Impact of Chronic Thrombocytopenia on Outcomes After Transcatheter Valvular Intervention and Cardiac Devices Implantation (From a National Inpatient Sample)

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To evaluate the impact of chronic thrombocytopenia (cTCP) on outcomes of transcatheter valvular procedures such as aortic valve implantation (TAVI), MitraClip, permanent pacemaker (PPM), implantable-cardioverter defibrillator (ICD), cardiac resynchronization therapy (CRT), left atrial appendage closure, and pericardiocentesis. Impact of cTCP on clinical outcomes following TAVI, Mitraclip, PPM, ICD, CRT, left atrial appendage closure, and pericardiocentesis procedures is not well described. Utilizing the National Inpatient Sample and (ICD-9-CM) procedural codes, we evaluated patients (age ≥18 years) who underwent these procedures, from January 1, 2009 to December 31, 2014, with or without cTCP as a chronic condition variable indicator. Propensity score matching model implemented to derive 2 matched groups. Propensity score matching created 47,292 and 47,351 hospitalizations matched pairs with and without cTCP, respectively. Patients with cTCP were older (mean age, 74.27 vs 72.26 years; absolute standardized differences [ASD] = 15.6) and less likely to be female (36.76% vs 43.74%, ASD = −14.31). They experienced higher in-hospital mortality (3.0% vs 2.0%; odds ratio [OR], 1.53; 95% confidence interval [CI], 1.27 to 1.83) and higher odds of vascular injury requiring surgery (2.63% vs 1.10%; OR, 2.43; 95% CI, 1.93 to 3.05). Postoperative hematoma and bleeding were 2-fold higher (4.57% vs 2.24%; OR, 2.08; 95% CI, 1.77 to 2.45) and 3-fold higher (6.34% vs 2.45%; OR, 2.69; 95% CI, 2.31 to 3.13) respectively among cTCP patients. They had greater health-care cost ($47,163 vs $35,763, p <0.0001) and longer hospital stay (mean 9.26 days vs 6.84 days, p <0.0001). In conclusion, cTCP patients had higher risk of complications after TAVI, MitraClip, PPM, ICD, CRT, left atrial appendage closure, and pericardiocentesis, including a 1.5-fold increased risk of in-hospital mortality. **(Am J Cardiol 2019;124:1601−1607)**

Bleeding is a feared complication in various cardiac interventions. Chronic thrombocytopenia (cTCP), platelet count of <150,000 cells/ml, has an incidence of 2.5% to 4% and is known to increase the risk of bleeding.[1]

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Methods

Our study utilized the National Inpatient Sample (NIS) of the Health Care Utilization Project (HCUP) created by the Agency for Healthcare Research and Quality (AHRQ). Data were obtained from January 1, 2009 to December 31, 2014. The NIS is the largest publicly available all-payer inpatient health care database in the United States.[2] In 2012, the NIS was redesigned to improve the precision of national estimates, and now it consists of a 20% random sample of discharges selected from 100% of the participating hospitals. To facilitate estimation of national prevalence, hospital and discharge weights are provided with information necessary to calculate the variance of the estimates and to account for changes in the sampling methodology, the AHRQ developed new discharge weights known as trend weights for use with NIS.[3] We evaluated all adult patients (age ≥18 years) who underwent permanent pacemaker (PPM), implantable-cardioverter defibrillator (ICD), cardiac resynchronization therapy (CRT), transcatheter aortic valve implantation (TAVI), Mitral clip, left atrial

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appendage closure, and pericardiocentesis with or without cTCP, as a chronic condition variable indicator. We identified these patients using the International Classification of Diseases-Ninth Revision, Clinical Modification (ICD-9-CM) procedural codes (supplemental Table 1). TCP is generally defined as platelets count of <150,000 cells/ml of blood. In the NIS, this diagnosis is based on inclusion as an ICD code and the exact lab values are not available. To identify cTCP, we used a chronic condition indicator variable, which identifies a diagnosis that was present for at least a year from the index admission. This population was weighted using the prespecified weights in the NIS to estimate the national prevalence. Patients with periprocedural TCP, or for whom the chronic condition indicator variable indicated that cTCP was present for <1 year before procedure and those with thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, those who underwent percutaneous coronary intervention and those who had concomitant coronary artery bypass graft, mitral valve surgery pulmonary valve surgery, tricuspid valve surgery, atrium or ventricular septum defect closure during index admission were excluded (supplemental Table 1).

We obtained data on patient characteristics and hospital-level characteristics from the NIS. Clinical outcomes were compared among patients who underwent the named procedures with and without cTCP. The main endpoint was assessment of in-hospital mortality. Secondary outcomes include platelet transfusions, vascular complications (injury to blood vessel, arteriovenous fistula, retroperitoneal hematoma, and vascular complications requiring surgical intervention), cardiac tamponade, acute kidney injury, bleeding complication requiring transfusions, postprocedural sepsis, and postprocedural acute cerebrovascular accident. These complications were identified by ICD-9-CM diagnosis and procedure codes (supplemental Table 1).

We identified demographic and comorbid factors as covariates. Demographic variables were age, sex (male, female), race (White, Black, Hispanics, and other races), health insurance (Medicare, Medicaid, Private, Self-pay, and others), income (stratified into 4 based on average household income of the zip-code of residence), region (Northeast, Midwest, South, and West), hospital teaching status (rural, urban nonteaching, and teaching). After identifying many comorbid variables involving the entire body-system, we computed the modified Elixhauser comorbidities index to summarize these comorbid variables into a number.[4] Assessment of healthcare resources was performed by comparing nonroutine home discharge rate, cost, and length of stay.

Hospital cost information was obtained from the hospital accounting reports collected by the Centers for Medicare, and Medicaid Services.[5] To account for the effect of inflation on hospital charges, we used data from the Bureau of Labor Statistic's medical care component of the Consumer Price Index (CPI) and presented the data in 2017 US dollars.[6]

We derived national estimates using the hospital-level trend/discharge weights included in the NIS by AHRQ. Data were analyzed with Statistical Analysis System (SAS V.9.4, SAS Institute Inc, Cary, NC), accounting for the stratified sampling design with appropriate keywords as recommended by HCUP-NIS.[7,8] The adjusted odds ratio (AOR) was reported for logistic models and adjusted mean ratio (AMR) for negative binomial and gamma models. Mean (with standard deviation) and frequency were respectively used to summarize normally distributed variables and categorical variables respectively. We used absolute standardized differences (ASD) to compare the baseline characteristics. ASD (calculated as the differences in means or proportions divided by a pooled estimated of the SD) is not as sensitive to sample size compared with traditional significance testing and is useful in identifying clinically meaningful differences. An ASD of >10% is considered clinically meaningful.[9]

A propensity score matching model was developed to derive 2 matched groups for comparative outcome analysis to account for potential confounding factors and reduce the effect of selection bias. We performed multivariate logistic regression cTCP as the outcome variable, and all comorbidities in Table 1 and patient-level NIS weights were used as covariates.[10]

Thereafter, the cTCP cases were greedy-matched to no cTCP controls, in a ratio 1:1, using propensity scores generated from the initial multivariate model. A caliper width of <0.01*SD of the logit of the propensity scores was used as the cutoff during the match process. After the matching, we examined ASD for each variable between the 2 groups to assess the efficacy of the propensity score model.[11] Finally, we compute regression models, with cTCP as a primary predictor, the propensity score as a covariate for tighter confounder adjustment, and each of our outcomes as the dependent variable in the models. The distributions of each of these models were specified to match those of the outcomes-logistic, gamma and negative binomial for binary, cost, and length of hospital stay respectively.

Results

Of 1,304,376 hospitalizations aged ≥18 years who underwent noncoronary cardiac procedures from 2009 to 2014 in the United States, 56,258 (4.31%) had cTCP. Those who had cTCP were on an average approximately 2 years older compared with those without (mean age, 74.27 vs 72.26 years; ASD = 15.6) and they were less likely to be female (36.76% vs 43.74% ASD = −14.31). There were no significant differences in racial distribution or socioeconomic status between those with cTCP and those without (ASD < 10). cTCP patients were more likely to be Medicare beneficiaries and less likely to have private insurance. The prevalence of atrial fibrillation, peripheral artery disease, deficiency anemia, congestive heart failure, chronic renal failure, chronic liver disease, and those on maintenance dialysis was higher in those with cTCP compared with those without (ASD > 10). cTCP patients exhibited a higher burden of Elixhauser comorbidities as represented with Elixhauser score ≥4 (47.62% vs 28.39%; ASD = 46.39) (Table 1). Propensity score matching created 47,292 and 47,351 hospitalizations matched pairs with and without cTCP respectively. Matching achieved similar baseline characteristics between the 2 groups (ASD < 10 for all) (Table 2).

Following propensity score matching, compared with patients without cTCP, those who had cTCP experienced

Table 1
Baseline characteristics of older participants admitted for noncoronary cardiac procedures by chronic thrombocytopenia status − unmatched

Variable	Thrombocytopenia		Total	¥ASD
	Yes	No		
No. of observation, unweighted	**11,454 (4.31%)**	**255,305**	**266,759**	
No. of observation, weighted	56,258	1,248,118	1,304,376	
Age (year) mean (SD)	74.27 (13.27)	72.17 (13.59)	72.26 (13.58)	**15.6**
Female	36.76%	43.74%	43.43%	**−14.31**
White	76.47%	76.85%	76.83%	
Black	10.44%	11.05%	11.02%	
Hispanic	7.26%	6.79%	6.81%	
Asia	2.37%	2.12%	2.13%	
Dyslipidemia*	48.69%	49.11%	49.09%	−0.96
Prior myocardial infarction	12.54%	13.10%	13.07%	1.48
Prior percutaneous coronary intervention	10.61%	11.30%	11.27%	−2.28
Prior coronary artery bypass grafting	15.28%	13.79%	13.86%	4.26
Prior pacemaker	3.75%	2.41%	2.47%	7.72
Atrial fibrillation	43.96%	37.31%	37.60%	**13.52**
Chronic obstructive pulmonary disease	24.12%	20.22%	20.38%	9.49
Carotid artery disease	3.18%	2.47%	2.50%	4.26
Prior cerebrovascular disease	10.48%	10.08%	10.10%	1.15
Hypertension	71.74%	69.77%	69.85%	4.16
Peripheral vascular diseases	14.89%	9.66%	9.88%	**15.98**
Hypothyroidism	16.77%	15.18%	15.25%	4.26
Diabetes mellitus	33.81%	31.85%	31.93%	4.27
Obesity*	12.10%	11.71%	11.73%	1.26
Anemia	35.77%	15.89%	16.75%	**46.86**
Heart failure	52.45%	42.20%	42.64%	**20.69**
Renal failure	35.01%	20.38%	21.01%	**33.29**
Liver disease	5.37%	1.32%	1.49%	**13.57**
On maintenance dialysis	4.33%	1.96%	2.07%	**13.57**
Smoking	25.11%	24.32%	24.35%	1.91
Alcohol abuse	3.56%	2.10%	2.16%	8.91
Long-term anticoagulation use	10.24%	11.32%	11.28%	-3.40
Weekend admission	18.40%	16.71%	16.78%	4.73
ITP	3.60%	0.00%	0.16%	**27.30**
Elixhauser score*				**46.39**
• −1	11.36%	23.04%	22.51%	
• −2 to 3	41.02%	48.56%	48.22%	
• ≥4	47.62%	28.39%	29.28%	
Hospital bed size				7.09
- Small	7.98%	0.25%	9.20%	
- Medium	21.78%	22.04%	22.03%	
- Large	70.24%	68.71%	68.78%	
Expected primary payer				**12.74**
- Medicare	78.28%	73.20%	73.41%	
- Medicaid	4.77%	5.05%	5.04%	
- Private	13.70%	17.79%	17.61%	
- Other	3.25%	3.96 %	3.93%	
Median household income in quartile				7.60
- 1st	25.28%	26.38%	26.34%	
- 2nd	25.49%	26.35%	26.31%	
- 3nd	25.17%	24.73%	24.75%	
- 4th	24.07%	22.53%	22.60%	
Hospital region				**10.41**
- Northeast	18.16%	22.04%	21.87%	
- Midwest	24.08%	23.18 %	23.22%	
- South	38.41%	36.42%	36.51%	
- West	19.34%	18.35%	18.39%	
Hospital teaching status				**10.28**
-Rural	4.83%	6.34%	6.27%	
-Urban, nonteaching	34.52%	37.45%	37.33%	
-Urban, teaching	60.65%	56.21%	56.40%	

(*continued*)

Table 1 (***Continued***)

Variable	Thrombocytopenia		Total	¥ASD
	Yes	No		
Procedures				
-TAVI	10.35%	1.97%	2.34%	35.13
-Percutaneous mitral valve repair	0.51%	0.18%	0.19%	5.68
-Left atrial appendage device	0.17%	0.15%	0.15%	0.62
-Automatic cardioverter/defibrillator	16.59%	18.85%	18.75%	−5.78
-Cardiac resynchronization therapy-Pacer	10.41%	12.87%	12.76%	−7.72
-Cardiac resynchronization therapy-Defibrillator	3.02%	2.59%	2.61%	2.42
-Insertion of pacemaker (single, dual chamber)	54.01%	58.43%	58.24%	−8.74
-Pericardiocentesis	6.81%	5.48%	5.54%	5.64

¥ASD indicates absolute standardized difference; calculated as differences in means or proportions divided by a pooled estimate of the SD. *Dyslipidemia: Disorders of lipid metabolism. *Obesity: ICD-9-CM codes: 278.0, 278.00, 278.01, Discharge does not have these DRGs: Nutrition/Metabolic (296-298).

significantly higher in-hospital mortality (3.0% vs 2.0%; odds ratio [OR], 1.53; 95% confidence interval [CI], 1.27 to 1.83). There were also significantly higher odds of vascular injury requiring surgery (2.63% vs 1.10%; OR, 2.43; 95% CI, 1.93 to 3.05), acute kidney injury (29.55% vs 22.90%; OR, 1.44; 95% CI, 1.44 to 1.54), and device infection (1.82% vs 1.25%; OR, 1.70; 95% CI, 1.39 to 2.07) among those that had cTCP. Postoperative hematoma and bleeding requiring transfusion were almost 2-fold higher (4.57% vs 2.24%; OR, 2.08; 95% CI, 1.77 to 2.45) and 3-fold higher (6.34% vs 2.45%; OR, 2.69; 95% CI, 2.31 to 3.13) respectively among patients who had cTCP, whereas the incidence of cardiac tamponade (3.32% vs 3.32%; OR, 1.01; 95% CI, 0.86 to 1.18), hemorrhagic stroke (0.44% vs 0.43%; OR, 1.00; 95% CI, 0.65 to 1.54), and ischemic stroke (2.25% vs 2.02%; OR, 1.13; 95% CI, 0.93 to 1.38) was similar in the 2 groups.

Among patients surviving to discharge, those with cTCP were less likely to be discharged home and more likely to require skilled nursing facility or home health services at discharge. Health care resources were more utilized in cTCP cohorts with significantly higher cost ($47,163 vs $35,763, p <0.0001) and longer hospital stay (mean 9.26 days vs 6.84 days, p <0.0001) (Table 3).

Discussion

The prevalence of cTCP is 2.5% and 4% in the general population.[12] In the current study population, the prevalence of cTCP was 4.3%. Patients with cTCP tend to be older in age and have significantly higher prevalence of noncardiac comorbidities, namely chronic liver and chronic renal diseases as well as deficiency anemias (Table 1), whereas having comparable conventional cardiovascular risk factor profiles. Similarly, congestive heart failure, pervious cerebrovascular disease, peripheral arterial disease as well as atrial fibrillation were more prevalent among patients with cTCP (Table 1), underscoring the value of propensity score matching to correct for observed variation in baseline characteristics as well as cardiac and noncardiac comorbidities. Table 2 reveals that this was successfully achieved in both matched groups.

Despite propensity score matching overall in-hospital mortality was significantly higher in cTCP group (OR 1.53, 95% CI 1.27 to 1.83) in a study conducted by Ayoub et al, which evaluated the impact of cTCP on PCI outcome,[13] cTCP was associated with increased mortality. Similar results were found in an older study.[14] However, it appears that cTCP has direct effect on mortality following cardiac procedures. One of the limitations of the current study is that we had to utilize propensity score matching to correct for observed variables that would potentially affect the outcome, but it is not possible to achieve the same effect of prospective randomization which also corrects for unobserved variables.

Interestingly, a retrospective study done at the Mayo clinic illustrated no difference in hospital mortality and bleeding events among patients with and without cTCP undergoing PCI.[15] However, comparing the current study population with those patients undergoing coronary interventions (PCI) may be challenging as latter group typically require special antiplatelet management that could modulate confound interpretation of complications in patients with cTCP. As expected, the cTCP group had significantly higher incidence of postoperative bleeding and hematoma formation requiring blood transfusion. Both were almost 2-fold higher in the cTCP group. The most common noncoronary procedure among the study group was device implantations, and it was evident that the dreadful complication of device infection was significantly more associated with cTCP. This might be due to more procedural manipulations needed to achieve hemostasis. Also, this group of patients might have reduced overall immune response and hence more risk of postoperative infections.

In the current study, we also observed that cTCP was associated with increased likelihood of postoperative vascular access complications necessitating surgical repair. Although the direct link between thrombocytopenia and the need for surgical repair might not be apparent, it is safe to speculate that postoperative bleeding/hematoma formation was threatening enough to necessitate surgical repair to control bleeding.

A separate subanalysis of TAVI subgroup, being the only procedure included in this analysis requiring large-bore arterial access, was undertaken (supplemental Table 2).TAVI patients with cTCP had more significant vascular injury requiring surgery, postoperative hematomas and bleeding requiring transfusion. Of note, cTCP was not associated with increased risk of cardiac tamponade. Albeit somewhat

Table 2
Baseline characteristics of older participants admitted for noncoronary cardiac procedure by chronic thrombocytopenia status − matched 1:1

Variable	Thrombocytopenia		¥ASD
	Yes	No	
No. of observation, unweighted	9,637	9,637	
No. of observation, weighted	47,292	47,351	
Age - year, mean (SD)	74.43 (13.13)	74.09 (12.71)	2.65
Female	37.24%	36.95%	0.64
Race/Ethnicity			3.83
- White	76.65%	76.21%	
- Black	10.36%	10.20%	
- Hispanic	7.26%	7.96%	
- Asia	2.39%	2.42%	
Dyslipidemia	49.66%	49.59%	0.12
Prior myocardial infarction	12.73%	13.00%	−0.80
Prior percutaneous coronary intervention	10.86%	10.44%	1.25
Prior coronary artery bypass grafting	15.75%	15.28%	1.32
Prior pacemaker	3.95%	3.59 %	1.86
Atrial fibrillation	44.69%	45.06 %	−1.06
Chronic obstructive pulmonary disease	25.02%	24.44%	1.20
Carotid artery disease	3.40%	3.31%	0.46
Prior cerebrovascular disease			0.13
Hypertension	74.19%	74.06%	0.00
Peripheral vascular diseases	15.65%	15.72%	−0.26
Hypothyroidism	17.49%	17.13%	0.74
Diabetes mellitus	35.10%	35.72%	−1.30
Obesity	12.72%	12.83%	−0.25
Anemia deficiency	37.22%	36.96%	0.73
Congestive heart failure	53.95%	53.37%	−0.50
Renal failure	36.41%	36.63%	−0.30
Liver disease	5.62%	4.91%	0.32
On maintenance dialysis	4.59%	4.00%	2.87
Smoking	25.57%	25.07%	1.19
Alcohol abuse	3.64%	3.37%	1.47
Long term anticoagulation use	10.29%	10.34%	−0.14
Weekend admission	18.49%	18.94%	−0.93
Elixhauser score*			4.60
- 1	10.99%	9.99%	
- 2−3	40.84%	42.57%	
- ≥4	48.17%	47.44%	
Hospital bed size			0.00
- Small	7.63%	7.59%	
- Medium	22.06%	22.28%	
- Large	70.31%	70.13%	
Expected primary payer			6.89
- Medicare	78.63%	78.71%	
- Medicaid	4.69%	4.72%	
- Private	13.50%	13.40%	
- Other	3.17%	3.18%	
Median household income in quartile			2.83
- 1st	25.23 %	25.49%	
- 2nd	24.77 %	24.59%	
- 3rd	25.03 %	25.06%	
- 4th	24.97 %	24.85%	
Hospital region			3.16
- Northeast	19.44 %	20.11%	
- Midwest	19.96 %	19.59%	
- South	40.22 %	40.44%	
- West	20.38 %	19.87%	
Hospital teaching status			0.00
-Rural	4.18 %	3.96%	
-Urban, nonteaching	35.75 %	35.90%	
-Urban, teaching	60.07 %	60.14%	

¥ASD indicates absolute standardized difference; calculated as differences in means or proportions divided by a pooled estimate of the SD.

Table 3
Impact of cTCP on outcomes

	Chronic thrombocytopenia		Odd ratio/Average* (95% CI)	p Value
	Yes	No		
Primary outcome				
In-patient mortality	3.01 %(291)	2.00 %(192)	1.53 (1.27, 1.83)	<.0001
Secondary Outcomes				
Vascular injury requiring surgery	2.63 %(251)	1.10 %(104)	2.43 (1.93, 3.05)	<.0001
Bleeding requiring transfusion	6.34 %(606)	2.45 %(238)	2.69 (2.31, 3.13)	<.0001
Cardiac tamponade	3.32 %(321)	3.32 %(318)	1.01 (0.86, 1.18)	0.935
Hemorrhagic stroke	0.44 %(42)	0.43 %(41)	1.00 (0.65, 1.54)	1.000
Ischemic stroke	2.25 %(216)	2.02 %(195)	1.13 (0.93, 1.38)	0.214
Acute kidney Injury	29.55%(2845)	22.90 %(2189)	1.44 (1.35, 1.54)	<.0001
Acute kidney injury requiring dialysis	2.78 %(268)	1.67 %(163)	1.70 (1.39, 2.07)	<.0001
Device infection	1.82 %(175)	1.25 %(123)	1.47 (1.17, 1.86)	0.001
Postoperative hematoma	4.57 % (438)	2.24 %(215)	2.08 (1.77, 2.45)	<.0001
Nonroutine discharge	54.65%(5245)	43.85%(4207)	1.56 (1.47, 1.65)	<.0001
Platelet transfusion	5.61 %(539)	0.95 % (94)	6.23 (4.98, 7.80)	<.0001
Cost − mean ($)	47, 163	35, 763	1.32 (1.29, 1.35)	<.0001
Length of stay − mean (days)	9.26	6.84	1.35 (1.32, 1.39)	<.0001

unexpected, this might be explained by the fact that operators possibly exercised extracaution in wire manipulations to preempt the risk of perforation and cardiac tamponade, given a previous knowledge of the diagnosis of cTCP.

Interestingly the incidence of postoperative stroke (whether ischemic or hemorrhagic) was similar in both matched groups. This is in sharp contradistinction to an increased incidence in ischemic strokes after PCI in patients with cTCP.[13] The obvious explanation is that in our study group most of the procedures did not necessitate left heart catheterization, intraprocedural anticoagulation or antiplatelet therapies thus attenuating both embolic and hemorrhagic risk (with the exception of TAVI). We would like to out point that chronic thrombocytopenia is a rather heterogeneous entity as there is evidence that the gravity of bleeding may depend upon the underlying cause for cTCP. Fatal bleeding is more common in patients with thrombocytopenia complicating myelodysplastic syndrome (MDS),[16] whereas chemotherapy-induced thrombocytopenia was not associated with significant bleeding except for very low platelet counts below 10×10^9/L.[17] In a large series of ICU patients, the severity of thrombocytopenia served as a biomarker for higher rates of bleeding and death.[18] Our study has a few limitations. As acknowledged earlier, a retrospective study with propensity score matching would correct for observed variables that might affect the outcome. However, this would never be as good as a dedicated prospective randomized study which would additionally, correct for nonobserved variables. Lack of medication data as well as cause and severity of cTCP is a significant limitation. In conclusion, in this cohort of patients, chronic thrombocytopenia was associated with higher risk of complications after TAVI, MitraClip, PPM, ICD, CRT, left atrial appendage closure and pericardiocentesis, including a 1.5-fold increased risk of in-hospital mortality.

Conflict of Interest

None of the authors have any conflicts of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.08.012.

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