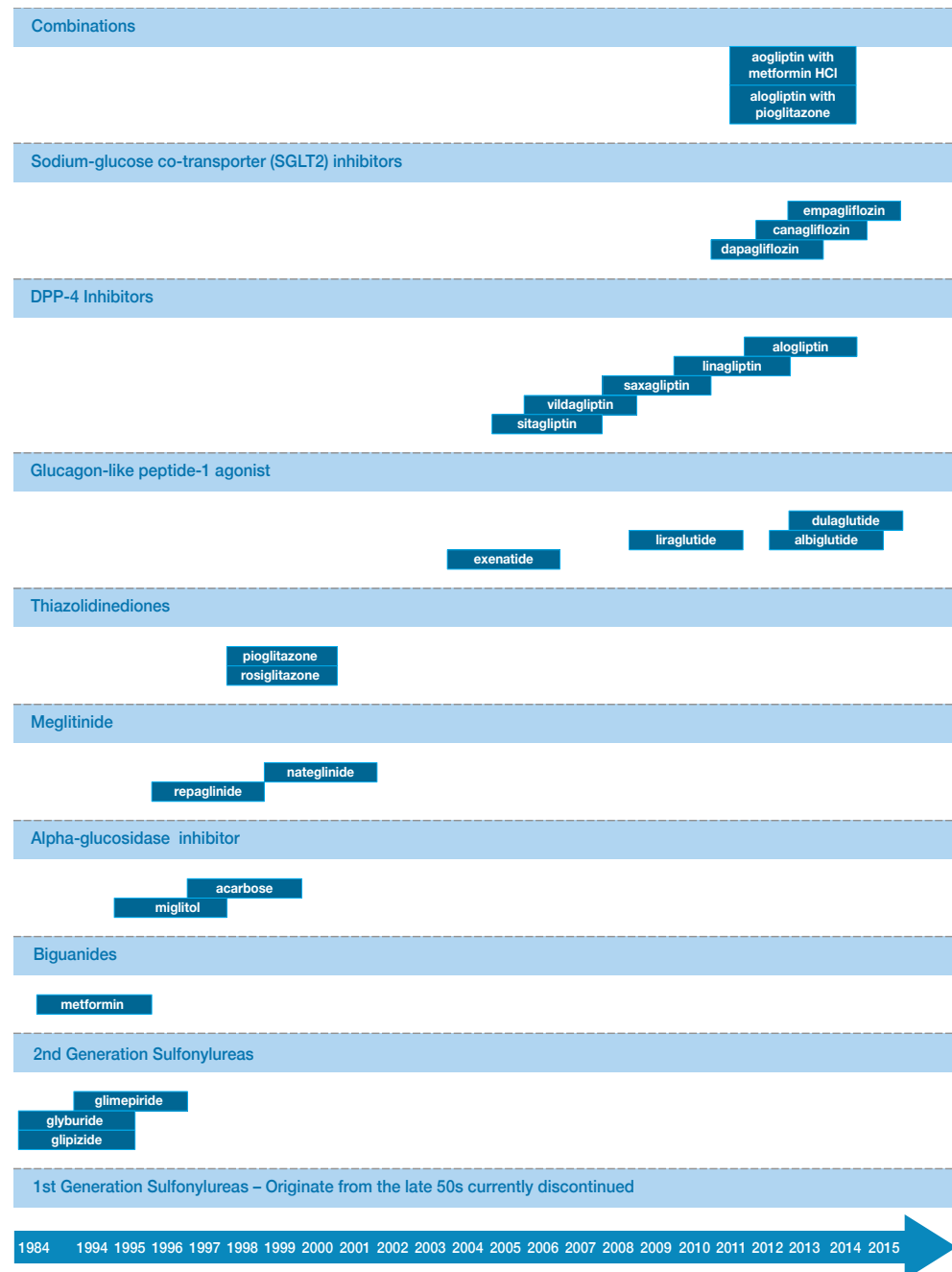
41 Gromada (1995), 'Effects of the hypoglycaemic drugs repaglinide and glibenclamide on ATP-sensitive potassium channels and cytosolic calcium levels in beta TC3 cells and rat pancreatic beta cells' *Diabetologia*, Vol.38, 1025-1032.

42 Halimi (2008), 'Combination treatment in the management of type 2 diabetes: focus on vildagliptin and metformin as a single tablet', *Vascular Health and Risk Management*, vol. 4, iss. 3, 481-492.

43 Doyle and Egan (2007), 'Mechanisms of Action of GLP-1 in the Pancreas' *Pharmacology & Therapeutics*, vol. 113, iss. 3, 546-593.

- **Dipeptidyl-peptidase-4 (DPP-4) inhibitors**, inhibit degradation of hormones that are involved in increasing insulin release.⁴⁴ Examples include saxagliptin and alogliptin.
- **Sodium-glucose co-transporter (SGLT2) inhibitors** are a class of glucose-lowering drugs which provide fully insulin-independent mechanism of action to managing the glycemic levels of a patient (by blocking glucose reabsorption in the kidney).⁴⁵ Examples include canagliflozin and dapagliflozin.

Figure 4: Development of OADs over time



Source: CRA analysis

44 Thornberry and Gallwitz (2007), 'Mechanism of action of inhibitors of dipeptidyl-peptidase-4 (DPP-4)', PubMed, vol. 23, iss. 4, 4790486.

45 Valentine (2012), 'The role of the kidney and sodium-glucose cotransporter-2 inhibition in diabetes management', Clinical Diabetes, vol.30, iss. 4, 151.

Insulin

Hypoglycaemic agents all try to influence the body's secretion of insulin. Insulin however, is itself also used to treat T2D patients and is typically used after poor control on OADs. Insulin is classified according to the length of action, which determines whether it is used as basal or bolus insulin. Basal insulin is used to keep blood glucose at consistent levels when fasting, while bolus insulin is taken at meal times to control blood glucose after meals.⁴⁶ Molecular makeup (animal, human and analogue) also differentiates the insulins. At present, human and analogue insulins are the most commonly used.⁴⁷ Insulin therapy is classified into several different types:⁴⁸

- **Rapid-acting (analogue) insulin:** injected either just before, with, or after food, with a peak at between 0 and 3 hours. Generally lasts between 2 and 5 hours. Examples are aspart and lispro.
- **Short-acting (human) insulin:** injected 15 to 30 minutes before meals to compensate for the rise in blood glucose levels caused by eating. This type has a peak action of 2 to 6 hours and last up to 8 hours. Examples are regular insulin Novolin R and Humulin R.
- **Intermediate-acting (human) insulin:** taken once or twice a day in combination with short – or fast-acting insulins to provide a background insulin level. Their peak is between 4 and 12 hours and can last up to 30 hours. NPH insulin is an example.
- **Long-acting (analogue) insulin:** as with intermediate-acting insulin, injected to provide background insulin in combination with short – or fast-acting insulin. Does not have a peak action and does not need to be taken with food. Examples are glargine and detemir.
- **Ultra long-acting (analogue) insulin:** Like long-acting insulins, they do not need to be taken with food and do not have a peak action. These are taken once a day, at any time, and provide insulin for up to 42 hours. An example is degludec.⁴⁹
- **Premix insulin:** a biphasic insulin that provides basal and bolus coverage without having to be injected separately. The basal coverage can be in the form of intermediate – or long-acting insulins, while bolus coverage can be in the form of short – or rapid-acting insulin.

Although the first commercialisation of animal derived insulin began in the 1920s, we focus on synthetic “human” insulin. Figure 5 demonstrates the evolution of FDA-approved insulin therapies.

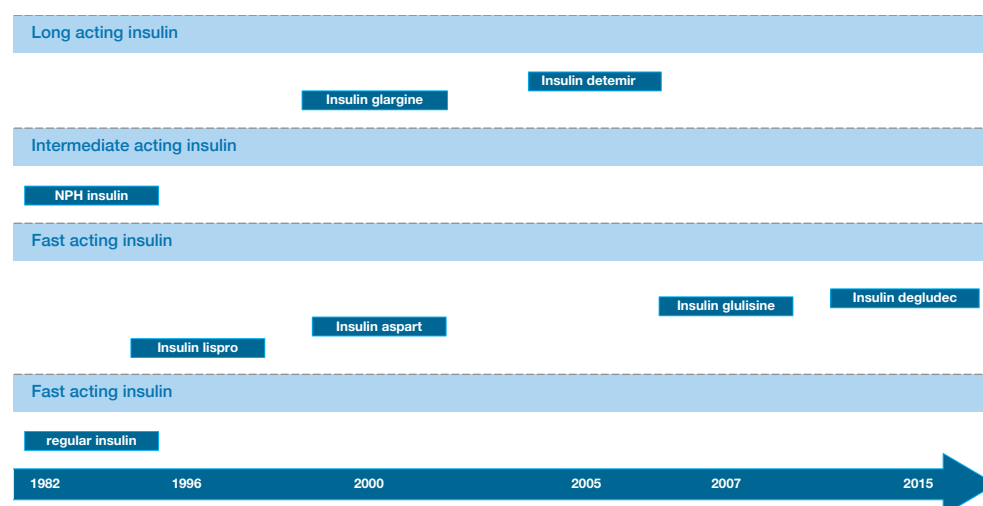
46 Diabetes UK, 'Basal bolus – basal bolus injection regimen', <http://www.diabetes.co.uk/insulin/basal-bolus.html>

47 Diabetes UK, 'The three groups of insulin', Diabetes UK guide to diabetes: <https://www.diabetes.org.uk/Guide-to-diabetes/Treatments/Insulin/>. [Accessed on 28 October 2015].

48 Diabetes UK, 'The main types of insulin', Diabetes UK guide to diabetes: <https://www.diabetes.org.uk/Guide-to-diabetes/Treatments/Insulin/>. [Accessed on 28 October 2015].

49 Diabetes UK, 'Insulin,' Diabetes UK Guide to diabetes: <https://www.diabetes.org.uk/Guide-to-diabetes/What-is-diabetes/Diabetes-treatments/Insulin/>. [Accessed on 28 October 2015].

Figure 5: Development of insulin medicines over the last thirty years

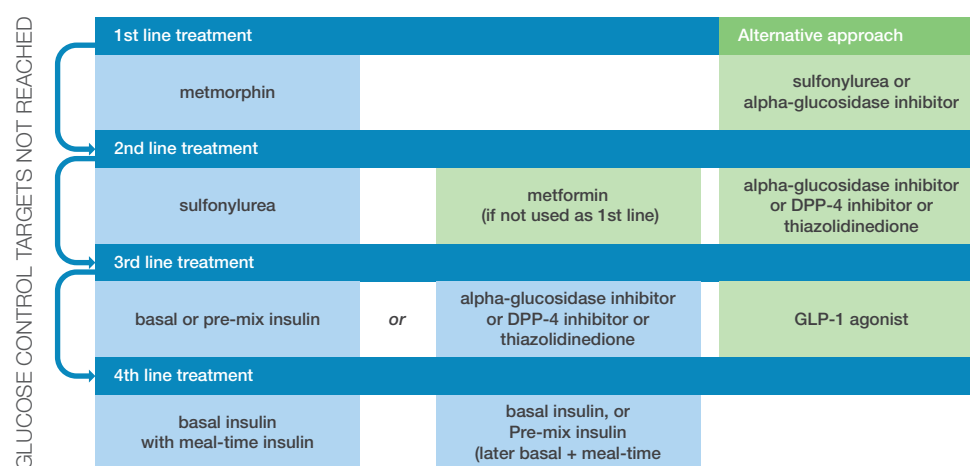


Source: CRA analysis

RECOMMENDED FIRST-LINE TREATMENT FOR DIABETES IN IDF GUIDELINES

The International Diabetes Federation introduced its first 'Global Guideline for Type 2 Diabetes' in 2005. The guidelines were developed based on clinical elements, cost-effectiveness, and resources of less-wealthy countries. The guidelines were last reviewed in 2012.⁵⁰ Figure 6 shows how different medicines should be used in sequences if glucose control targets are not reached.

Figure 6: IDF diabetes guidelines, 2012



Source: International Diabetes Federation (2012) 'Global Guideline for Type 2 Diabetes', IDF, 2012 Clinical Guidelines Task Force. Note: Limited care principles are the same as recommended care; however, attention must be given to cost and generic alternatives (e.g. human insulins can provide most of the gains that are achieved with analogue insulins). Comprehensive care also follows the same principles, but more expensive therapies and insulins may be considered.

The IDF guideline confirms what has been also established in literature, that people with diabetes often need multiple anti-diabetic medicines to adequately control blood glucose,⁵¹ illustrating that both patented and off-patent medicines are of value to patients.

⁵⁰ International Diabetes Federation (2012) 'Global Guideline for Type 2 Diabetes', IDF, 2012 Clinical Guidelines Task Force.

⁵¹ Leichter S & Thomas S (2003). "Combination medicine in diabetes care; an opportunity that merits more attention." Clinical Diabetes. Vol. 21 No. 4 pp 175-178.

2.1. ACCESS TO MEDICINES FOR DIABETES

The first issue to examine is the relative access in our HIC and MIC countries to the innovative medicines described above.

All major diabetes treatments are available in the selected HICs, with some differences in uptake for the latest anti-diabetics.

To determine the degree of access in China, we first examine the introduction of diabetes medication in the Chinese Essential Drug List (EDL), the use of clinical guidelines on the treatment of diabetes, the existence of a national strategy to fight against diabetes, and the existing evidence on access to treatments for diabetes in China.

The introduction of diabetes medication in the Chinese EDL

Insulin and OADs were included in the Chinese EDL in 2002 (see Table 2). China's 2002 EDL includes OADs from the meglitinide and thiazolidinediones class, which have been removed from the 2012 edition of the EDL.⁵² The bulk of OADs fall within the second-generation sulfonylureas class. This is the oldest of the classes, and even with new classes available, the majority of hypoglycaemic medicines on China's 2012 EDL are within this category.⁵³ The 2002 EDL does not provide further detail on the type of insulin, but the 2012 EDL specifies that insulins encompass short-acting, intermediate-acting, and premix animal and human insulins. Analogue insulins were not included in the 2012 EDL.

Table 2: Year of introduction of treatment classes for diabetes in Chinese EDL 2002 & 2012

TREATMENT CLASS	YEAR OF INTRODUCTION
Sulfonylureas	2002
Biguanides	2002
AGI	2002
Meglitinide	2002*
Thiazolidinediones	2002*
GLP-1 agonist	-
DPP-4 inhibitor	-
Sodium-glucose co-transporter inhibitor	-
Insulin	2002

Source: CRA analysis using Chinese 2002 and 2012 Essential Drugs List. Note: *Indicates that the a molecule in the class was introduced in that year, but is not included in the 2012 EDL

52 Chinese National Essential Drug List, 2002. Available at <http://www.sda.gov.cn/gyja438/x07.htm>, <http://www.sda.gov.cn/gyja438/x04.htm>, and <http://www.sda.gov.cn/gyja438/x11.htm>. [Accessed on 23.10.2015].

53 Chinese National Essential Drug List, 2012. Available at <http://itrade.gov.il/china-en/2013/04/23/national-essential-medicine-list-2012-edition-released/>. [Accessed on 23.10.2015].

The use of clinical guidelines on the treatment of diabetes

The Chinese Diabetic Society (CDS) is the leading national diabetes organisation in China. The CDS's mission is to prevent and treat diabetes through education, research, and the instilling of good medical practice.⁵⁴

The CDS developed the first Chinese diabetes treatment guidelines in 2000 based on the 1997 American Diabetes Association (ADA) guidelines and WHO 1999 guidelines. The CDS guidelines were updated in 2004, 2008, 2009 and 2013. They provide guidance on aspects of diabetes treatment such as diagnosis, classification, treatment goals and diabetes management.^{55,56}

Chinese national strategy to fight against diabetes

Since 2003, the CDS has run a project nationwide promoting the 'Chinese Guidelines of Diabetes Prevention and Treatment' (Guideline Promotions) which is one of two branches of the China National Diabetes Management Program (CNDMP). The objective of the CNDMP is to establish an effective model for the prevention, detection and treatment of diabetes across different regions in China.⁵⁷ As part of the 'Guideline Promotions', China started a five-year programme to train healthcare professionals and specifically 8,600 doctors (3,600 doctors in 36 major cities and 5,000 in smaller cities). A total of 11,128 professionals were trained in 441 counties, of which 5,550 were doctors (3,050 short of the original aim).^{58,59}

In addition to the CNDMP, the Chinese Ministry of Health (MoH) and the Development and Reform Commission signed the 'China National Plan for Non-Communicable Diseases Prevention and Treatment (2012-2015)'. As a result, the MoH has launched a number of action plan for diabetes along with other diseases such as cancer, cardiovascular disease, and chronic obstructive pulmonary disease.⁶⁰

As this national initiative comes to its end, the Chinese government is in the process of developing a further 5-year plan on non-communicable diseases. However, the details of the plan has not yet been finalised.⁶¹

Given the efforts of the Chinese government on addressing diabetes, we turn to examine the access of treatments for diabetes in China.

54 Chinese Diabetes Society website: <http://www.cdschina.org/english/page.jsp?id=33>.

55 Wang (2011), 'Diabetes Care in China Impacts of Traditional Chinese Medicine (TCM) and Insurance on Quality and Utilization', Pardee Rand Graduate School dissertation.

56 中华医学会糖尿病学分会 (2014). "中国 2 型糖尿病防治指南 (2013 年版)". Chin J Endocrinol Metab, October 2014, Vol. 30, No. 10. Available at: <http://www.endocrmetab.com/fileup/PDF/2014-10-893.pdf>. [Accessed on 26.10.2015].

57 Chinese Diabetes Society, (2010), 'The Promotion of the Chinese Guideline of Diabetes Prevention and Treatment in China', Chinese Diabetes Society.

58 Chinese Diabetes Society, (2010), 'The Promotion of the Chinese Guideline of Diabetes Prevention and Treatment in China', Chinese Diabetes Society.

59 World Diabetes Foundation (2015). "National diabetes programme WDF02-036". Available at: <http://www.world-diabetesfoundation.org/projects/china-wdf02-036>. [Accessed 28.10.2015].

60 WHO (2013), 'Cardiovascular diseases', WHO Representative Office China, Available at: <http://www.wpro.who.int/china/mediacentre/factsheets/cvd/en/index.html>. [Accessed on 28 October 2015].

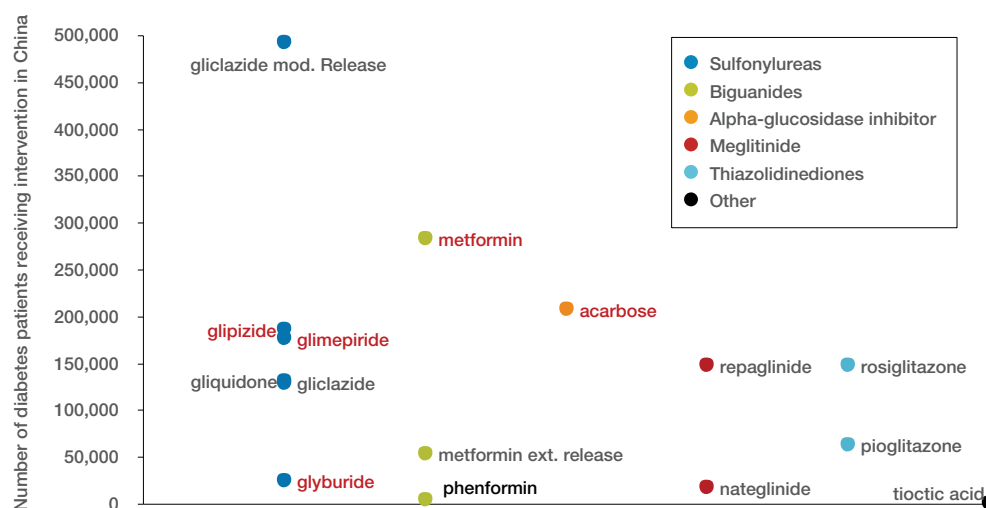
61 Wang (2015). "2015第六届慢病管理大会6月9日开幕". Available at: <http://www.ncd.org.cn/Article/index/id/4439>. [Accessed on 04.11.2015].

The existing evidence on access to treatments for diabetes in China

A study by IMS Health (IMS) estimates anti-diabetic medication usage in China in 2008.⁶² The study uses WHO's 'defined daily dose' (DDD) to calculate the number of patients receiving treatment based on the total anti-diabetic drugs use in the hospital setting.

Sulfonylureas are the most commonly used medicine class in China with over one million patients receiving this treatment. This is followed by biguanides with only 341,376 users (Figure 7). Another study found that biguanides (i.e. metformin) are the most prescribed first-line OADs in China, followed by first-generation drugs from the AGI and meglitinide classes, which had a 37.6% penetration rate (compared to 1.3% in the United States). The newer classes, namely DPP-4 inhibitors and GLP-1 agonists, has limited uptake in China (2.7% of the patient population, compared to 42% in the United States). This corroborates three of the data points in Figure 7 and supports the hypothesis that drugs included in EDLs are commonly used within the population.⁶³

Figure 7: Estimated number of patients receiving OADs in China by molecule, 2008



Source: CRA analysis using IMS, (2009), 'Examining diabetes and anti-diabetic medication use in low – and middle – income countries using the IMS core diabetes model', Core Center for Outcomes Research. Note: Medicines are grouped by class on the x-axis; medicines in red represent those on the Chinese Essential Drug List (2012 version)

As seen in Figure 8, human and animal insulins are the most popular types of insulins used in China. The use of the newer analogue insulin class is still very limited by comparison. Interestingly, insulin use is higher in China compared to the United States (35.9% vs. 20%), which the study attributes to poor blood sugar control of T2D patients in China.⁶⁴

62 Hospitals are the primary drug dispensers in China as pharmacies mainly sell OTC drugs and traditional Chinese medicines.

63 IPSOS (2013), 'Majority of type 2 diabetes patients in China yet to benefit from latest generations of oral treatment'.

64 IPSOS (2013), 'Majority of type 2 diabetes patients in China yet to benefit from latest generations of oral treatment'.

Figure 8: Estimated number of patients receiving insulins in China, 2008



Source: CRA analysis using IMS, (2009), 'Examining diabetes and anti-diabetic medication use in low – and middle – income countries using the IMS core diabetes model', Core Centre for Outcomes Research. Note: Insulins are grouped by class on the x-axis; medicines in red represent those on the Chinese Essential Drug List (2012 version)

A more recent study by Lu et al (2015) that looked at the uptake of new anti-diabetes medications using IMS sales data for China up to 2012 has similar findings. In terms of market share⁶⁵, newer anti-diabetic medications such as DPP-4 inhibitors only make up 0.15% of the market, which is dominated by biguanides (34.64%), alpha glucose inhibitors (27.35%), and sulfonylureas (20.80%).⁶⁶

There are very few studies estimating the extent of access to anti-diabetic medication in China and the available evidence suggests that access remains a problem. If we use the IMS data above and assume that a diabetic patient will be on only one therapy over the period of a year (i.e., one type of OAD or one type of insulin) and compare this with the 2007 IDF diabetes prevalence estimates for China, then there were at most 6.5% of diabetes patients receiving some sort of diabetes therapy (although this is likely to be an overestimation for a number of reasons).⁶⁷ In other words, even with these generous assumptions, 93.5% of diabetics did not receive therapy in 2008 in China. This could be in part attributed to the low compliance of prescription practices to the CDS guidelines. A survey of 1,028 physicians by Ji et al (2014) found that even though 83% of surveyed physicians were “aware” of CDS guidelines on the care for T2D, only over half (52%) of physicians actively complied to CDS guidance and prescribed OAD monotherapy.⁶⁸

65 Market share is the percentage of the total market volume based on volume sold in standard units per 1000 population. IMS Health defines a standard unit as the smallest common dose of a product form: one tablet or capsule for oral formulations.

66 Lu, C., et al (2015). "Uptake of new antidiabetic medications in three emerging markets: a comparisons between Brazil, China and Thailand." J. Pharm. Policy Pract. Vol 8, Issue (1). Available at: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4343056/>. [Accessed on 26.10.2015]

67 First, we used 2007 data, as 2008 data is not available. Given the positive trend experienced in China, we believe that in 2008 the population would have been bigger. Second, by using the whole diabetes population, we assume that all patients are at the same stage of the disease. Finally, patients will not necessarily be on only one therapy. For example, it is common for T2D patients to be on an OAD and insulin therapy, while those in the later stages of the disease may be on two types of insulin therapy.

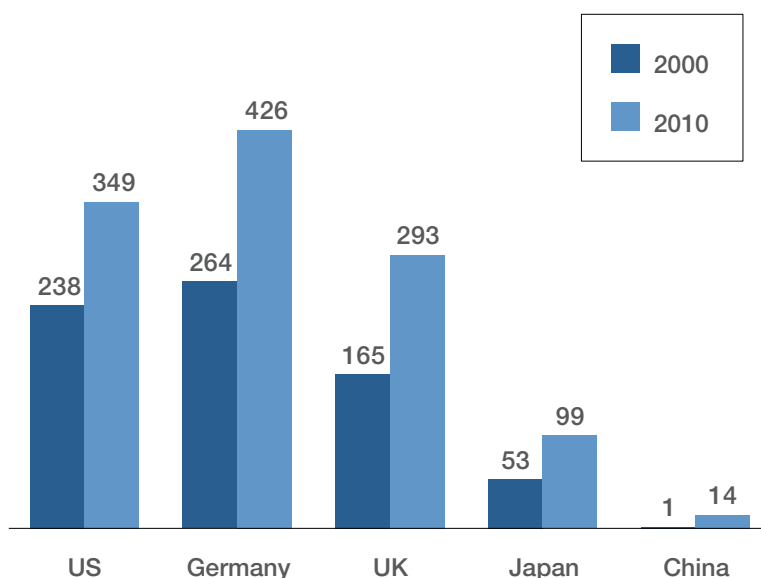
68 Ji L, Newman, J., Lu, JM, and Cai XL. (2014). "Understanding the standard of care in the treatment of type 2 diabetes in China: results from a national survey." Chinese Medical Journal 127 (20): 3524-3529. Available at: http://124.205.33.103:81/ch/reader/view_abstract.aspx?file_no=20140826&flag=1. [Accessed 26.10.2015].

Since the adoption of the Chinese National Plan for Non-Communicable Diseases Prevention and Treatment 2012-2015, there have been signs that suggest access to anti-diabetic care is improving. Most recently, a 2015 analysis of treatment data amongst 993 diabetic urban, migrant, and rural middle aged and older adults in the China Health and Retirement Longitudinal Study found that on average 62.9% of patients received Western medicine treatment for diabetes (< 8% being insulin therapy).⁶⁹ As China is preparing a further 5-year plan to address NCDs, access to anti-diabetic treatment should continue to improve in China.⁷⁰

A comparison of access to diabetes treatment in HICs and China

Unsurprisingly, we find that diabetes therapies, both old and new classes, are widely available within the HICs. Although insulin and oral hypoglycaemic drugs are included in the Chinese EDL, they tend to be from the older classes. For example, drugs from the AGI and meglitinide classes had a 37.6% penetration rate, while the newer DPP-4 inhibitors and GLP-1 agonists had only 2.7% penetration. By contrast, in the United States the former has only a 1.3% penetration rate, while the newer OADs have 42% penetration.⁷¹ Use of insulins in China has increased dramatically in the last 10 years due to increased prevalence of or access to insulin, but it is still low compared to HICs (see Figure 9).

Figure 9: Insulin consumption in selected countries – average insulin units per inhabitant



Source: Novo Nordisk (2011), 'The global diabetes care market'.

69 Xu, HZ., Luo, JF., and Wu, B. (2015). "Self-reported diabetes treatment among Chinese middle-aged and older adults with diabetes: Comparison of urban residents, migrants in urban settings and rural residents". Available at: <http://www.sciencedirect.com/science/article/pii/S235201321500006X>. [Accessed 26.10.2015].

70 Wang (2015). "2015第六届慢病管理大会6月9日开幕". Available at: <http://www.ncd.org.cn/Article/index/id/4439>. [Accessed on 04.11.2015].

71 IPSOS (2013), 'Majority of type 2 diabetes patients in China yet to benefit from latest generations of oral treatment'.

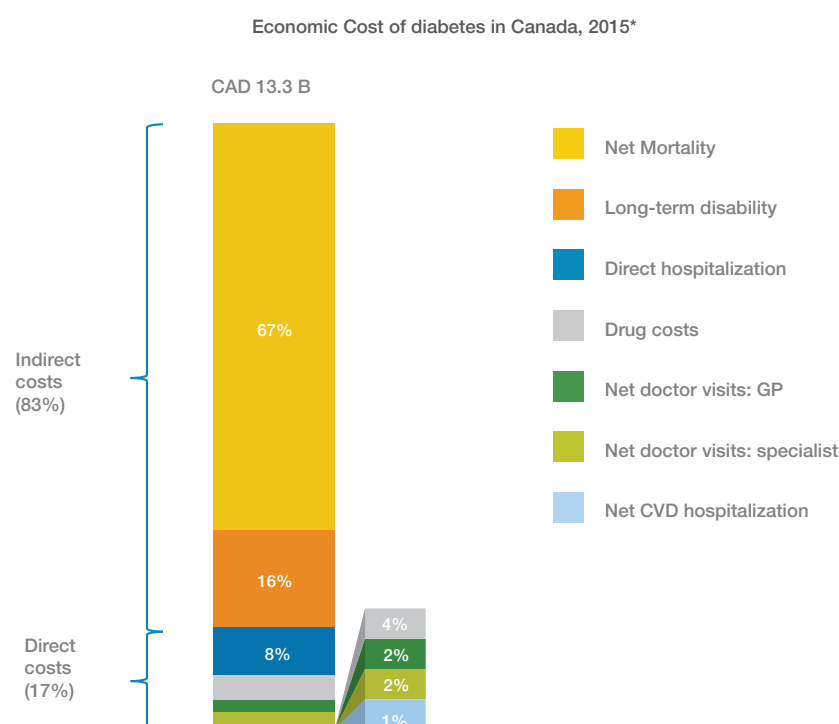
2.2. THE VALUE OF TREATMENT FOR DIABETES

In this section we first provide an overview of the benefits that diabetes treatments have brought to HICs, focusing on recent literature published in HICs, and we then see if the same effects have been found in China.

THE BENEFITS OF DIABETES DRUGS ACHIEVED WITHIN HICS⁷²

The economic burden of diabetes has been estimated in a number of HICs. These show that the economic burden is substantial and largely represented by indirect costs. For the United Kingdom in 2012, it was estimated that the total indirect costs due to lost productivity is close to £9 million.⁷³ In the same year, the total cost of diabetes in the United States was US\$245 billion, of which US\$176 billion was attributed to direct medical costs and a significant US\$69 billion to reduced productivity.⁷⁴ Similarly, the indirect cost of diabetes in Canada represented 83% of total costs. The total cost of diabetes was CA\$13.3 billion, of which direct costs (i.e., medical costs) amounted to CA\$2.3 billion in 2015 (Figure 10).

Figure 10: Economic burden of diabetes in Canada, in CAD, 2015



Notes: + 2010 CAD dollars \$12.2 billion inflated to 2015 CAD dollars with Bank of Canada inflation calculator Source: Canadian Diabetes Association (2009), 'An economic tsunami the cost of diabetes in Canada'. Note: CAD – Canadian dollars.

72 We have chosen to use Australia, Canada and the UK as the HIC comparators. There is extensive data available in Europe from "Diabetes expenditure, burden of disease and management in 5 EU countries". This is available at <http://www.lse.ac.uk/LSEHealthAndSocial-Care/research/LSEHealth/MTRG/LSEDiabetesReport26Jan2012.pdf>. [Accessed 26.10.2015]

73 Hex et al. (2012). "Estimating the current and future costs of Type 1 and Type 2 diabetes in the UK, including direct health costs and indirect societal and productivity costs." Diabetic Medicine Available at: <http://onlinelibrary.wiley.com/doi/10.1111/j.1464-5491.2012.03698.x/abstract> [Accessed on 26.10.2015].

74 American Diabetes Association. (2014). "Statistics about diabetes – National Diabetes Statistics Report 2014". Available at <http://www.diabetes.org/diabetes-basics/statistics/#sthash.RexOT7Wx.dpuf>. [Accessed 26.10.2015]

Therapeutic/Clinical benefits

The link between the use of diabetes drugs and the reduction of mortality rates in developed economies has been extensively studied. Prevention of T2D has been shown to bring therapeutic benefits as it reduces the complications and other risks associated with the disease. Indeed, a recent report developed by Diabetes Australia that reviewed the most relevant publications on the clinical benefits of treating diabetes, found the following:^{75,76}

- A United Kingdom study found that effective treatment of T2D reduced the probability of complications such as heart attack (by more than 50%), stroke (by 44%) and serious deterioration of vision (by up to 33%). The study's definition of 'effective treatment' included close monitoring and control of blood glucose levels, blood pressure and lipids.^{77,78} This would be achieved through several forms, including diabetes therapy.
- A 10-year study in Denmark demonstrated that by intervening simultaneously on multiple factors when treating T2D (glucose, blood pressure, cholesterol, etc.), the risks of developing severe complications were reduced by about 50% over 13 years.⁷⁹
- Diabetes-related complications are a major driver of service use and can multiply costs per patient. For example, about 34% of the total hospital in-patient days for diabetes patients are due to cardiovascular disease.⁸⁰ Similarly, end-stage renal disease has been shown to increase costs by as much as 771%.⁸¹

Controlling costs in the healthcare system

There are many studies that have estimated the cost associated with untreated diabetes.⁸² There have been a number of estimates of the cost savings that could be achieved if both preventive and appropriate management of diabetes were implemented. In Canada, the direct and indirect costs were estimated using a scenario where the diabetes incidence rates fell by 2% yearly. In such a situation, direct costs would decrease by 9% by 2020, with the greatest decline being from reduced GP and specialist visits due to improved diabetes education and management (see Figure 11). The authors did not project the effect of reduced complications on costs

75 Shaw, et al (2012), 'Diabetes: the silent pandemic and its impact on Australia', Baker IDI, Diabetes Australia and Juvenile Diabetes Research Foundation. It is worth noting that most of the sources cited by Diabetes Australia were also used by the Canadian Diabetes Association

76 Canadian Diabetes Association (2009), 'An economic tsunami. The cost of diabetes in Canada'.

77 The diabetes control and complications trial research group (1993), 'The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus', *New England Journal of Medicine*, 329; Nathan et al (2005), 'Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes', *New England Journal of Medicine*, 353; UKPDS group (1998), 'Intensive blood-glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes IKPDS33', *The Lancet*, 352.

78 The UKPDS was the largest clinical research study in diabetes conducted at the time and it is still a reference that is used within most of the diabetes associations.

79 Gaede, et al (2008), 'Effect of a multifactorial intervention on mortality in Type 2 diabetes', *New England Journal of Medicine*, 359.

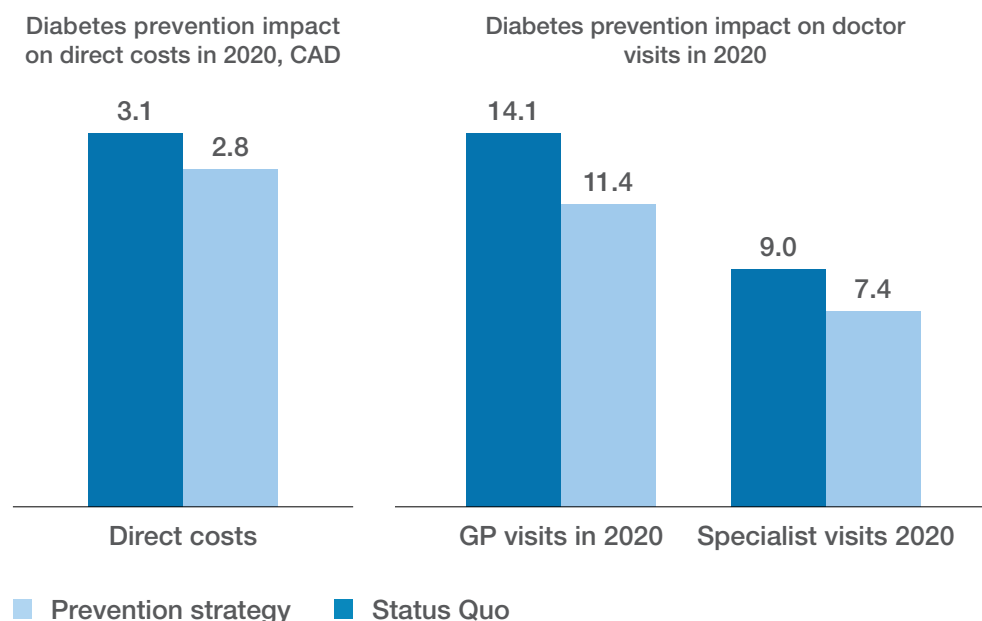
80 "Economic Costs of Diabetes in the US in 2007". American Diabetes Association. *Diabetes Care* 2008; 31:596-615.

81 Jonsson B. "Revealing the Cost of Type II Diabetes in Europe". *Diabetologia* 2002; 45:S5-S12

82 For example, costs estimates for gangrene treatment, ulcer treatment and lower limb amputation were provided in Bakker K et al. "Practical Guidelines on the Management and Prevention of the Diabetic Foot". *Diabetes Metab Res Rev* 2012; 28(Suppl 1):225-231.

of hospitalisation, amputation (which is estimated by the IDF as more than 25 times greater in patients with diabetes), or medication use.⁸³

Figure 11: Diabetes prevention program impact on direct costs and doctor visits in Canada, 2020



Source: Canadian Diabetes Association (2009), 'An economic tsunami. The cost of diabetes in Canada'

Wider benefits to society

In terms of wider benefits, we have not found evidence related directly to T2D. However, a study in England estimated the cost savings related to type 1 diabetes (T1D) if patients had their blood sugars tightly controlled.⁸⁴ The authors estimated that if T1D patients were administered intensive glucose control, an average of 10 deaths per year could be avoided in the first five years, with an average annual value for the English economy of £10 million. This represents an annual average of 400 years of life lost (YLL) and a total of 1,400 avoidable DALYs lost, costing the economy £40 million each year. These numbers become bigger when examining the effects in the long run. Table 3 summarises the results.⁸⁵

⁸³ Canadian Diabetes Association (2009), 'An economic tsunami. The cost of diabetes in Canada'.

⁸⁴ For the purposes of the study, the authors consider type 1 diabetes patients to be receiving intensive therapy if: insulin is administered at least three times a day (or with an insulin pump); insulin dosage, dietary intake and exercise adjustment according to results of self-monitoring of blood glucose; self-monitoring of blood glucose is administered at least four times per day; there is a monthly measurement of HbA1c, a monthly visit at the diabetic centre, and specialist calls during the month to review regimens.

⁸⁵ Airolidi, et al. (2006), 'Estimating health and productivity gains in England from intensive glucose control in Type 1 diabetes', LSE Working Paper, 2046-4614.

Table 3: Avoidable productivity losses in England from intensive glucose control in T1D

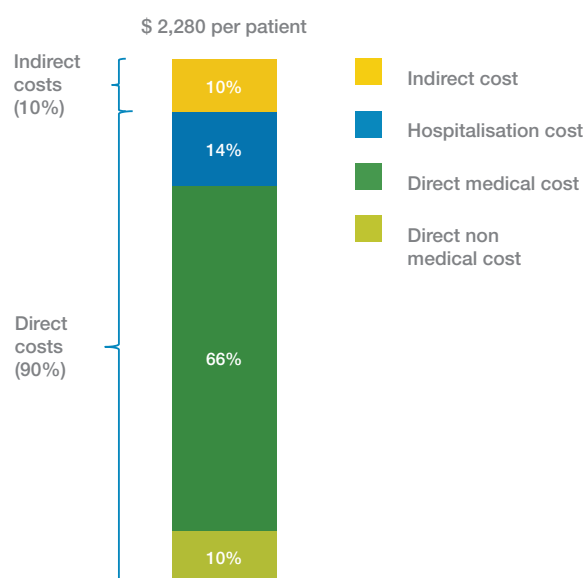
Annual average	DURING THE FIRST FIVE YEARS		IN THE LONG RUN	
	Absolute numbers	In value (million)	Absolute numbers	In value (million)
Avoidable deaths	10	£10	400	£450
Avoidable YYL	400	--	12,500	--
Avoidable discounted DALYs or QALY gains	1,400	£40	16,500	£ 450

Source: Airolidi, et al. (2006), 'Estimating health and productivity gains in England from intensive glucose control in Type 1 diabetes', LSE Working Paper, 2046-4614

The benefits of diabetes drugs achieved in China

Similar estimates of the economic burden of diabetes have been undertaken in China. Compared to HICs, the economic burden of diabetes in China largely comes from direct costs. As shown in Figure 12, indirect costs, which include productivity loss, account for around 10% of the average annual cost per diabetic patient in China. This is a much lower proportion than that of Canada, where indirect cost accounts for 67% of diabetes' economic burden.⁸⁶ Furthermore, it was estimated in one study that over a patient's lifetime, 53% of the direct costs could be attributed to diabetes-related complications.⁸⁷

Figure 12: Average annual cost per patient with diabetes in China, in USD, 2015*



Notes: *USD 2007 \$1986.80 inflated to 2015 USD using inflation estimates from Congressional Budget Office and Office of Management & Budget ; Source: Wang et al (2009), 'Type 2 diabetes mellitus in China: A preventable economic burden', The American Journal of Managed Care, 15, 9

⁸⁶ Canadian Diabetes Association (2009), 'An economic tsunami. The cost of diabetes in Canada'.

⁸⁷ Palmer JL et al (2012), 'Direct medical costs of diabetes mellitus in China: annual cost of illness and long-term projections using a validated diabetes model.' ISPOR 5th Asia-Pacific Conference 2012.

Therapeutic/Clinical benefits

There is emerging evidence of the reduction in morbidity or mortality in China from anti-diabetic medication. In particular, the following studies show that anti-diabetic medication reduces long term complications like diabetic retinopathy and microvascular disease and increases quality of life and life expectancy.

- A five-year prospective study on 453 diabetic retinopathy progression in patients with T2D in China found that patients with “well-controlled” blood glucose had slower progression rates to diabetic retinopathy than patients with higher HbA1C levels. Specifically, HbA1c levels lower than 5.2% had the lowest progression rate (19.6%) while patients with HbA1c levels over 6.4% had a much higher progression rate (76.8%).⁸⁸
- A study among T2D patients in China suggested that screening for T2D could reduce microvascular disease by 25%, with a greater reduction in people with good glycaemic control (A1C value greater than 9%).⁸⁹
- A six – month study on 8,578 patients starting or switching to biphasic insulin aspart 30 found that insulin improved glycaemic control and health-related quality of life. At the start of the study, only 88.4% and 77.3% reported no problems with mobility and pain or discomfort, by the end of the study, these percentages rose to 91.4% and 82.8% respectively.⁹⁰
- A study sponsored by Novo Nordisk projected the long-term (30 years) cost of converting patients who were also on OADs from insulin glargine to insulin detemir in China. The study found that the switch would increase patients’ life expectancy by 0.06 years (an increase from 11.46 years to 11.52 years) and 0.48 quality-adjusted life years. Perhaps more significantly, the switch is projected to reduce end-stage renal complications by 6.37%.⁹¹
- Palmer et al (2008) examined the effect of switching patients from biphasic human insulin to biphasic insulin aspart 30 in diabetes patients. The study found that the switch improved discounted life expectancy by 0.38 years per patient (9.91 years vs. 9.53 years) and quality-adjusted life expectancy by 0.91 years (6.32 vs. 5.41).⁹²

88 Jin PY et al. (2015). “A five-year prospective study of diabetic retinopathy progression in Chinese Type 2 Diabetes patients with “well-controlled” blood glucose”. PLoS ONE 10(4) Available at: <http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0123449>. [Accessed on 26.10.2015].

89 Wang et al (2009), ‘Type 2 diabetes mellitus in China: A preventable economic burden’, American Journal of Managed Care, 15,9.

90 Yang, WY (2014). “Improvements in quality of life associated with biphasic insulin aspart 30 in type 2 diabetes patients in China: results from the A1cheive® observational study”. Available at: <http://www.biomedcentral.com/content/pdf/s12955-014-0137-9.pdf>. [Achieved 26.10.2015].

91 Yang et al (2012), ‘Cost-effectiveness of switching patients with type 2 diabetes from insulin glargine to insulin detemir in Chinese setting: a health economic model based on the PREDICTIVE study’, Value in Health, 15: S56-S59.

92 Palmer et al (2008), ‘Cost-effectiveness of switching to biphasic insulin aspart in poorly-controlled type 2 diabetes patients in China’, Adv Ther 25(8): 752-774.

Controlling costs in the healthcare system

There is also a growing body of evidence of the health care savings that stem from anti-diabetes treatment.

- A pre-post intervention study in a South China teaching hospital found that pharmaceutical care from a clinical pharmacist led to a reduction in drug cost per patient per day (reduced from €254.74 to € 219.85) even though the change in hospital length of stay was not significant (16.35 vs. 15.91 days).⁹³
- Wang et al (2009) estimated that if 95% of T2D patients adhered to metformin therapy it could result in \$6.4 billion in savings of direct costs by 2030. Screening for T2D in the general population, having glycaemic control among patients with A1C levels over 8%, and controlling blood pressure could save at least \$1,309 per patient in annual direct medical costs.⁹⁴
- One of the major diabetes manufacturers reported that the lifetime cost of treatment and management of T2D patients with diabetes under control is higher than that of patients whose diabetes is not under control (105,000 DKK vs. 84,000 DKK), however, the lifetime cost of complications is lower for those whose T2D is under control (49,000 DKK vs. 66,000 DKK).⁹⁵

Two studies looked at the use of specific insulins and found cost savings from reduced diabetes-related complications.

- A study projected the long-term (30 years) cost of converting patients who were also on oral anti-diabetic drugs (OADs) from insulin glargine to insulin detemir in China. The study found that switching to insulin detemir+OAD from insulin glargine+OAD would increase diabetes drug and management costs by US\$400 per patient, but decrease the cost of treating complications by US\$820 per patient. The net savings from switching to insulin detemir was US\$420 per patient over a period of 30 years.⁹⁶
- A study in China examined the effect of switching patients from biphasic human insulin to biphasic insulin aspart 30, where the bolus insulin is an insulin analogue rather than human insulin. The study found that the switch increased the total direct medical cost per patient by 1,751 CNY, due to higher pharmacy and management costs (+19,007 CNY), but this was offset by reduced diabetes-related complication costs (-17,254 CNY). The incremental cost-effectiveness ratio per QALY gained with biphasic insulin aspart 30 compared to biphasic human insulin was 1,926 CNY.⁹⁷

93 Xin, C, Ge, X, Yang, X, Lin M, Jiang C, and Xia Z. (2014) "The impact of pharmaceutical care on improving outcomes in patients with type 2 diabetes mellitus from China: a pre - and post-intervention study." *International Journal of Clinical Pharmacology* 36 (5) pp. 936-938. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24993458> [Accessed on 26.10.2015].

94 Wang et al (2009), 'Type 2 diabetes mellitus in China: A preventable economic burden', *American Journal of Managed Care*, 15, 9.

95 Novo Nordisk (2011), 'Changing diabetes in China', *The Blueprint for Change Programme*, February 2011.

96 Yang et al (2012), 'Cost-effectiveness of switching patients with type 2 diabetes from insulin glargine to insulin detemir in Chinese setting: a health economic model based on the PREDICTIVE study', *Value in Health* 15: S56-S59.

97 Palmer et al (2008), 'Cost-effectiveness of switching to biphasic insulin aspart in poorly-controlled type 2 diabetes patients in China', *Adv Ther* 25(8): 752-774.

Wider benefits to society

Evidence of the socio-economic benefits of diabetes therapy in China is still scarce. Although authors acknowledge that the major hazards of diabetes are complications that can result in disability and early death, there is limited evidence quantifying the socio-economic cost that could be avoided if patients were appropriately treated in China. This is likely due, in part, to lower indirect costs (e.g. productivity loss) in China compared to the cost of treatment, unlike in HICs, where indirect costs constitute a fairly large portion of the societal cost of diabetes.

Wang et al (2009) estimated that a 95% adherence to metformin therapy among T2D patients could save between \$0.4 and \$0.5 billion in indirect costs, which includes lost income by patients and family members and the cost of hiring care providers. The low proportion of indirect cost savings as a proportion of total savings (around 6.9%) is likely due to the high unemployment rate of the study group (more than 83% unemployed) coupled with low individual income (at least 68% with less than \$260 monthly income).⁹⁸

One of the major diabetes manufacturers stated that the improved products and services they provide saved 140,000 life years in 2010, a number that is expected to grow at an annual rate of 30%, reaching more than 500,000 years in 2015. It is also predicted that type 2 diabetics whose diabetes is controlled are expected to have lower lifetime lost productivity compared to those whose diabetes is uncontrolled (34,000 DKK vs. 50,000 DKK).⁹⁹

2.3. THE VALUE OF MEDICINES FOR DIABETES IN HICS AND MICS

Diabetes is a lifelong disease that requires the complex and delicate management of glycaemic control and prevention of acute long-term complications. Studies have shown that appropriate treatment, close monitoring and behavioural changes can delay or prevent the progression.¹⁰⁰ It is one of the most common NCDs in the world, with similar prevalence rates in HICs and MICs as of 2012. In 2014, the number of individuals aged between 20-79 suffering from diabetes was significantly larger in MICs (96 million in China alone) compared to HICs (52 million in Europe) simply due to relative size of populations.¹⁰¹

There has been considerable advance in the development of medicines available for treating diabetes. Diabetes is normally treated by using insulin therapy as a replacement therapy and/or by controlling blood glucose levels with OAD. The IDF recommends metformin as a first-line treatment, and other glucose control agents such as sulfonylurea as a second-line treatment. Newer OADs such as AGI, meglitinides and

98 Wang et al (2009), 'Type 2 diabetes mellitus in China: A preventable economic burden', *American Journal of Managed Care*, 15,9.

99 Novo Nordisk (2011), 'Changing diabetes in China', *The Blueprint for Change Programme*, February 2011.

100 Wang (2011), 'Diabetes care in China. Impacts of Traditional Chinese Medicine (TCM) and insurance on quality and utilization', dissertation for doctoral degree at the Pardee RAND Graduate School.

101 Prevalence of diabetes in Europe is 7.87% and prevalence in China is 9.32%. International Diabetes Federation. Title of subordinate document. In: *Diabetes Atlas 6th ed. 2014 Update*. http://www.idf.org/sites/default/files/Atlas-poster-2014_EN.pdf.

thiazolidinediones were introduced in the early 1990s, and further innovative agents such as GLP-1 agonists and DPP-4 inhibitors were launched in the mid-2000s.

Diagnosis, treatment and management of diabetes are very well defined in HICs. The access to treatment in MICs appears significantly less complete. Diabetes care in China has limited infrastructure, and the delivery of healthcare varies considerably by location. Furthermore, access to monitoring is also limited. The Diabcare-China study of T2D, which aimed to describe diabetes control, management and complication status had over 2700 participants and found:^{102,103}

- More than half of the people with diabetes had poor blood glucose control (glycaemic control).
- Half of the people had their HbA1C (an indicator of long-term blood glucose levels) measured in the last 12 months.
- About three in five people with diabetes had poor metabolic control, showing above-average levels of triglycerides and LDL cholesterol (so-called 'bad' cholesterol).

Indeed, overall glycaemia control remains poor. In a recent study of 9,065 patients across 26 Chinese medical centres between 2010 and 2012, only 32.6% of all patients had glycaemia control that matched American Diabetes Association or Chinese HbA1c levels.¹⁰⁴

However, insulin and oral hypoglycaemic drugs are included on the Chinese EDL, meaning that some treatments are available. Additionally, the Chinese government launched the Chinese National Plan for Non-Communicable Diseases Prevention and Treatment 2012-2015, which set out aims to develop a plan for NCDs including diabetes.¹⁰⁵

We found evidence that diabetes therapies have brought value in HICs in terms of clinical benefits and reduction of healthcare costs, as well as wider socio-economic benefits such as the avoidance of DALYs lost. Diabetes treatments have also yielded clinical benefits in China when they were used, and there is evidence that effective treatment results in savings to the health system. Treatment has also been shown to reduce lost productivity among diabetics in China, although since indirect costs were a smaller portion of the societal cost of diabetes in China compared to HICs, the savings per person is not as significant. Table 4 below shows these results.

102 The Diabcare-China study collected data between 1998 and 2006 from people with diabetes at 30 specialist centres across China. Available at: <http://professional.diabetes.org/Content/Posters/2008/p922-P.pdf>.

103 Pan (2005), 'Diabetes care in China: meeting the challenge', *Diabetes Voice*, 50,2.

104 Chen R. et al (2015). "Glycemic control rate of T2DM outpatients in China: A multi-centre survey." *Med Sci Monit* 21: 1440-1446. Available at: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4448594/> [Accessed 26.10.2015]

105 China MoH. (2012) "China National Plan for NCD Prevention and Treatment (2012-2015)." Available at: http://www.chinacdc.cn/en/ne/201207/t20120725_64430.html. [Accessed 26.10.2015].

Table 4: Evidence on the value of treatment for diabetes: HIC vs. China

	HICS	CHINA
Therapeutic/clinical value	✓	✓
Controlling costs	✓	✓
Wider benefits	✓	Limited

Source: CRA analysis

3

POLICY IMPLICATIONS

In the previous section, we have set out the evidence for the value of innovative treatments delivered in HICs and MICs. In this chapter, we draw a number of policy implications from the evidence.

THE ESTABLISHMENT OF A POLICY PRIORITY

For diabetes, political prioritisation appears important, particularly where the main limitation preventing the benefits of innovative treatments from being brought to MICs is healthcare infrastructure. Only in recent years have we seen more attention paid to diabetes. We have seen the establishment of the CDS Chinese National Diabetes Management Programme (2003-2010), the Chinese National Plan for Non-Communicable Diseases Prevention and Treatment which includes diabetes (2012-2015) and seen the periodic update of diabetes treatment guidelines.^{106,107,108} In parallel, we have seen the awareness of recommended diabetes treatment amongst physicians rise to over 80%.¹⁰⁹ As the government develops another 5-year national initiative for NCDs, we expect to see improvements in access to anti-diabetic treatment and management.¹¹⁰

We recognise that the establishment of these national diabetes initiatives is not sufficient in itself to bring about value; indeed there are other factors affecting patient access to innovative medicines.

Policy implication: Ensuring that the widest population receives the value of innovative medicines often requires a national programme to increase awareness

There is not a simple relationship between whether we can observe value and the intellectual property protection.

There are both patented and off-patent anti-diabetic medications and both provide value. Indeed, the IDF guideline and published literature recognise that people with diabetes often need multiple anti-diabetic medicines to adequately control blood glucose.^{111,112}

106 World Diabetes Foundation (2015). "National diabetes programme WDF02-036". Available at: <http://www.world-diabetesfoundation.org/projects/china-wdf02-036>. [Accessed 28.10.2015].

107 Wang (2011), 'Diabetes Care in China Impacts of Traditional Chinese Medicine (TCM) and Insurance on Quality and Utilization', Pardee Rand Graduate School dissertation.

108 中华医学会糖尿病学分会 (2014). "中国 2 型糖尿病防治指南 (2013 年版)". Chin J Endocrinol Metab, October 2014, Vol. 30, No. 10. Available at: <http://www.endocrmetab.com/fileup/PDF/2014-10-893.pdf>. [Accessed on 26.10.2015].

109 Ji L, Newman, J., Lu, JM, and Cai XL. (2014). "Understanding the standard of care in the treatment of type 2 diabetes in China: results from a national survey." Chinese Medical Journal 127 (20): 3524-3529. Available at: http://124.205.33.103:81/ch/reader/view_abstract.aspx?file_no=20140826&flag=1. [Accessed 26.10.2015].

110 Wang (2015). "2015第六届慢病管理大会6月9日开幕". Available at: <http://www.ncd.org.cn/Article/index/id/4439>. [Accessed on 04.11.2015].

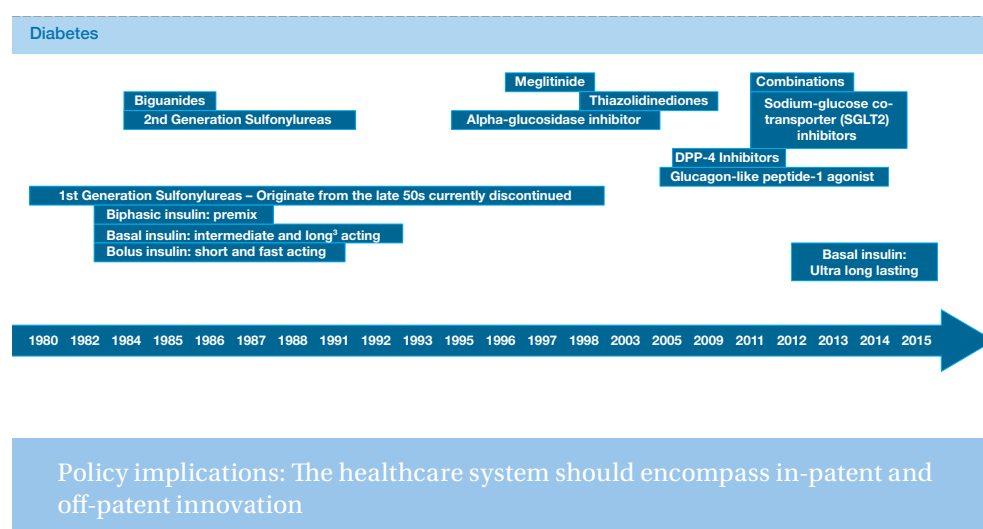
111 Leichter S & Thomas S (2003). "Combination medicine in diabetes care; an opportunity that merits more attention." Clinical Diabetes. Vol. 21 No. 4 pp 175-178.

112 International Diabetes Federation (2012) 'Global Guideline for Type 2 Diabetes', IDF, 2012 Clinical Guidelines Task Force.

In this report, all major diabetes treatments are available in the selected HICs, with some differences in uptake for the latest anti-diabetic medicines.¹¹³ However, we also find evidence suggesting that the uptake of newer anti-diabetic innovations such as GLP-1s, DPP4s, and SGLT-2s (Figure 13) is low in China.¹¹⁴ Indeed, only older OADs and insulin are included in the 2012 Chinese EDL.¹¹⁵

While older off-patented medicines might be less costly, innovative patented medications can provide additional therapeutic benefit (for example, new SGLT-2s could lower risks for certain complications in diabetic patients but are more costly than older anti-diabetic medicines like sulfonylureas). Given the benefits of diabetes medicines on health outcomes, much more benefit could be achieved if both patented and off-patent medicines are accessible.

Figure 13: Therapy areas by class



THE LEVEL OF INFRASTRUCTURE REQUIRED TO ADOPT INNOVATION

We find evidence of therapeutic benefits in HICs and China but there is scope for further clinical benefits from anti-diabetic treatment in China.

In both HICs and China, we find that effective treatment, composed of treatment access, management and monitoring reduces diabetes-related complications such as heart attacks (by 50% in one UK study)¹¹⁶, and diabetic retinopathy (significantly lower

113 For example, in the UK there is access to all major classes of anti-diabetic treatment. Available at: <https://www.medicinescomplete.com/about/>

114 Lu, C., et al (2015). "Uptake of new antidiabetic medications in three emerging markets: a comparisons between Brazil, China and Thailand." J. Pharm. Policy Pract. Vol 8, Issue (1). Available at: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4343056/>. [Accessed on 26.10.2015]

115 Chinese National Essential Drug List, 2012. Available at <http://trade.gov.il/china-en/2013/04/23/national-essential-medicine-list-2012-edition-released/>. [Accessed on 23.10.2015].

116 The diabetes control and complications trial research group (1993), 'The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus', New England Journal of Medicine, 329; Nathan et al (2005), 'Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes', New England Journal of Medicine, 353; UKPDS group (1998), 'Intensive blood-glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes IKPDS33', The Lancet, 352.

progression rates in patients with well-controlled HbA1c levels)¹¹⁷. However, we also observe that diabetes care and management remains wanting, as 3 in 5 people with diabetes have poor glucose control and only about half of all people with diabetes have had a blood glucose test in the last year.^{118,119} Diabetes is a therapy area that requires an availability of specialists or sophisticated technology and in China, there is a lack of primary care infrastructure to properly manage diabetes.¹²⁰

The benefit of innovative anti-diabetic medication is in part due to access but also depends on supporting healthcare infrastructure. Without patients being tested and appropriately managed, it is not possible to increase the appropriate use of medicine and, unsurprisingly, we are then unlikely to observe benefits from innovative medicines in MICs.

This implies that the value of innovative medicines, especially for NCDs, requires integrated policies in developing infrastructure to test and manage patients, as well as access to innovative medicines.

Policy implications: For medicines to deliver value, there needs to be appropriate healthcare infrastructure; this works best when integrated programmes are used to ensure diagnosis, testing, access to medicines and maintenance of patients on a course of treatment

A WIDE DEFINITION OF VALUE SHOULD BE RECOGNISED

As set out in the previous chapter, innovative medicines have delivered a broad range of benefits affecting not only patients but also the healthcare system and the society in general. We tested this directly by comparing the composition of benefits delivered in a MIC versus a HIC.

Treatment of diabetes has brought a wide range of benefits within HICs, with diabetes drugs reducing diabetes-related mortality rates within HICs and helping to reduce direct healthcare costs associated with the disease. To some extent, the same is true in China, and we have seen therapeutic benefits from anti-diabetic medicines.

But the evidence for wider benefits to society is considerably weaker. For HICs, there was only indirect evidence (from Type 1 diabetes) suggesting that intensive glucose control would save an average of 10 deaths per year, and provide an annual value of £10 million to the British economy.¹²¹ For China, there are estimates of cost-savings

117 Jin PY et al. (2015). "A five-year prospective study of diabetic retinopathy progression in Chinese Type 2 Diabetes patients with "well-controlled" blood glucose". PLoS ONE 10(4) Available at: <http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0123449>. [Accessed on 26.10.2015].

118 The Diabcare-China study collected data between 1998 and 2006 from people with diabetes at 30 specialist centres across China. Available at: <http://professional.diabetes.org/Content/Posters/2008/p922-P.pdf>.

119 Pan (2005), 'Diabetes care in China: meeting the challenge', Diabetes Voice, 50,2.

120 Novo Nordisk. "Improving the quality of diabetes care in China." Available at: http://www.changingdiabetesbarometer.com/docs/CDB_CHINA_GP_FINAL.pdf. [Accessed 04.11.2015].

121 Airolidi, et al (2006). "Estimating health and productivity gains in England from intensive glucose control in Type 1 diabetes." LSE Working Paper, 2046-4614.

per patient for particular types of management – care from pharmacies,¹²² or a specific type of insulin.¹²³ But, we have yet to see any aggregate evidence of societal benefits of diabetes in China. Thus, there remains considerable scope over the long term for HIC and MIC health authorities to refine their approaches to assessing the value of modern medicines from a national perspective. We would recommend therefore a modest investment of central resources in building better epidemiological and cost data bases to support the development of modern methods of evaluating the relative value of alternative therapies.

Policy implication: In both HICs and MICs, medicines should be assessed according to the value they deliver directly to patients, to the healthcare system, and to the wider society.

122 Xin, C, Ge, X, Yang, X, Lin M, Jiang C, and Xia Z. (2014) “The impact of pharmaceutical care on improving outcomes in patients with type 2 diabetes mellitus from China: a pre – and post-intervention study.” *International Journal of Clinical Pharmacology* 36 (5) pp. 936-938. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24993458> [Accessed on 26.10.2015].

123 Yang et al (2012), ‘Cost-effectiveness of switching patients with type 2 diabetes from insulin glargine to insulin detemir in Chinese setting: a health economic model based on the PREDICTIVE study’, *Value in Health* 15: S56-S59.

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