Original Article

Korean J Health Promot 2022;22(1):40-47 • pISSN: 2234-2141 • eISSN: 2093-5676
http://dx.doi.org/10.15384/kjhp.2022.22.1.40

당뇨 환자의 메트포민 복용과 암 발생 억제 효과: 불멸의 시간 편향 통제를 중심으로

서화정

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Effect of Immortal Time Bias Controlled Metformin for Cancer Development in Diabetic Patients

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Background: This study aimed to determine the effectiveness of metformin as first line oral hypoglycemic agent in diabetes patients in inhibiting cancer incidence, on the basis of the sample cohort supplied by the National Health Insurance Service, and to ascertain the effects of time-related bias on the results.
Methods: A *t*-test was performed to compare the time taken for cancer development between the compliant and non-compliant metformin users and the non-metformin users. Survival analyses for cancer patients, regarding the period time until cancer incidence, were performed according to metformin use through three models: model 1 adjusted for age and sex; model 2 further adjusted for body mass index, cholesterol, and smoking status; and model 3 further adjusted for hypertension.
Results: The odds ratio for cancer development was 1.11 times higher for the non-metformin users (6,997) than for the metformin compliant users (16,132), which was significant at the 0.1 significance level. The age, sex, body mass index, cholesterol, smoking status, and hypertension-adjusted hazard ratio was 0.86.
Conclusions: This study has confirmed that metformin is effective in delaying cancer development for patients at risk of cancer rather than in inhibiting cancer incidence itself, by strict application of metformin exposure, with which immortal time biases are controlled. It is therefore necessary to manage compliance with an agent, as well as to prescribe metformin for patients at high risk of cancer, giving consideration to the risk factors for cancer development (old age, being male) instead of focusing on metformin prescription, with the objective of inhibiting cancer development.
Korean J Health Promot 2022;22(1):40-47

Keywords: Diabetes mellitus, Neoplasms, Medication adherence, Selection bias, Cohort studies

INTRODUCTION

The methods of controlling blood glucose for diabetics include the correction of lifestyles based on diet control, exercise prescription, oral hypoglycemic agent (OHA) medication, and insulin therapy.[1] The possible agents for OHA monotherapy include metformin, sulfonylurea, dipeptidyl peptidase-4 (DPP-4) inhibitors, and thiazolidinedione (TZD).

■ Received: Dec. 13, 2021 ■ Revised: Feb. 11, 2022 ■ Accepted: Feb. 15, 2022
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■ This study was supported by Gachon University and Gil Hospital (FRD2017-09-02) and funded by the Ministry of Science, ICT & Future Planning (NRF-2017R1A2B4006545).

Of these, metformin has been found to be more effective in many ways than sulfonylurea or TZD.[2] A great deal of research has recently been conducted on the effectiveness of metformin in inhibiting cancer incidence for diabetics.[3-7] Mechanism of action of metformin in cancer focuses on inhibiting growth stimuli and metabolic processes within cancer cells, and in altering cancer cell growth.[8] The metformin users had a lower hazard ratio (HR) for cancer incidence than the non-metformin users. HR for cancer incidence was very low: 0.83 for breast cancer,[9] 0.38 for pancreatic cancer,[10] and 0.68 for colon cancer.[3] Reportedly, the cancer-related hospitalization rate for type 2 diabetes patients was 2-7 times as high as for the non-diabetic patients in South Korea.[11]

As regards the OHA combination therapy used by diabetics, its effectiveness in inhibiting cancer incidence is a crucial theme in this research. However, if the subjects not exposed to the agent are categorized into the exposure group and vice-versa, distorted results could ensue. In an observational study using cohort data, several biases related to time are likely to affect results.[12] In particular, for the purpose of evaluating the effects of an agent, it is most of all important to accurately define the exposure of subjects to the agent. The validity of cohort research can depend heavily on how the likelihood of having these biases occur is controlled. The results of the existing research disadvantageously failed to reflect the duration of exposure to an agent or to correct compliance with it due to the characteristics of the claim data for South Koreans covered by the National Health Insurance and the healthcare beneficiaries.[13]

This study is conducted in the following ways: first, it uses cohort data concerning large claims for health insurance; second, it strictly applies the minimum dosage period for categorization into the agent exposure group to remove the effects of the definition of compliance with the agent on time biases; and third, it analyzes the differences in cancer incidence between the metformin users and the non-metformin users while the biases are controlled. By doing this, the likelihood of time biases from the cohort study is removed, making the procedure more valid.

METHODS

1. Data collection

This study used sample cohort data supplied by the National Health Insurance Service (NHIS). The NHIS sample cohort includes data concerning health insurance claims for approximately 1 million persons, which make up 2% of the whole nation. Participants were included in the study on the date of their first health screening examination (baseline examination). This study then excluded participants who had claims for cancer between January 1, 2002 and the baseline screening examination.[14]

2. Criteria and definitions

1) Immortal time bias

"Immortal time" is the follow-up period during which, in some studies, the outcomes of interest cannot occur.[15] Immortal time bias is an error that can frequently occur in a cohort observational study when the period of failing to be exposed to the agent is classified as that of being exposed to it. The determinants of immortal time bias are definition of exposure (to the agent) and index date setting. Analysis performed after simply removing immortal time bias can lead to selection bias because it results in a different time for cohort entry from the non-exposure group.[16] In the drug effectiveness literature, various cohort designs may result in immortal time bias.[17]

To avoid any immortal time bias, it is necessary to control the effects of biases by removing the period in which the target results cannot be obtained: immortal time. The medication possession ratio (MPR) was used to control immortal time biases. The MPR is used to determine if a pa-

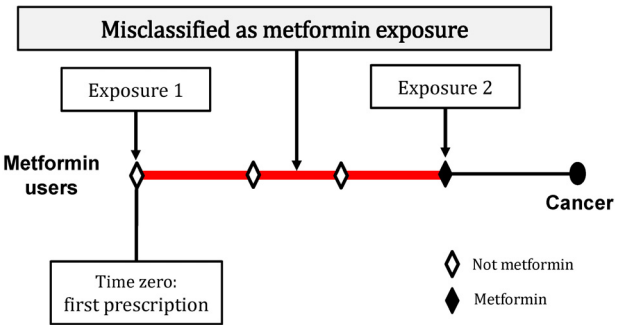

Figure 1. Immortal time bias controlled model.

tient has continued to take full medication by estimating the ratio of the number of prescription days to the reference period (Figure 1).[18]

2) Metformin users (compliant and non-compliant patients) and non-metformin users

In this study, the patients continuously taking metformin (including when OHA such as sulfonylureas, TZD, and DPP-4 inhibitors were prescribed together, not metformin alone) for 80% of 180 prescription days over one year after the first prescription, which is the reference for full exposure to the agent, were regarded as compliant metformin users. Those taking it for <80% of 180 prescription days were regarded as non-compliant metformin users. Those who were not using any dose of metformin were regarded as non-metformin users, forming the control group.

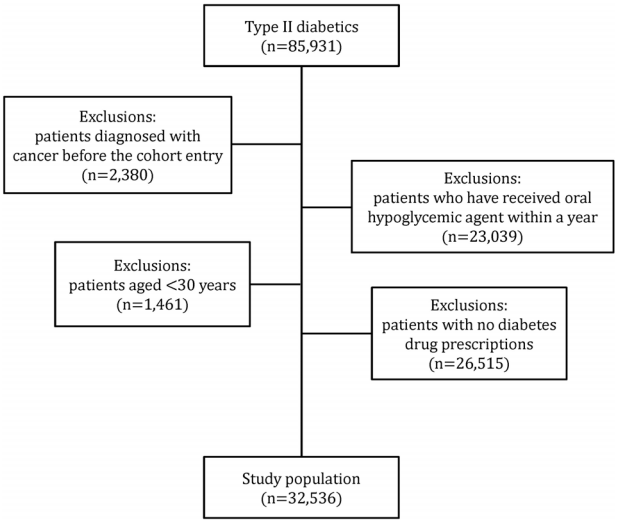

Figure 2. Flow diagram of study population selection.

3. Study design

The diabetics in this study were patients with a fasted blood glucose ≥126 mg or a (primary) disease code of E10-E14 and who had prescription of an anti-diabetes agent and ≥4 claims for a (secondary) disease code of E10-E14 on an annual basis. Newly diagnosed patients were defined as those who had never received prescription of any other OHA within a year after the first prescription and had no claim for diabetes-related disease codes (Figure 2). Patients with type 1 diabetes diagnosed with cancer before the cohort entry were excluded from the research. To reduce errors that could result from the differences in age and anti-diabetes medication, patients aged <30 years at the time of cohort entry were excluded from the analysis. Finally, 32,536 out of 85,931 patients were included in the study.

Table 1. Characteristics of the study population

	Metformin			
	Yes		No	Total
	MPR ≥80%	MPR <80%	MPR=0%	
Sex				
Male	8,784 (49.5)	5,212 (29.4)	3,758 (21.2)	17,754 (54.6)
Female	7,348 (49.7)	4,195 (28.4)	3,239 (21.9)	14,782 (45.4)
Age, y				
<65	13,205 (57.9)	7,556 (33.1)	2,044 (0.9)	22,805 (70.1)
≥65	2,927 (30.1)	1,851 (19.0)	4,953 (50.9)	9,731 (29.9)
Cancer diagnosis				
No	15,187 (49.7)	8,879 (29.0)	6,504 (21.3)	30,570 (94.0)
Yes	945 (48.1)	528 (26.9)	493 (25.1)	1,966 (6.0)
Insulin				
No	15,388 (50.1)	8,993 (29.3)	6,362 (20.7)	30,743 (94.5)
Yes	744 (41.5)	414 (23.1)	635 (35.4)	1,793 (5.5)
Total	16,132 (49.6)	9,407 (28.9)	6,997 (21.5)	32,536 (100.0)

Values are presented as number (%).
Abbreviation: MPR, medication possession ratio.

4. Statistical analysis

Frequency analysis was performed to determine the characteristics of subject distribution, whereas mean analysis and *t*-test were carried out to compare the time taken for cancer development between the compliant and non-compliant metformin users and the non-metformin users.

A logistic regression model was used to measure the relative impact of the predictors of cancer development and the risk of cancer by metformin use. Cox regression analysis was performed to determine the effects of metformin use on time taken for cancer incidence, taking into account age and sex (model 1), as well as such checkup factors as body mass index (BMI), cholesterol, and smoking status (model 2), with hypertension added (model 3). All analyses were conducted by using R version 4.2 (R Core Team, Vienna, Austria) statistical software.

RESULTS

1. Participant characteristics

The general characteristics of the participants are presented in Table 1. In Table 1, 25,539 patients (78.5%) took at least one dose of metformin (compliant patients with a MPR ≥80% and non-compliant patients with an MPR <80%) and 6,997 (21.5%) did not take any dose of metformin. Seventeen thousand seven hundred fifty-four patients (54.6%) were male and 14,782 (45.4%) were female; 22,805 (70.1%) were aged <65 years; 1,966 (6.0%) were diagnosed with cancer; and 1,793 (5.5%) received insulin prescription (Table 1).

Table 2. Period from first prescription to cancer diagnosis

Group	Mean	Std. Err	Std. Dev	95% CI	*P*
Metformin (≥80%)	2,148.06	22.72	698.45	2,103.47 to 2,192.65	
Metformin (<80%)	2,096.62	31.00	712.43	2,035.72 to 2,157.53	
Metformin none	1,827.73	38.40	852.67	1,752.28 to 1,903.18	
MD (≥80% vs. <80%)	51.43			-23.99 to 126.86	0.180
MD (≥80% vs. none)	320.33			232.75 to 407.91	<0.001
MD (<80% vs. none)	268.89			172.04 to 365.75	<0.001

Abbreviatons: CI, confidence interval; MD, mean difference; Std. Dev, standard deviation; Std. Err, standard error.

Table 3. Factors associated with cancer development in model with uncontrolled bias (metformin; never vs. ever)

	Cancer development		OR (95% CI)	*P*
	Yes	No		
Age at diagnosis, y				
<65	1,269 (64.5)	24,445 (80.0)	2.39 (2.23-2.57)	<0.001
≥65	697 (35.5)	6,125 (20.0)	1 (ref.)	
Sex				
Male	1,222 (62.2)	16,532 (54.1)	1.62 (1.51-1.73)	<0.001
Female	744 (37.8)	14,038 (45.9)	1 (ref.)	
Insulin				
Yes	122 (6.2)	1,671 (5.5)	1.09 (0.95-1.25)	0.371
No	1,844 (93.8)	28,899 (94.5)	1 (ref.)	
Medication compliance				
Metformin				
Never	493 (25.1)	6,504 (21.3)	1.12 (1.04-1.21)	0.043
Ever	1,473 (74.9)	24,066 (78.7)	1 (ref.)	

Values are presented as number (%) unless otherwise indicated.
Abbreviations: CI, confidence interval; OR, odd ratio; ref., reference.

2. Onset of cancer in diabetic patients

Time taken for cancer development was investigated in the group diagnosed with cancer (n=1,996): metformin compliant patients, non-compliant patients, and non-metformin users (Table 2). After the first prescription, the compliant patients took an average of 2,148 days (95% confidence interval [CI], 2,103.47-2,192.65), the non-compliant patients took an average of 2,096 days (95% CI, 2,035.72-2,157.53), and the non-metformin users took an average of 1,827 days (95% CI, 1,752.28-1,903.18). The mean difference was 320 days between the compliant and the non-metformin patients (95% CI, 232.75-407.91; *P*<0.001) and 268 days between the non-compliant and the non-metformin patients (95% CI, 172.04-365.75; *P*<0.001).

3. Risk factors for cancer development

Logistic regression analysis was performed for comparison of the risk of cancer development by metformin use. In model with uncontrolled bias, a comparative analysis of the risk of cancer development was performed between the metformin users (ever) and the non-metformin users (never). In model with controlled bias, a comparative analysis of the risk of cancer development was performed between the compliant patients (≥80%) and the non-metformin users. Age, sex, and insulin injection were considered as controlling factors.

The analysis in model with uncontrolled bias found that age and sex affected cancer development/diagnosis (Table 3). The odds ratio for cancer incidence was 2.39 times higher for the patients aged <65 than for those aged ≥65 (95% CI,

Table 4. Factors associated with cancer development in model with uncontrolled bias (metformin; MPR ≥80% vs. MPR=0%)

	Cancer development		OR (95% CI)	*P*
	Yes	No		
Age at diagnosis, y				
<65	933 (64.9)	17,255 (79.4)	2.24 (2.07-2.43)	<0.001
≥65	505 (35.1)	4,466 (20.6)	1 (ref.)	
Sex				
Male	891 (62.0)	11,651 (53.7)	1.58 (1.47-1.72)	<0.001
Female	547 (38.0)	10,040 (46.3)	1 (ref.)	
Insulin				
Yes	177 (12.3)	1,284 (5.9)	1.08 (0.93-1.26)	0.495
No	1,261 (87.7)	20,407 (94.1)	1 (ref.)	
Medication compliance				
Metformin				
MPR=0%	493 (34.3)	6,504 (30.0)	1.11 (1.02-1.20)	0.092
MPR ≥80%	945 (65.7)	15,187 (70.0)	1 (ref.)	

Values are presented as number (%) unless otherwise indicated.
Abbreviations: CI, confidence interval; MPR, medication possession ratio; OR, odd ratio; ref., reference.

Table 5. Hazard ratios (HRs) for incident cancer associated with diabetes

Parameter	Case	Model 1		Model 2		Model 3	
		HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Metformin							
MPR=0%	6,997 (30.25)	1 (ref.)		1 (ref.)		1 (ref.)	
MPR ≥80%	16,132 (69.75)	0.797 (0.71-0.89)	<0.001	0.853 (0.73-0.99)	0.044	0.860 (0.74-0.99)	0.045

Values are presented as number (%) unless otherwise indicated.
Model 1: adjusted for age (<65 or ≥65) and sex (female or male); model 2: further adjusted for body mass index (continuous), cholesterol (continuous), smoking (never, past, and now); model 3: further adjusted for hypertension (ever or never).
Abbreviations: CI, confidence interval; MPR, medication possession ratio; ref., reference.

2.23-2.57; P<0.001) and 1.62 times higher for men than for women (95% CI, 1.51-1.73; P<0.001). The odds ratio for cancer incidence was 1.12 times higher for the non-metformin users than for the metformin users (P=0.043), which was significant at the 0.05 significance level.

The analysis in model with controlled bias shows that age and sex affected cancer incidence/diagnosis (Table 4). The odds ratio for cancer development was 2.24 times higher for patients aged <65 than for those aged ≥65 (95% CI, 2.07-2.43; P<0.001) and 1.58 times higher for men than for women (95% CI, 1.47-1.72; P<0.001). The odds ratio for cancer development was 1.11 times higher for the non-metformin patients than for the metformin compliant patients (P=0.092), which was insignificant at the 0.05 significance level but significant at the 0.1 significance level.

Cox regression analysis was performed to determine the effects of metformin use (>80%) on the time taken for cancer incidence among 1,966 cancer patients, of which 945 were compliant patients and 493 were non-metformin patients. The age and sex adjusted HR (model 1) was 0.797 (95% CI, 0.71-0.89). The age, sex, BMI, cholesterol, and smoking status adjusted HR (model 2) was 0.853 (95% CI, 0.73-0.99). The fully adjusted HR (model 3) was 0.860 (95% CI, 0.74-0.99) (Table 5). Table 6 shows the HR for each variable adjusted for model 1, model 2, and model 3.

Table 6. Details of hazard ratios for incident cancer associated with diabetes

Variable	HR (95% CI)	P
Model 1		
Age (<65 years)	1.000	
Age (≥65 years)	1.003 (0.90-1.12)	0.955
Metformin (no)	1.000	
Metformin (yes)	0.797 (0.71-0.89)	<0.001
Sex (female)	1.000	
Sex (male)	1.068 (0.96-1.19)	0.224
Model 2		
Age (<65 years)	1.000	
Age (≥65 years)	0.991 (0.85-1.15)	0.908
Metformin (no)	1.000	
Metformin (yes)	0.853 (0.73-0.99)	0.044
Sex (female)	1.000	
Sex (male)	1.030 (0.89-1.18)	0.333
BMI	1.010 (0.99-1.03)	0.345
Cholesterol	1.010 (1.00-1.01)	0.030
Smoke (never)	1.000	
Smoke (past)	0.940 (0.75-1.19)	
Smoke (now)	0.880 (0.73-1.07)	0.447
Model 3		
Age (<65 years)	1.000	
Age (≥65 years)	0.980 (0.86-1.15)	0.806
Metformin (no)	1.000	
Metformin (yes)	0.860 (0.74-0.99)	0.045
Sex (female)	1.000	
Sex (male)	1.090 (0.88-1.17)	0.319
BMI	1.010 (0.99-1.03)	0.306
Cholesterol	1.010 (1.00-1.01)	0.030
Smoke (never)	1.000	
Smoke (past)	0.940 (0.74-1.19)	
Smoke (now)	0.880 (0.73-1.07)	0.423
Hypertension (yes)	1.000	
Hypertension (no)	1.050 (0.89-1.24)	0.542

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio.

DISCUSSION

Metformin is recommended as a first-line therapy because it not only has better monotherapeutic effects than the other types of OHA but also has better therapeutic effects in combination with other types of OHA.[19] In this study, the risk of cancer development and time taken for cancer development were compared between the compliant patients with the MPR ≥80% and the non-metformin users among the diabetics using an anti-diabetes agent to determine the effectiveness of metformin as OHA in preventing cancer.

Research on the long-term effectiveness of an agent can give clarity to the minimum duration of medication a patient needs to have before being under its influence.[20] When the effectiveness of an agent or the survival duration is estimated, overestimation may occur as immortal time is included in the follow-up period.[21]

For 16,132 diabetics observed in the general South Korean population, the compliant patients (MPR ≥80%) were at slightly lower risk of cancer development than the non-metformin users after controlling immortal time biases, which were insignificant at the 5% significance level (P=0.092) but significant at the 10% level. When the immortal time biases were not controlled, the risk of cancer development was statistically significant for metformin users (MPR >0%) than for non-metformin users (P=0.043).

The analysis of the effects of an inhaled beta-agonist on

the prognoses of cardiovascular disease confirmed that the rate ratio was significant at 0.73 (95% CI, 0.57-0.93), when immortal time was not removed, and insignificant at 0.98 (95% CI, 0.77-1.25), when it was removed.[22] The study on the effects of statin on the progression of diabetes verified that HR was significant at 0.74 (95% CI, 0.58-0.95), when immortal time was not removed, and insignificant at 1.97 (95% CI, 1.53-2.52), when it was removed.[23] In this study's[24] example, standard Cox regression provided moderate evidence of reduced risk of death for patients who received oseltamivir (HR, 0.52; 95% CI, 0.29-0.95). In contrast, a time-dependent Cox model showed no evidence of reduced risk of death for patients receiving oseltamivir (HR, 0.87; 95% CI, 0.48-1.61).

The study on the effects of metformin on the progression of diabetes found that metformin compliance (MPR >80%) is highly effective in inhibiting cancer development by delaying it for ≥10 months on average.

The risk factors for cancer development are age (≥65 years) and sex (male) (P<0.001).[25] Also, the higher the level of cholesterol is, the shorter the period of time taken for cancer incidence is. The remarkable result is that about 50% of the patients aged ≥65 years received metformin prescription, which is significantly lower than for those aged <65 years (approximately 90%). This is because attention is paid to metformin prescription for the aged, who suffer its side-effects, such as anorexia, impaired renal functions, higher creatinine index, and increased estimated glomerular filtration rate (eGFR). In general, metformin therapy is reportedly inappropriate for elderly patients who are weak, have anorexia nervosa, are underweight, or have impaired kidney or liver functions because elderly patients having type 2 diabetes are exposed to diverse comorbidities.[26]

This study has confirmed that when immortal time biases are controlled (by applying the minimum intake period strictly), metformin might be effective in inhibiting cancer development itself. Specifically, metformin is effective in delaying cancer development.

This study has the following limitations: since a specific carcinoma was not selected and defined as a resulting variable, such a definition could have affected the results. For cancer development, there are diverse variables to be controlled according to carcinoma. For example, lung cancer can involve tuberculosis and chronic obstructive pulmonary disease;[27,28] breast cancer can involve post-menopausal hormone therapy;[29] and liver cancer can involve hepatitis C and hepatitis B.[30] However, because this study did not specify a carcinoma to observe, it failed to fully control the confounding variables in cancer development as outcome. Like most of the studies using data concerning claims, this study cannot investigate over-the-counter drugs or uncovered therapies.

요 약

연구배경: 본 연구는 국민건강보험공단에서 제공한 표본코호트를 기반으로 당뇨 환자들에게 가장 먼저 고려되는 경구혈당강하제인 메트포민의 암 발생 억제 효과를 확인하고, 시간에 따른 편향이 암에 미치는 영향을 확인하는 것을 목적으로 하였다.

방법: 메트포민 순응군, 비순응군과 비복용군의 암 발생 기간 비교를 위해 t-test를 실시하였다. 메트포민 복용에 따른 암 발생 위험도를 예측하는 변인들의 상대적 영향력을 측정하기 위해 로지스틱 회귀모형을 수행하였다. 암 발생까지의 기간에 대한 메트포민 복용 효과의 분석을 위해 콕스 회귀분석을 수행하였다.

결과: 메트포민 복용군이 비복용군에 비하여 평균적으로 320일 늦게 발생하였다. 메트포민 비복용군(n=6,997)이 메트포민 순응군(n=16,132)보다 암 발생 오즈비가 1.11배(P=0.092) 측정되었다. 연령, 성별, 체질량지수, 콜레스테롤, 흡연 및 고혈압을 보정한 모델 3의 위험비는 0.86이었다.

결론: 본 연구는 불멸의 시간 편향을 통제함으로서 최소 복용 기간을 엄격하게 적용함에 따라 메트포민이 암 자체를 억제하는 것보다 암 위험이 있는 환자의 암 발병을 지연시키는 데 효과적임을 확인하였다. 암 발생 위험인자들(고령, 남성)을 고려해야 하며, 메트포민 비복용군, 높은 콜레스테롤 등 암 발생 기간에 대한 위험이 높은 환자들에게 약제에 대한 순응도 관리가 필요하다.

중심 단어: 당뇨병, 암, 약물 순응도, 표본선택편의, 코호트 연구

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