Overview of Therapeutic Inertia in Diabetes: Prevalence, Causes, and Consequences

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Many people with diabetes do not achieve individualized treatment targets. Therapeutic inertia, the underuse of effective therapies in preventing serious clinical end points, is a frequent, important contributor to this failure. Clinicians, patients, health systems, payors, and producers of medications, devices, and other products for those with diabetes all play a role in the development of therapeutic inertia and can all help to reduce it.

The prevalence of total diabetes in the United States was 14% from 2013 to 2016, with a 9.7% prevalence of diagnosed diabetes and a 4.3% prevalence of undiagnosed diabetes (1). An estimated 1.5 million new cases are diagnosed every year (2). In 2017, the total estimated cost of diabetes was $327 billion; adjusted for inflation, this represents a 26% increase from 2012 to 2017 (3).

Type 2 diabetes, which accounts for 90–95% of all diabetes, is a progressive disease characterized by insulin resistance in most patients and impaired and declining β-cell function in virtually all (4). As a result, most patients require progressive intensification in therapy to reach and maintain glycemic goals. It is well established that meeting glycemic targets reduces the risk of development and progression of microvascular and probably macrovascular complications (5). Edelman and Polonsky (6) noted that, despite multiple randomized controlled trials documenting the risks of glucose elevated above goal over time, a large armamentarium of treatment options, and the availability of new technologies, many individuals are still unable to achieve their glycemic targets.

An analysis from the National Health and Nutrition Examination Survey reported that only ~50% of American patients with diabetes were able to achieve an A1C <7.0% (7). The Healthcare Effectiveness Data and Information Set examined health plans from >171 million Americans in 2014 and reported that 40% of commercially insured health maintenance organization patients and 30% of government-insured patients achieved an A1C <7.0% (8). Given the progressive nature of type 2 diabetes, the risks of elevated A1C, and the increasing costs of diabetes, it is of paramount importance to understand the barriers to achieving glucose targets.

One such barrier is therapeutic inertia, which can be driven by the physician, the patient, or both. In addition, the health care system, payers, and producers of antihyperglycemic therapies and diabetes medical devices can all potentially play a role. The aim of this review is to provide an overview of therapeutic inertia in patients with diabetes, including its prevalence, causes, and consequences or outcomes.

The term "clinical inertia" has been used since the early years of this century. Allen et al. (9) proposed that clinical inertia includes three factors: physician factors, patient factors, and office system factors. Clinical inertia denotes underuse of effective therapies in preventing serious clinical end points despite abundant evidence showing the benefit of those therapies. In 2015, Reach (10) offered a description of clinical inertia that included the following: "There is an implicit or expert guideline, the physician is aware of the guideline, the physician believes the guideline applies to the patient, the physician has the resources to apply the guideline, and all these conditions are met, but the physician does not follow the guideline in the case of the patient." However, it has been noted that clinical inertia in some cases may represent a clinical safeguard and may be considered appropriate if the guidelines do not apply to a specific patient (4,11). This has been referred to as "apparent clinical inertia" (4). Clinician inaction can also occur because of a lack of knowledge of appropriate care, and this can also be considered clinical inertia. Moreover, clinical inertia should not be termed "clinician inertia" because it is well documented that clinical inertia is not always a failure

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of the clinician but is often related to patient factors (e.g., denial of having disease, lack of medication taking, or low health literacy) or system factors (e.g., limited access for follow-up or limited clinic staff) (4). In recent years, it has been proposed that "therapeutic inertia" is more appropriate specifically to describe the failure to advance or deintensify treatment, whereas the broader concept of clinical inertia includes not only escalation or deintensification of therapy but also issues such as failure to screen, make appropriate referrals, and manage risk factors and complications (12). For this reason, the term "therapeutic inertia" will be used moving forward.

The American Diabetes Association (ADA) recently launched a new initiative focused on overcoming therapeutic inertia (13). Phase 1 of this multiyear activity began with a summit of key stakeholders on 28 November 2018 in Arlington, VA. The objectives of that meeting were to identify and assess issues related to therapeutic inertia, address barriers, and develop solutions and next steps that will have a significant impact on long-term outcomes.

Prevalence of Therapeutic Inertia

Research conducted in many countries has demonstrated the high prevalence of therapeutic inertia. Khunti et al. (14) demonstrated in a retrospective cohort study based on 81,573 patients with type 2 diabetes in the U.K. Clinical Practice Research Datalink database that it took more than 3 years to intensify from one oral antihyperglycemic drug to two oral agents in patients with an A1C >7.0%. A study in urban African Americans showed that diabetes treatment was only intensified at 50% of clinic visits despite patients not being at goal (15). The Diabetes in Canada evaluation demonstrated that nearly 50% of patients with type 2 diabetes in primary care practice had an A1C above target. This study went a step further by surveying primary care providers (PCPs) and asking how they planned to help patients attain their target A1C. Only 56% intended to intensify therapy or refer to a specialist (16). In another analysis of the U.K. Clinical Practice Research Datalink database, among 15,000 patients, the median time to initiate insulin in patients prescribed multiple oral agents was 7.7 years, despite a mean A1C >8.0% and patients being on two or more oral antihyperglycemic agents (17). The DAWN Japan Study (18) used a questionnaire-based survey with Japan Diabetes Society certified specialists and noncertified specialists to assess physician barriers to insulin initiation. The mean A1C in patients under the care of the surveyed physicians was 7.5%. Only 27% of the cohort were on insulin. Multiple reasons for not starting insulin were deemed to be clinically significant, including lack of staff to assist with explanations to patients, concerns about using insulin therapy in the elderly, and difficulty providing guidance and education to patients regarding insulin injections. A 2016 study in the United Kingdom revealed that only 30.9% of patients on basal insulin with an A1C >7.5% had their treatment plan intensified with either bolus insulin, premixed insulin, or a glucagon-like peptide 1 (GLP-1) receptor agonist (19).

Overtreatment and failure to deintensify therapy are other components of therapeutic inertia especially important in older adults with type 2 diabetes who are at high risk for hypoglycemia and adverse consequences from hypoglycemia (12,20). Studies have also documented therapeutic inertia related to other treatment goals in patients with diabetes, including blood pressure and dyslipidemia (21,22).

Causes Contributing to Therapeutic Inertia

As previously stated, the drivers of therapeutic inertia are complex and can be broadly divided into three categories: provider-related, patient-related, and health system–related (9), although payer- and industry-related factors also contribute. Understanding the various contributions of and interplay among factors in each category is essential to finding effective solutions.

Provider-Related Factors

In 2001, Phillips et al. (23) defined therapeutic inertia as clinicians recognizing that patients are not meeting defined targets in the management of chronic disease states, including hypertension, dyslipidemia, and diabetes, but still not changing care to meet these targets. They described three provider-related factors that lead to therapeutic inertia: overestimation of quality of care, use of soft excuses to avoid intensification, and lack of materials, time, and training to appropriately escalate care to meet recommended targets. Others have used this definition and its three proposed factors to further examine the reasons contributing to health care providers' reluctance to intensify treatment when clinically appropriate (5,9,24).

Despite the known association between achievement of glycemic targets and the prevention or delay in the development or progression of diabetes-related complications (25,26), clinicians often do not set glycemic, blood pressure, and lipid goals with patients and then initiate and titrate medical management to meet such goals (24,27). The consequences of treatment delays include shorter time to development of diabetes-induced retinopathy (28) and increased rates of cardiovascular (CV) events, including myocardial infarction (MI), heart failure, (HF) and stroke (29).

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Not advancing therapy when indicated may in part be due to ever-evolving guidelines and goals of therapy (9). In 2012, the ADA and the European Association for the Study of Diabetes (EASD) released a joint position statement on the management of hyperglycemia for people with type 2 diabetes that emphasized the need for a patient-centered approach to care that includes individualized treatment goals and glycemic targets (30). Since that time, new therapies and evidence from U.S. Food and Drug Administration (FDA)-mandated CV safety trials have become available and incorporated into updates released in 2015 and 2018 (31,32), which echoed the need for a patient-centered approach with an emphasis on shared decision-making between clinicians and patients. The 2018 ADA/EASD update specifically recommends prioritization of patient-centered care that takes into consideration patient-specific factors, including cultural beliefs, cognitive impairment, attitude, and support system. This approach also recommends early consideration of history of CV disease (CVD) and chronic kidney disease (CKD), as well as life expectancy, risk for hypoglycemia, and costs to further guide and individualize treatment.

The ADA also publishes annual *Standards of Medical Care in Diabetes* guidelines to define treatment targets and guide decision-making; however, after metformin as first-line therapy for most patients, the choice of second-line agents has sometimes not been as well defined (33). However, recent ADA guidelines have become more specific than in previous years in stratifying recommendations for patients with atherosclerotic CVD, congestive HF, or CKD or when avoidance of hypoglycemia or weight gain is important or cost is an issue.

Per the ADA, A1C testing should be repeated 3 months after a change in treatment or every 6 months in those meeting therapeutic goals. Nevertheless, decisions still often rely on clinician judgment. Decision-making is made more difficult as the number of antihyperglycemic medications increases. With this increase in medications comes changes to insurance formularies that can be difficult, if not impossible, to keep track of, as well as requirements for prior authorization for certain, especially newer, medications that can further delay their availability. To assist PCPs, the ADA publishes an annual abridged version of the *Standards of Medical Care in Diabetes* for PCPs (34).

The American Association of Clinical Endocrinologists and the American College of Endocrinology have for some years recommended early use of combination antihyperglycemic therapy when a single agent is unlikely to achieve goal glycemia (35). Fixed-dose or single-pill combinations and fixed-ratio injectable combinations of basal insulin and a GLP-1 receptor agonist can facilitate the use of combination therapy, may help patients achieve glycemic targets sooner, and can also reduce some of the burden of multiple medications and copayments for patients (36,37).

The need for patient-centered management must be considered in a real-world context in which several factors affect the decision to intensify therapy. Parchman et al. (38) demonstrated that competing demands, including time constraints, multiple diagnoses, and patient concerns, limit changes in antihyperglycemic medications during primary care visits. This has also been described in the context of patients redirecting clinical encounters toward different concerns and further limiting provider time to discuss advancing diabetes therapy (24).

Lack of knowledge and resources also delays treatment intensification, particularly insulin initiation. Studies comparing PCPs to specialists have shown that specialists are more likely than PCPs to initiate insulin and GLP-1 receptor agonists earlier in the course of therapy. Shah et al. (39) compared 591 specialist-treated patients to 1,911 nonspecialist-treated patients and found that less than half in both groups had treatment intensification (45.1 vs. 37.4%), with specialists more likely to initiate insulin than nonspecialists. Barriers to initiation of injections were lack of time and support staff to train patients in injection technique, glucose monitoring, and hypoglycemia recognition and treatment. These concerns may also extend to starting GLP-1 receptor agonists, which are also more likely to be started by specialists or PCPs with larger diabetes practices (40).

Communication issues between health care providers and patients can also limit effective diabetes management and medication intensification. First, clinicians may have incorrect perceptions regarding the reasons for patients' reluctance to start insulin or a GLP-1 receptor agonist. For many patients, the fear of becoming dependent on insulin or a misunderstanding of the severity of disease outweighs the physical fear of injections and injection discomfort that physicians perceive to be the more significant sources of concern (41). This perception may lead to inadequate education and understanding about the disease process and the importance of meeting glycemic targets. Tarn et al. (42) conducted an observational study that included physician and patient surveys along with videotaped outpatient encounters of visits in which a new medication was started. They observed that clinicians only said the name of new medications 74% of the time and explained the purpose in 87% of encounters. Adverse events were reviewed in 35% of visits, and explicit dosing instructions were given only 55–58% of the time.

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This finding is particularly relevant when initiating insulin because patients and physicians share concerns regarding the risks of hypoglycemia and weight gain, as well as starting or adding to already complex medication plans. For example, some older adults may be prescribed as many as 20 medications daily, making the addition of multiple daily injections daunting (43). A study among 2,000 patients with diabetes in the Veterans Administration health care system examined the association between patients' perceptions of their physicians' communication style and their participation in shared decision-making in relation to self-reported diabetes management and found that effective communication was more important in enhancing diabetes self-management than was shared decision-making (44). Mechanisms to improve communication between clinicians and patients are thus crucial to improving patient care, particularly when initiating higher-risk medications such as insulin.

Patient-Related Factors

As with the physician-related factors contributing to therapeutic inertia, patient-related factors are complex and can make management of diabetes challenging for patients, their families, and health care professionals. Difficulty in making changes to lifestyle and taking medications is common and is a significant contributor to the challenge of meeting glycemic targets. A study comparing the change in A1C in patients started on a GLP-1 receptor agonist or a dipeptidyl peptidase 4 (DPP-4) inhibitor in randomized controlled trials and in real-world settings using claims data found a smaller reduction in A1C in claims data than in randomized trials for patients treated with either a GLP-1 receptor agonist (−0.52 vs. −1.30%) or a DPP-4 inhibitor (−0.51 vs. 0.068%). An analysis of the reasons for this difference found less frequent medication taking to be the cause in 75% of cases (45).

Not taking medications as prescribed or following lifestyle recommendations certainly contribute to patients not achieving glycemic targets and are in turn often attributable to other factors that can add to therapeutic inertia, including medication side effects and cost. A potential strategy to increase rates of medication-taking is to link pharmacy data to electronic medical records to notify health care providers if patients have not refilled medications. This information can facilitate dialogue about medication side effects or intolerance, cost concerns, and lack of perceived efficacy.

The term "psychological insulin resistance" was coined to describe patients' refusal to start insulin therapy when recommended by a clinician. Polonsky et al. (46) conducted a survey of 708 patients with type 2 diabetes who were not on insulin to better understand the reasons behind resistance to insulin therapy. Of these participants, 28% reported unwillingness to take insulin if prescribed. Commonly cited concerns included potential permanence of therapy, complex and restrictive plans, fear of hypoglycemia, and inadequate diabetes self-management education and support (DSMES). There is also often the belief that progression to insulin therapy marks a failure on the part of patients or their clinicians to control disease rather than an understanding that type 2 diabetes is often associated with progressive β-cell failure that can ultimately require insulin (5,46). Concerns about weight gain and other medication side effects, especially hypoglycemia, contribute to patients' reluctance to start, continue, or consistently take new medications (5). Indeed, patients who experience hypoglycemia after initiating insulin therapy have an increased risk of discontinuing the therapy (47). Sometimes, patients have unrealistic expectations about the effects of medications (e.g., the amount of weight loss they are likely to have with a GLP-1 receptor agonist or a sodium–glucose cotransporter 2 inhibitor) and may discontinue the medication when those expectations are not met.

Patient-specific issues can also contribute to therapeutic inertia and are often not recognized or appropriately addressed by treating clinicians. Depression is very common among people with diabetes, with reported rates as high as 17.8% compared with 9.8% in those without diabetes, and patients with depression are more likely to have concerns related to initiation of insulin (48,49). Older adults may struggle with dexterity and vision impairment, limiting their ability to monitor glucose and use injectable medications (50). Cost is also a concern for many patients and must be considered when choosing therapy, particularly given the large difference between the cost of older versus newer antihyperglycemic therapies (51). It has been demonstrated that patients with lower incomes and higher out-of-pocket costs are likely to forego or be less likely to take diabetes medications. However, other factors such as depression, beliefs regarding medications, and dissatisfaction with medication information also contribute to patients' medication-taking decisions (49,52). Understanding barriers to patients' willingness or ability to engage in therapy is therefore essential to improving outcomes and increasing medication-taking.

System-Related Factors

Several health system–level issues can lead to difficulty in achieving therapy goals in people with diabetes. Medicare began providing coverage for diabetes self-management training (its term for DSMES) in 2000. However, in 2010, only 5% of patients with newly diagnosed diabetes

participated in DSMES in the year after being diagnosed. Differences in utilization may be based on sex, race, age, comorbidities, location, and provider availability (53). Similar findings were demonstrated in a privately insured cohort, in which only 6.8% of newly diagnosed patients received DSMES in the year after diagnosis (54). The low rates of participation in education may be in part due to lack of access to DSMES programs. In 2016, 62% of nonmetropolitan counties did not have a DSMES program, with lower rates in counties with higher numbers of people with diabetes and percentages of uninsured or unemployed residents (55).

As noted previously, lack of knowledge about guidelines or a lack of clear guidelines, differences among guideline recommendations from various organizations (56), and changing targets can contribute to clinician uncertainty about intensifying medication plans. This confusion is further complicated by the cost of medications and changing formulary constraints, which are out of the control of patients and providers but often influence care. For example, nonmedical switching (NMS) is a term used to describe the change in a patient's prescribed medication to an alternative (not a generic) medication for reasons related to price, insurance coverage, formulary changes, and other administrative reasons (57). In a recently published study, patients with NMS used significantly fewer antihyperglycemic products compared with patients without NMS (58). Thus, therapy abandonment was a major unintended consequence. Time constraints placed on providers, as well as a lack of institutional organization of care, may further limit the health care system's ability to provide consistent and effective care tailored to individual patients' needs (5,24).

Taken together, many factors exist at the patient, provider, and health-system levels that affect the ability to deliver care to patients with diabetes. These all contribute to the existing problem of therapeutic inertia and in turn have a large impact on outcomes for patients with diabetes.

Therapeutic Inertia Outcomes

As noted above, lack of following medication plans is an important contributor to therapeutic inertia. Medication-taking is crucial to attaining and maintaining target glycemic levels, which in turn is associated with lowering risks for short- and long-term health complications for patients. Data collected from 11,272 veterans with type 2 diabetes from April 1994 to May 2006 demonstrated a strong link between medication-taking and glycemic levels (59). Some of the effects of above-target A1C levels due to infrequent medication-taking include an increase in total medical costs, increased use of acute care resources, and higher rates of short- and long-term medical complications. In 2016, Boye et al. (60) showed that a 1% increase in medication-taking among 1,000 patients resulted in all-cause savings of $65,464 over 3 years. A meta-analysis performed in 2017 by Khunti et al. (61) included three studies examining the association between medication-taking and all-cause mortality and found a pooled relative risk of 0.72 (95% CI 0.61–0.82, $P < 0.001$) for all-cause mortality when medication-taking was compared with not taking medication.

An analysis of the relationship between medication-taking and outcomes using Truven's Medicare Supplemental Database from 1 July 2009 to 30 June 2014 (60) focused on three main outcomes: total medical costs, the use of acute care resources, and acute health complications. Researchers assessed the percentage of days an individual received at least one glucose-lowering agent during the analysis period (60). Total costs, including outpatient costs, acute care costs, and drug costs, were inversely proportional to the level of medication-taking: $73,009 with <20% medication-taking and $44,185 with >80% medication-taking (60). The use of acute care resources was lower with better medication-taking. When medication-taking was <20%, the probability of hospitalization was 56.22% and the probability of emergency department visits was 72.02% compared with a probability of hospitalization of 37.43% and of emergency department visits of 54.18% in the cohort with >80% medication-taking during the observation period (60). Although drug costs were higher with >80% medication-taking, total costs were much lower because of lower acute care costs. The probability of acute complications was 24.11% with <20% medication-taking and 13.02% with >80% medication-taking (60). Acute complications included diagnoses of hyperglycemia, hypoglycemia, and diabetic/hypoglycemic coma. Acute complications leading to hospitalization had further consequences in older adult patients because they sometimes needed long-term nursing care after a short hospital stay and often had readmissions resulting in higher medical costs (60).

Similar results were seen in an older study published in 2005, demonstrating decreased total medical costs with increased medication-taking in a retrospective cohort observation of 137,277 patients <65 years of age (62). Hospitalization risk significantly decreased from 30% with medication-taking of 1–19% to 13% with medication-taking of 80–100% (62).

The long-term complications of therapeutic inertia in people with diabetes are also significant and can include diabetes-related retinopathy and other microvascular events, as well as MI, HF, and stroke. One retrospective cohort study

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performed in Thailand showed that failure to intensify medical treatment within 3 months after an initial A1C measurement >9.0% was associated with a rate of new or progressive diabetes-related retinopathy of 10 cases per 1,000 person-months versus 2.2 cases per 1,000 person-months in the group with treatment intensification (28). Another retrospective cohort study analyzed data from the U.K. Clinical Practice Research Datalink database from January 1990 to December 2012 (29). In patients with an A1C >7.0% who did not receive intensification of treatment within 1 year of diagnosis, the risks of MI, HF, stroke, and a composite of CV events were increased by 67, 64, 51, and 62%, respectively, compared with patients who received intensification of treatment within 1 year (29). A delay in intensification of treatment among patients diagnosed with CVD before their diagnosis of diabetes was associated with an increased risk of HF and CV events, but not of MI or stroke (29). A similar effect was seen in a cohort study conducted among individuals with newly diagnosed type 2 diabetes between 1997 and 2013 with 10 years of survival. Those with an A1C ≥6.5% during the first year after diagnosis were found to have increased risks of both microvascular and macrovascular events, and those with an A1C ≥7.0% had increased mortality (A1C 7.0 to <8.0%, HR 1.290 [95% CI 1.104–1.507]) (63). The mechanisms for increased macrovascular events associated with hyperglycemia are not fully understood, although oxidative stress, inflammation, and thrombosis are among those proposed (64–66).

Early intervention in patients who did not achieve glycemic targets with metformin monotherapy was associated with the achievement of goal A1C levels in a shorter period of time in a Cleveland Clinic study (67). Achieving glycemic targets earlier in the diabetes disease process can have long-term benefits, as shown in the 10-year follow-up of the U.K. Prospective Diabetes Study, in which a continued reduction in microvascular risk and appearance of reductions in the risks for MI and all-cause mortality were observed (68). Similarly, early intervention with a GLP-1 receptor agonist in patients on basal insulin who had glucose values above target showed better clinical and economic outcomes (69). This study categorized patients into three groups: early, delayed, and no intensification. In the early-intensification group, a GLP-1 receptor agonist was added within 0–6 months after basal insulin was initiated, whereas in the delayed-intensification group, a GLP-1 receptor agonist was added 7–24 months after basal insulin was initiated. Clinical outcomes showed A1C decreases of 1.01% in the early-intensification group, 0.68% in the delayed-intensification group, and 0.20% in the no-intensification group (69). The study also showed a decreased rate of hypoglycemia in patients who received treatment with a GLP-1 receptor agonist, whereas patients in the no-intensification group had an increased rate of hypoglycemia. Total health care costs decreased in the early-intensification group, in contrast to an increase in total health care costs in the no-intensification group. These clinical and economic benefits further support early intervention to achieve glycemic targets.

In an attempt to achieve earlier therapy intensification, one study used a model of intervention called Stepping Up in the primary care setting to improve rates of glucose levels at target (70). The Stepping Up model of care included a practice nurse (a highly trained nurse who works along with a general practitioner) to lead the discussion with patients about intensifying treatment with insulin, simple clinical protocols for insulin initiation and titration, and finally mentoring by a registered nurse with diabetes educator credentials. The results of the study showed that, at the end of 1 year, 70% of the patients in the intervention group had started taking insulin, whereas only 22% of the patients in the control group had started taking insulin (70). Interventions such as this can play an important role in helping patients to meet glycemic targets by reducing therapeutic inertia. Many other strategies are being employed in attempts to combat therapeutic inertia. These strategies include digital apps and online coaching services for patients; innovations in diabetes care within health care systems; and new technologies, including automated insulin delivery systems and an FDA-approved software program using an artificial intelligence algorithm to analyze retinal camera images uploaded to a cloud server, which provides a screening decision without the need for a clinician to also interpret the image or results (71).

Summary

Therapeutic inertia is a common occurrence in the care of people with diabetes and impairs the ability of patients with diabetes to attain and maintain glycemic targets, which in turn increases risks for the development and progression of diabetes-related complications. Clinicians, patients, health systems, payers, and industry entities developing diabetes medications, devices, and other products all can play a role in reducing therapeutic inertia.

DUALITY OF INTEREST

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AUTHOR CONTRIBUTIONS

S.L.K., J.D., and S.P. researched data, wrote the manuscript, contributed to discussion, and reviewed/edited the manuscript. L.B. contributed to discussion and reviewed/edited the manuscript. S.L.K. is the guarantor of this work and, as such, had full access to all the references cited and takes responsibility for the integrity of the review and the accuracy of the data analysis.

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