Unprotected left main coronary stenting as alternative therapy to coronary bypass surgery in high surgical risk acute coronary syndrome patients

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Unprotected left main coronary stenting as alternative therapy to coronary bypass surgery in high surgical risk acute coronary syndrome patients

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Abstract: Acute coronary syndrome has a high mortality rate that dramatically increases in the presence of left main coronary artery (LMCA) disease. Over the past decades, coronary artery bypass graft (CABG) surgery has been commonly accepted as the standard of care for patients with LMCA stenosis and is still considered the first-line treatment in current practice guidelines. Percutaneous coronary intervention (PCI) of protected and unprotected LMCA has gained popularity and is increasingly utilized with comparable outcomes to CABG in randomized controlled trials. In-stent restenosis and the need for revascularization provide the main obstacle to LMCA revascularization. The advent of better PCI equipment, stents, ablative devices, intravascular ultrasound, hemodynamic support devices and antithrombotic agents have ignited a renewed interest in the practice of LMCA PCI, especially for high surgical risk patients who are neither candidates nor agreeable to CABG surgery. Herein, we review the studies comparing unprotected LMCA stenting with CABG surgery in regard to 3 main endpoints: mortality, major adverse events and the incidence of repeat revascularization.

Keywords: left main coronary artery disease, left main stenting, left main stenosis

Introduction

Coronary artery disease is the leading cause of death worldwide. left main coronary artery (LMCA) stenosis is a high-risk condition that represents a major challenge for interventional cardiologist. The incidence of significant LMCA stenosis is about 5% in chronic angina and 7% in recent myocardial infarction (MI) [Stone and Goldschlager, 1979; DeMots *et al.* 1977] mostly in combination with multivessel disease. The large area of myocardium affected in LMCA disease results in extensive MI, cardiogenic shock and increased mortality. The estimated incidence of cardiogenic shock in patients with MI is approximately 7–10%; the mortality rate from cardiogenic shock is approximately 80-90% without revascularization, which improves to almost 50% at 30 days with early revascularization [Goldberg *et al.* 1999; Hochman *et al.* 1999]. This high mortality results from pump failure and malignant ventricular tachyarrhythmias [Goldberg *et al.* 1978; Spiecker *et al.* 1994]. The SHOCK (SHould We Emergently Revascularize Occluded Coronaries for Cardiogenic ShocK) trial demonstrated that the mean time from MI to revascularization was 24.3 hours in the coronary artery bypass graft (CABG) group compared with 7.4 hours in the percutaneous coronary intervention (PCI) group, and from shock to revascularization was 11.3 hours in the CABG group and 3.8 hours in the PCI group [Lee *et al.* 2008]. Significant LMCA disease has a mortality rate of approximately 50% if treated medically, and improves to 3.5% after CABG surgery [Nayak *et al.* 2000]. For many decades, CABG surgery has been considered the gold standard for revascularization of LMCA lesions [Smith *et al.* 2006, 2001] based on previous randomized and observational studies [Chaitman *et al.* 1981]. Its survival benefit compared with medical treatment has been well established [European Coronary Surgery Study Group, 1980].

Protected LMCA is defined by the presence of a patent bypass graft to the left anterior descending artery (LAD) or left circumflex artery (LCX), or the presence of collateral vessels from the

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right coronary artery (RCA). Over the past decade, stenting of the LMCA has been increasingly utilized in certain high surgical risk patients averting the need for CABG surgery. However most studies were performed with small samples, in single centers, and after short-term follow up. The main concern with unprotected LMCA stenting is the periprocedural complications including dissection, thrombosis, in-stent restenosis (ISR) and the need for revascularization. The increased elastic and smooth muscle fiber within LMCA makes recoil and restenosis a feared problem after balloon angioplasty. However, the recent advances in PCI equipment, drug eluting stents (DESs), ablative devices, intravascular ultrasound (IVUS) and hemodynamic support devices, in addition to the evolution of dual antiplatelet therapy (DAPT), have spread optimism to accept LMCA percutaneous revascularization as a reasonable alternative for CABG surgery.

Studies reported 0–4% in-hospital mortality for LMCA stenting [Agostoni *et al.* 2005; Chieffo *et al*. 2005; Valgimigli *et al.* 2005; Silvestri *et al.* 2000; Takagi *et al.* 2002], which is comparable with the 3.5% postoperative mortality in LMCA disease treated with CABG surgery [Keogh, 2002]. However, due to the estimated 22% incidence of ISR reported in PCI-treated patients [Park *et al*. 1998], LMCA disease is primarily managed by CABG. Three single-center observational studies [Chieffo *et al*. 2006; Lee *et al.* 2006; Palmerini *et al*. 2006] and a small-scale randomized trial [Buszman *et al.* 2008] have concluded that there is no statistically significant difference in the intermediate term mortality between LMCA stenting and CABG for LMCA disease. The catheter-based reperfusion of unprotected left main stenosis during an acute MI, the ULTMA (Unprotected Left Main Trunk Intervention Multi-center Assessment) registry found that patients with LMCA disease who underwent stenting were sicker than their CABG counterparts, which might explain the better long-term results with CABG surgery [Marso *et al.* 1999]. The work by Wu and colleagues confirmed the same findings [Wu *et al.* 2008]. The outcome of the SYNTAX (SYNergy between PCI with TAXus and cardiac surgery) trial, the first randomized controlled trial with all-comers design that compared CABG with PCI using DESs for LMCA and three-vessel coronary artery disease (CAD) [Morice *et al.* 2010], demonstrated comparable safety and efficacy with both approaches but with a trade-off for higher incidence of repeat revascularization at 1-year in the PCI group. However, in subgroup analysis according to the number of additionally affected vessels and the complexity of lesions (SYNTAX score) the sample was unacceptably small. A few months later, a randomized study on 201 patients concluded that DESs were inferior to CABG with regard to freedom from major adverse cardiovascular events (MACE) and repeat revascularization but with no significant difference in death or MI [Boudriot *et al.* 2011]. Other comparative studies showed a trend towards favorable early outcome of PCI in comparison with CABG and agreed with the associated increased incidence of revascularization. The complexity of coronary anatomy is a main obstacle for LMCA PCI. Although it is reasonable that CABG surgery is more effective for patients with more complex coronary anatomy, this needs to be supported by randomized trials. In some centers, PCI has now become a feasible alternative for patients with LMCA disease who are neither candidates nor agreeable to CABG surgery. Herein, we review the literature in regard to the main outcomes of unprotected LMCA stenting compared with CABG surgery for patients with LMCA disease.

Review of literature

We reviewed the literature for studies that compared the outcome of CABG *versus* PCI in treating LMCA disease. The review is based on data published in scientific journals indexed by the PubMed and Medline databases using the following keywords: 'unprotected left main stenting', 'left main stenosis' and 'CABG *versus* stenting for left main disease'. Articles in English were included up to August 2011. A total of 18 studies were found and data for three main endpoints were compiled: major adverse cardiovascular and cerebrovascular events (MACCE); long-term mortality; and target vessel revascularization (TVR).

Incidence of revascularization in both groups

It is clear that most studies agreed that TVR was significantly higher in patients with LMCA disease treated with PCI. ISR has been the major contributing factor to the inferiority of PCI in treating LMCA disease. Incidence of restonosis at 6 months has been found to reach 25.7% [Colombo *et al.* 2004] and is mainly observed in patients with distal bifurcated LMCA disease, which has a prevalence of 36.9% [Das and Meredith, 2007; Giannoglou *et al* 2006]. TVR is six-fold higher in patients with bifurcational

stenosis compared with nonbifurcational lesions [Valgimigli *et al.* 2006]. Distal bifurcational lesions have been associated with higher incidence of restenosis at the origin of the LCX in three major studies [Chieffo *et al.* 2005; Valgimigli *et al.* 2005; Park *et al.* 2005]. One study evaluated the outcome of stenting of LMCA in regard to the site of lesion and concluded a significant increase in MACE at 1 year ($p = 0.014$) and 2 years ($p = 0.002$) in the group with distal bifurcated lesions [Chen *et al.* 2009]. Kim and colleagues found a significantly lower angiographic restenosis and TVR with the use of DESs compared with bare metal stents (BMSs) [5.4% versus 12.1%; hazard ratio (HR) 0.40; 95% confidence interval (CI) 0.22–0.73; $p = 0.003$] [Kim *et al.* 2009]. However, a major concern since the evolution of DESs is stent thrombosis [Omar *et al.* 2012], which is especially important when more than one DES is used with overlapping struts increasing drug dosage and impairing re-endothelialization [Finn *et al.* 2005]. For this reason, the US Food and Drug Administration has warned that the risk of stent thrombosis may outweigh the benefits of DES in off-label use such as for patients with unprotected LMCA stenosis.

Another factor explaining the increased incidence of revascularization in the PCI group is the significantly higher rate of follow-up angiography. In one study, 73% of patients in the PCI group *versus* 14.6% in the CABG group received coronary angiography, underestimating the number of patients with asymptomatic graft stenosis or occlusion [Seung *et al.* 2008]. Moreover, LMCA disease is frequently associated with significant calcification and other multivessel stenoses [Price *et al.* 2006].

Is there any mortality benefit with either approach?

The Society of Thoracic Surgeons (STS) National Database reported an in-hospital mortality of 3.9% in patients with LMCA disease undergoing CABG surgery [STS, 1999] and the Cleveland clinic foundation reported an in-hospital and 1-year mortality of 2.3% and 11.3%, respectively [Ellis *et al.* 1998]. These numbers were comparable with patients undergoing PCI for unprotected LMCA disease. As is clear from Table 1, most studies did not find a statistically significant difference in long-term mortality between PCI and CABG despite the complexity of patient population in the PCI group. One study showed a significant survival benefit [Wu *et al.* 2008] with a mortality rate (when including all patients from 1 January 2000 to 31 December 2004) of 5.93% in CABG *versus* 17% in PCI patients (HR 0.32, CI 0.14–0.71; $p = 0.003$). However, in the DES era (between 10 January 2003 and 31 December 2004), the difference in mortality between the PCI and CABG group was insignificant (HR = 0.73, $p = 0.69$). Interestingly, in a later study, there was a trend toward lower mortality after PCI compared with CABG with propensity score analysis ($p = 0.06$); however, results did not reach significance [Wu *et al.* 2010].

The 5-year survival after PCI or CABG for LMCA disease was evaluated by two studies [Park *et al.* 2010; Chieffo *et al.* 2010], which found no significant difference between both approaches. Mortality in the elderly patients >75 years was evaluated in three studies [Ghenim *et al.* 2009; Rittger *et al.* 2011; Palmerini *et al.* 2007]. After adjusting for the propensity score, patients treated with DESs had a nonsignificant trend towards better survival (HR = 0.81, 95% CI 0.37–1.81) [Palmerini *et al.* 2007].

Predictors of mortality were determined by several studies. Kim and colleagues demonstrated that high surgical risk represented by high EuroSCORE or Parsonnet score were independent predictors of death or myocardial infarction after PCI for unprotected LMCA disease [Kim *et al.* 2008]. Brener and colleagues showed two predictors of mortality at 3 years to be a high Euroscore (HR 1.33, 95% CI 1.16-1.54; $p < 0.001$) and diabetes mellitus (HR 1.96, 95% CI 1.24–3.09; $p = 0.004$) [Brener *et al.* 2008]. In one study, the predictors of mortality at 2 years were: peripheral vascular disease, left ventricular ejection fraction and acute coronary syndrome (ACS) [Palmerini *et al.* 2007]. Reduced left ventricular systolic function was the most significant independent predictor of mortality in another study (HR 14.9, 95% CI 5.5–40.0, $p < 0.001$) [Mäkikallio *et al.* 2008].

MACCE and major adverse events

Three studies demonstrated a significant benefit for CABG over PCI in LMCA disease with regards to MACCE [Kang *et al.* 2010; Serruys *et al.* 2009; White *et al.* 2008]. The increase in MACCE was essentially driven by an increase in revascularization rate. Other studies failed to show any benefit

Table 1. A compilation of the three major outcomes from studies utilizing PCI *versus* CABG for treatment of LMCA disease.

Study	*N* (PCI arm)	Stent type	MACCE	Long-term mortality	Revascularization	Conclusion
Lee *et al.* [2006]	50	DES	At 30 days, 17% in CABG *versus* 2% in PCI, $p < 0.01$. MACCE-free survival at 6 months and 1 year was 83% and 75% in the CABG group *versus* 89% and 83% in the PCI group, $p = 0.2$	Freedom from death at 1 year: 85% in CABG *versus* 96% in PCI, $p = 0.18$	Freedom from TVR at 1 year 95% in CABG *versus* 87% in PCI, $p = 0.22$	DES is not associated with increased immediate or medium-term complications compared with CABG.
Sanmartin *et al.* [2007]	96	DES	At 30 days 2.1% in PCI and 9% in CABG, $p = 0.03$. However, at 1 year, 10.4% in PCI and 11.4% in CABG, $p = 0.5$ (NS)	At 1 year, 5.2% in PCI *versus* 8.4% in CABG, $p = 0.37$	5.2% in PCI *versus* 0.8% in CABG, $p = 0.02$	PCI provided similar clinical results at midterm compared with CABG
Palmerini *et al.* [2007]	98	DES	Incidence of 2-year MI was 6% in CABG and 4% in DES, $p = 0.11$	15% in CABG *versus* 13% in PCI, $p = 0.74$	3% in CABG *versus* 25% in PCI, $p < 0.0001$	No mortality difference between CABG and PCI. TLR higher in PCI group.
Wu *et al.* [2008]	135	DES and BMS		At 2 years, 5.93% in CABG *versus* 17% in PCI, $p = 0.005$	27.4% in PCI *versus* 5.9% in CABG, $p < 0.001$	CABG is associated with lower risk of long-term death and repeat revascularization compared with PCI.
White *et al.* [2008]	120	DES*	MACCE higher in PCI group. HR 1.83, CI 1.01 → 3.32, $p = 0.05$	HR in PCI *versus* CABG 1.93, CI 0.89 → 4.19, $p = 0.1$		Propensity-adjusted risk of mortality does not differ between PCI- and CABG-treated groups.
Buszman *et al.* [2008]	52	DES and BMS	PCI had lower 30-day risk of MAE ($p < 0.006$) and MACCE ($p = 0.03$) and shorter hospitalization ($p < 0.0007$) but total MACCE-free 1-year survival was comparable	1-year survival 98.1% in PCI *versus* 92.5% in CABG, $p = 0.37$	28.8% in PCI *versus* 9.43% in CABG, $p = 0.01$	PCI group had a favorable early outcome in comparison with CABG group. After 2 years, MACCE-free survival was similar, with trend towards better survival with PCI.
Makikallio *et al.* [2008]	49	DES		4% in PCI *versus* 11% in CABG, $p = 0.136$		PCI for selected LMCA disease patients results in short- and midterm outcomes comparable with CABG.
Brener *et al.* [2008]	97	DES and BMS**		3-year mortality 15% in CABG *versus* 20% in PCI, $p = 0.14$	4.6% of the PCI group required revascularization	PCI had 3-year survival similar to CABG.
Serruys *et al.* [2009]	903	PES	17.8% in PCI *versus* 12.4% in CABG, $p = 0.002$. Higher risk of stroke in CABG group 2.2% *versus* 0.6% in PCI, $p = 0.003$	4.4% in PCI *versus* 3.5% in CABG, $p = 0.37$	13.5% in PCI *versus* 5.9% in CABG, $p < 0.001$	CABG remains the gold standard of care for patients with LMCA disease due to lower rates of combined endpoint of MACCE at 1 year.

Table 1. (Continued)

Study	*N* (PCI arm)	Stent type	MACCE	Long-term mortality	Revascularization	Conclusion
Ghenim *et al.* [2009]	105	DES	At 1 year, 13.9% in CABG *versus* 14.9% in PCI, $p = 0.841$ ***		1% in CABG *versus* 13.9% in PCI, $p < 0.001$	In patients with high probability of being treated with PCI (old age, high Euroscore, high creatinine, single vessel disease), MACCE was significantly lower. Incidence of repeat revascularization is significantly higher in PCI group.
Wu *et al.* [2010]	131	DES¶	27% in PCI *versus* 22% in CABG, $p = 0.42$	4.6% in PCI *versus* 9.4% in CABG; propensity score–adjusted HR 0.34, $p = 0.06$	18% in PCI *versus* 9% in CABG, $p = 0.02$. However, ischemic TVR was not significantly different between both groups, $p = 0.15$	At 4-year follow up, MACCE were similar in both PCI and CABG groups, with a trend toward lower mortality after PCI. DES were associated with a higher TVR but ischemic TVR was comparable in both groups.
Morice *et al.*[2010]	357	PES	13.7% in CABG *versus* 15.8% in PCI, $p = 0.44$. Stroke significantly higher in CABG arm 2.7% *versus* 0.3%, $p = 0.009$	At 1 year, all-cause mortality was 4.4% in CABG *versus* 4.2% in PCI, $p = 0.88$	11.8% in PCI *versus* 6.5% in CABG, $p = 0.02$	Revascularization with PCI was comparable with CABG at 1 year.
Park *et al.* [2010]	1102	DES and BMS ¶¶	HR of PCI *versus* CABG 1.1 (CI 0.74 → 1.38. $p = 0.94$ ¶¶¶	At 5 years, HR for PCI *versus* CABG was 1.02 (CI 0.74 → 1.39), $p = 0.91$	HR of PCI *versus* CABG 4.55 (CI 2.88 → 7.2, $p < 0.001$	At 5 years, there was no significant difference in death or MAACE, but higher revascularization in PCI group.
Chieffo *et al.* [2010]	107	DES ‡	At 5 years, 32.4% in PCI *versus* 38.3% in CABG. Adjusted OR 1.57, $p = 0.18$	At 5 years, cardiac death 11.9% in CABG *versus* 7.5% in PCI, adjusted OR 0.502, $p = 0.24$	TVR 28% in PCI *versus* 8.4% in CABG. Adjusted OR 4.41, $p = 0.0004$	At 5 years, there was no difference in MACCE between PCI and CABG but PCI had less composite endpoints of death, MI and/or stroke. CABG had benefit of less intervention.
Kang *et al.* [2010]	205	DES ‡‡	35.1% in PCI *versus* 21.8% in CABG. $p = 0.001$	14.1% in PCI *versus* 12.1% in CABG, $p = 0.428$	22.4% in PCI *versus* 5.1% in CABG, $p < 0.001$	PCI is safe comparable to CABG but with the added risk of increased repeat revascularization.
Shimizu *et al.* [2010]	64	DES ‡‡‡	At 2 years, MACCE-free survival 82.2% in CABG *versus* 62.6% in PCI, $p = 0.033$	At 2 years, overall survival 91.9% in PCI *versus* 93.4% in CABG, $p = 0.288$	23.4% in PCI *versus* 1.6% in CABG	CABG is more cost-effective and can still be the first revascularization strategy. Total hospitalization costs were lower in CABG group ($p = 0.013$).

(Continued

Table 1. (Continued)

Study	*N* (PCI arm)	Stent type	MACCE	Long-term mortality	Revascularization	Conclusion
Boudroit *et al.* [2011]	100	SES	MACE 19% in PCI and 13.9% in CABG, noninferiority $p = 0.19$	2% in PCI *versus* 5% in CABG, noninferiority $p < 0.001$	14% in PCI *versus* 5.9% in CABG, noninferiority $p = 0.35$	PCI with DES was inferior to CABG at 12 months with respect to repeat revascularization and freedom from MACE.
Rittger *et al.* [2011]	95	DES $	MACE 13.7% in CABG *versus* 14.7% in PCI, adjusted $p = 0.16$	At 12 months, 6.8% in CABG *versus* 4% in PCI, adjusted $p = 0.27$	TLR was 1.5% in CABG *versus* 10.5% in PCI, adjusted $p = 0.001$	DES is feasible with a short- and intermediate term outcome comparable with CABG.

* 91 SES and 29 PES.
** 37 patients received BMS and 55 received DES (30 SES and 25 PES) and balloon angioplasty alone was performed in 5 patients.
*** Patients in the subgroup with a high probability of being treated by PCI, the probability of MACCE was significantly lower in the PCI group after adjustment for age, presence of diabetes, left ventricular ejection fraction, Euroscore, and creatininemia: OR = 0.16 [0.04–0.69), $p = 0.013$.
¶ 126 patients received SES and 5 ZES.
¶¶ 318 and 784 patients received BMS and DES respectively; out of DES, 77% received SES and 23% received PES.
¶¶¶ HR were obtained among the propensity-matched patients.
‡ 52 had PES and 55 had SES.
‡‡ Most PCIs were performed with SES and PES and ZES were used in 7 patients.
‡‡‡ SES in 61 patients and PES in 3 patients.
$ 85 patients received a SES and 10 cases received another DES.
HR, hazard ratio; MACCE, major adverse cardiovascular and cerebrovascular events; MACE, major adverse cardiovascular events; MI, myocardial infarction; N, number; NS, nonsignificant; OR, odds ratio; PES, paclitaxel-eluting stent; RR, relative risk; SES, sirolimus-eluting stent; TLR, target lesion revascularization; TVR, target vessel revascularization; ZES, zotarolimus-eluting stent.

in MACCE for CABG over PCI including the landmark SYNTAX trial [Morice *et al.* 2010].

Although MACCE was greater in the PCI group (HR 1.83, 95% CI 1.01 to 3.32; $p = 0.05$) in the study by White and colleagues, MACCE-free survival was not different in propensity-matched individuals [White *et al.* 2008]. On the other hand, several studies found a significant increase in stroke risk in the CABG group. Serruys and colleagues concluded that the rate of stroke was significantly higher with CABG (2.2% *versus* 0.6% with PCI; $p = 0.003$) even after adjustment for confounding variables including carotid artery disease and other stroke risk factors [Serruys *et al.* 2009]. In the SYNTAX trial, stroke was also significantly higher at 1 year in the CABG arm (2.7% in CABG *versus* 0.3 in PCI; $p = 0.009$).

Furthermore, some studies showed a statistically significant lower risk of major adverse events (MAEs) and MACCE in the PCI group at 30 days. Buszman and colleagues demonstrated a lower incidence of MAEs in the PCI group at 30 days (8% in PCI *versus* 28% in CABG, 95% CI 0.64–0.94; $p = 0.006$) and lower MACCE (2% in PCI *versus* 13% in CABG, 95% CI 0.79–0.99; $p = 0.003$) in addition to shorter hospitalization; $p = 0.0007$ [Buszman *et al.* 2008]. Sanmartín and colleagues showed a decreased incidence of MACCE at 30 days in the PCI group (2.1% in PCI *versus* 9% in CABG; $p = 0.03$) [Sanmartín *et al.* 2007]. In another study the 30-day MACCE was 2% in the PCI group *versus* 17% in the CABG group in addition to longer hospitalization of the CABG group ($p < 0.01$) [Lee *et al.* 2006]. In all three studies, however, long-term MAE- and MACCE-free survival were comparable in both groups [Buszman *et al.* 2008; Sanmartín *et al.* 2007; Lee *et al.* 2006].

In the SYNTAX study, predictors of MACCE at 1 year were emergent revascularization, diabetes mellitus and higher Euroscore, whereas female gender was associated with significantly reduced MACCE [Morice *et al.* 2010]. Bifurcation involvement was determined to be a predictor of MACE in another study (HR 12.9, 95% CI 1.36–122.45; $p = 0.0259$) [Kim *et al.* 2008]. Lee and colleagues determined the predictors of MACCE to be Parsonnet score, diabetes mellitus and MI [Lee *et al.* 2006]. Another factor found to affect MACCE was whether CABG was performed on-pump *versus* off-pump. In-hospital MACCE was lower in patients with off-pump surgery (19.6%

versus 36% with on-pump CABG; $p = 0.04$) and this benefit was maintained at 1 year (MACCE 30.3% *versus* 43% with on-pump CABG; $p = 0.15$) [Chieffo *et al.* 2006].

Conclusion

The review emphasizes that stenting of LMCA disease can be a therapeutic option, with promising short- and intermediate-term results, in high surgical risk patients presenting with ACS due to LMCA disease. The safety profile suggested by these observational and randomized trials suggest that PCI for LMCA disease might be an alternative to CABG surgery in patients with significant comorbidities increasing their surgical risk if the patient is willing to accept the higher incidence of repeat revascularization. Further randomized trials are mandatory to directly address the safety and long-term outcome of LMCA stenting.

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The authors declare no conflicts of interest in preparing this article.

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