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Brief report

Barriers to effective insulin treatment: the persistence of poor glycemic control in type 2 diabetes

Stuart A. Ross
University of Calgary, Calgary, Alberta, Canada

Hugh D. Tildesley
University of British Columbia, Vancouver, British Columbia, Canada

John Ashkenas
SCRIPT, Toronto, Canada

Address for correspondence:
Dr. Stuart A. Ross, University Of Calgary Medicine, #102, 5940 MacLeod Trail, Calgary, AB T2H 2G4.
Tel.: +1 403 288-3224;
drstuartaross@gmail.com

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Abstract

Background:
Contrary to longstanding recommendations on type 2 diabetes (T2D) management, the de facto standard of care in Canada includes lag times of many years prior to introducing effective glycemic control. Even patients transitioned to insulin may continue to experience poor glycemic control, with attendant diabetic complications, suggesting poor adherence or inadequate dose titration.

Objective:
To identify barriers to timely and effective use of insulin in T2D.

Methods:
PubMed searches were conducted to find research articles on insulin initiation, adherence and intensification. Also, because recent data on the consequences of intensive glycemic control may be taken as justification for relaxing glycemic targets, a secondary search on this literature was conducted, including the UKPDS and ACCORD trials, plus post hoc and meta-analyses of these data. No formal evaluation of level of evidence was conducted while researching this narrative literature review.

Findings:
Timely, effective glycemic control remains an important clinical goal but is complicated by patient, physician and treatment factors. Patient barriers to accepting insulin initiation include fear of hypoglycemia, injections and weight gain, and reluctance to accommodate the inflexible timing of scheduled insulin doses. Adherence issues, including dose omission, are common and are associated with some of the same factors. Fear of hypoglycemia also underlies many physicians' reluctance to prescribe insulin. Caregivers' failure to provide training or answer questions about insulin's risks and benefits was also associated with low patient adherence. Poor communication may also be at fault when patients on insulin fail to titrate or intensify their treatment adequately. Conversely, glycemic control can be significantly improved by facilitating ongoing communication between patients and caregivers.

Discussion:
Although innovations in injectable therapy for T2D may help address the current pattern of poor glycemic control, improved communication between patients and caregivers is also a powerful approach and can be implemented with existing therapies.

Introduction

Current guidelines call for physicians to address a patient's poor glycemic control within several months of making a diagnosis of type 2 diabetes (T2D)[1]. In reality, however, diabetes care is far from meeting this standard, and, at least in Canada, there is little evidence of recent progress.

The Diabetes in Canada Evaluation study (DICE)[2], conducted in 2002–2003, identified a pattern of clinical inertia in the routine management of T2D, such that only half of patients were achieving target glycemic control (defined by a glycated hemoglobin [A1c] value <7.0%). Overall, 17% of prevalent patients had 'inadequate' control (A1c ≥8.4%), and this proportion increased with disease duration, with parallel increases in diabetes complications (macrovascular complications, including angina and a history of myocardial infarction [MI]; and microvascular disease, including neuropathy, nephropathy, cataracts and retinal disease).

In the years following DICE, several similar studies have been carried out, with similar implications about T2D management in general practice. The Diabetes Registry to Improve Vascular Events (DRIVE) study, conducted in 2005–2006, found that half of patients achieved the A1c target, while 9% of patients had very poor control (A1c ≥9%)[3]. While some DRIVE patients were on insulin, nearly one-third were treated with a single oral antihyperglycemic drug (OAD) or had no pharmacotherapy at all, suggesting considerable room for improvement if more ambitious management were implemented.

In addition, two recent studies highlighted the long lag prior to initiation of insulin among Canadian T2D patients. We[4] reported a mean 10.3-year lag between diagnosis and first insulin use, with a mean A1c of 9.0% at the time of insulin initiation. A chart audit by Harris *et al.* (2010) also suggested that patients experienced inadequate treatment and poor glycemic control, likely for some years. On average, patients in the Harris study had been diagnosed with T2D for 9 years before receiving insulin, and they began insulin treatment with a mean A1c of 9.5% and a considerable burden of diabetes complications[5].

In this brief report, we consider evidence that insulin is initiated too late in the course of T2D management and is used sub-optimally, with limited adherence and delayed intensification. We also discuss various barriers to timely and effective use of insulins, including recent clinical data that may be misinterpreted as licence to leave patients in a state of poor glycemic control. Finally, we explore the possible benefits of innovative therapies and of improved communication between patient and caregiver, as means of helping insulin-treated patients reach appropriate glycemic targets safely.

Methods

PubMed searches were conducted in February 2011, using the following terms: insulin, hypoglycemia, adherence, persistence, compliance, initiation, titration, intensification, and omission. Additional articles were chosen from the authors' personal libraries or were found by consulting the reference list of relevant reviews. Forward searching, to identify subsequent work where key papers were cited, was conducted using Web of Science (Institute for Scientific Information).

Additional PubMed searches on the benefits and risks of intensive glycemic control were carried out using the names of relevant trials, including ACCORD, ADVANCE, and VADT.

No formal evaluation of levels of evidence was conducted in the course of researching this narrative literature review.

Is insulin up to the job?

Many of the patients described in the Harris chart review remained under poor glycemic control >3 years after they received their first prescription for insulin. While the mean A1c level declined from 9.5% to 7.9% in this time, one-fifth of patients still had A1c in excess of 9%, and the prevalence of micro- and macrovascular complications climbed from 74% to 94%[5]. These findings offer a sharp reminder of the need to establish glycemic control earlier in disease progression, as recommended by various authorities[1,6].

The persistence of poor control in this patient group presents a puzzle, since insulin's potential to reduce glycemic exposure has no theoretical limits. In our view, there are only two general explanations for an individual's A1c remaining at 9% after 3 years of insulin. First, the patient may not be taking insulin injections or may be taking them irregularly. Second, the patient or physician may have failed to titrate or intensify the treatment adequately to effect a change in glycemic exposure in the face of disease progression. We cannot distinguish between these two scenarios. As discussed below, both are plausible, given what is known of real-world T2D care, where various physician-, patient- and treatment-related barriers prevent the timely introduction and effective use of insulin[7].

Adherence to insulin

Several forms of insulin non-adherence can be distinguished by consulting pharmacy records. For instance, 'primary non-adherent' patients are those who simply fail to fill their first prescription[8]. This pattern can be distinguished from poor persistence, in which patients discontinue treatment at some point and fail to refill their prescription. Frequent dose omission[9], which may be deliberate or accidental, can account for a pattern of continuous but infrequent refills[10].

The full extent and clinical impact of adherence problems in T2D are difficult to assess. As would be anticipated, low adherence to OADs[11] or insulin[12] is consistently

associated with poor glycemic control and failure to meet glycemic targets. Beyond this, patient surveys and retrospective analyses help paint a picture of the non-adherent patient and of the clinical and communications problems that caregivers face in managing T2D.

Karter *et al.* (2010) searched pharmacy records from a U.S. health management organization (HMO) and interviewed patients who had filled or failed to fill a new prescription for insulin. Primary non-adherent patients typically cited fears of social limitations and of hypoglycemia, and they expressed uncertainty about their own ability to make dose adjustments. Compared with their primary adherent counterparts, they were significantly less likely to understand the balance of risks and benefits of insulin treatment or to have received insulin self-management training. This last observation suggests that the barriers to primary adherence can be addressed by redoubling efforts at patient education[8].

Similar themes came up in a recent survey by Peyrot *et al.* (2010) on dose omission, in which most insulin-treated diabetics acknowledged skipping doses, with 20% saying they do so regularly[13]. Among the factors associated with self-reported dose omission were the perceived intrusiveness of insulin treatment and dissatisfaction with the injections themselves. Respondents who claimed that they need to plan their day around insulin injections and that insulin injections interfere with activities of daily living were significantly more likely than other patients to omit doses. Likewise, the perception of insulin injections as painful or embarrassing was associated with dose omission, as was a large number of daily injections[13]. Poor adherence has been reported before in T1D and T2D patients with more complex treatment regimens[14].

Fear of hypoglycemia and weight gain

Fear of hypoglycemia is a common basis for patients' reluctance to initiate insulin treatment[15] and also for physicians to delay insulin initiation in patients with poor glycemic control[16]. Hypoglycemia, specifically the risk of severe nocturnal hypoglycemia, is indeed the major dose-limiting effect of all insulins and certain OADs. The true incidence of severe hypoglycemia in T2D is hard to gauge from the literature, since operational definitions for severity of hypoglycemic events vary, and retrospective studies generally depend on the accuracy of patient self-reporting[17,18]. Incidence of hypoglycemia is generally lower in T2D than in T1D patients, although the difference diminishes with longer disease duration[19]. Recent studies using continuous glucose monitoring have established that episodes of low glycemia (including nocturnal events) occur more frequently than was known from analyses depending on clinical symptoms and/or older monitoring approaches[20,21].

Although fear of hypoglycemia has been identified as a key factor in dose omission by T1D patients, this association was not evident in the Peyrot *et al.* study[13]. However, the relationship between hypoglycemia and adherence is likely to be complex, as others have noted. For instance, a perverse consequence of poor adherence may be that patients are placed at increased risk of hypoglycemia when their insulin dose is increased inappropriately to compensate for an apparent lack of efficacy.

Weight gain is another adverse consequence of the transition to insulin treatment. Like hypoglycemia, it looms large in the thinking of both patients and caregivers and is widely cited as a reason for delaying insulin initiation[22]. The physiological basis of this response is not well understood, since normal insulin production does not cause weight gain. Some authors have speculated that weight gain is related to the fear of hypoglycemia, because patients rightly or wrongly perceive a need to snack defensively to maintain blood sugar in the normal range. This explanation is unlikely to be complete, because insulin analogues differ from one another with regard to weight gain. Among the various basal insulins and analogues, both insulin glargine and detemir offer long-term stable action over approximately 24 hours, with a corresponding reduction in hypoglycemia risk relative to NPH insulin[23]. However, detemir is associated with minimal weight gain and, in many patients, weight stability or weight loss, unlike either NPH insulin or glargine[22,23].

As discussed below, both basal insulin analogues are associated with greater treatment persistence than is seen with NPH insulin[9].

Persistence with injectable therapies

In an HMO pharmacy-based study of injectable treatments for T2D, Cooke *et al.* (2010)[9] examined patients' records of continuing to refill their prescriptions. The authors reported that persistence with NPH insulin was significantly lower than with basal insulin analogues (glargine or detemir) or with the incretin mimetic exenatide.

Because this study measured persistence only for an 'index' treatment (i.e., an agent that was prescribed for the first time during the study period), it identified patients who were changing treatment under a doctor's care, along with those who were allowing their care to lapse. Nevertheless, this finding is consistent with other data on patient adherence, as well as with comparative clinical data. Although NPH insulin is as effective as each of the available basal analogues, it is associated with greater risk of hypoglycemia, including nocturnal hypoglycemia[23]. Choice of basal analogue therapy and use of incretin agents may also help address patients' concerns about weight gain[22,24,25]. Thus, the selection of therapeutics

may directly influence patients' willingness to stay on therapy.

Do we still need glycemic control?

The benefits of establishing glycemic control early in the disease process have been known for some time. In T2D, the clearest long-term evidence came from the UK Prospective Diabetes Study (UKPDS), which followed a population of patients starting treatment immediately upon diagnosis of T2D[26]. Patients were randomized to intensive treatment (OADs and/or insulin treatment targeting a fasting blood glucose [FBG] of 6 mmol/L) or to conventional treatment (primarily lifestyle interventions maintaining FBG <15 mmol/L).

Over the course of the UKPDS, which extended >12 years for some subjects, reduced glycemic exposure led to significant improvements on multiple outcomes: mortality, macrovascular events such as MI and stroke, and microvascular events such as retinopathy. The benefits of intensive control came at the cost of weight gain and increased risk of hypoglycemia, a recognized treatment-limiting consequence of sulfonylureas and insulins, which were used by most of the intensively treated patients in the study[26].

A later follow-up study of the same UKPDS patients showed an additional long-term benefit of tight glycemic control, namely a significant 15% reduction of MI and a 17% reduction of diabetes-related deaths in patients who had been originally randomized to the intensive treatment arm of the study. This observation was all the more striking because the earlier difference in glycemic control was lost early in the follow-up period, but mortality and other benefits of prior good control continued to accrue[27].

The benefits seen in the UKPDS and UKPDS follow-up studies[26,27] provide direct evidence that early, effective glycemic control reduces mortality and morbidity in T2D. It is important to recognize that nothing in the subsequent literature contradicts or undermines these conclusions, although other studies raise important questions about how widely the conclusions can be generalized. In the post-UKPDS literature, various studies have revisited the hypothesis that intensive treatment to control glycemia improves survival or macro- or microvascular outcomes. The later studies attempted to extend the lessons of UKPDS beyond newly diagnosed patients[26] to patients with some years of prior diabetes. The subjects in these later trials (ADVANCE[28] and ACCORD[29], among several others; reviewed in Zhang *et al.*, 2010[30]) began their treatment at greater risk of death from the complications of diabetes, compared with UKPDS patients at baseline. Furthermore, the definition of intensive treatment varied across studies, although in each case it required more aggressive management than was attempted in UKPDS. Hence, it is not surprising that the apparent clarity of the lesson from UKPDS[7] is missing from the newer literature[31].

Nevertheless, a few consistent points have emerged from these studies and from related meta-analyses[30,32–34]. First, intensive treatment worked as expected; all studies found significantly lower A1c in intensively treated patients, relative to conventionally treated patients. Second, none of the studies that followed UKPDS documented significant mortality benefits associated with intensive treatment; indeed, ACCORD was terminated early because of higher all-cause mortality in the intensively treated group[30,32–34]. Third, intensively treated patients in UKPDS and all of the later studies had significantly higher risk of hypoglycemia. Fourth, the rate of fatal and non-fatal MI was consistently reduced with intensive treatment, a beneficial effect that was statistically significant in meta-analyses and in ACCORD[29,32,34]. Finally, intensive control was associated with improvement in certain microvascular outcomes, such as incident nephropathy[28,35].

Thus, even in patients with longstanding disease, intensive control as attempted in these various studies appears to offer some consistent benefits. Whether this approach is generally appropriate for patients with longstanding disease remains a topic of debate[6,36,37]. In print[37] and elsewhere, some physicians have expressed doubts about the appropriateness of treating T2D patients to target, in light of the mortality data from ACCORD.

However, recent reanalyses of ACCORD offer some important insights into the unexpectedly high mortality seen with intensive treatment in that study. For instance, it was initially suggested that rapid reduction of A1c (as occurred in the intensive treatment arm of ACCORD) might be harmful in itself. However, later analysis made it clear that patients with rapid A1c reduction were not at elevated risk of death. On the contrary, excess mortality in ACCORD was seen primarily in patients who responded slowly or weakly to intensive treatment[38]. Consistent with this finding, there was a nearly linear relationship between risk of death and average A1c over the course of intensive treatment, suggesting that patients who begin with or quickly achieve better glycemic control and lower A1c values are less likely to experience adverse consequences. Moreover, a parallel effect was seen with regard to hypoglycemia: risk of severe hypoglycemia was also significantly reduced among ACCORD patients with lower average A1c[39,40]. Hence, it appears that both of these adverse outcomes (mortality and severe hypoglycemia) might be minimized by selecting individuals with lower A1c for intensive treatment. This suggestion is consistent with data from UKPDS, where patients were included at early stages of T2D.

Based on the findings from ACCORD and related studies, it may be reasonable to identify patients with poor

control who fail to respond to treatment and to consider these patients for individualized (i.e., less ambitious) treatment goals. However, there is no justification from any of these studies for allowing patients to reach a state of severely degraded glycemic control in the first place. The benefits of good glycemic control, as established in the UKPDS, emerge gradually and are maintained over the course of years. Timely, effective treatment of patients with short T2D duration and mild A1c elevation should therefore be encouraged. This approach is likely to be more effective in bringing patients to target. The recent analyses suggest it may also be safer than aiming for the same outcomes in patients with longstanding disease and severely elevated A1c.

Overcoming barriers to intensification

Because T2D is progressive, dose titration and treatment intensification are needed to ensure that insulin therapy confers long-term benefits. Caregivers need to understand and be able to teach patients about these steps; their failure to do so is a significant barrier to effective management.

Does it matter how we start?

Physicians should be reassured that many good insulin titration schemes have been described and tested; all are easy to implement, and all step the patient up gradually to improved glycemic control while continually monitoring for treatment-induced hypoglycemia[1,41–43]. Patients may be instructed to use any of these schemes so that they can titrate their own insulin dose to reach a specified target range for fasting glycemia. One such scheme, recommended by the Canadian Diabetes Association, is shown in Figure 1.

With evidence of OAD failure, a common first step is to initiate once-daily basal insulin using NPH or analogues[1,23,44]. This approach may be justified, even for some patients who will eventually need intensification to more complex regimens, because it allows the patient to gain confidence with glucose monitoring and dose adjustment. The recent Treat Type 2 Diabetes to Target (4-T) study[45] provided a direct comparison of three different insulin initiation and intensification strategies, using basal or fast-acting insulin analogues or premixes, in insulin-naive patients with longstanding (median 9 years) T2D. Reassuringly, all three strategies led to a mean 1.2–1.4% point drop in A1c over 3 years. At least two of the three (basal with intensification to basal–bolus treatment, and twice-daily premix with intensification to three times daily) were also associated with acceptable hypoglycemia rates. Weight gain was least in patients randomized to basal insulin therapy.

Can we innovate our way to better treatment adherence?

There are various commonly cited explanations for the slow introduction and inadequate intensification of insulins in common clinical practice (Table 1), as well as for poor treatment adherence, and it is easy to ascribe blame to doctors, patients or both. However, the properties of insulins themselves should also be considered. Despite years of effort to make insulin injection as quick, discreet and close to painless as possible[46], patient studies show that acceptance is limited by lifestyle factors, including the inflexible timing of most treatment regimens. A survey of participants in the 4-T study found that, as patients' regimens were intensified up to even five daily injections, their anxiety centered on the risk that they would need to self-inject in public in order to time their treatment properly[47].

In the context of the 4-T study, there was no indication that patients' anxiety decreased their treatment adherence, but the acceptability of the regimen may be an important aspect of treatment success in routine practice[46]. Indeed, there is much basis for optimism that expanding therapeutic options for diabetes may lead to better adherence or reduce patients' resistance to moving beyond OAD therapy. For instance, just as the available basal insulin analogues are associated with reduced risk of hypoglycemia[23], it is possible that newer insulins could reduce the risk still further[48]. In addition, some of the current difficulty in establishing good glycemic control may resolve with the introduction of newer antihyperglycemic therapies, such as the incretin agents. The injected incretin agents, liraglutide and exenatide, are not associated with hypoglycemia, and they typically cause weight loss rather than gain[25]. These agents may be used as monotherapy or in combination with various oral agents, and some researchers are beginning to explore their use in conjunction with insulin treatment[25,49].

What can we do now?

In addition to the benefits that may arise from innovative therapeutics, considerable progress could be made by improving communication between caregivers and patients. We have recently shown that Internet-based contact can dramatically improve patients' glycemic control[50]. In this study, patients on insulin were randomized to either maintain their therapy, with no additional physician contact, or stay in regular contact with an endocrinologist via the Internet. The endocrinologist reviewed patients' glucose monitoring data, suggested additional monitoring and treatment adjustments, and offered encouragement. The patients with Internet-based physician contact experienced a significant and sustained improvement in glycemic control over 6 months, with a decline in mean A1c from 8.8% to 7.6% ($p = 0.001$), while

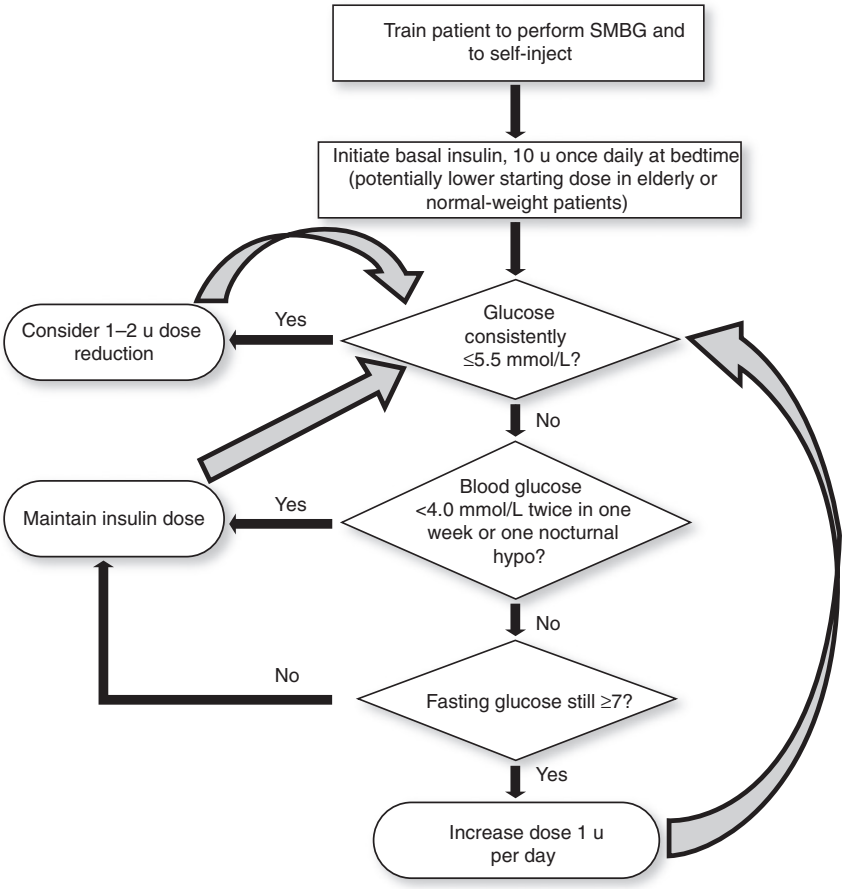

Figure 1. A sample insulin titration algorithm targeting fasting blood glucose levels between 4.0 and 7.0 mmol/L. This sample algorithm, based on Canadian Diabetes Association guidelines[1], may be used to titrate once-daily basal insulin (NPH insulin or insulin analogues). Although the process is straightforward, patients will require initial training to ensure that they can perform self-monitoring of blood glucose, and ongoing support to ensure that they do so regularly, at least once daily in the fasting state. Many other easy-to-implement algorithms have been tested that, like this one, allow the patient to increase insulin dose slowly to the point where it helps bring hyperglycemia under control, while constantly monitoring for evidence of hypoglycemia[41,42].

Table 1. Common barriers to timely introduction and effective use of insulins in T2D.

Patient barriers	Physician barriers
Sense of failure associated with disease progression	Benign neglect
Fear of complex insulin regimens	Fear of complex insulin regimens
Fear of hypoglycemia	Fear of hypoglycemia
Fear of weight gain	Fear of weight gain
Fear or needles/injections	Lack of time/resources
Embarrassment at need for injections in public	Need for referrals

A1c in the usual-care group declined non-significantly from 8.5% to 8.4%[50]. Insulin dose did not differ significantly between treatment arms, either before or after the intervention[50], and the improved control in the intervention group was not accompanied by instances of severe hypoglycemia (Tildesley and Ross, unpublished). The benefits of improved physician access proved to be reversible in a follow-up study, suggesting that continued or at least longer-term interaction may be needed for patients to use insulin more effectively and safely[51]. Nevertheless, the key point remains that for many T2D patients, safe and effective control might be within reach if barriers to communication could be removed, allowing caregivers to help their patients optimize their use of insulin.

Conclusion

Delayed introduction and inadequate use of insulin in T2D are complex problems with roots in patient and physician

attitudes and misconceptions, as well as in the limitations of the older therapeutics. As we have stressed above, it remains crucial for patients to achieve and maintain effective glycemic control, particularly early in the development of the disease. Multiple strategies for insulin dose adjustment are available for this purpose, both for routine dose titration and for treatment intensification in the face of inevitable disease progression. The choice among these strategies may be less important than the commitment to apply them promptly and remain on them over the long term. Patient education is a key responsibility for caregivers when patients are first prescribed insulin. Effective follow-up is no less important, and physicians should be encouraged to monitor their patients' glucose test results and dose adjustment carefully, as frequently as is practical.

As innovative products enter the market, and as guidance on glycemic targets and patient selection continues to be refined, it should be possible to make diabetes therapies more effective, safer, more acceptable and less intrusive. However, even with existing approaches, improved communication between patients and caregivers has extraordinary potential to optimize insulin therapy, improve glycemic control and ultimately reduce mortality and morbidity associated with T2D.

Transparency

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