

When to initiate renal replacement therapy: The trend of dialysis initiation

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Abstract

The timing of renal replacement therapy for patients

with end-stage renal disease has been subject to considerable variation. The United States Renal Data System shows an ascending trend of early dialysis initiation until 2010, at which point it decreased slightly for the following 2 years. In the 1990s, nephrologists believed that early initiation of dialysis could improve patient survival. Based on the Canadian-United States Peritoneal Dialysis study, the National Kidney Foundation Dialysis Outcomes Quality Initiative recommended that dialysis should be initiated early. Since 2001, several observational studies and 1 randomized controlled trial have found no beneficial effect when patients were placed on dialysis early. In contrast, they found that an increase in mortality was associated with early dialysis initiation. The most recent dialysis initiation guidelines recommend that dialysis should be initiated at an estimated glomerular filtration rate (eGFR) of greater than or equal to 6 mL/min per 1.73 m². Nevertheless, the decision to start dialysis is mainly based on a predefined eGFR value, and no convincing evidence has demonstrated that patients would benefit from early dialysis initiation as indicated by the eGFR. Even today, the optimal dialysis initiation time remains unknown. The decision of when to start dialysis should be based on careful clinical evaluation.

Key words: End-stage renal disease; Renal replacement therapy; Dialysis; Estimated glomerular filtration rate; Creatinine clearance; Survival

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Core tip: In the United States, the number of patients who were placed on dialysis early increased dramatically from 1996 to 2010 and then decreased slightly. To investigate the proper timing of renal replacement therapy (RRT), we reviewed the literature and found that the results from different studies were conflicting, so that the optimal time of dialysis initiation remained unknown. Early initiation of RRT may contribute to the

current high incidence of RRT. If properly delayed RRT initiation is demonstrated to be safe for patients, this strategy may reduce the high incidence of RRT.

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INTRODUCTION

Over the past 2 decades, the numbers of patients with uremia and patients who have received renal replacement therapy (RRT) have increased worldwide. At the same time, the percentage of patients who initiated dialysis early increased dramatically from 1996 to 2010^[1], which might have contributed to the high incidence of end-stage renal disease. RRT initiation can be intentionally delayed with careful monitoring. Delaying the initiation of RRT might be a strategy to reduce the incidence of RRT, if it is safe for patients. To investigate the effects of RRT timing on patient outcome, we conducted a literature review; we report its results in this paper.

RRT TRENDS

The early dialysis initiation trend

Twenty years ago, dialysis was not initiated until patients had life-threatening or severe symptoms of uremia. Emergency dialysis was needed for resistant hyperkalemia, with the emergence of metabolic acidosis. In 1995, Hakim *et al.*^[2] identified the indicators for RRT initiation: Patients with pericarditis, fluid overload, pulmonary edema, hypertension, advanced uremic encephalopathy, clinically significant coagulopathy, persistent and severe nausea and vomiting and who were poorly responsive to drug therapy should be placed on RRT immediately. If conservative non-dialysis management was ineffective for the following manifestations, the initiation of RRT was also suggested: (1) a general but fairly severe decline in quality of life (QOL), including vomiting, resistance and severe pruritus; and (2) decreased attentiveness, memory, cognitive abilities and depression that could affect the interpersonal relationships of the patient.

Hakim's standard was mainly based on clinical symptoms, and the timing of RRT initiation was apparently late. The point at which dialysis is initiated should be neither too late nor too early. If dialysis is started too late, patients risk the complication of uremia, which leads to low QOL and a higher risk of mortality. Dialysis is not a physiological process. As such, It (1) places the patient under the dangers of complications related to the RRT process; (2) accelerates the reduction of endogenous renal function^[3], especially for elderly or frail patients with high rates of comorbidities; and

(3) provokes or aggravates depression and other psychosocial problems. All of the above conditions correlate with an increased risk of mortality^[4,5].

In the 1990s, the initiation of early dialysis was determined by the estimated glomerular filtration rate (eGFR), in accord with a Modification of diet in renal disease (MDRD) equation; the criterion was an eGFR greater than or equal to 10 mL/min per 1.73 m². Many researchers in the academy thought that early dialysis initiation would improve patient QOL and patient survival by reducing the complication of dystrophy. Furthermore, it was also believed that a decreased glomerular filtration rate GFR at dialysis initiation was associated with an increased probability of hospitalization and death^[6-9]. They held the idea that early dialysis initiation was indispensable for preventing and reversing the deteriorated nutritional status associated with progressive uremia. The National Dialysis Cooperative Study^[9] introduced the Kt/V_{urea} metric as a predictor of morbidity and mortality. Then, in 1996, the Canadian-US Peritoneal Dialysis (CANUSA) study^[10] recommended a potential renal survival benefit of a weekly Kt/V_{urea} of greater than 2.0 [peritoneal creatinine clearance (CC) of > 70 L per 1.73 m²]. This threshold is equivalent to a CC of 9-14 mL/min per 1.73 m². Based on the CANUSA study, the National Kidney Foundation Dialysis Outcomes Quality Initiative hemodialysis Adequacy Guideline (1997)^[11] recommended that dialysis be initiated when the GFR decreased to 10.5 mL/min per 1.73 m² unless the normalized protein nitrogen appearance was more than 0.8 g/kg and the patient had a stable weight and a good appetite. Since then, the majority of national and international guidelines have promoted early dialysis for patients with deteriorating nutritional status and with symptoms or co-morbidities^[12]. The Canadian Society of Nephrology (CSN) (1999)^[13] suggested that dialysis be initiated when eGFR less than 12 mL/min per 1.73 m² in the presence of uremia symptoms or malnutrition. In the meantime, the indicator for dialysis initiation changed from the Kt/V_{urea} to the eGFR. The European Renal Best Practice (ERBP) (2002)^[14] advocated for closer supervision of high-risk patients (those with eGFR < 15 mL/min per 1.73 m² plus symptoms and signs, the inability to control hydration status or blood pressure, and progressive nutritional status deterioration). High-risk patients, such as diabetics, may benefit from an earlier start. In 2006, the Kidney Dialysis Outcomes Quality Initiative (KDOQI)^[15] updated these guidelines and suggested that RRT be considered when eGFR of < 15.0 mL/min per 1.73 m². Particular clinical considerations and certain characteristic complications may prompt the initiation of therapy before the onset of end-stage renal disease (ESRD). When the eGFR is greater than 15.0 mL per minute, RRT may also be warranted for patients with coexisting conditions such as diabetes or with symptoms of uremia.

All of the studies and guidelines mentioned above support early dialysis, and they have all been promoted

Table 1 Study and recommendations that support early dialysis initiation

Study/recommendations	Year	Time/eGFR (mL/min per 1.73 m ²)	Journal
CANUSA study	1996	9 to 14	<i>J Am Soc Nephrol</i>
NECOSAD study	2001	No beneficial effect of earlier dialysis initiation	<i>Lancet</i>
NKF-DOQI	1997	10.5	<i>Am J Kidney Dis</i>
CSN	1999	< 12	<i>J Am Soc Nephrol</i>
KDOQI	2006	< 15.0	<i>Am J Kidney Dis</i>

eGFR: Estimated glomerular filtration rate.

as conventional wisdom (CW)^[2,9,12]. The CW can be summarized as follows: (1) low levels of dialytic and endogenous renal clearance are associated with improved morbidity and mortality; (2) nutrition can be improved with the early initiation of dialysis; (3) dialysis should be initiated earlier in diabetics than in nondiabetics; and (4) dialysis initiated at eGFRs below 6 mL/min per 1.73 m² is potentially dangerous.

The trend toward early initiation of dialysis can also be seen internationally. According to the United States Renal Data System (USRDS)^[1], with the eGFR calculated using the chronic kidney disease epidemiology calculation (CKD-EPI equation) (CKD-EPI eGFR, mL/min per 1.73 m²), the percentage of ESRD patients who started RRT at higher eGFR levels increased steadily from 1996 until 2010. In 1996, 9.48% of patients initiated RRT with an eGFR of 10–14.9 mL/min per 1.73 m², and only 3.01% had an eGFR > 15 mL/min per 1.73 m². In 2010, these percentages had more than doubled (to 27.85% and 14.71%, respectively). This phenomenon was more prominent in the elderly dialysis population. The percentage of incident ESRD patients who started dialysis at an eGFR < 5 mL/min per 1.73 m² decreased from 34.4% in 1996 to 12.6% in 2010^[1]. In Beijing, the percentage of patients who initiated hemodialysis with an eGFR > 10 mL/min per 1.73 m² rose gradually from 13.2% to 20.7% between 2007 and 2010^[16]. In Europe^[17], dialysis initiation when eGFR > 10.5 mL/min per 1.73 m² had risen from 16.4% to 23.6% between 1999 and 2003. The United Kingdom Renal Registry data^[18] showed that, between 1997 and 2010, the mean eGFR at dialysis initiation increased from 6.2 to 8.7 mL/min per 1.73 m². In data from the Canadian Organ Replacement Registry^[19], the percentage of patients who started peritoneal dialysis at an eGFR > 10.5 mL/min per 1.73 m² rose from 29% (95%CI: 26%–32%) to 44% (95%CI: 41%–47%) between 2001 and 2009. The average eGFR at dialysis initiation increased from 9.3 ± 4.6 to 10.7 ± 6.1 mL/min per 1.73 m² (Figure 1 and Table 1).

Studies and recommendations that support late dialysis initiation

Recently, certain registry and observational studies that included a total of > 900000 analyzable patients all demonstrated that late dialysis initiation was associated

with improved survival^[14,20].

The Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)^[21] showed that, though not significant (adjusted HR = 1.66; 95%CI: 0.95–2.89), the early group (which was initiated according to the first KDOQI guidelines) gained an estimated survival benefit of 2.5 mo vs late starters after 3 years of dialysis. In the NECOSAD study, the eGFR was calculated from timed urine collections (as the mean of urea and CC). However, there was a delay of at least 4.1 mo before dialysis initiation in the late-start group^[21]. After taking the lead time bias (discussed below) into account, there was no beneficial effect of earlier dialysis initiation. In 2002, Traynor *et al*^[22] also found that there was no significant survival benefit from earlier initiation of dialysis and that patients who started dialysis with a lower estimated CC survived longer. More recent observational data^[17,23–34] found a comorbidity-adjusted survival disadvantage for early dialysis initiation, as 12 studies found an increase in mortality associated with early dialysis initiation. Beddhu *et al*^[23] found that for each 5 mL/min increase of the MDRD eGFR, the associated risk of death was 27% higher (HR = 1.27; *P* < 0.001). However, this phenomenon was not observed for the CC value. In a Chinese study in Taiwan^[29], the median eGFR level at dialysis initiation was 4.7 mL/min per 1.73 m² from July 2001 to December 2004 in > 23000 incident patients. Based on the eGFR level at dialysis initiation, patients were divided into quintiles, and the best survival was observed at < 3.29 mL/min per 1.73 m². In another report, the best survival was achieved in patients with eGFRs of between 0 and 5 mL/min per 1.73 m² among American subjects. This study included 81176 uremic subjects, aged 20–64 with no substantial comorbidities other than hypertension, from the USRDS dataset^[27]. In 2012, Yamagata *et al*^[31] analyzed 20854 patients who had started RRT in 1989 and 1990 and found that the timing of RRT initiation had no impact on the long-term prognosis after adjustments were made for co-morbid conditions. In 2014, Crews *et al*^[33] found that, compared with patients who started at a lower eGFR, patients with early dialysis initiation at an eGFR ≥ 10 mL/min per 1.73 m² showed greater mortality and more frequent hospitalization, even after adjusting for comorbid conditions. In 2014, a study of 310932 patients who had started dialysis between 2006 and 2008^[32] demonstrated that no harm or benefit was associated with early dialysis initiation. A meta-analysis of cohort studies and trials by Susantitaphong *et al*^[34] found that a 1 mL/min per 1.73 m² increase in the GFR at dialysis initiation was associated with 3%–4% higher all-cause mortality after adjustment for comorbid conditions.

Possible explanations for the conflicting results

Previous studies provide reproducible evidence that dialysis initiation with higher eGFR is associated with increased mortality. However, these studies also have

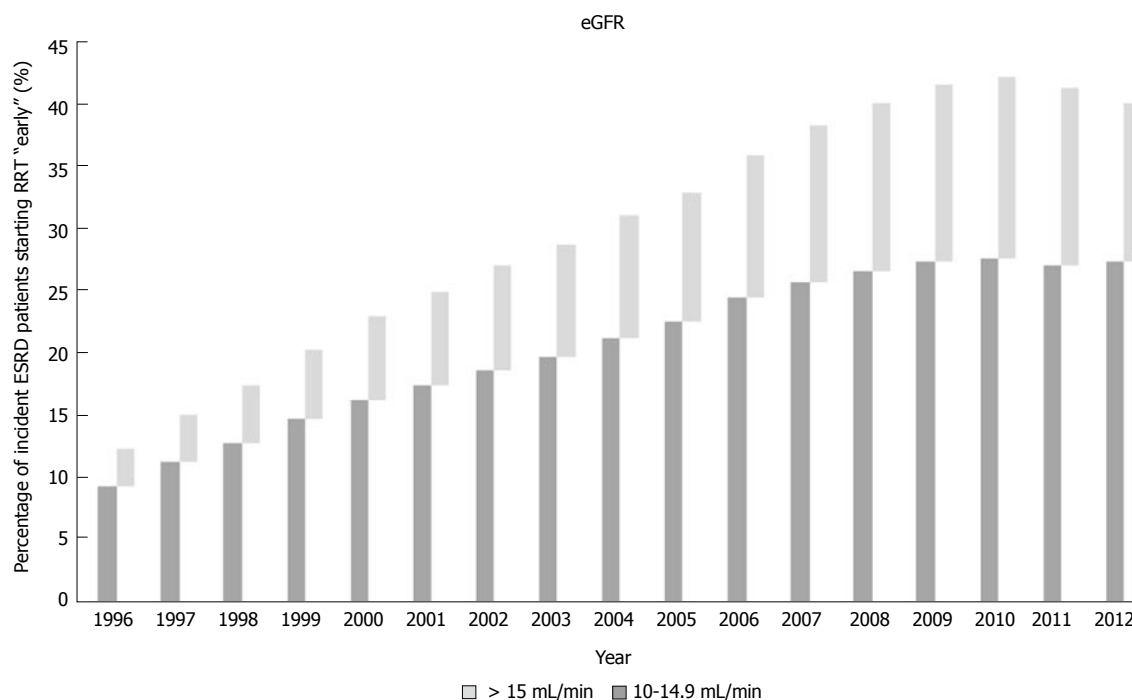


Figure 1 Percentage of patients initiating renal replacement therapy “early” in the United States during the years 1996-2012. Data from the United States Renal Data system. eGFR calculated using the CKD-EPI equation [CKD-EPI eGFR (mL/min per 1.73 m²)]. ESRD: End-stage renal disease; eGFR: Estimated glomerular filtration rate.

shortcomings. The limitations of the prior studies are discussed below.

Inaccurate eGFR values

The decision to initiate RRT has relied heavily on the eGFR^[12]. The ERBP^[23] concluded that creatinine-based measures of the eGFR in pre-dialysis patients were fundamentally flawed and were thus invalid. In studies using GFR measures that were based on 24-h urine urea and/or creatinine clearance, the adverse effect of early initiation was not found. The MDRD equation accounts for the average loss of muscle over time with age (sarcopenia) but does not account for unusual body habitus or diet. In other words, the MDRD equation may be erroneous for patients with ESRD. Craig *et al.*^[35] concluded that, when compared with the reference standard radionuclide GFR (rGFR), the MDRD equations performed poorly in patients with advanced renal failure, while the Cockcroft-Gault (CG) equation showed a smaller bias and was more accurate. In this study, an intravenous injection of 51Cr-EDTA (3 MBq) was used for the measurement of rGFR, and plasma samples were taken approximately 120 and 240 min later. The study recommended using the CG equation when the rGFR method is unavailable. It must be kept in mind that the differences between the GFR methods may greatly influence the decision for RRT initiation^[36].

There are possible explanations for falsely overestimated eGFR. First, patients with low muscle mass due to inactivity or malnutrition have a lower creatinine generation rate, which would overestimate the true residual renal function (RKF). Second, fluid overload

would dilute patient serum creatinine levels. All such patients would have higher co-morbidity rates and lower serum creatinine levels. The serum creatinine-based eGFR might overestimate the true GFR in the above patients and thus risk including such patients in the “earlier” start groups^[14] when they should in fact start late.

Elderly or frail patients were more likely to start dialysis early

Patients with symptoms or co-morbidities were more likely to be started on dialysis early. The multivariate adjustment for co-morbidities indeed decreased the benefit of initiating dialysis with a low eGFR, but the effects did not disappear. The most common reason to initiate dialysis early was a nutritional decline. Compared with nondiabetic dialysis patients, the association of an early start with higher mortality was much stronger among patients with diabetes^[26]. It was confirmed that patients with low comorbidity burdens showed reduced survival compared to higher starting eGFR values^[17,22-27,29].

Lead time bias

Unfortunately, the studies that support early dialysis initiation fail to take the effect of the lead time bias into consideration. The lead time bias is related to the initiation time of treatment within the duration of the disease. The prolonged survival may be due merely to earlier diagnosis and treatment. Alternatively, it may be expected that earlier disease detection would be correlated with longer survival. After eliminating the

effect of the lead time bias, the NECOSAD study^[21] demonstrated that there was no beneficial effect of earlier dialysis initiation.

High-risk patients may die before dialysis initiation in the late group

Some studies only included patients who actually started dialysis. Those who died before dialysis had been initiated (possibly because of uremia) were excluded. In other words, the late-start subjects may not suffer from severe disease who died before the initiation of dialysis. Only the fittest patients who survived long enough were included in the late-start groups.

Treatment time on RRT

Mortality might be a result of "insufficient" dialysis. Long treatment times (> 4 h per session) and more frequent dialysis sessions reduced the risk of low albumin, which is correlated with decreased mortality^[37,38].

Cardiovascular comorbidities and infection

Early-dialysis patients were more likely to die in the hospital. Compared with patients who underwent conservative management, patients who underwent dialysis expected longer days in the hospital and were more likely to die in the hospital, especially when debilitated, frail, or elderly^[39]. In the first year of hemodialysis, deaths were mainly due to cardiovascular disease and infection^[1]. The all-cause mortality, cardiovascular disease mortality, and mortality due to other causes peaked in month 2 and then decreased thereafter^[13]. Dialyzed patients had twice the rate of sudden death, which was connected with ultrafiltration volumes, decreased blood pressure, lower Kt/V_{urea}, and low potassium concentrations^[40]. Cardiovascular disadvantages can also appear when accompanied with life-threatening diseases such as pulmonary edema. The risk of infection was associated with the modality and access type. In a study of 55 inpatients who underwent tunneled hemodialysis catheter (TDC) removals, 36.4% had proven bacteremia, 41.8% had a fever and 20% had clinical signs of sepsis with hemodynamic instability or respiratory failure^[41]. The risk of TDC is thus apparent. Once a patient has started dialysis, the risks of all forms of infection are much higher, and the patient is more likely to have septicemia, which is especially prevalent among elderly patients.

The IDEAL study

The randomized controlled trial of early vs late initiation of dialysis (IDEAL) study^[42] showed no difference in mortality between the early and late groups. The early group was expected to start dialysis when the CC (calculated with the CG equation) was 10-14 mL/min per 1.73 m², and the late group was expected to start dialysis at 5-7 mL/min per 1.73 m². It was allowed to start dialysis based on clinical indications, disregardfulness CC in either group. The average CC values were 12.0 and 9.8 mL/min per 1.73 m² at the

time of dialysis initiation in the early and late groups, respectively. Compared with the early group, the late group showed a 6-mo delay in initiation. However, 76% of the patients who were allocated to the late group actually commenced dialysis with a higher CC, and the mean difference in the estimated GFR between the late and early groups was only 2.2 mL/min. The gap between the 2 groups was too small to generate a difference in the mortality rates. However, for some patients, who started RRT after their eGFR values dropped below 5-7 mL/min per 1.73 m², no harm was detected. In other words, initiating dialysis late might be safe for some patients with fluid overload or other accompanying complications if they are carefully monitored.

Recommendations that support late dialysis

Notably, most patients are symptomatic and need to be dialyzed in a GFR range of 6-9 mL/min per 1.73 m². Many guidelines, including the ERBP 2002^[14], the Australia 2005^[43] and the United Kingdom 2009^[44], recommend that RRT should be initiated before the GFR reaches 6 mL/min per 1.73 m². The ERBP 2002^[14] recommends that dialysis preparation should be initiated at a GFR of 8 mL/min per 1.73 m² and that dialysis must be initiated at a GFR of 6 mL/min per 1.73 m². Caring for Australians with Renal Impairment (2005)^[43] recommends that dialysis should be initiated when the GFR is less than 10 mL/min per 1.73 m² if symptoms of uremia or complications such as malnutrition are present or when the GFR is less than 6 mL/min per 1.73 m² in the absence of symptoms or complications. The United Kingdom Renal Association 2009^[44] recommends RRT initiation when the eGFR is less than 6 mL/min per 1.73 m², even if the patient is asymptomatic. The 2012 Kidney Disease Improving Global Outcomes^[45] suggests that dialysis should be initiated when the eGFR is approximately 5-9 mL/min per 1.73 m². The CSN 2014 clinical practice guidelines^[46] suggest that chronic dialysis should be initiated when the eGFR drops to 6 mL/min per 1.73 m², even if there are no clinical indications. However, the existing guidelines do not specify a dialysis initiation point (with respect to eGFR or serum creatinine level). In the USRDS^[1], the percentage of incident ESRD patients who began RRT at higher eGFR levels decreased slightly in 2011 and again in 2012. The percentage of patients who began RRT at an eGFR \geq 10 mL/min per 1.73 m² decreased from 42.6% in 2010 to 40.5% in 2012, and the percentage of patients who initiated RRT at an eGFR < 5 mL/min per 1.73 m² rose from 12.6% in 2010 to 13.7% in 2012 (Table 2).

CONCLUSION

There is still considerable doubt with respect to the optimal timing of dialysis initiation in uremic populations. The timing of dialysis is often affected by multiple factors, including age, diabetes mellitus, individual desire, socioeconomic status, personal beliefs, and

Table 2 Study and recommendations that support late dialysis initiation

Ref./ recommendations	Year	Time/eGFR (mL/min per 1.73 m ²)	Journal
Beddhu <i>et al</i> ^[23]	2003	5-mL/min increase of the associated risk of death was 27% higher	<i>J Am Soc Nephrol</i>
Chinese Taiwan study	2010	< 3.29	<i>Nephrol Dial Transplant</i>
Rosansky <i>et al</i> ^[27]	2011	Between 0 to 5	<i>Arch Intern Med</i>
Yamagata <i>et al</i> ^[31]	2012	No difference	<i>Ther Apher Dial</i>
Crews <i>et al</i> ^[33]	2014	< 10	<i>J Am Soc Nephrol</i>
Susantitaphong <i>et al</i> ^[34]	2014	1 mL increase 3%-4% higher all-cause mortality	<i>Am J Kidney Dis</i>
Scialla <i>et al</i> ^[32]	2014	No difference	<i>Kidney Int</i>
ERBP	2002	8, and to be sure at 6	<i>Nephrol Dial Transplant</i>
Australia	2005	Evidenced symptoms or complications: < 10, no symptoms or complications < 6	
United Kingdom	2009	< 6	
K/DIGO	2012	5-9	
CSN	2014	< 6	<i>CMAJ</i>

eGFR: Estimated glomerular filtration rate.

the patient's cultural and educational background. Initiating dialysis early based solely on a single objective measurement (specific level of GFR) can be harmful. Most patients begin dialysis because of renal failure-related symptoms. Importantly, dialysis therapy is not innocuous, and it does not replace all the functions of the kidney. Compared with patients who received dialysis, the native Kt/V_{urea} of an able-bodied man is more than 15-fold higher. Some scholars believe that the biggest advantage of dialysis is the alleviation of fluid overload. Thus far, we lack validated and objective measures of the uremic state that could be used to guide the timing of dialysis initiation. Currently, the established guidelines for the timing of dialysis are based on the conclusions of many observational studies. Data from randomized controlled trials that establish optimal timing for RRT are lacking. The time at which dialysis is initiated must be individualized, and further studies are required to explore a comprehensive, systematic dialysis index that is associated with the GFR, with symptoms, and with assumed indications for dialysis initiation.

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