



# From history to reality: sodium glucose co-transporter 2 inhibitors – a novel therapy for type 2 diabetes mellitus

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## Introduction

Type 2 diabetes is a progressive metabolic disorder characterised by insulin insensitivity, relative insulin deficiency and consequent hyperglycaemia.<sup>1</sup> The International Diabetes Federation estimated a global diabetes prevalence for 2010 of 285 million, representing 6.4% of the world's adult population, with a prediction that by 2030 the number of people with diabetes will have risen to 438 million, 85–90% of this being type 2 diabetes.<sup>2</sup> Type 2 diabetes is a major risk factor for developing both microvascular complications (retinopathy, nephropathy and neuropathy) and macrovascular complications (ischaemic heart disease, cerebrovascular disease and peripheral vascular disease).<sup>3</sup> The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that effective glycaemic control reduced the rates of these complications.<sup>4–6</sup>

The pharmacotherapy for type 2 diabetes until the last decade only consisted of biguanides, sulphonylureas, and insulin. These 'older' drugs were used in the UKPDS and, although effective, were limited by gastrointestinal side effects, hypoglycaemia and weight gain.<sup>4,5</sup> The last 10 years have seen a rapid increase in the number of blood glucose-lowering agents which have become available including thiazolidinediones (in 2000), dipeptidylpeptidase-4 (DPP-IV) inhibitors (in 2007) and glucagon-like peptide-1 (GLP-1) mimetics (in 2007). Whilst these

## ABSTRACT

The human kidney has a key role in the regulation of blood glucose predominantly by reabsorption of glucose from the glomerular filtrate via sodium glucose co-transporter 2 (SGLT-2) channels. These are expressed in the proximal renal tubules and are blocked by SGLT-2 inhibitors, which are novel pharmacological agents currently in development. Specific SGLT-2 inhibition results in significant increases in renal glucose excretion causing a net calorie loss and consequent weight loss, coupled with a lowering of blood glucose due to removal of glucose from the circulation. The main side effect of SGLT-2 inhibitors appears to be an increase in genital infections, although concerns remain about the potential adverse effects of dehydration and electrolyte imbalance. Dapagliflozin is the SGLT-2 inhibitor that is the furthest along in development, and is currently in phase III clinical trials.

In this review article we consider the role of the kidney in glucose homeostasis in normal and diabetic subjects. We also review the history and concept of SGLT-2 inhibition, and discuss the future potential clinical utility of this promising new class of drugs. Copyright © 2010 John Wiley & Sons.

*Practical Diabetes Int* 2010; 27(7): 311–316

## KEY WORDS

sodium glucose co-transporter 2 inhibitors; SGLT-2 inhibitors; dapagliflozin; renal glucose reabsorption

drugs have undoubtedly increased the pharmacotherapeutic armamentarium available to diabetes health care professionals, they also have their own limitations. These include cardiovascular safety concerns, weight gain, anaemia, oedema and fracture risk with thiazolidinediones.<sup>7,8</sup> Although GLP-1 mimetics result in modest weight loss, they are injectable therapies and cause side effects of nausea and vomiting.<sup>9</sup> Oral incretin-based therapies (DPP-IV inhibitors) are well tolerated; however, they are merely weight-neutral.<sup>9</sup> Therefore there is no ideal pharmacological blood glucose-lowering agent to treat type 2 diabetes, and consequently a necessity for additional treatments to be developed remains.

## The kidney: under-recognised role in glucose homeostasis

The important role of the kidney in physiological glucose homeostasis is often overlooked. It helps to regulate blood glucose by gluconeogenesis, by utilisation of glucose from the circulation, and by reabsorption of glucose from the glomerular filtrate. These homeostatic mechanisms are altered in type 2 diabetes which may contribute to hyperglycaemia.<sup>10</sup>

Renal gluconeogenesis occurs via the production of glucose from precursors such as lactate and glutamine.<sup>11–13</sup> In the fasted state, about 20–25% of glucose released into the circulation is derived from the kidney, and this proportion increases with a longer duration of

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**Received:** 19 July 2010

**Accepted in current form:** 22 July 2010

## REVIEW

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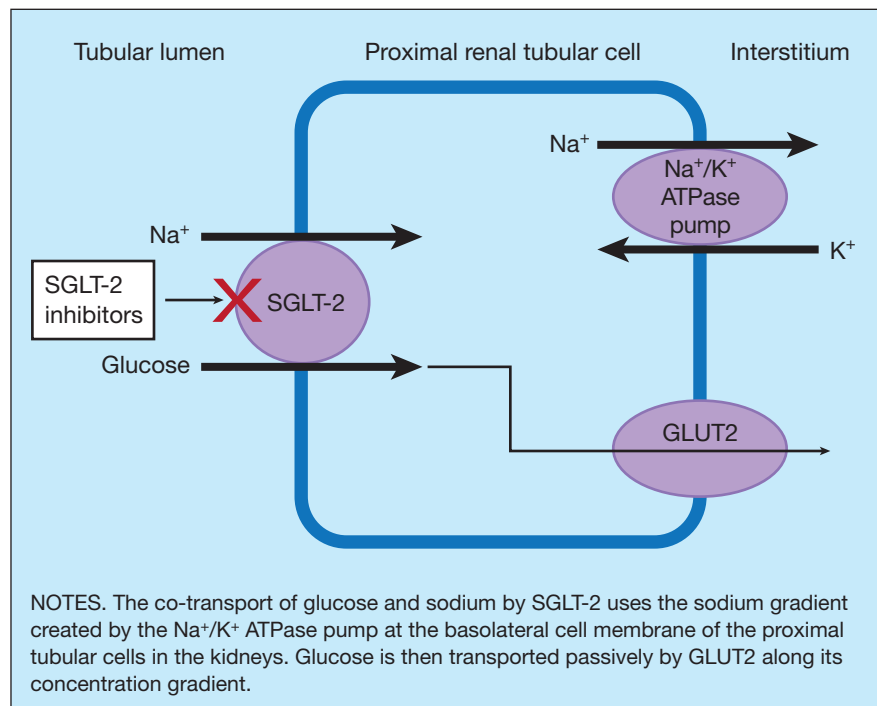


fasting, as glycogen stores in the liver become depleted (meaning the glycogenolysis cannot occur and that the majority of glucose released into the circulation is derived from gluconeogenesis).<sup>12</sup> However, in the post-prandial state, renal gluconeogenesis increases and is responsible for approximately 60% of glucose release into the circulation. This is associated with a significant reduction of hepatic gluconeogenesis and the cessation of glycogenolysis in order to replenish hepatic glycogen stores.<sup>14</sup> Patients with type 2 diabetes have been shown to have significantly increased rates of renal gluconeogenesis in both the fasting and post-prandial states.<sup>15</sup>

After an overnight fast, about 10% of glucose utilised by the body is taken up by the kidneys, and this proportion increases in the post-prandial state. This utilisation of glucose by the kidney is predominantly by the renal medulla.<sup>10,11,14</sup> Renal glucose uptake is increased in both the fasting and post-prandial states in type 2 diabetes mellitus.<sup>15</sup>

Renal glucose reabsorption is the principal means by which the kidney regulates glucose homeostasis. Usually about 180g of glucose is filtered by the kidneys every day; however, almost all of this is reabsorbed into the circulation by means of sodium glucose co-transporters (SGLTs).<sup>10</sup> SGLTs transport sodium and glucose into cells using the sodium gradient produced by sodium/potassium ATPase pumps at the basolateral cell membranes as shown in Figure 1. This is in contrast to the glucose transporters (GLUTs) which allow passive transport of glucose along its concentration gradient.<sup>16</sup> Approximately 10% of renal glucose reabsorption occurs via SGLT-1, a high-affinity, low-capacity glucose/galactose transporter which is located in the S3 segment of the proximal convoluted tubule (and also in the small intestine).<sup>17,18</sup> The majority (90%) of glucose is reabsorbed by SGLT-2 which is a high-capacity, low-affinity glucose transporter expressed on the S1 and S2 segments of the proximal tubule.<sup>17,19</sup> In normal physiology, as plasma glucose levels increase, there are corresponding proportionate

**Figure 1.** Site and mechanism of action of SGLT-2 inhibitors



increases in the amount of glucose filtered by the glomerulus and the amount of filtered glucose that is reabsorbed. This occurs until plasma glucose reaches a threshold level (11mmol/L), and above this level the proportion of filtered glucose that is reabsorbed decreases resulting in an increase in the amount of glucose excreted in the urine, causing glucosuria.<sup>20</sup> In type 2 diabetes, this threshold glucose is increased and glucosuria only occurs at higher plasma glucose levels than would be required to produce an equivalent effect in non-diabetic subjects.<sup>21</sup> This contributes to the hyperglycaemia of type 2 diabetes and provides a potential target for therapeutic intervention.

### Mechanism of action of SGLT-2 inhibitors

Phlorizin is a bitter white glycoside which acts as a non-selective inhibitor of SGLT-1 and SGLT-2, and was isolated from the root bark of the apple tree by French chemists in 1835. In the late 19th century, the observation that the bitter taste of phlorizin was similar to that of anti-malarial treatments led to its use in the treatment of malaria and other infectious diseases, and at this time it was noted that high doses of phlorizin caused

glycosuria.<sup>22</sup> Since then, phlorizin has been shown to normalise blood glucose levels in pancreatectomised diabetic rat models, but it has not been developed as a glucose-lowering drug due to a combination of its poor bioavailability and poor side-effect profile, which is likely to be a result of its non-selective action (its metabolite, phloretin, inhibits SGLT-1 in the intestinal mucosa causing malabsorption of glucose and galactose).<sup>23,24</sup>

Specific SGLT-2 inhibitors, which are analogues of phlorizin, are a new class of drugs some of which are in phase III clinical studies. They work independently to insulin and selectively inhibit SGLT-2 thereby preventing glucose reabsorption from the glomerular filtrate. This class of drugs effectively reduce the renal threshold for glucose and cause glucosuria, and so lead to net calorie loss and potentially have minimal risks of hypoglycaemia and weight gain.<sup>16</sup>

### SGLT-2s in clinical development

#### Dapagliflozin

Dapagliflozin is the SGLT-2 inhibitor, developed by Bristol-Myers Squibb and AstraZeneca, which is currently the furthest along in development,



and is the first with published phase III trial results.

Phase I clinical data have confirmed that dapagliflozin has a pharmacokinetic profile of a once-daily drug producing dose-dependent increase in glycosuria. It also has good bioavailability when administered orally, reaching a maximum plasma concentration within two hours of administration with a mean half-life ranging from 11.2–16.6 hours.<sup>25</sup>

Phase IIa data have shown that dapagliflozin, administered at 5mg, 25mg or 100mg doses, inhibited approximately 40% of renal glucose reabsorption when compared to baseline, resulting in glucose excretion of up to 70g per day.<sup>26</sup>

In a phase IIb multiple-dose study, 389 patients with type 2 diabetes were randomised to receive one of five different doses of dapagliflozin (2.5mg, 5mg, 10mg, 20mg or 50mg), metformin or placebo. At 12 weeks, all dapagliflozin groups achieved significant reductions in mean HbA<sub>1c</sub> of -0.55% to -0.90%, compared to -0.18% (placebo), and -0.73% (metformin). Dapagliflozin also induced glycosuria with daily urinary loss of approximately 200–300kcal, resulting in weight loss of -2.5 to -3.4kg, compared to -1.2kg (placebo) and -1.7kg (metformin). There was a higher incidence of genital infections in the dapagliflozin patients, especially at higher doses.<sup>27</sup>

Another phase IIb study randomised 71 patients with type 2 diabetes treated with insulin to placebo, 10mg dapagliflozin or 20mg dapagliflozin. Subjects continued to receive their oral antidiabetic agents and 50% of their pre-study daily insulin dose. At week 12, dapagliflozin 10mg and 20mg groups achieved HbA<sub>1c</sub> reductions of -0.70% and -0.78% respectively, and reductions of total body weight of -4.5kg and -4.3kg respectively (compared to mean -1.9kg weight loss with placebo). There were more genital infections and also minor hypoglycaemic events reported with dapagliflozin than with placebo.<sup>28</sup>

An analysis of two phase II studies compared 151 early-stage (less than one year duration of diabetes) patients with 58 late-stage (more than 10 years' duration of diabetes)

patients with type 2 diabetes who were randomised to receive placebo, 10mg dapagliflozin or 20mg dapagliflozin. Comparable reductions in HbA<sub>1c</sub> and body weight were demonstrated in both the early-stage and late-stage patients with dapagliflozin treatment.<sup>29</sup>

The first published phase III clinical trial with dapagliflozin studied 546 metformin-treated patients with type 2 diabetes and suboptimal glycaemic control. Subjects were randomised to receive either one of three doses of dapagliflozin (2.5mg, 5mg or 10mg) or placebo. At six months there were mean HbA<sub>1c</sub> reductions of -0.67% (-0.81 to -0.53,  $p=0.0002$ ), -0.70% (-0.85 to -0.56,  $p<0.0001$ ), -0.84% (-0.98 to -0.70,  $p<0.0001$ ) and -0.30% (95% CI, -0.44% to -0.16%) in the 2.5mg dapagliflozin, 5mg dapagliflozin, 10mg dapagliflozin and placebo groups respectively. There were no differences in the rate of hypoglycaemia among patients in the dapagliflozin and placebo groups; however, genital infections were more frequent in the dapagliflozin groups (2.5mg, 11 patients [8%]; 5mg, 18 patients [13%]; 10mg, 12 patients [9%]) than in the placebo group (seven patients [5%]).<sup>30</sup>

A number of phase III studies with dapagliflozin are currently in progress, as monotherapy and also as an add-on therapy to metformin, glimepiride, DPP-IV inhibitors, thiazolidinediones and insulin. A phase III study is also ongoing in subjects with moderate renal impairment. In addition, another phase III study looking at the effects of dapagliflozin on blood pressure in diabetic patients with inadequately controlled hypertension is planned.<sup>31</sup>

#### Canagliflozin

Canagliflozin, developed by Johnson & Johnson, is another compound currently in phase III studies. Data from phase II studies have been presented at the recent American Diabetes Association (ADA) 70th Scientific Sessions (summarised in Table 1). A number of phase III studies are underway, as monotherapy and as add-on therapy to metformin. Phase III studies are also in progress to determine efficacy and safety in

patients with moderate renal impairment, in older (55–85 years of age) patients and a cardiovascular safety study as required by recent FDA recommendations for registration of new glucose-lowering drugs.<sup>32</sup>

#### BI 10773

This molecule from Boehringer Ingelheim Pharmaceuticals is currently undergoing phase II studies in combination with metformin and insulin.<sup>33</sup> Some early data regarding this compound were presented at the recent ADA 70th Scientific Sessions (summarised in Table 1).

#### ASP1941

This novel compound, developed by Astellas Pharma Inc, is in phase II trials.<sup>34</sup> Data from these showing significant reductions in fasting glucose and body weight have been presented at the ADA's 70th Scientific Sessions (see Table 1).

#### Remogliflozin etabonate

This is a GlaxoSmithKline product. Early dose ranging data have been presented in abstract form only.<sup>35</sup> There are no ongoing studies registered for this compound.

#### AVE 2268

This compound is in development by Sanofi-Aventis. A phase II study looking at it as add-on therapy in patients not adequately controlled on metformin was completed in 2008.<sup>36</sup> The results of this study are awaited. There are no registered ongoing studies with this compound.

#### Ongoing concerns and adverse effects

Individuals with the rare condition, familial renal glucosuria (FRG) caused by mutations of the gene coding SGLT-2, have a decreased renal threshold for glucose. Subjects with FRG exhibit varying degrees of glycosuria (in some cases losing up to 100g glucose per day in the urine); however, they are asymptomatic and do not have an increased risk of urinary tract infections.<sup>37</sup> They also do not become hypoglycaemic or dehydrated.<sup>37,38</sup> This model of SGLT-2 inhibition is therefore reassuring in terms of adverse effects. However, extrapolation from



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the mechanism of action of SGLT-2 inhibitors raises the possibility of side effects such as dehydration and electrolyte loss, although this is generally not supported by preclinical phase I and II studies, or currently published phase III evidence.<sup>25–27,30</sup>

Nevertheless, one of the phase II studies with dapagliflozin reported a single case of dehydration and renal impairment which resolved on oral rehydration and withholding their ACE-inhibitor and diuretic treatment.<sup>28</sup> It must be remembered

that, in contrast to individuals with FRG, a relatively high proportion of patients with diabetes may be treated with diuretics (particularly thiazides) and ACE-inhibitors which could theoretically increase the risk of these side effects. In addition,

**Table 1.** Summary of recently presented SGLT-2 abstracts from the proceedings of the American Diabetes Association 70th Scientific Sessions, 25–29 June 2010, Orlando, Florida

Compound	Citation	Results
<b>Dapagliflozin</b>	Wilding JPH, <i>et al.</i> , Abst 78-OR and Abst 21-LB	Reductions in HbA <sub>1c</sub> of -0.9% and body weight of -1.67kg in patients poorly controlled with insulin with 10mg dose over 24 weeks
	Parikh S, <i>et al.</i> , Abst 563-P	Data analysed from 3 dapagliflozin studies showed significant improvements in glycaemic control regardless of the duration of diabetes and background medication
<b>Canagliflozin</b>	Sha S, <i>et al.</i> , Abst 568-P and Abst 76-OR	Increased glycosuria and decreased renal threshold for glucose excretion in 126 subjects in 2 weeks. Reduced 24-hr plasma glucose, fasting plasma glucose and weight (1–1.5kg more than placebo). Dose-dependent increases in glycosuria in healthy volunteers
	Schwartz S, <i>et al.</i> , Abst 564-P	29 subjects, poorly controlled on insulin, showed reductions in HbA <sub>1c</sub> of -0.92% and body weight of -1.2kg after 28 days
	Rosenstock J, <i>et al.</i> , Abst 77-OR	451 patients on metformin randomised to sitagliptin, placebo or various doses of canagliflozin. HbA <sub>1c</sub> reduced by -0.71% and weight by -2.3kg with 300mg canagliflozin, compared to -0.56% and 0.4kg with 100mg sitagliptin
	Polidori D, <i>et al.</i> , Abst 646-P	Beta-cell function assessed by HOMA2-B% improved significantly after 12 weeks
	Sarich T, <i>et al.</i> , Abst 567-P	Dose-dependent increase in glycosuria and weight loss of up to -3.5kg in obese individuals at 14 days. No changes in plasma glucose, insulin levels or self-reported appetite and satiety
	Ueta K, <i>et al.</i> , Abst 608-P	Improved hepatic glucose metabolism by a reduction of glucokinase expression, thus preventing hyperglycaemic glucotoxicity in male ZDF rats
<b>ASP1941</b>	Kashiwagi A, <i>et al.</i> , Abst 75-OR; Schwartz S, <i>et al.</i> , Abst 566-P	Reduced HbA <sub>1c</sub> , fasting blood glucose levels and body weight with good safety and tolerability in patients with type 2 diabetes
	Veltkamp SA, <i>et al.</i> , Abst 565-P	Rapidly absorbed with a median t max of 1.0 to 2.3 hrs and showed a dose-dependent glycosuric effect in healthy volunteers without impacting on mean plasma glucose levels. Mean half-life ranged from 11–15 hrs
<b>BI 10773</b>	Port A, <i>et al.</i> , Abst 569-P	Favourable pharmacokinetics, pharmacodynamics and tolerability results in healthy volunteers
	Seman L, <i>et al.</i> , Abst 571-P; Heise T, <i>et al.</i> , Abst 629-P	Well tolerated and reduced daily mean and post oral glucose tolerance test of blood glucose levels in patients with type 2 diabetes
	Grempler R, <i>et al.</i> , Abst 1793-P	Showed that the body weight reduction induced was due to decreasing body fat and not body water or protein content in experimental models of obesity



diabetic subjects with renal impairment or autonomic neuropathy may potentially be less able to cope with even small amounts of fluid and electrolyte loss. Ongoing phase III studies should provide evidence as to the efficacy and safety of SGLT-2 inhibitors in renal impairment.

From the most current evidence, the most notable side effect of SGLT-2 inhibitors appears to be an increased risk of genital infections.<sup>27,28,30</sup> The glycosuria produced by these drugs provides a scientific rationale for this adverse effect; however, this is not seen in FRG. Nevertheless, it may be that this is only observed in subjects with diabetes, as they have an impaired cellular immunity making genital infections both more common and more severe.<sup>39-41</sup> These would be the main side effects to look out for, and the results of the ongoing phase III studies should provide more data.

An increase in parathyroid hormone levels has been seen in a dapagliflozin phase II study, although, reassuringly, vitamin D levels and urine calcium excretion remained comparable to the placebo group.<sup>27</sup>

SGLT-2 has been shown to be expressed in the placenta in an *in vitro* study and hence is unlikely to be tested or licensed for use in pregnancy.<sup>16</sup>

The cardiovascular effects of long-term SGLT-2 inhibition are as yet unknown. As with all drug therapies for diabetes, establishing cardiovascular safety is paramount, and this should be demonstrated in phase III studies before this class of drugs can gain approval from licensing agencies.

### Potential clinical utility of SGLT-2 inhibitors

SGLT-2 inhibitors cause glucose lowering and weight loss. This makes them a potential future therapeutic option in patients with type 2 diabetes who are overweight or obese. Subjects with type 2 diabetes have been shown to have a higher exchangeable body sodium, and this propensity to retain sodium may contribute to the pathophysiology of the high prevalence of hypertension in diabetes.<sup>42</sup> Therefore, one can argue that potentially the urinary

### Key points

- The kidney performs an important role in glucose homeostasis
- Sodium glucose co-transporter 2 inhibitors (SGLT-2 inhibitors) prevent reabsorption of glucose in the proximal tubule. This results in an increase in glycosuria, lowering of blood glucose, and weight loss
- Side effects include an increase in genital infections. Concerns also exist regarding the potential for dehydration and electrolyte abnormalities
- Data from well designed clinical trials are needed to confirm the efficacy and safety of these promising new glucose-lowering agents

sodium loss resulting from inhibition of SGLT-2 and the osmotic diuretic effect caused by glycosuria produced by these drugs, may have some advantages in patients with type 2 diabetes, particularly in those who also have hypertension.

Assuming SGLT-2 inhibitors succeed in reaching the market, then future guidance from the National Institute for Health and Clinical Excellence (NICE) will be a major determinant of future prescribing in the UK. As the tariff price of this class of drugs and the results of ongoing phase III studies are not known, it is not possible to pre-empt NICE guidance. However, one may speculate that as a new class of drugs in which development costs will need to be recouped, they are likely to be priced at a premium. As NICE makes decisions based on cost-effectiveness, it seems improbable that these agents will be recommended for use as either first-line therapy (instead of metformin) or second-line therapy (instead of sulphonylureas). It seems more likely that the main utility of these drugs will be as an add-on therapy in an already crowded third-line marketplace. Bearing this in mind, it is disappointing that there are no registered phase III studies with insulin or GLP-1 mimetics as active comparators, nor indeed any active phase III studies looking at their effects when used as triple therapy in conjunction with metformin/sulphonylureas. However looking beyond third-line therapy, there is potential promise of some utility for SGLT-2 inhibitors to be used as insulin sparing agents. This has been suggested in recently published phase II evidence with dapagliflozin which showed improvements in glycaemic control despite reducing the dose of insulin by 50%.<sup>28</sup>

In summary, SGLT-2 inhibitors are an exciting and promising new class of drugs for the treatment of type 2 diabetes. They have the potential to be a useful addition to existing therapies; however, data from further well designed clinical studies are needed to confirm their safety and efficacy.

### Acknowledgments

We would like to thank Katrina Yates and the Medical Information department of Bristol-Myers Squibb.

### Conflict of interest statement

NG has previously given lectures or attended meetings sponsored by MSD, Eli Lilly, Takeda, Novo Nordisk and Bristol-Myers Squibb. Any honoraria from these meetings are paid either to the departmental diabetes education and research trust fund, or to other registered charities. NG is also the principal investigator for a SGLT-2 study sponsored by Boehringer Ingelheim.

JW has been a consultant and clinical trialist for several companies developing SGLT-2 inhibitors as treatment for diabetes.

SN has been a co-investigator for clinical trials with several SGLT-2 inhibitors.

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## CONFERENCE NOTICE

## 1st International Diabetes and Obesity Forum Annual Conference (IDOF 2010)

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