

Apolipoprotein E Genotype and Cardiovascular Diseases in the Elderly

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Published online: 16 July 2010

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Abstract The apolipoprotein E (APOE) genotype is a genetic risk factor for dementia, Alzheimer’s disease, and cardiovascular disease (CVD). It includes three alleles (e2, e3, e4) that are located on chromosome 19q3.2. The e3 allele is the most common and is more common in people of Northern European ancestry and less common in those of Asian ancestry. Those with at least one e4 allele are at increased risk for CVD outcomes. It is well established that the presence of an e4 allele is linked to higher low-density lipoprotein cholesterol levels, even at young ages. Even though most CVD occurs in older people, there are few studies of the effects of APOE on CVD in older people. This review addresses recent research on the links between APOE, CVD, and vascular mechanisms by which APOE may affect CVD in the elderly.

Keywords Apolipoprotein E · Cardiovascular disease · Elderly

Introduction

In 2006, cardiovascular diseases (CVD) accounted for 34.3% of all deaths in the United States [1] (approximately

the deaths of 831,000 people). In that year, there were an estimated 74 million people with high blood pressure, nearly 18 million with coronary heart disease (CHD), and 6.4 million with strokes. The vast majority of these events and diagnoses occur among people aged ≥ 65 years, such that the prevalence of heart disease and stroke in people over 65 years of age is nearly four times higher compared with people aged 18 to 64 years [2]. Personal health care expenditures in 2005 for Medicare recipients for heart disease, stroke, and hypertension totaled nearly \$50,000 per person [3]. According to statistics published by the National Center for Health Statistics, the prevalence of these conditions in the United States in people aged ≥ 65 years declined by about 20% between 1999 and 2006. However, it is likely that death from CVD in people with these conditions is simply being postponed, and that the decline in the death rates will lead to a potential future increase in CVD morbidity in people over the age of 80 years [1] because those who would have died instead survive with their condition and contribute to the overall population burden of CVD-related chronic conditions [1]. Treatments for CVD and prevention of risk factors for CVD have become more effective and more widely used. Statin drugs were used by 24 million Americans in 2003 and 2004 and their use is higher among people with higher levels of low-density lipoprotein cholesterol (LDL-C) who are aged ≥ 75 years than among those aged 20 to 39 years [4]. Cigarette smoking is a prime example of this kind of change, as prevalence of smoking has declined and in 2006 to 2008, 23% of those over age 18 years were current smokers compared with nearly 40% of those over 65 years of age.

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Studies of coronary heart disease, lipids, and coronary atherosclerosis from 2000 to 2010

Study	Year	Cases/sample or controls	Age range, y	Ethnic group	Design	APOE allele	Outcome	Risk estimate (95% CI)
Slooter et al. [20]	2004	185/6852	55+	Europeans	Cohort	e3/e4 or e4/e4	MI	1.0 (0.7–1.4) 1.7 (0.8–3.6)
Ward et al. [21 ^a]	2009	2712/22,169	40–79	Europeans	Cohort	Any e4 ^a	CHD	1.09 (1.0–1.19)
Scuteri [11]	2001	104/730	21–96	US white men	Cohort	Any e4 ^a	Coronary events	2.01 (1.4–3.1)
Volcik et al. [19]	2006	447/12,491	45–64	US whites and blacks	Cohort	Any e4 ^a	CHD	Whites: 1.07 (0.94–1.21) Blacks: 1.13 (0.91–1.40)
Lahoz et al. [42]	2001	242/1668	11–65	US white men	Cohort	Any e4 ^a	CVD	1.46 (0.99–2.15)
Lahoz et al. [42]	2001	121/1739	9–62	US white women	Cohort	Any e4 ^a	CHD	1.36 (0.78–2.38)
Bennett et al. [16]	2007	37,850/82,727 ^c	NA	Mixed studies	Meta-analysis of 121 case-control studies with 500+	Any e4 ^a	CHD	1.06 (0.99–1.13)
Song et al. [13]	2004	15,492/32,965	NA	Mixed studies	Meta-analysis of 48 case-control studies	Any e4 ^a	CHD	1.42 (1.26–1.61)
Anand et al. [14]	2009	25,348/51,484	30–64	Asian, European, Arab, Nepalese	Case control	e4 ^a	MI	1.07 (1.01–1.28)
Keavney et al. [15]	2004	4685/3420	30–64	UK whites	Case control	Per e4 allele vs e2/e3	Nonfatal MI	1.16 (1.06–1.27)
Georgoulas et al. [22]	2009	410	40–87	Greek	Patient group	Any e4 ^a	Myocardial perfusion SSS > 2 ^b	35.8 (13.1–98.1)
Frikke-Schmidt et al. [43]	2000	940/9241	20–80	Danish men	Case-referent	e4/e3 ^a	IHD	1.16 (0.96–1.41)
Liu et al. [17]	2003	385/373	40–84	US men	Nested case control	Any e4 ^a	MI	0.93 (0.63–1.37)
Mooijaart et al. [18]	2006	546	85	Dutch	Cohort	e4/e3 modified by plasma APOE	Cardiovascular death	Intermediate plasma APOE: 2.81 ^c (1.02–7.74) High plasma APOE: 4.25 ^c (1.38–13.0)

APOE apolipoprotein E; *CHD* coronary heart disease; *CVD* cardiovascular disease; *IHD* ischemic heart disease; *MI* myocardial infarction; *SSS* summed stress score; *UK* United Kingdom; *US* United States

^a Versus e33

^b Severity of perfusion defect under stress

^c Intermediate and high plasma ApoE

Studies of stroke, hypertension, and carotid atherosclerosis from 2000 to 2010

Study	Year	Cases/sample or controls	Age range, y	Ethnic group	Design	APOE	Outcome	Risk estimate (95% CI)
McCarron et al. [44]	1999	9 studies	NA	Japanese, Canadian, European	Meta-analysis of 9 case-control studies	Any e4 ⁺	Ischemic CVD	1.68 (1.36–2.09)
Slooter et al. [20]	2004	149/6852	55 +	Dutch	Cohort	e3/e4 e4/e4	Ischemic stroke	0.9 (0.6–1.3) 0.6 (0.1–2.5)
van Vliet et al. [34]	2007	99/561	85+	Dutch	Cohort	e3/e4 ⁺	Stroke	3.01 (1.34–6.74)
Wang et al. [45 ^a]	2009	396/396	57 (mean)	Han Chinese	Case control	Any e4 ⁺	Stroke	1.50 (1.13–1.91)
Sturgeon et al. [46]	2007	180/5054	45–64	US white men	Cohort	Any e4 ⁺	Ischemic stroke	0.98 (0.70–1.38)
Sturgeon et al. [46]	2007	97/1499	45–64	US black men	Cohort	Any e4 ⁺	Ischemic stroke	0.77 (0.49–1.24)
Banerjee et al. [47]	2007	6107	50–70	Asian	Meta-analysis	Any e4 ⁺	Stroke	1.47 (1.00, 2.15)

Lahoz et al. [42]	2001	242/1668	11–65	US white men	Cohort	Any e4 ⁺	CVD	1.46 (0.99–2.15)
Niu et al. [10]	2009	1812/1762	40+	Asian	Meta-analysis of 6 case-control studies	Any e4 ⁺	Hypertension	1.97 (1.11–3.52)
Volcik et al. [19]	2006	15,792	45–64	US white and black	Cohort	Any e4 ⁺	Carotid IMT (mean [SE]) ^a	e4: 0.74 (0.003)
Debette et al. [48]	2006	5856	65+	European	Cohort	e4/e4 vs. e33	Carotid plaque	2.12 (1.27–3.53)
Beilby et al. [49]	2003	1109	27–77	Australian white men	Cross-sectional	e4/e4 e3/e4	Carotid plaque	2.85 (0.49–16.6) 1.79 (1.01–3.17)

APOE apolipoprotein E; *CVD* cardiovascular disease; *IMT* intimal media thickness

^a $P < 0.05$ versus e33

The apolipoprotein E (APOE) genotype is a genetic risk factor for dementia, Alzheimer's disease, and CVD. It is among the more common genotypes. It includes 3 alleles (e2, e3, e4) and 6 genotypes (e22, e23, e24, e33, e34, e44) that occur on chromosome 19q3.2. The e3 allele is the most common of the three and may be considered an ancestral allele. The e4 allele is more common in people of Northern European ancestry and lower in those of Asian ancestry [5]. Those with at least one e4 allele are at increased risk for CVD outcomes, and homozygosity for e4 (ie, e4/e4) increases risk further. It is well established that the presence of an e4 allele is linked to higher LDL-C levels; this is found even at younger ages, and LDL-C increases more rapidly with age in those with the e4 allele [6].

Apolipoprotein E is often found to interact with environmental risk factors, such as smoking or diet, to increase risk. Compared with e2 or e3, the e4 allele may contribute to earlier and higher mortality, which in turn contributes to a lower occurrence of the e4 allele in older compared with younger people [7–9]. Apolipoprotein E is often reported to modify the effects of environmental risk factors such as diet, smoking, or physical activity on cardiovascular outcomes.

Multiple individual studies, reviews, and meta-analyses have previously examined and summarized the influence of the APOE genotype on the risk of CVD. Most studies have focused on CHD, atherosclerosis, hypertension, and ischemic stroke, and some mechanistic studies have evaluated the role of lipids and inflammation in the links between apolipoprotein e4 and vascular outcomes. This review includes only studies published after 1998 that were sufficiently large to have statistically significant effects. In addition, only studies for which the referent or target population was identifiable were selected. This review is divided into studies examining 1) cerebrovascular diseases, including ischemic stroke, hypertension, or carotid atherosclerosis; and 2) studies examining CHD, lipids, and coronary atherosclerosis. Only studies in which there were older

adults were included, with the exception of a longitudinal study of young adults modeling change over time in LDL-C in relation to apolipoprotein E [6]. Only a few studies that are restricted to older populations (age ≥ 65 years) have been done of the effects of apolipoprotein E on these outcomes. Most studies include middle-aged individuals with smaller numbers of older individuals, and they do not report apolipoprotein E effects by age strata or test interactions between apolipoprotein E and age. Therefore, information about the differences between younger and older people in the effects of apolipoprotein E on vascular outcomes is limited. The effects of population heterogeneity by nationality, race, or ethnicity on apolipoprotein E and vascular outcomes is addressed in a number of recent studies.

Stroke

Ischemic stroke is the most common form of stroke and the most frequent stroke outcome studied in relation to apolipoprotein e4. Three of the publications included here did not distinguish ischemic from hemorrhagic stroke. Overall, the risk of ischemic stroke in those with an e4 compared with an e3 allele ranges from a risk of 0.77 (95% CI, 0.49–1.24) in US middle-aged black men [46] to 3.01 (95% CI, 1.34–6.74) in Dutch people over the age of 85 years [34]. Among studies of people of Asian origin, the elevated risk of stroke associated with apolipoprotein e4 is more consistent (around 1.50 for e4 vs e3) than in people of European origin, in whom it ranges from 0.90 to 1.68 in samples of middle-aged individuals [20, 44].

Hypertension and carotid atherosclerosis are common mechanisms related to stroke risk. Only one recent study has examined the association between apolipoprotein e4 and hypertension [10], yielding a risk of 1.97 (95% CI, 1.11–3.52) in a meta-analysis of six cohort studies of Asians [46]. In addition, four studies in various population groups have reported significant increases in carotid atherosclerosis or carotid plaques in those with an e4 compared with an e3

allele [19, 48, 49]. Of all the studies of apolipoprotein E and cerebrovascular disease that we reviewed, only four were restricted to people over the age of 55 years and none examined age-specific effects or tested interactions between apolipoprotein E and age [20, 34, 47, 48].

Notable among these studies are the following. 1) The only study to focus on elderly people (age ≥ 85 years) found that the effects of the e3/e3 and e3/e4 genotypes on stroke were mediated by plasma apolipoprotein E levels [34]. In e3/e4 carriers, a 1-SD difference in plasma apolipoprotein E was associated with a threefold increase in stroke risk ($P=0.002$). In the e3/e3 genotype, this risk was 1.95 ($P=0.002$). Stroke risk in e2 carriers was not mediated by plasma apolipoprotein E. 2) A meta-analysis of six studies of hypertension risk including only Asian participants that compared the e3 to the e4 allele found that the odds of hypertension were elevated in e4 carriers [47]. The summary estimate was more consistent than studies of Europeans. It is possible that there is less subpopulation heterogeneity in this group of Asian studies than in European studies.

Coronary Heart Disease

In the current literature, several large cohort studies report that the apolipoprotein e4 allele is associated with an increased risk of CHD, with a risk ranging between 1.1 and 2.0 [11–16]. Six of the 13 found a significantly increased risk of CHD in e4 carriers. Three of the 13 studies found no association between the e4 allele and CHD [17–19]. Mooijaart et al.'s study [18] was the only population-based study we found that restricted enrollment to elderly participants who were Dutch and ≥ 85 years of age. Some of these studies may have lacked power to detect differences in CHD risk due to small sample size.

In a Dutch cohort study of 6852 men and women 55 years of age were followed for up to 8 years, the authors reported that the e4 allele was weakly associated with myocardial infarction, with e3/e4 individuals experiencing no increased risk (RR=1.0; 95% CI, 0.7–1.4) compared with e3/e3 individuals [20]. In the same study, e4/e4 individuals, who made up a small proportion of the sample ($n=162$), experienced an increased risk that was not statistically significant (relative risk=1.7; 95% CI, 0.8–3.6) [20].

In a cohort study of 25,630 English men and women aged 40 to 79 years who were followed for up to 11 years, individuals with the e4 allele experienced a slightly higher risk for CHD (hazard ratio=1.09; 95% CI, 1.0–1.19) [21]. This relation was mediated by the ratio of low-density lipoprotein (LDL) to high-density lipoprotein (HDL); adding this variable to the regression models changed the

hazard ratio to 1.06 (95% CI, 0.95–1.18), but the association remained statistically significant.

A cohort study of 1094 Swedish men and women 75 years or older at baseline who were followed for up to 18 years found Individuals with the e4 allele were significantly more likely to die than individuals who were homozygous for the e3 allele over the 18 years of follow-up (RR=1.22; 95% CI, 1.07–1.41) [9]. The authors investigated whether this relation was modified by ischemic heart disease or dementia. They found that increased risk of mortality was mediated by dementia but not by ischemic heart disease, but gender was an effect modifier.

A 2007 meta-analysis of 121 large studies found that individuals with the e4 allele had a slightly higher risk of CHD (odds ratio=1.06; 95% CI, 0.99–1.13) [16]. There are very few large studies examining the role of apoe4 in relation to coronary atherosclerosis. One study of patients aged 61 years (mean) who underwent exercise-rest myocardial perfusion single positron emission computed tomography (SPECT) reported that individuals who were homozygous for e3 and e4 and individuals who were heterozygous for e4 had significantly higher values of a summed stress score (SSS) compared with those who were heterozygous for the e3 allele ($P<0.001$) [22]. After adjustment for demographic and clinical risk factors, both APOE genotypes were independent predictors, with a cumulative contribution for the prediction of SSS and summed difference score. All APOE4 genotypes had higher levels of abnormal SSS, indicating they are linked to coronary atherosclerosis.

Cardiovascular Mechanisms

Lipids

Many studies have found that individuals with the apolipoprotein e4 allele have higher plasma LDL levels than individuals without the apolipoprotein e4 allele [16, 18, 19, 21, 23]. For example, work by Giltay et al. [23] reported that LDL-C was significantly ($P<0.001$) lower in those with the e2/e2 or the e3/e2 genotype (mean of 3.2 mmol/L [95% CI, 3.0–3.5]) than in those with the e3/4 (mean of 4.1 mmol/L [95% CI, 3.9–4.2]) or e4/e4 genotype (mean of 4.5 mmol/L [95% CI, 3.9–5.2]). Similarly, high-density lipoprotein cholesterol (HDL-C) was significantly ($P<0.001$) higher in those with the e2/e2 (mean of 1.31 mmol/L [95% CI, 1.25–1.37 mmol/L]) and e3/e2 genotypes (mean of 1.24 mmol/L [95% CI, 1.14–1.34]) than in those with the e4/e3 (mean of 1.20 [95% CI, 1.16–1.23]) or the e4/e4 (mean of 1.17 [95% CI, 1.01–1.34]) genotypes.

It is less clear whether this apolipoprotein-related increase in LDL leads to an increased risk of CVD. Two recent cohort

studies suggest that plasma lipid levels mediate the relationship between apolipoprotein e4 genotypes and CHD [15, 21]. However, three of these studies reported that the apolipoprotein e4 allele is associated with significantly higher plasma LDL levels but not associated with CHD. In a 2007 meta-analysis of 82 large case-control studies, e4/e3 individuals had 0.13 mmol/L (95% CI, 0.09–0.16) higher mean plasma LDL levels than e3/e3 individuals [16], and in a cohort of 22,279 European men aged 70 to 89 years at baseline, e4 carriers had significantly higher plasma LDL levels than non-e4 carriers (mean difference of 0.23 mmol/L [95% CI, 0.09–0.37]) over 15 years of follow-up [24].

A Dutch cohort study enrolled 561 individuals aged 85 years and followed them for an average of 4.2 years [18]. On average, plasma LDL-C levels were significantly higher in e4/e3 individuals than in e3/e3 individuals (4.14 mmol/L [95% CI, 3.96–4.32] vs 3.70 mmol/L [95% CI, 3.60–3.80]; $P < 0.001$). Over the course of the study, 68 participants died of CVD. The authors reported that e4/e3 and e4/4 carriers experienced a nonsignificant increased risk for cardiovascular mortality compared with e3/e3 individuals. The results of this study suggest that in the elderly, higher plasma LDL levels may not be associated with CVD. However, this study may have lacked power to detect differences in cardiovascular mortality due to smaller sample size.

A nested case-control study found significantly higher mean plasma LDL levels in individuals with the e3 allele compared with e3/e3 individuals (mean of 3.51 mmol/L [95% CI, 3.37–3.65] and 3.64 mmol/L [95% CI, 3.56–3.72], respectively), but the authors did not find an increased risk of first myocardial infarction in e4 carriers compared with e3/e3 individuals (odds ratio=0.87; 95% CI, 0.62–1.23) [17].

Change in Exposure to Lipids and Other CVD Risk Factors with Age

Risk factors for CVD tend to change with aging due to changes in lifestyle, selective survival, or age-dependent physiologic changes. There are also cohort effects representing time-dependent changes in exposure to risk factors. As an example, higher serum total cholesterol and LDL-C are well-accepted as risk factors for CHD in middle age and early old age, but this association may disappear or reverse at older ages [25]. Raiha et al. [25] reported in a cohort of 347 people aged ≥ 65 years that elevated total serum cholesterol did not predict vascular mortality but was a predictor of survival from death due to nonvascular causes. In fact, lower lipid levels were associated with poorer survival and higher with better survival from vascular mortality, and the effects of apolipoprotein e4 on death were unrelated to lipid levels. Current lipid levels in the elderly do not accurately represent lifetime exposure because many lifestyle factors (smoking, heavy alcohol use) that influence lipids change with age and

these changes may modify lipid levels with advancing age [26]. To the extent that APOE genotypes tend to interact with vascular risk factors, changes in these risk factors can modify risk. Smoking is lower in elderly populations compared with younger groups (21% vs 9.3% in 2008). Some of this may be a cohort effect, due to selective survival of nonsmokers or due to smoking cessation. For these reasons, the impact of apolipoprotein e4 on vascular outcomes may be attenuated in elderly individuals if exposures vary by age and over time. Thus, at older ages, the deleterious effects of apolipoprotein e4 may not be exclusively mediated by dyslipidemia but also by other mechanisms.

Inflammation

Considerable evidence now exists linking inflammatory responses to an increased risk of CHD and stroke [27–30]. Inflammatory responses also increase in individuals with chronic conditions, so inflammation is as likely to be a marker of disease as a cause.

Inflammatory responses may be affected by the APOE genotypes. C-reactive protein, which is variously linked to CHD, varies by APOE genotype such that carriers of e2 and those with the e3/e3 genotype have higher levels of C-reactive protein than those with e3/4 or e4/e4 [31, 32, 41]. In the very elderly (≥ 90 years of age), the e4 allele is linked to a decreased C-reactive protein response compared with younger people [33].

Fibrinogen, sometimes shown to be a CHD risk factor, is higher in elderly people with e3/e4 versus e3/e3 or e4/e4. Apolipoprotein e4 carriers have higher levels of the inflammatory cytokine interleukin (IL)-1 β and lower levels of its receptor antagonist. Tumor necrosis factor- α , and IL-6 are downregulated by the e4 allele. Plasma apolipoprotein E in very old people provokes an inflammatory response that may be independent of the genotypes e4/e4 or e3/e4 [34].

Homocysteine is a sulfur amino acid that is variably linked to stroke and to ischemic heart disease and sometimes to dementia [35]. A recent meta-analysis suggested that homocysteine is only a modest predictor of stroke and ischemic heart disease. Although the presence of apolipoprotein e4 may be associated with higher risk of stroke and ischemic heart disease, no studies have evaluated whether the apolipoprotein e4 allele modifies the effects of homocysteine on risk of stroke or of ischemic heart disease. Work by Ravaglia et al. [36] in an elderly Italian cohort study found that e4 carriers were less likely than noncarriers to have high homocysteine and were also less likely to have high C-reactive protein. The implications of these results for stroke or ischemic heart disease risk are not clear; it may be that neither homocysteine nor C-reactive protein are biochemical pathways by which APOE genotype influences the risk of stroke or ischemic heart disease. It is also possible that selective

survival mechanisms result in impaired immune response in carriers of apolipoprotein e4 alleles in old age [32, 37].

Statins Use and APOE Genotype

Statin use has increased rapidly over the past 10 to 15 years for the purpose of lowering LDL-C levels and preventing CHD and possibly stroke. Statins are highly effective in lowering LDL-C and may also affect inflammation [38]. Although apolipoprotein E is linked to LDL-C, relatively few studies have been able to evaluate the effectiveness of statin therapy in those with the e4 allele compared with the e3 or e2 allele. A genome-wide association study was conducted on a sample of 1984 men with a mean age of 62 years [39]. They were enrolled in a randomized trial to test the effects of low-dose versus high-dose statins on cardiovascular outcomes. This trial evaluated 17 single nucleotide polymorphisms in relation to LDL-C response to treatment over an 8-week period. Of these, only APOE genotypes met study criteria; the least LDL-C change occurred in those with an e4/4 genotype and the largest change occurred in those with an e2/2 genotype. In a series of patients with and without familial hypercholesterolemia, the effects were tested of apolipoprotein E on lipid response to either atorvastatin for those with familial hypercholesterolemia or to fenofibrate in those without familial hypercholesterolemia [40]. Among those with familial hypercholesterolemia, the largest change occurred in those with the e2 allele (46-mg/dL decline) and the smallest change occurred in carriers of the e4 allele (34.5-mg/dL decline; comparison of baseline to post-treatment in both alleles was $P < 0.0001$). Among those without familial hypercholesterolemia, a similar pattern of change in LDL-C did not occur and the results were similar for carriers of e2, e3 and e4 alleles.

Conclusions

Our summary of recent research on the effects of the APOE genotypes on CVD in the elderly reveals a complex system of relationships. APOE genotypes clearly influence lipids and potentially inflammation, and may be linked to atherosclerosis and hypertension. However, the association of these biomarkers with CVD outcomes is altered in the elderly, in part by age- and time-dependent changes in exposure. The occurrence of APOE4 genotypes in older populations has been seen to decline as well. From a population perspective, this may mean that the fraction of CVD cases attributable to apolipoprotein e4 may be smaller and that the ability of e4 to influence CVD risk by increasing LDL-C is more limited. There are few studies of these issues in elderly people, and most of the research includes middle-aged individuals. This age inclusion would

tend to attenuate the ability to observe age-specific effects. The more recent research has provided some information about subpopulation heterogeneity in the occurrence of e4 alleles and about related differences in effects on CVD. The work by Niu et al. [10] is of particular value as it is one of the only studies on e4 and hypertension in Asians.

The efficacy of active lipid-lowering interventions such as statin use or diet on CVD may or may not be affected by genetic risk factors such as apolipoprotein E. Most trials are not designed to test whether the apolipoprotein genotypes affect treatment efficacy. Given that in some populations e4 carriers comprise as much as 25% of the population, this is an important omission. Clearly, more research is needed that can help to elucidate the mechanisms by which apolipoprotein E affects CVD in older populations.

Disclosure No potential conflicts of interest relevant to this article were reported.

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