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Is Pretreatment with Beta-Blockers Beneficial in Patients with Acute Coronary Syndrome?

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Key Words

Acute coronary syndrome · Acute myocardial infarction · β-Receptor blockers · β-Blockers · In-hospital mortality · AMIS

Abstract

Objectives: The role of β-blockers in the treatment of hypertension is discussed controversially and the data showing a clear benefit in acute coronary syndromes (ACS) were obtained in the thrombolysis era. The goal of this study was to analyze the role of pretreatment with β-blockers in patients with ACS. ***Methods:*** Using data from the Acute Myocardial Infarction in Switzerland (AMIS Plus) registry, we analyzed outcomes of patients with β-blocker pretreatment in whom they were continued during hospitalization (group A), those without β-blocker pretreatment but with administration after admission (group B) and those who never received them (group C). Major adverse cardiac events defined as composed endpoint of re-infarction and stroke (during hospitalization) and/or in-hospital death were compared between the groups. ***Results:*** A total of 24,709 patients were included in the study (6,234 in group A, 12,344 in group B, 6,131 in group C). Patients of group B were younger compared to patients of group A and C (62.5, 67.6 and 68.4, respectively). In the multivariate analysis, odds ratio for major adverse cardiac events was 0.59 (CI 0.47–0.74) for group A and 0.66 (CI 0.55–0.83) for group B, while group C was taken as a reference. ***Conclusions:*** β-Blocker therapy is beneficial in ACS and they should be started in those who are not pretreated and continued in stable patients who had been on chronic β-blocker therapy before.

Introduction

While the role of β-receptor-blocking agents (β-blockers) has been challenged recently as a first choice in the treatment of systemic hypertension [1, 2], β-blockers remain recommended medications for patients with chronic coronary artery disease [3], especially those after acute myocardial infarction (AMI) [4–6].

In 1999, Freemantle et al. [7] assessed the role of β-blockers in a large meta-analysis of 54,234 patients with myocardial infarction. They found that β-blockers are effective in the long-term secondary prevention after myocardial infarction, reporting a 23% reduction in the odds of death in long-term trials (95% CI 15–31%). Similar long-term results were reported by the β-blocker pooling

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research group [8] and the Cooperative Cardiovascular Project [9].

The impact of β-blocker treatment on early outcomes after myocardial infarction has been discussed controversially. Freemantle et al. [7] did not observe a positive short-term effect of β-blockers administered immediately after AMI (4% reduction in the odds of death; –8 to 15%).

Also, the role of early intravenous β-blocker therapy has been disputed. While early studies performed in patients without reperfusion therapy demonstrated a mortality benefit [10, 11], studies in the thrombolysis era showed no survival benefit [12, 13] or even an increased mortality [14]. However, in the study by Pfisterer et al. [14], atenolol was used, a β-blocker which has been widely criticized lately, especially in hypertension trials.

Administration of intravenous β-blockers before primary percutaneous coronary intervention (PCI) was found to enhance myocardial recovery and reduce 30-day mortality in patients with AMI undergoing primary PCI [15]. A pooled analysis of 3 prospective trials showed that pretreatment with β-blockers has an independent beneficial effect on short-term clinical outcomes in patients undergoing primary angioplasty for AMI [16]. In the most recent study, which analyzed the role of β-blockers in the treatment of AMI, 45,000 patients were randomized to intravenous (continued with oral) metoprolol therapy or placebo. The rate of death, re-infarction or cardiac arrest was similar between both groups in this study [17].

One of the mechanisms how β-blockers could potentially improve prognosis in ACS is heart-rate reduction [18, 19]. However, the concept of sole heart-rate reduction is discussed controversially after the publication of the BEAUTIFUL trial, which failed to reduce cardiovascular mortality in stable patients with coronary artery disease (CAD) and reduced left ventricular function, although reducing the rates of fatal and nonfatal myocardial infarction in these patients [20].

Since the short-term effect of early administration of β-blockers in patients with unstable angina or AMI remains controversial and little is known about the early outcome of AMI patients already treated with β-blockers, there is need for further investigation.

Using data from the Acute Myocardial Infarction in Switzerland (AMIS Plus) registry, a large national registry of ACS, we have analyzed the effect of previous β-blocker therapy on the outcome of patients with ACS. Our hypothesis was that in patients with ACS, previous β-blocker therapy does not offer additional benefit to a β-blocker therapy started after admission.

Methods

The AMIS Plus Registry

The AMIS Plus project is a nationwide prospective registry of patients admitted with ACS to hospitals in Switzerland. The registry began in 1997, and patient recruitment has been ongoing since. Participating centers, ranging from community institutions to large tertiary facilities, provide blinded data for each patient through a standardized Internet- or paper-based questionnaire. The details of the AMIS Plus Project have been published elsewhere [21–24].

Patients

The AMIS Plus registry included all patients with ACS: AMI defined by characteristic symptoms and/or ECG changes and cardiac marker elevation (either total creatine kinase or creatine kinase MB fraction at least twice the upper limit of normal or troponin I or T above individual hospital cutoff for myocardial infarction), ACS with minimal necrosis (symptoms or ECG changes compatible with ACS and cardiac marker level lower than cutoff for myocardial infarction) and unstable angina (symptoms or ECG changes compatible with ACS and normal cardiac markers). Patients were also categorized as having ST-segment elevation ACS (STEMI) or non-ST-segment elevation ACS (NSTEMI) based on initial ECG findings. Classification of STEMI included evidence of ACS as above and ST-segment elevation and/or new left bundle branch block on the initial ECG. NSTEMI included patients with ischemic symptoms, ST-segment depression or T-wave abnormalities in the absence of ST-elevation on the initial ECG. Valid data since 1997 on pretreatment and early treatment with β-blockers were available and those data were analyzed. Baseline characteristics and outcomes are compared between patients on chronic β-blocker therapy (group A), patients without β-blocker pretreatment and in whom β-blocker therapy was started after admission (group B), and patients without β-blocker pretreatment who were not started on a β-blocker when admitted (group C). Major adverse cardiac event (MACE) was defined as a composed endpoint of re-infarction, stroke and/or in-hospital death. Comorbidities of the patients were assessed using the Charlson index [25]. In March 2005, the AMIS Plus questionnaire was revised and more angiographic parameters were added (for example: vessel treated, left ventricular ejection fraction, thrombolysis in myocardial infarction flow at the end of PCI).

Statistical Analyses

Data are presented as percentages of valid cases for discrete variables and as means ± SD and/or median for continuous variables. Differences in baseline characteristics were compared using t test and χ^2 tests. A p value of <0.05 was considered significant. User-defined missing values are treated as missing. Statistics for each table are based on all cases with valid data in the specified ranges for all variables in each table. Odds ratios (OR) with 95% CI for OR of in-hospital mortality were calculated using logistic regression models. The following factors were included in the multivariate analysis: β-blocker treatment, age, gender, history of coronary artery disease, hypertension, diabetes, dyslipidemia, smoking, overweight, ST-segment elevation, Charlson score, Killip class and use of PCI. SPSS software (version 15.0; SPSS Inc., Chicago, Ill., USA) was used for all statistical analyses.

Table 1. Baseline characteristics of the study population

	All ACS patients (N = 26,964)	ACS patients with valid data on BB (N = 26,159)			p between groups
		group A previous and continued BB (n = 6,234)	group B BB on admission (n = 12,344)	group C never BB (n = 6,131)	
Mean age, years[1]	65.6 (13.2)	67.6 (12.0)	62.5 (13.1)	68.4 (13.6)	<0.001
Male patients, %	72.3	70.9	75.5	69.0	<0.001
STEMI, n/N	15,807/26,881 (58.8)	2,961/6,216 (47.6)	7,696/12,326 (62.4)	3,835/6,108 (62.8)	<0.001
CAD, n/N	8,692/22,226 (39.1)	3,520/5,575 (63.1)	2,534/10,025 (25.3)	1,676/4,793 (35.0)	<0.001
Diabetes, n/N	5,207/26,045 (20.0)	1,483/6,094 (24.3)	1,893/12,002 (15.8)	1,302/5,911 (22.0)	<0.001
Hypertension, n/N	14,717/25,794 (57.1)	4,877/6,105 (79.9)	5,350/11,833 (45.2)	2,927/5,809 (50.4)	<0.001
Dyslipidemia, n/N	13,800/24,136 (57.2)	4,024/5,764 (69.8)	6,109/11,272 (54.2)	2,516/5,233 (48.1)	<0.001
Smoking, n/N	9,616/25,356 (37.9)	1,658/5,891 (28.1)	5,247/11,916 (44.0)	2,093/5,622 (37.2)	<0.001
Obesity, n/N	4,110/21,470 (19.1)	1,142/5,204 (21.9)	1,847/10,155 (18.2)	795/4,464 (17.8)	<0.001
Antithrombotic therapy	aspirin	5,913/6,229 (94.9)	12,024/12,333 (97.5)	5,482/6,122 (89.5)	<0.001
	clopidogrel	3,353/6,206 (54.0)	6,632/12,298 (53.9)	2,591/6,116 (42.4)	<0.001
	UFH	3,989/6,197 (64.4)	9,080/12,305 (73.8)	4,288/6,117 (70.1)	<0.001
	LMWH	1,941/5,333 (36.4)	3,578/9,755 (36.7)	1,264/4,577 (27.6)	<0.001
	GP IIb/IIIa	1,544/5,347 (28.9)	3,716/9,779 (38.0)	1,341/4,579 (29.3)	<0.001

Numbers in parentheses are percentages, unless indicated otherwise. BB = β-Receptor-blocking agents; CAD = coronary artery disease.

[1] Figures in parentheses are SD.

Results

From 26,964 registered patients between January 1st 1997 to December 31st 2007, 24,709 patients (91.6%) had valid data on previous and/or early treatment with β-blockers. For 2,255 patients (8.4%), treatment with β-blockers was unknown or data were missing.

7,684 patients (29.4%) had previous β-blocker therapy, and in 6,234 of these patients this therapy was continued after admission (group A; in 1,450 patients β-blockers were stopped after admission); in 12,344 (47.2%) patients β-blocker therapy was started at admission (group B); 6,131 (23.4%) patients never received β-blocker therapy (group C). Baseline characteristics of the study population are shown in table 1. The mean age of all patients was 65.6 years (±13.2) and 72.3% of them were males. Patients of group A were significantly older than patients of group B (67.6 vs. 62.5 years, $p < 0.001$) but had a similar age as patients of group C (68.4 years).

Patients of group A had a higher proportion of diabetes (24.3 vs. 15.8% in group B and 22% in group C, $p < 0.001$) and a higher proportion of arterial hypertension (79.9 vs. 45.2% in group B and 50.4% in group C).

The rate of STEMI was higher in patients of groups B and C (62.4 and 62.8%) compared to patients of group A (47.6%, $p < 0.001$).

The anti-thrombotic therapy is shown in the bottom part of table 1. Patients from group C received less aspirin and less clopidogrel than those of group A and B.

In table 2, the Killip classifications of the patients are summarized. Patients of group B were more likely to be in Killip class I (84.5%) compared to patients of group A (77%) and patients of group C (66.1%).

Table 3 summarizes the reperfusion therapies for ACS patients in the AMIS Plus population. A reperfusion therapy (thrombolysis or primary PCI) was performed in 45.8% of patients of group A, 55.9% of patients of group B and 48% of patients of group C. Primary PCI was the predominant reperfusion therapy in all groups.

Median door-to-balloon times for PCI-treated patients were 193 min for group A, 117 min for group B and 109 min for group C ($p < 0.001$). Median door-to-needle time for thrombolysis-treated patients was 35 min in group A and 30 min in group B and C ($p = 0.032$).

In table 4, the complications and outcome of ACS patients during hospitalization are demonstrated. Patients of group B had similar rates or cardiogenic shock (3.8 vs.

Table 2. Killip classification

	All ACS patients (N = 26,964)	ACS patients with valid data on BB (N = 26,159)			p between groups
		group A: previous and continued BB (n = 6,234)	group B: BB on admission (n = 12,344)	group C: never BB (n = 6,131)	
Class I	76.9	77.3	84.5	66.1	<0.001
Class II	16.1	17.7	12.7	20.2	<0.001
Class III	4.5	4.0	2.0	8.5	<0.001
Class IV	2.5	1.0	0.8	5.2	<0.001

BB = β-Receptor blocking agents. Between BB groups $p < 0.001$.

Table 3. Reperfusion therapy

	All ACS patients (N = 26,964)	ACS patients with valid data on BB (N = 26,159)			p between groups
		group A: previous and continued BB (n = 6,234)	group B: BB on admission (n = 12,344)	group C: never BB (n = 6,131)	
No reperfusion, %	48.8	54.2	44.1	52.0	<0.001
Thrombolysis, %	10.2	6.7	12.7	9.7	<0.001
Primary PCI, %	41.0	39.1	43.2	38.3	<0.001

BB = β-Receptor-blocking agents. Between BB groups $p < 0.001$.

Table 4. Complications and outcome of ACS patients in the AMIS Plus Registry

	All ACS patients (N = 26,964)	ACS patients with valid data on BB (N = 26,159)			p
		previous and continued BB (n = 6,234)	BB on admission (n = 12,344)	never BB (n = 6,131)	
Cardiogenic shock, n/N	1,909/26,603 (7.2)	227/6,161 (3.7)	469/12,200 (3.8)	832/6,046 (13.8)	<0.001
Re-infarction, n/N	637/26,540 (2.4)	156/6,152 (2.5)	236/12,185 (1.9)	170/6,025 (2.8)	<0.001
Cerebrovascular event, n/N	279/26,349 (1.1)	56/6,111 (0.9)	80/12,071 (0.7)	90/5,995 (1.5)	<0.001
MACE, n/N	2,430/26,396 (9.2)	399/6,113 (6.5)	613/12,078 (5.1)	930/6,015 (15.5)	<0.001
In-hospital mortality, n/N	1,890/26,964 (7.0)	256/6,234 (4.1)	394/12,344 (3.2)	808/6,131 (13.2)	<0.001

Numbers in parentheses are percentages. BB = β-Receptor-blocking agents.

3.7% in group A) but lower rates than group C (13.8%, $p < 0.001$). Re-infarction rates were 2.5% in group A, 1.9% in group B and 2.8% in group C.

Unadjusted MACE rates were similar in patients with β-blocker therapy on admission (group B) compared to those with previous β-blocker therapy (group A) (5.1 vs. 6.5%) but lower than those who never received β-blockers (group C, 15.5%).

The unadjusted in-hospital mortality was 4.1% for group A, 3.2% for group B and 13.2% for group C.

In table 5, a multivariate logistic regression for major adverse cardiac events is shown. Factors increasing the MACE OR are age, STEMI, a higher Killip Class, the history of CAD, diabetes and an increasing Charlson score. The OR for β-blocker therapy on admission (group B) was 0.66, while the OR for previous β-blocker therapy (group A) was 0.59.

Table 5. Multivariate logistic regression for MACE

	OR	95% CI	p
Previous and continued β-blocker therapy	0.59	0.47–0.74	<0.001
β-Blocker therapy at admission	0.66	0.55–0.83	<0.001
Age (per year)	1.04	1.04–1.05	<0.001
Gender	1.16	0.97–1.39	0.112
STEMI	1.55	1.30–1.86	<0.001
Killip			
II	1.67	1.35–2.07	<0.001
III	2.50	1.82–3.44	<0.001
IV	15.6	11.3–21.7	<0.001
Hypertension	0.84	0.70–1.01	0.069
Dyslipidemia	0.79	0.67–0.94	0.009
Smoking	1.22	1.00–1.50	0.055
Charlson score 1	1.42	1.13–1.79	0.003
Charlson score 2	1.72	1.32–2.24	<0.001
Charlson score ≥3	2.21	1.73–2.83	<0.001
Primary PCI	0.59	0.49–0.72	<0.001

Discussion

We analyzed a large population of patients with ACS who are prospectively registered in the AMIS Plus database. The majority of the patients (71%) with ACS in Switzerland receive β-blocker therapy (either pretreated and continued or started during hospitalization). The proportion of β-blockers' use in our population is slightly lower compared to the proportion reported in the Worcester Heart Attack Study where in 1999, 82% of the patients received this therapy after AMI [26].

The unadjusted MACE and in-hospital mortality rate were slightly better in patients with β-blocker therapy started after admission, compared to those who had a chronic β-blocker therapy or those who never received a β-blocker (table 4). However, it's important to recognize the fact that there were significant differences between the different β-blocker groups (table 1). One of the most important factors was age. Patients with previous β-blocker therapy and those who never received a β-blocker were more than 5 years older than patients with β-blocker therapy started after admission. It is well known that age increases the risk for adverse outcomes after non-invasive and invasive therapies for AMI [27, 28]. One of the reasons for this phenomenon is probably the lower use of guideline-recommended medical and interventional therapies in elderly patients [23]. Increased percutaneous coronary intervention rates have been associated with decreased mortality among patients with ACS who present with cardiogenic shock or STEMI in Switzerland [29, 30].

Further factors possibly explaining higher MACE rates are the higher prevalence of diabetes and coronary artery disease in patients pretreated with β-blocking agents than those without a β-blocker therapy. A factor favoring a worse outcome in patients with β-blocker therapy after admission is the higher proportion of STEMI in this group (62.4 vs. 47.6% in patients with previous β-blocker therapy).

Since the baseline characteristics of the groups were different, we performed a multivariate logistic regression analysis, which included the Charlson comorbidity score and is shown in table 5. According to this analysis, both previous β-blocker therapy and β-blocker therapy after admission are beneficial in patients with ACS. This multivariate analysis favors pretreatment with β-blockers indicating a 41% reduction of OR with a 95% CI of 0.47–0.74.

What could be the impact of these results when dealing with patients who present with ACS? Patients with β-blocker pretreatment in whom this therapy is continued after admission do at least as good (or even better) than patients without pretreatment, in whom β-blockers are started after admission. In 1,045 of 7,684 patients (13.6%) with previous β-blockers, this therapy was stopped after admission. Despite the fact that we do not know the exact reasons why clinicians stopped β-blockers, we can assume that this was for hemodynamic reasons.

The latest large prospective trial analyzing the role of β-blockers in AMI found that they reduce the risk of reinfarction and ventricular fibrillation but increase the risk of cardiogenic shock, especially during the first day after admission [17].

When cautiously interpreted, our data call for a tailored approach. Patients who are pretreated with β-blockers and who present with ACS should further receive their β-blocker if they are hemodynamically stable since this medication has the potential to decrease their MACE rate to as much as 41%. Patients without β-blocker pretreatment who are hemodynamically stable should receive this therapy soon after presentation for ACS.

In our study, patients who never received a β-blocker therapy had very high rates of MACE. This is explained by their comorbidities (age, diabetes, prevalence of known CAD, lower use of aspirin and clopidogrel) but might also be related to the fact that they never received β-blockers (a proven beneficial therapy for ACS).

Limitations

We are aware that these are registry data, which should be interpreted with caution. Since the baseline characteristics of the different β-blocker groups were so different, a comparison of the outcomes is difficult and remains challenging despite the use of multivariate logistic regression.

Additionally, we cannot provide data which types of β-blockers and in which dose they were used. Global data about baseline ejection fraction are not available for most of the patients and this limits the interpretations of the data since ejection fraction affects patient's response to treatment with β-blockers.

Conclusions

This study confirms the potential benefit of β-blockers in patients with ACS. β-Blockers have the potential to markedly reduce in-hospital mortality and MACE rates in ACS patients. Hemodynamically stable patients without β-blocker pretreatment should receive them upon admission, and this therapy should be continued in those already on β-blockers.

Appendix

AMIS Plus Participants 1997–2007

The following hospitals participated from 1997–2007 in the AMIS registry on which this report is based (in alphabetical order): Affoltern am Albis, Bezirkspital (F. Hess), Altdorf, Kantonsspital (R. Simon), Altstätten, Kantonales Spital (P.J. Hangartner/M. Rhyner), Aarau, Kantonsspital (P. Lessing), Baden, Kantonsspital (M. Neuhaus/U. Hufschmid), Basel, Kantonsspital (P. Hunziker), Basel, St. Claraspital (C. Grädel), Bern, Beau-Site Klinik (A. Schönfelder), Bern, Inselspital (B. Meier/S. Windecker), Biel, Spitalzentrum (H. Schläpfer), Brig-Glis, Oberwalliser Kreisspital (D. Evéquoz), Bülach, Spital (R. Pampaluchi/A. Ciurea-Löchel/M. Kruhl/A. Vögele), Burgdorf, Regionalspital Emmental (D. Ryser), Chur, Rätisches Kantons- und Regionalspital (P. Müller), Chur, Kreuzspital (V. Wüscher/R. Jecker), Davos, Spital (G. Niedermaier), Dornach, Spital (A. Koelz/H. Lederer), Flawil, Kantonales Spital (T. Langenegger/J. Haarer), Frauenfeld, Kantonsspital (H.P. Schmid), Fribourg, Hôpital cantonal (B. Quartenoud), Frutigen, Spital (S. Moser/K. Bietenhard), Genève, Hôpitaux universitaires (HUG) (J.M. Gaspoz/P.F. Keller), Glarus, Kantonsspital (W. Wojtyna), Grenchen, Spital (P. Schlup/A. Oestmann/B. Oertli/R. Schönenberger), Grosshöchstetten, Bezirksspital (C. Simonin), Heiden, Kantonales Spital (R. Waldburger), Herisau, Kantonales Spital (P. Staub/M. Schmidli), Interlaken, Spital (P. Sula/E.M. Weiss), Jegenstorf, Spital (H. Marty), La Chaux-de-Fonds, Hôpital (H. Zender), Lachen, Regionalsspital (I. Poepping/C. Steffen), Langnau im Emmental, Regionalspital (J. Sollberger/A. Hugi), Laufenburg, Gesundheitszentrum Fricktal (E. Koltai), Lugano, Cardiocentro Ticino (G. Pedrazzini), Luzern, Kantonsspital (P. Erne), Männedorf, Kreisspital (J. von Meyenburg/T. Luterbacher), Martigny, Hôpital régional (B. Jordan), Mendrisio, Ospedale regionale (A. Pagnamenta), Meyrin, Hôpital de la Tour (P. Urban), Monthey, Hôpital du Chablais (P. Feraud), Montreux, Hôpital de Zone (E. Beretta), Moutier, Hôpital du Jura bernois (C. Stettler), Münsingen, Regionales Spital Zentrum (F. Repond), Münsterlingen, Kantonsspital (F. Widmer), Muri, Kreisspital für das Freiamt (A. Spillmann/F. Scheibe/K. Rudaz-Schwaller), Nyon, Group. Hosp. Ouest lémanique (R. Polikar), Olten, Kantonsspital (S. Bassetti), Rheinfelden, Gesundheitszentrum Fricktal (H.U. Iselin), Rorschach, Kantonales Spital (M. Pfister/A. Fischer), Samedan, Spital Oberengadin (P. Egger), Sarnen, Kantonsspital Obwalden (T. Kaeslin), Schaffhausen, Kantonsspital (R. Frey), Schlieren, Spital Limmattal (B. Risti/V. Stojanovic/T. Herren), Schwyz, Spital (P. Eichhorn), Scuol, Ospidal d'Engiadina Bassa (G. Flury/C. Neumeier), Solothurn, Bürgerspital Solothurn (P. Hilti/A. Grât/R. Schöneneberger), St. Gallen, Kantonsspital (W. Angehrn/H. Rickli), Sursee, Spital (S. Yoon), Tiefenau, Tiefenauspital (P. Loretan), Thun, Spital (U. Stoller), Thusis, Krankenhaus (U.P. Veragut), Uster, Spital (D. Maurer/J. Muntwyler/J. Hellermann), Uznach, Kantonales Spital (A. Weber), Wädenswil, Schwerpunktspital Zimmerberg-Horgen (G. Garzoli/B. Kälin), Walenstadt, Kantonales Spital (H. Matter/D. Schiesser), Wetzikon, GZO Spital (M. Graber), Winterthur, Kantonsspital (A. Haller), Wolhusen, Kantonales Spital (M. Peter), Zofingen, Spital (H.J. Vonesch/H.J. Meier/S. Gasser), Zollikerberg, Spital (P. Siegrist/R. Fatio), Zug, Kantonsspital (M. Vogt/D. Ramsay), Zürich, Klinik im Park (O. Bertel), Zürich, Universitätsspital Zürich (F. Eberli/M. Maggiorini), Zürich, Stadtspital Triemli (O. Bertel/F. Eberli), Zürich, Stadtspital Waid (M. Brabetz/S. Christen).

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