A tale of two insulins: Understanding basal insulin therapy in type 2 diabetes
Swinnen, S.G.H.A.

Citation for published version (APA):
Insulin therapy for type 2 diabetes

Sanne G.H.A. Swinnen, Joost B.L. Hoekstra and J. Hans DeVries

Diabetes Care 2009;32:S253-S259
Introduction
A number of landmark randomised clinical trials established that insulin therapy reduces microvascular complications (1,2). In addition, recent follow-up data from the U.K. Prospective Diabetes Study (UKPDS) suggest that early insulin treatment also lowers macrovascular risk in type 2 diabetes (3). Whereas there is consensus on the need for insulin, controversy exists on how to initiate and intensify insulin therapy. The options for the practical implementation of insulin therapy are many. In this presentation, we will give an overview of the evidence on the various insulin regimens commonly used to treat type 2 diabetes.

Secondary analyses of the aforementioned landmark trials endeavoured to establish a glycaemic threshold value below which no complications would occur. The UKPDS found no evidence for such a threshold for HbA1c, but instead showed that better glycaemic control was associated with reduced risks of complications over the whole glycaemic range (‘the lower the better’) (4). For the management of type 2 diabetes, this resulted in the recommendation to ‘maintain glycaemic levels as close to the non-diabetic range as possible’ (5). However, in contrast to the UKPDS, the Kumamoto study observed a threshold, with no exacerbation of microvascular complications in patients with type 2 diabetes whose HbA1c was <6.5%, suggesting no additional benefit in lowering HbA1c below this level (2). Moreover, the intensive glycaemia treatment arm of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, targeting HbA1c <6.0%, was discontinued because of higher mortality in this group compared with the standard therapy group targeting HbA1c from 7.0 to 7.9% (6). Therefore, the American Diabetes Association (ADA) recommendation of an HbA1c target <7.0% seems the most balanced compromise at present (7).

Another important conclusion of the UKPDS was that the risk reductions in long-term complications were related to the levels of glycaemic control achieved, rather than to a specific glucose-lowering agent (1). This has left health care providers and patients with the difficult task of choosing from the wide variety of glucose-lowering interventions currently available. When considering the effectiveness, tolerability and cost of the various diabetes treatments, insulin is not only the most potent, but also the most cost-effective intervention (8). Although insulin has no upper dose limit and numerous trials established that glycaemic goals could be attained by using adequate insulin doses (5,8), in clinical practice,
many patients have elevated HbA1c levels and experience years of uncontrolled hyperglycaemia (9). Moreover, the Steno-2 Study demonstrated that only a minority of patients reached the intensive HbA1c target of <6.5%, compared with a far greater percentage of patients who reached the respective intensive treatment goals for blood pressure and serum lipid levels (10). Apparently, the initiation and intensification of insulin therapy is not as straightforward and simple as we had hoped. In accordance with the ADA and the European Association for the Study of Diabetes (EASD) (5,7), we advocate an algorithmic approach for the start and adjustment of insulin treatment, with modifications for individual patients as needed. This review contains an overview of the currently available insulin preparations and an outline of the merits and disadvantages of the various regimens commonly used for the initiation and intensification of insulin therapy in patients with type 2 diabetes. Our aim is to assist clinicians in designing individualised management plans for insulin therapy in type 2 diabetic patients.

**Human insulin and its analogues**

Insulin therapy with the conventional mealtime and basal insulin preparations has many shortcomings. First, the absorption of regular human insulin from the subcutaneous (s.c.) tissue is slow and the metabolic action takes effect only 30 to 60 min after injection and peaks after 2 to 3 h. Consequently, treatment with regular insulin is associated with postmeal hyperglycaemia and an increased risk of late-postprandial hypoglycaemia. Second, the conventional basal NPH insulin has a distinct peak glucose-lowering effect, has a duration of action considerably shorter than 24 h, and is absorbed from the s.c. tissue at variable rates. These pharmacodynamic limitations predispose users to elevated glucose levels before breakfast and nocturnal hypoglycaemia (11,12). To overcome these difficulties, insulin analogues with a modified amino acid sequence from the human insulin molecule were developed. The three rapid-acting analogues (aspart, glulisine, lispro) are absorbed more quickly than regular insulin because of reduced self-association. Their onset of action is within 15 min after s.c. injection and they have a faster and greater peak action. Insulin glargine, the first long-acting insulin analogue to reach the market, was initially proclaimed to have the ideal ‘peakless’, nearly 24-h duration of action (13). However, these initial pharmacodynamic studies raised some criticism, and it should be concluded that there is no such thing as a ‘peakless’ insulin preparation (12,14,15). Nevertheless, both long-acting
insulin analogues (detemir and glargine) have a limited peak effect and a longer mean duration of action compared with NPH insulin (with glargine having a slightly longer action than detemir [13,16,17]).

It was expected that the rapid-acting and long-acting analogues, which more closely approximate physiological insulin secretion, would confer important clinical benefits (11). With respect to type 2 diabetes, the topic of this review, it is important to note that most patients with type 2 diabetes have residual endogenous insulin secretion in the context of insulin resistance. Therefore, the rationale for imitating the insulin secretion pattern of human physiology is less convincing than in type 1 diabetes. Indeed, in patients with type 2 diabetes the rapid-acting analogues were not found to be superior to regular insulin in reducing HbA1c levels or rates of overall hypoglycaemia (18). The clinical benefits of the long-acting insulin analogues compared with NPH insulin are limited to a reduction in (nocturnal) hypoglycaemia (19).

**When should insulin therapy be initiated?**

Type 2 diabetes is a progressive disease, and thus, ultimately this question will arise for many of our patients. Unfortunately, there is no unequivocal answer, which was nicely illustrated by a recent interactive case vignette. The polling results demonstrated once again that the management of patients with type 2 diabetes uncontrolled by two oral glucose-lowering agents is controversial. Furthermore, the preferred treatment option was found to be related to the respondents’ locations and self-reported specialties (20).

Traditionally, there has been a stepwise introduction of glucose-lowering interventions, with the final ‘step’ of insulin therapy being administered 10 to 15 years after diagnosis (8). Both patients and physicians are often reluctant to start insulin because of fears of painful injections, hypoglycaemia and weight gain (21,22). Additional reasons for ‘psychological insulin resistance’ among patients are negative beliefs about insulin treatment permanence, restrictiveness, low self-efficacy, personal failure and illness severity (22). Drawback of the stepwise approach is that the introduction of successive interventions after treatment failure is often delayed, exposing patients to many years of uncontrolled hyperglycaemia (9). Another reason for a more rapid response to treatment failure is that lowering glycaemia has been shown to improve insulin resistance as well as endogenous insulin secretion (23). This was recently confirmed by Weng et al., who found
that a brief course of insulin therapy in subjects with newly diagnosed type 2 diabetes not only restored, but also maintained, β-cell function, resulting in prolonged glycaemic remission. Interestingly, remission rates were significantly higher in the intensive insulin groups than in the intensive oral therapy group (24). However, Weng’s findings need to be confirmed, and also for reasons of practicality and patients’ acceptance, we advocate stepwise diabetes treatment, provided that ‘an HbA1c of ≥7.0% serves as a call to action to initiate or change therapy’ (5). Moreover, the response to this call should be swift; given the great (cost-)effectiveness, we advocate the initiation of insulin when glycaemic goals are not attained after 2 to 3 months of maximally dosed dual oral therapy. For patients intolerant to one or more oral glucose-lowering agents and who do not achieve glycaemic control with oral monotherapy, as well as those with a personal preference, earlier initiation of insulin is indicated. It is noteworthy that rapid addition of insulin therapy is supported by numerous studies showing improved treatment satisfaction and quality of life for type 2 diabetic patients who had started using insulin (25,26).

How should insulin therapy be initiated?

**Basal insulin**

The ‘treat-to-target’ clinical trials established that the addition of basal insulin to existing oral glucose-lowering therapy achieves good glycaemic control in the majority of patients with type 2 diabetes (27-29). According to the ADA/EASD algorithm for the management of type 2 diabetes, insulin could be initiated with either once-daily NPH insulin or a long-acting insulin analogue (5). For several reasons we consider NPH insulin the preferred option. As previously mentioned, the relative benefit of the long-acting insulin analogues is limited to a reduction in (nocturnal) hypoglycaemia (19). Moreover, this advantage is relevant to only a minority, since most patients with type 2 diabetes starting insulin therapy do not experience hypoglycaemia at all (12). A recent meta-analysis that included six randomised comparisons of NPH and glargine found event rates for self-monitored blood glucose (SMBG) confirmed symptomatic hypoglycaemia <3.6 mmol/l (65 mg/dl) of only 138 and 91 events per 100 patient-years for these insulins, respectively, in insulin-naive type 2 diabetic patients who achieved an HbA1c of 7.0% (30). Finally, in this era of relentlessly increasing incidence rates for type 2 diabetes, physicians cannot afford to disregard the elevated cost of
the newer insulin preparations. In the U.S., the average retail price of a 10 ml vial of the long-acting insulin analogues is $105 compared with $53 for a vial of NPH insulin (31). In this respect, clinicians should realise that when they stop prescribing conventional insulin preparations, with established beneficial effects, they provide a pretext for the manufacturers to withdraw these drugs from the market. Recent examples of such industry responses to low demand are the withdrawal of Novolin R penfills in the U.K. and of Novolin 70/30 in several European countries. Thus, to recapitulate, given its cost-effectiveness, we consider NPH insulin the preferred agent for the initiation of insulin therapy in type 2 diabetes. However, if dose titration is limited by (nocturnal) hypoglycaemia, a switch to a long-acting insulin analogue should be tried.

There is doubt as to whether a once-daily dose of insulin detemir will help as many people achieve good control as NPH insulin and glargine. In a ‘treat-to-target’ trial with twice-daily detemir administration, an endpoint HbA1c of 6.8% was reached (28). In other studies, a second daily detemir injection was required in 34 to 55% of study subjects because of pre-dinner hyperglycaemia or nocturnal hypoglycaemia (29,32). In the only reported trial that investigated the efficacy of once-daily insulin detemir, HbA1c remained above the currently recommended glycaemic goal with an endpoint level of 7.4%, both for NPH insulin and detemir (33), compared with end-of-study HbA1c <7.0% with once-daily glargine and NPH in the original ‘treat-to-target’ trial (27). Rather than possible insufficiency of a once-daily dose of insulin detemir, these discrepant outcomes are likely to be explained by diversity in study design, such as different titration targets and titration frequency. This is supported by Fig. 1a and b, which show the relationship between the reduction in HbA1c level and endpoint insulin dose, and between HbA1c reduction and the frequency of patient contact, respectively, in nine randomised trials investigating insulin initiation with basal insulin (27-29,32-37). Both graphs show clear dose-response relationships, suggesting that substantial decreases in HbA1c can be achieved provided that the daily insulin dose and the contact frequency are adequate. The only way to finally determine whether once-daily detemir injection is appropriate for the treatment of type 2 diabetes is to conduct a clinical trial, ideally comparing once-daily detemir and glargine in patients with baseline HbA1c levels of ~8.5%. Such a study could also assess whether higher detemir dosages are needed to obtain the same level of glycaemic control as with insulin glargine, as was demonstrated in two of the
aforementioned studies in which detemir was administered twice-daily (28,29,38). This trial could also confirm the proclaimed reduction in weight gain associated with insulin detemir.

Figure 1 Relationships between mean endpoint daily insulin dose (a) and the frequency of patient contact (clinical visits and telephone contacts combined) (b) and mean reduction in HbA1c, and between mean endpoint daily insulin dose and mean weight gain (c), during nine randomised trials investigating insulin initiation with NPH insulin, insulin detemir or insulin glargine. Included studies are Bretzel et al. (34), Fritsche et al. (35), Hermansen et al. (28), Holman et al. (32), Philis-Tsimikas et al. (33), Riddle et al. (27), Rosenstock et al. (29), Yki-Järvinen et al. (36) and Yki-Järvinen et al. (37) (Fig. 1a and c). Figure 1b does not include Holman et al., since this publication did not specify the number of interim telephone contacts. Two trials (28,35) did not report mean endpoint daily insulin dose as units/kg/day. We calculated the desired figures from the mean endpoint dose reported as units/day and mean body weight at study end. Three studies (Riddle et al. and the two studies of Yki-Järvinen et al. [27, 36,37]) did not report reduction in HbA1c. We calculated these values from mean baseline and endpoint HbA1c levels.
Titration and timing of basal insulin

After the recent unexpected finding of increased mortality in the intensive glucose-lowering therapy group of the ACCORD study, which might be partly related to the rate of the reduction in HbA1c (6), clinicians may now be more reserved to lower glucose levels promptly. However, we still feel that in addition to timely initiation, rapid titration of the dose is indispensable for successful insulin therapy. The ACCORD study solely included patients at high risk for cardiovascular disease, in whom very low HbA1c levels were reached by using up to four or five different classes of glucose-lowering drugs. In contrast, in less selected patients treated with stable doses of one or two oral agents, simple titration algorithms targeting fasting plasma glucose ≤5.6 mmol/l (100 mg/dl) can safely achieve HbA1c of 7.0% (27). A patient-driven algorithm, with patients increasing their insulin dose by two or three units every three days, as long as their fasting plasma glucose remains above target, constitutes a practical approach that has been shown to be equally or more effective than physician-led titration (39,40).

Regarding the timing of injection in once-daily basal insulin regimens, administration of NPH in the evening appears to be superior to morning injection (11,25). Studies examining the injection time of the long-acting insulin analogues showed conflicting results. One study conducted with insulin glargine found greater reductions in HbA1c and nocturnal hypoglycaemia with morning compared with evening injection (35), whereas a larger comparison of morning vs. evening glargine with an identical study design did not find any difference (both studies investigated this issue against a background of glimepiride once-daily) (41). A morning administration of insulin detemir was associated with lower glucose levels during the day and a trend toward a reduced risk of nocturnal hypoglycaemia compared with evening injection (33). From these discrepant data, it can be concluded that when nocturnal hypoglycaemia limits dose titration of evening detemir or glargine, administration in the morning could be attempted.

Other options for the initiation of insulin therapy

The recent Treating to Target in Type 2 Diabetes (4-T) study compared the introduction of basal insulin at bedtime to insulin initiation with either biphasic insulin twice-daily or prandial insulin before meals (32). The biphasic and prandial insulin regimens provided better glycaemic control than once-daily basal insulin
(escalated to twice-daily in 34% of patients) but at the expense of increased risks of hypoglycaemia and weight gain. Although biphasic insulin reduced HbA1c levels to the same extent as prandial insulin, the latter regimen was associated with the most hypoglycaemic episodes and the highest weight gain (32). Therefore, and considering that to date there is no clinical trial evidence supporting the specific lowering of postprandial glucose levels when aiming to lower cardiovascular risk in type 2 diabetes, initiation with prandial insulin is generally not a first-choice approach when starting insulin in type 2 diabetic patients. This was confirmed by a recently reported direct comparison of once-daily insulin glargine vs. thrice-daily insulin lispro in insulin-naive patients (34). Finally, also regarding feasibility in clinical practice and patients’ acceptance, three injections per day is the least attractive option for initiation of insulin therapy.

Although many are accustomed to initiation with biphasic insulin, we generally recommend the addition of once-daily basal insulin to oral therapy for several reasons. First, the lower HbA1c levels reached with biphasic insulin comes at the expense of increased risks of hypoglycaemia and weight gain (32,42,43). Second, and as aforementioned, trials with systematic dose titration demonstrated that once-daily basal insulin achieves the currently recommended glycaemic levels in many patients with type 2 diabetes (27,29). In this respect, it has frequently been argued that in patients with badly controlled hyperglycaemia (e.g. HbA1c >8.5% at the start of insulin therapy), treatment with once-daily basal insulin alone would not attain glycaemic goals (11,32,33). However, the LANMET study proved otherwise. In this clinical trial, HbA1c levels decreased from 9.1% at baseline to 7.1% with combination therapy of bedtime insulin glargine or NPH insulin and metformin (36). Finally, it seems likely that insulin initiation by means of one (basal) injection may also facilitate patients’ acceptance of insulin initiation.

**Combined therapy with oral agents**

As discussed at the first Controversies in Obesity, Diabetes and Hypertension (CODHy) Meeting, the rationale for combining insulin with oral therapy is minimisation of the adverse effects of insulin treatment, i.e. hypoglycaemia and weight gain (44). Combination of insulin with metformin is indeed associated with better glycaemic control, fewer hypoglycaemic events and less weight gain than treatment with insulin alone (45). Therefore, metformin should be continued when
patients are initiated on insulin therapy (i.e. providing there are no intolerable side effects). Data concerning the combination of insulin with either sulfonylureas alone, or with both metformin and sulfonylureas, compared with insulin-alone treatment regimens, are ambiguous (46). The only consistent advantage of such combined therapy is reduced insulin dose requirements, which may result in less daily injections, easier dose titration and improved compliance (46). However, these potential benefits must be balanced against the side effects and higher cost of continuing sulfonylureas together with metformin compared with treatment with metformin and NPH insulin alone -although not vs. long-acting insulin analogues and metformin alone (31,46)- and the possibility of reduced patient adherence when increasing numbers of pills are prescribed (47). An ongoing randomised trial comparing the continuation of sulfonylureas in combination with metformin and insulin glargine vs. discontinuation of sulfonylureas with this combination regimen in insulin-naive type 2 diabetic patients will hopefully provide further evidence regarding this issue (www.controlled-trials.com number: ISRCTN29335793).

**Intensification of insulin therapy**

*When should insulin therapy be intensified?*

Due to progressive β-cell decline, treatment with once-daily basal insulin alone will eventually fail to maintain glycaemic control in a substantial number of patients with type 2 diabetes. When the recommended HbA1c level of <7.0% is not reached, or maintained despite successful basal insulin dose titration maintaining fasting plasma glucose ≤5.6 mmol/l (100 mg/dl), or when aggressive titration is limited by hypoglycaemia, treatment should be intensified by adding insulin injections.

*How should insulin therapy be intensified?*

The available options for additional insulin injections include a second injection of basal insulin, prandial insulin before one or more meals, or a switch to biphasic insulin. The choice between intensification of basal insulin vs. the introduction of prandial or biphasic insulin should be individualised based on patients’ diurnal blood glucose profiles. When considering the profiles obtained with NPH insulin or long-acting insulin analogue once-daily, the effect appears to wane during the day,
even in patients starting insulin therapy, i.e. with remaining endogenous insulin secretion (33,37,48). These patients could benefit from adding a second injection of basal insulin (48). However, in the context of declining endogenous insulin secretion, daytime hyperglycaemia is usually related to elevated postprandial glucose levels, favouring the initiation of prandial or biphasic insulin.

Two recent studies established that in patients not achieving adequate glycaemic control with once-daily basal insulin, basal-bolus therapy results in greater HbA1c reductions than biphasic insulin twice- or thrice-daily (49,50). However, when a more gradual intensification of insulin treatment is preferred, patients can be switched to biphasic insulin two, and subsequently three, times daily. The latter regimen has been shown to significantly improve HbA1c levels of patients previously treated with insulin glargine (50). Whether stepwise introduction of meal-time injections is as safe and effective as the rapid initiation of a full basal-bolus regimen is currently under investigation (51).

Finally, regarding the choice of prandial insulin, rapid-acting insulin analogues are not superior to regular insulin in reducing HbA1c levels or rates for overall and nocturnal hypoglycaemia, despite improving postprandial control (18). In some studies, treatment with rapid-acting analogues was associated with fewer severe hypoglycaemic episodes and improved treatment satisfaction (18), the latter probably being related to increased convenience because of injection immediately before meals. In conclusion, there is no compelling reason to overall favour rapid-acting insulin analogues over regular insulin in type 2 diabetes. Whereas in some countries the price of rapid-acting analogues has been lowered to the level of regular insulin, in others, it remains around twice as high (31).

**Continuous subcutaneous insulin infusion**

In patients with type 2 diabetes already using at least one daily insulin injection, the introduction of intensive insulin therapy with continuous subcutaneous insulin infusion resulted in comparable glycaemic control, weight gain and hypoglycaemia risk as multiple daily injection therapy (52,53). Although continuous subcutaneous insulin infusion was associated with greater improvements in treatment satisfaction in one study (53), we recommend that its use be restricted to selected patients in experienced centres only.
**Drawbacks of insulin therapy**

*Hypoglycaemia*

Intensive glucose-lowering therapy inevitably results in an increased rate of hypoglycaemia, which was once again confirmed in the recent ACCORD study with annualised rates of hypoglycaemic episodes requiring medical assistance of 3.1 and 1.0% in the intensive and standard therapy groups, respectively (6). Iatrogenic hypoglycaemia hampers tight glycaemic control and is considered the limiting factor in diabetes management (54).

Opinions are divided on the extent of the problem, with cited event rates for severe hypoglycaemia in insulin-treated type 2 diabetic patients ranging from between 1 and 3 (5) to between 10 and 73 per 100 patient-years (55). Of note, the relatively low rates were found in clinical trials (2,56), whereas the higher figures were reported in retrospective and population-based studies (57-59). The difference is probably explained by varying durations of disease or insulin therapy in the cited studies. The risks of mild and severe hypoglycaemia are very low among type 2 diabetic patients just beginning insulin therapy (30), and appear to increase with increasing durations of diabetes and insulin treatment (57-59).

To conclude, in type 2 diabetes, the frequency of hypoglycaemia is generally lower than that in type 1 diabetes (54). This is presumably the result of relative protection of type 2 diabetic patients against hypoglycaemia by residual endogenous (i.e. physiologically regulated) insulin and glucagon secretion, insulin resistance, and higher glycaemic thresholds for counterregulatory and symptomatic responses to hypoglycaemia (60,61). Therefore, when initiating insulin therapy, attempts to attain HbA1c goals should not be hampered too much by concerns about hypoglycaemia. However, iatrogenic hypoglycaemia appears to become a more frequent problem at the insulin-deficient stage of the disease, warranting more vigilance as the disease advances (54).

*Weight gain*

The ~2 to 4 kg increase in body weight associated with insulin therapy has traditionally been explained by reductions of glucosuria and resting energy expenditure when glycaemic control is improved (5,46). Other explanations are snacking to prevent, or in response to, hypoglycaemia or restoration of the weight loss usually preceding insulin initiation to the weight before onset.
of diabetes. In contrast, a recent study found that the mean weight gain of 1.8 kg in 23 type 2 diabetic patients during the first six months of insulin therapy was not accompanied by a change in glucosuria, resting energy expenditure or physical activity. The authors concluded that increased energy intake was the only plausible explanation for the observed weight increments (62). Although the mechanisms underlying insulin-associated weight gain are still not fully understood, it is thought to be proportional to the number of insulin injections or the total daily insulin dose (32,45,46). Interestingly, when considering studies investigating basal insulin initiation in type 2 diabetes, we found no evidence for such a dose-response relationship (Fig. 1c).

Finally, when directly comparing the mean increases in body weight during insulin initiation with NPH insulin vs. long-acting insulin analogues, insulin glargine is associated with similar weight gain (27,35-37). Treatment with insulin detemir, on the other hand, appears to result in less weight gain than NPH insulin (28,33). However, considering the limited magnitude of the reported weight-sparing effect, we still recommend NPH insulin for the initiation of insulin therapy in patients with type 2 diabetes.

Conclusions

Although insulin has no upper dose limit and numerous trials established that glycaemic goals can be attained by using adequate doses, in clinical practice, many patients experience years of uncontrolled hyperglycaemia. Because most type 2 diabetic patients have residual endogenous insulin secretion, the rationale for imitating the physiological insulin secretion pattern is less convincing than in type 1 diabetes. Glycaemic treatment should be stepwise with swift introduction of successive interventions after treatment failure (i.e. HbA1c ≥7.0%). Insulin should be initiated when HbA1c is ≥7.0% after 2 to 3 months of dual oral therapy. The preferred regimen for insulin initiation in type 2 diabetes is once-daily basal insulin. In addition to timely initiation, rapid titration of the dose is indispensable for successful insulin therapy. Hypoglycaemia risk is very low among type 2 diabetic patients just starting insulin therapy, making NPH insulin the most cost-effective drug.
When glycaemic goals are not attained despite successful basal insulin dose titration (i.e. fasting plasma glucose ≤5.6 mmol/l [100 mg/dl]), or when titration is limited by hypoglycaemia, treatment should be intensified by addition of prandial or biphasic insulin.

Duality of interest
Sanne G.H.A. Swinnen is employed by the Department of Internal Medicine of the Academic Medical Centre, Amsterdam, the Netherlands, partly through funding from Novo Nordisk and sanofi-aventis for the conduct of clinical trials. Joost B.L. Hoekstra has received honoraria for consultancy work from Novartis and sanofi-aventis. J. Hans DeVries has received honoraria for consultancy work as well as research funding from Novo Nordisk and sanofi-aventis.
References


