Managing Hyperglycemia in Patients With Type 2 Diabetes Mellitus: Rationale for the Use of Dipeptidyl Peptidase-4 Inhibitors in Combination With Other Oral Antidiabetic Drugs

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Objective: Type 2 diabetes mellitus is a chronic, progressive disease that necessitates comprehensive and individualized patient treatment strategies. Daily glycemic measures, including measures of postprandial glucose and fasting plasma glucose levels, in combination with measures of glycated hemoglobin (HbA1c) levels may be a more reliable indicator of blood glucose control and the long-term risk of complications than measures of HbA1c levels alone. Emerging treatment strategies for type 2 diabetes support the rationale for using dipeptidyl peptidase-4 (DPP-4) inhibitors in combination with other oral antidiabetic drugs for early and aggressive management of type 2 diabetes.

Data Sources: Information was gathered through a search of MEDLINE, Derwent Drug File, BIOSIS, and EMBASE databases for DPP-4 inhibitors and postprandial hyperglycemia in patients with type 2 diabetes.

Study Selection: Studies published from 2003 to the present and in any language were included. Additional sources were relevant conference poster presentations.

Data Synthesis: Early in the disease process, more intensive glucose-lowering intervention prior to the onset of advanced disease and cardiovascular events may be necessary to demonstrate effective reduction in macrovascular risk. Recent advances in pharmacotherapy allow physicians to target glucose excursions and variability. Data support the use of a combination of drugs with a complementary mechanism of action; to achieve an HbA1c level of less than 7% of total hemoglobin, use a drug with a primary mechanism of action that targets postprandial glucose levels in combination with a drug that primarily lowers fasting plasma glucose levels. Based on the glucose-dependent action of incretins, DPP-4 inhibitors demonstrate a low propensity for hypoglycemia, are generally weight neutral, and have a low risk of interactions with other drugs, which makes them appropriate candidates for combination therapy, particularly with other oral antidiabetic drugs including metformin, thiazolidinediones, and sulfonylureas.

Conclusion: The complementary mechanism of action of DPP-4 inhibitors with other oral antidiabetic drugs affords clinicians an effective and well-tolerated treatment option for early and more aggressive management of hyperglycemia in patients with type 2 diabetes.

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Type 2 diabetes mellitus is a chronic, progressive disease that requires patient treatment strategies that are comprehensive and individualized. Management of blood glucose levels is complex and critical for effective treatment of patients with type 2 diabetes. To achieve glycemic control, clinicians must consider several parameters of the patient profile such as age, disease duration, and associated complications, as well as metabolic characteristics such as weight, lipid levels, and blood pressure. Moreover, glycemic variables such as glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), and postprandial glucose levels are essential components of successful diabetes management.1 Fluctuations in postprandial glucose and FPG levels during a 24-hour period are believed to have a substantial adverse impact on long-term complications of diabetes. Thus, a patient-centric therapeutic regimen for patients with type 2 diabetes should be a priority and must be optimized for efficacy, safety, and tolerability, as well as adjusted for patient characteristics and comorbidities.

Managing Glycemic Control Implications of Recent Outcomes Studies

In studies on the management of glycemic control, data continue to mount that demonstrate the importance of the patient’s
individual disease-related characteristics. The link between glycemic control and vascular disease is currently an area of intense investigation, because evidence has been inconsistent. Recent outcomes studies that were designed to assess glycemic control and benefits in terms of vascular disease (ie, the Action to Control Cardiovascular Risk in Diabetes [ACCORD] trial, the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation [ADVANCE], the Hyperglycemia and Its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Patients With Type 2 Diabetes [HEART2D] study, and the Veterans Affairs Diabetes Trial [VADT]) failed to demonstrate a reduction in macrovascular complications. However, long-term (10-year follow-up) data from the United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that early glycemic control was associated with reduced risk of macrovascular events. Data were acquired 10 years after randomization had ended and demonstrated that early, aggressive lowering of blood glucose reduced the risk of myocardial infarction and all-cause mortality (Figure 1). Similarly, a 17-year follow-up of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) indicated that intensive glycemic control has long-term beneficial effects on risk of cardiovascular disease in patients with type 1 diabetes mellitus.

Although the results of the ACCORD trial, ADVANCE, the HEART2D study, and VADT showed no macrovascular benefit from intensive glucose-level reduction, the patients evaluated in these studies had established cardiovascular disease or at least one cardiovascular risk factor. In fact, the patients in the HEART2D study were treated within 21 days of an acute myocardial infarction. An earlier intervention to lower blood glucose levels, prior to the onset of advanced disease and macrovascular complications, may be necessary to effectively reduce the incidence of cardiovascular events. Further, glycemic control has been demonstrated to reduce macrovascular risk in the DCCT/EDIC study and the UKPDS. Taken together, these results suggest that perfor-

Figure 1. Reduced risk of myocardial infarction and all-cause mortality in initial United Kingdom Prospective Diabetes Study (UKPDS) and 10-year follow-up. Hazard ratios for patients in the UKPDS who experienced myocardial infarction (A and B) or who died of any cause (C and D) are shown for the sulfonylurea-insulin group compared with the conventional therapy (A and C) and for the metformin group compared with the conventional therapy group (B and D). The overall values at the end of the study, in 1997, are shown as black squares; annual values during the 10-year posttrial monitoring period are shown as gray diamonds. Numbers of first events in an aggregate outcome that accumulated in each group are demonstrated at 2-year intervals (vertical bars represent 95% confidence intervals). Source: Adapted with permission from Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008;359(15):1577-1589. Copyright 2008 Massachusetts Medical Society. All rights reserved.
mance of a long-term (10 years or more) follow-up study—such as the DCCT/EDIC and UKPD (vs studies that lasted 3½-5 years)—in patients with few disease complications may be needed to determine actual macrovascular benefit.

**Managing Glycemic Control on a Daily Basis**

Metabolic control and long-term glycemic management goals may be expressed in terms of percentage of HbA1c per total hemoglobin or estimated average glucose (see Appendix). In terms of managing glycemic control on a day-to-day basis, it is important to consider the patient’s individual glucose profile as reflected by FPG, postprandial glucose, and HbA1c levels. Although measurement of HbA1c levels remains the standard for monitoring glycemic control, HbA1c measurement provides a timed average and gives little or no indication of blood glucose range. Further, HbA1c measurement does not provide the magnitude or frequency of fluctuations in blood glucose observed over a 24-hour period. Daily measures of blood glucose levels (FPG and postprandial glucose) combined with measures of HbA1c may be a more reliable indicator of blood glucose control and the long-term risk of complications than measures of HbA1c alone.1

In patients with type 2 diabetes, FPG and postprandial glucose, as well as varying contributions of HbA1c contribute to the overall diurnal hyperglycemia, with varying contributions based on HbA1c levels. The contribution of postprandial glucose to hyperglycemia is greater in patients with mild or moderate diabetes (HbA1c up to 8.4%), with the relative postprandial glucose contribution decreasing with increasing HbA1c. In addition, postprandial hyperglycemia is prevalent early in the course of disease in patients with type 2 diabetes and may occur when HbA1c is less than 7%. However, FPG is a main contributor to overall diurnal hyperglycemia in patients with more severe diabetes (HbA1c more than 8.4%), with the relative contribution of FPG increasing with increasing HbA1c (Figure 2).10

To achieve overall glucose control, management of postprandial glucose levels is necessary. This finding was observed in a recent prospective intervention trial that demonstrated that control of postprandial glucose levels is essential if target HbA1c levels are to be achieved, and control of postprandial glucose levels has a greater impact on overall glycemic control than does control of FPG levels in patients with type 2 diabetes. Control of FPG levels is necessary yet insufficient for reaching the HbA1c target level of less than 7%, as recommended by the American Diabetes Association. Compared with decreases in FPG levels, decreases in postprandial glucose levels have allowed the percentage of patients who reach the HbA1c goal to nearly double.12 To effectively reach HbA1c goals, however, postprandial glucose levels, as well as FPG levels, need to be addressed. Most patients cannot maintain long-term glycemic control with monotherapy because of the progressive nature of and the multifaceted metabolic abnormalities associated with type 2 diabetes. As a result, many patients with type 2 diabetes will reach HbA1c targets only with combination therapy.14 To optimize therapy, specific combinations of antihyperglycemic agents should be selected on the basis of glucose-lowering efficacy, safety, and potential synergy of the combination. Typically, the greatest efficacy may be with drug combinations that provide different and complementary mechanisms of action that together target both postprandial glucose levels and FPG levels.
The majority of oral antidiabetic drugs function by lowering FPG levels through increasing the patient’s sensitivity to insulin or increasing the amount of insulin secreted.\textsuperscript{16,17} Sulfonylureas act through direct stimulation of insulin release from the pancreatic islet cells. Thiazolidinediones increase insulin sensitivity through enhanced insulin-stimulated glucose transport in skeletal muscle, decreased glucose absorption, and decreased glucose production in the liver, as well as through several mechanisms mediated by peroxisome proliferator–activated receptor-\(\gamma\). Metformin also increases insulin sensitivity, primarily through hepatic mechanisms; peripheral effects are moderate. Dipeptidyl peptidase (DPP)-4 inhibitors delay the degradation of glucagon-like peptide 1 to extend the action of glucose-dependent insulin secretion while also suppressing the release of glucagon (Figure 3).\textsuperscript{17} Evidence continues to mount, however, in support of a more prominent role for postprandial glucose regulation. Therapy targeted at lowering postprandial glucose levels has demonstrated improved glucose control and reduced progression of atherosclerosis and cardiovascular events.\textsuperscript{19} Furthermore, postprandial insulin secretion is not sufficient to suppress postprandial hyperglycemia in patients with type 2 diabetes. The prolonged action of endogenous incretin hormones through the inhibition of DPP-4 plays a clinically important role in the treatment of type 2 diabetes by improving postprandial glucose levels and ultimately HbA\textsubscript{1c} levels.\textsuperscript{20} Diabetes treatments that primarily lower postprandial glucose levels (ie, DPP-4 inhibitors) can be used in combination with other oral antidiabetic drugs, in particular insulin sensitizers, to enhance glycemic control. Incretin-based therapies, glucagon-like peptide-1 agonists, and DPP-4 inhibitors are newer treatment options that are associated with a low risk of hypoglycemia, are weight neutral, and function by mechanisms of action that complement those of current therapies.

**Managing Hyperglycemia With DPP-4 Inhibitors**

**Efficacy**

Inhibition of DPP-4 is emerging as a viable therapeutic option for patients with type 2 diabetes. The incretin hormones, glucagon-like peptide-1 and glucose-dependent insulinotropic peptide, act to augment insulin secretion and are released during postprandial nutrient absorption in the gastrointestinal tract. Incretin activity is extended via suppression of glucagon-like peptide-1 and glucose-dependent insulinotropic peptide degradation with DPP-4 inhibitors.\textsuperscript{20} As monotherapy, DPP-4 inhibitors (ie, alogliptin, saxagliptin, sitagliptin, vildagliptin) demonstrate approximately 0.5% to 1.0% reduction in HbA\textsubscript{1c} levels, and durability of that effect has been demonstrated with saxagliptin, sitagliptin, and vildagliptin.\textsuperscript{13,21-23} Treatment-naïve patients with type 2 diabetes (mean baseline HbA\textsubscript{1c} level of 8.4%) treated with vildagliptin (100 mg/d) for up to 2 years demonstrated a mean (standard deviation) reduction in HbA\textsubscript{1c} levels of 1.0% (0.1%).\textsuperscript{21} After completion of a double-blind, 54-week study to examine the long-term efficacy and safety of sitagliptin given in combination with metformin as initial therapy in patients with type 2 diabetes, 402 patients entered a 50-week extension of the study.\textsuperscript{22} After 104 weeks (2 years) of treatment, monotherapy with sitagliptin and initial combination therapy with sitagliptin plus metformin were shown to provide substantial and long-term improvements in glycemic control (mean change in HbA\textsubscript{1c} level, \(-1.2\%\) to \(-1.7\%\)).\textsuperscript{22} Similarly, in patients whose type 2 diabetes was inadequately controlled with metformin alone, saxagliptin (2.5, 5, or 10 mg)}
added to metformin provided sustained, clinically meaningful glycemic improvements compared with placebo during 102 weeks; the difference in HbA1c levels between study patients and control patients was \(-0.52\%\) to \(-0.72\%\).

The efficacy of DPP-4 inhibitors as add-on therapy to other oral antidiabetic drugs (ie, metformin, sulfonylureas, and thiazolidinediones), as well as in combination with metformin as initial therapy for newly treated type 2 diabetes, has been studied in a broad range of patients (Table). For example, the addition of 5 mg of saxagliptin, the approved usual clinical dose, to a thiazolidinedione in patients with type 2 diabetes whose glycemia was inadequately controlled with the thiazolidinedione alone demonstrated clinically meaningful and statistically significant improvements in glycemic control (as demonstrated by reductions in HbA1c, postprandial glucose, and FPG levels; \(P<.0001\)) relative to thiazolidinedione monotherapy. The DPP-4 inhibitor alogliptin, when added to thiazolidinedione therapy (with or without metformin or a sulfonylurea) also significantly improved glycemic control (as demonstrated by reductions in HbA1c levels; \(P<.001\)) in patients with type 2 diabetes. Furthermore, compared with metformin alone in treatment-naïve patients with type 2 diabetes, saxagliptin given concurrently (initial combination therapy) with metformin produced statistically significant improvements in glycemic parameters (HbA1c, postprandial glucose, and FPG levels; \(P=.0002\)). DPP-4 inhibitors approved by the US Food and Drug Administration (FDA), as well as those currently under FDA review and in phase 3 development as monotherapy and combination therapy, are shown in Figure 4.

**Safety and Tolerability**

When choosing an agent or combination of agents to optimize glycemic control, evaluation of short-term (hypoglycemia) and long-term (body weight, cardiovascular risk) safety and tolerability of the drug class is critical. Clinical data have shown DPP-4 inhibitors to be generally safe and well tolerated in patients with type 2 diabetes for up to 2 years of therapy,\(^{21-23,26,38-40}\) although an increase in upper respiratory tract infections and nasopharyngitis has been identified in patients who have been treated with the DPP-4 inhibitor class of compounds.\(^{41}\) Dipeptidyl peptidase-4 inhibitors are generally weight neutral and are associated with a low risk for hypoglycemia, which makes them attractive candidates for combination therapy from safety and tolerability perspectives, particularly with other oral antidiabetic drugs (ie, metformin, thiazolidinediones, and sulfonylureas).\(^{18,20}\)

**Body Weight**—As previously mentioned, DPP-4 inhibitors are generally weight neutral when used as monotherapy and in combination with other oral antidiabetic drugs. Short-term monotherapy trials demonstrated changes in patient body weight that were neither clinically relevant nor statistically significant relative to weight changes in patients who received placebo.\(^{39,42}\) A 2-year treatment with vildagliptin demonstrated a 0.5-kg (0.4-kg) mean increase in body weight.\(^{21}\) Similarly, only small decreases in body weight were demonstrated in patients receiving saxagliptin as an add-on to metformin after 102 weeks of therapy.\(^{23}\) The weight neutrality of DPP-4 inhibitors provides a therapeutic advantage compared with other oral antidiabetic drugs such as thiazolidinediones, which are generally associated with weight gain.

**Hypoglycemia**—The DPP-4 inhibitors are not associated with hypoglycemia, a common adverse effect seen with some of the other available oral antidiabetic drugs. A pooled analysis of hypoglycemic events from six randomized, double-blind, 24-week phase 3 clinical trials that involved treatment with monotherapy demonstrated hypoglycemic events similar to those of placebo for saxagliptin-treated subjects.\(^{43}\) As an add-on therapy to a sulfonylurea, saxagliptin demonstrated modest, nonsignificant increases in frequency of hypoglycemia, which is not uncommon when other oral antidiabetic drugs are added to a sulfonylurea.\(^{28}\) In patients with type 2 diabetes that is inadequately controlled with insulin, vildagliptin has been shown to reduce the frequency of hypoglycemia—in particular, severe hypoglycemia.\(^{44}\) Furthermore, vildagliptin has been shown not to accentuate sulfonylurea-induced hypoglycemia.\(^{45}\) It has been hypothesized that use of DPP-4 inhibitors results in a low incidence of hypoglycemia because of their potential glucose-sensing effects.\(^{46}\)

**Cardiovascular Risk**—An important concern regarding the use of antidiabetic agents is the associated risk of cardiovascular events.\(^{47}\) These concerns have been raised about several drugs used to treat type 2 diabetes—most recently rosiglitazone, which is a thiazolidinedione—and have been compounded by the recent results of the ACCORD trial, which demonstrated increased mortality in patients undergoing intensive glucose-lowering therapy. These concerns have been exacerbated by the unexpected results from ADVANCE, the VA Diabetes, and the HEART2D study, which demonstrated no cardiovascular benefit from intensive lowering of glucose levels.\(^{5,48}\) Therefore, it is important that larger, long-term trials are conducted with all classes of agents to further evaluate clinical benefits and risks associated with oral antidiabetic drugs.\(^{49}\) These studies and others prompted an FDA-appointed advisory committee to examine the issue of diabetes drugs and cardiovascular safety.

The FDA guideline recommends that for new antidiabetic treatments, studies must be performed to demonstrate whether the treatment increases cardiovascular risk. Specific study parameters are being determined on an individual basis.\(^{50}\) Notably, to my knowledge no DPP-4 inhibitor to date has demonstrated an increased risk of cardiovascular events. Saxagliptin was the first DPP-4 inhibitor to be reviewed by the FDA for cardiovascular safety. The FDA noted that saxagliptin was associated with no unacceptable cardiovascular risk. This
Table Results of Short-Term Treatment With a Dipeptidyl Peptidase-4 (DPP-4) Inhibitor in Combination With Other Oral Antidiabetic Agents

<table>
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<th>Study Baseline Fasting Plasma Glucose Level,*</th>
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*Placebo-corrected values.
†Postprandial glucose levels at 2 hours during oral glucose tolerance test.

Abbreviations: HbA1c, glycated hemoglobin; NA, not applicable.
### DPP-4 Inhibitors Status

<table>
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<td>Sitagliptin</td>
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<td>Vildagliptin</td>
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Decision was based on results of a clinical trial of more than 5000 patient-years that demonstrated no evidence of increased cardiovascular risk with saxagliptin treatment—either alone or in combination with other oral antidiabetic agents.51 The Cox proportional hazard ratio for major adverse cardiovascular events (MACE; stroke, myocardial infarction, or cardiovascular death, analyzed post hoc) and acute cardiovascular events (ACE; acute, clinically important events, including cardiac revascularization procedures) was 0.44 for MACE (95% confidence interval: 0.24-0.82) and 0.59 for ACE (95% confidence interval: 0.35-1.00). Additionally, evaluation of the clinical trials database of adverse event data from more than 3700 patients treated with vildagliptin revealed a favorable cardiovascular safety profile. The overall incidence of cardiovascular and cerebrovascular events for vildagliptin at a dose of 50 mg twice a day (0.6%) was less than that for placebo (1.3%, P<.05).52 In a pooled safety analysis from 12 clinical trials, there were no meaningful differences between sitagliptin-treated patients and control patients in the incidence of cardiovascular or ischemia-related adverse events.53

### Treatment Recommendations

The American College of Endocrinology / American Association of Clinical Endocrinologists diabetes consensus included DPP-4 inhibitors as preferred for first- and second-line treatment,54 particularly because of their effect on postprandial glucose levels and for patients for whom there are concerns of hypoglycemia. For example, in treatment-naive patients DPP-4 inhibitor monotherapy (for initial HbA1c levels of 6%-7%) and DPP-4 inhibitor combination therapy with or without metformin (for initial HbA1c levels of 7%-9%) are among the consensus recommendations. Dipeptidyl peptidase-4 inhibitors are proving to be advantageous early in the treatment paradigm when HbA1c is 8% or less and when reduction of postprandial hyperglycemia is most important.54 Moreover, if the HbA1c goal of less than 6.5% is not met in treated patients, a DPP-4 inhibitor can be added to metformin (with or without a sulfonylurea) or a thiazolidinedione.54 The American Diabetes Association/European Association for the Study of Diabetes guidelines note that the majority of patients with type 2 diabetes will require more than one antihyperglycemic agent over the course of their disease.13 The process of selecting agents to be used together must include consideration of glucose-lowering effectiveness and safety, as well as the additive effects of the particular combination of drugs.

### Conclusion

Type 2 diabetes is a progressive disease that necessitates critical management of blood glucose levels to prevent hyperglycemia and associated complications. New data from outcomes studies indicate that comprehensive treatment strategies must allow for patient characteristics and comorbidities for a clinical course of action to be successful. An individualized, patient-centric therapeutic regimen should be optimized for both tolerability and efficacy to allow glycemic control to be achieved safely.

According to findings from the long-term follow-up two prospective, observational studies (ie, UKPDS, DCCT), the risk of developing micro- and macrovascular complications decreases with early glucose control in patients with type 2 diabetes.67 Results of the primary study (UKPDS 35) suggest that the risk of these complications would be further reduced with HbA1c values in the normal range (less than 6%); however, any reduction in HbA1c levels would be expected to lower the risk of complications.56 Moreover, data from recent outcomes studies suggest that an earlier glucose-lowering intervention, prior to the onset of advanced disease and cardiovascular events, may be necessary to demonstrate effective reduction in macrovascular risk.67

Recent advances in pharmacotherapy allow physicians to target glucose excursions and variability. Daily assessment of glycemic status, including measures of FPG and postprandial glucose, may be a more reliable indicator of blood glucose control and the long-term risk of complications than measures of HbA1c levels alone.1 Control of FPG levels was shown to be necessary but insufficient for reaching HbA1c levels of less than 7%; decreases in postprandial glucose levels allowed nearly double the percentage of patients to reach the HbA1c goal than did decreases in FPG levels.12 Newer combinations of drugs—with complementary mechanisms of action that
target FPG and postprandial glucose to reduce hyperglycemia—together with earlier intervention may limit cardiovascular risk. These data support the need for earlier and more aggressive treatment regimens. Based on the glucose-dependent action of incretin hormones, DPP-4 inhibitors demonstrate a low propensity for hypoglycemia and act in a weight-neutral manner, making them attractive candidates for combination therapy. Prolonged incretin actions through the use of DPP-4 inhibitors play a clinically important role in the treatment of type 2 diabetes by improving postprandial glucose, FPG, and, ultimately, HbA1c levels. The complementary mechanism of action of DPP-4 inhibitors with other oral antidiabetic drugs affords clinicians an effective and tolerable drug choice when using combination regimens for management of hyperglycemia in patients with type 2 diabetes.

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References


Appendix

Method for estimating the average glucose level in the blood on the basis of the percentage of glycated hemoglobin in total hemoglobin.

The HbA₁c-Derived Average Glucose, or ADAG, study demonstrated a linear relationship between HbA₁c level and average glucose level in a clinically relevant range of glycemia. As a result, the study group derived a formula for converting the HbA₁c level to an estimated average glucose level (eAG) in either milligrams per deciliter, eAG = 28.7 × HbA₁c - 46.7, or in millimoles per liter, eAG = 1.59 × HbA₁c - 2.59, where HbA₁c is the percentage of glycated hemoglobin in total hemoglobin.

Because the estimated average glucose value is provided in the units of measure that are used in self-monitoring blood glucose systems (ie, milligrams per deciliter or millimoles per liter), the value is helpful to both patients and health care practitioners for use as a teaching tool in clinical practice. For example, an HbA₁c target of 7.0% is equivalent to an estimated average glucose value of 154.2 mg/dL or 8.5 mmol/L.