

An analysis of mortality rates with dual-antiplatelet therapy in the primary prevention population of the CHARISMA trial

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Aims To examine the unanticipated, excess mortality observed in patients randomized to clopidogrel and aspirin vs. aspirin alone in the prespecified 'asymptomatic' subgroup of CHARISMA, we investigated whether dual-antiplatelet therapy may be associated with adverse cardiovascular (CV) events in a primary prevention population.

Methods and results Of 15 603 patients enrolled, 3284 were initially categorized as asymptomatic with CV risk factors, but 995 had a prior CV event, leaving 2289 patients to represent the primary prevention cohort. This subset was compared with 13 148 symptomatic patients with established vascular disease and both were evaluated for CV death and bleeding. A multivariate analysis analysed predictors of CV death in this group. No post mortem data were available. Compared with aspirin alone, a significant increase in CV death ($P = 0.01$) was observed in patients receiving dual-antiplatelet therapy in the asymptomatic population. Within the primary prevention cohort, this excess CV death was not significant ($P = 0.07$). Multivariate analysis of the primary prevention group showed a trend towards excess CV death ($P = 0.054$; HR 1.72; CI 0.99–2.97) with dual-antiplatelet therapy (aspirin plus clopidogrel). Other independent predictors of CV death included increasing age, hypertension, atrial fibrillation, and a history of heart failure. There was a non-significant increase in moderate or severe bleeding ($P = 0.218$) with dual-antiplatelet therapy; thus, bleeding was an unlikely explanation for the excess event rate.

Conclusion These findings do not support the use of dual-antiplatelet therapy with clopidogrel and aspirin in a primary prevention population. In this subgroup analysis, CV death occurred more frequently than anticipated. The cause of this apparent harm is not elucidated, may represent play of chance, but requires further prospective evaluation.

Introduction

Aspirin has been shown to be efficacious in the secondary prevention of cardiovascular disease (CVD)¹ and may be a viable strategy for primary prevention after appropriate risk stratification.^{2–4} Dual-antiplatelet therapy with aspirin and clopidogrel also has a well-defined role in the secondary prevention of CVD. The Clopidogrel in Unstable Angina to

Prevent Recurrent Events (CURE) trial showed that dual therapy decreased coronary events by 20% compared with aspirin.⁵ This strategy was then proven to be beneficial in the post-percutaneous coronary intervention (PCI) population in the PCI-CURE substudy and the Clopidogrel for the Reduction of Events During Observation (CREDO) trial.^{6,7} Subsequently, the Clopidogrel as Adjunctive Reperfusion Therapy—Thrombolysis in Myocardial Infarction (CLARITY—TIMI 28) trial and the Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) established the efficacy of aspirin and clopidogrel in patients with ST-elevation

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Kaplan–Meier curves were created to summarize time to CV death and GUSTO severe bleeding. Log-rank *P*-values are presented comparing clopidogrel plus aspirin vs. aspirin alone for time to CV death and Pearson χ^2 test for bleeding. All analyses were performed using SAS 8.2 (SAS Institute, Cary, NC, USA).

Results

The study population consisted of 2289 primary prevention patients with CV risk factors. Baseline characteristics for the original cohort of asymptomatic and symptomatic patients as well as for the primary prevention and secondary prevention patients are outlined in *Table 1*. The patients in the primary prevention group were significantly different from those in the secondary prevention group in every characteristic except for age. Of note, compared with the secondary prevention group, the primary prevention group had a significantly increased proportion of females, current smokers, hypertensives, hypercholesterolaemics, diabetics, and patients with increased body mass index and a lower proportion of patients with a history of atrial fibrillation and heart failure. Within the primary prevention population, the demographic comparison between patients randomized to aspirin plus placebo and the dual-antiplatelet strategy is given. In this group, patients receiving aspirin plus placebo compared with aspirin and clopidogrel were well matched except for a significant increase in diabetics in the dual-antiplatelet group (85.5 vs. 88.3% respectively, *P* = 0.048).

In terms of medications, the patients in the asymptomatic group were treated very differently from the symptomatic patients—a finding which held true after patients with a prior CV event were removed from the asymptomatic group (*Table 2*). In comparison, the asymptomatic and primary prevention groups were treated more frequently with diuretics, calcium-channel blockers, angiotensin converting enzyme-inhibitors, angiotensin II receptor blockers, and anti-diabetic agents. Conversely, they were treated less frequently with nitrates, beta-blockers, and statins. Within the primary prevention group, patients on aspirin and placebo vs. aspirin and clopidogrel received comparable therapy.

The unadjusted data reveal no difference in CV death between aspirin and placebo vs. aspirin and clopidogrel in the symptomatic group (*P* = 0.34; *Table 3*). In the asymptomatic group, the rate of CV death for single vs. dual-antiplatelet therapy are 2.2 and 3.9%, respectively (*P* = 0.01). The primary prevention group shows directionally similar rates of CV death of 1.8% with aspirin plus placebo and 3.0% with aspirin plus clopidogrel (*P* = 0.07; *Figure 1*). In addition, there are reduced stroke events in the clopidogrel arm seen in the symptomatic group which is significant in the secondary prevention group (*P* = 0.04).

In the CHARISMA trial, there was a non-statistically significant 20% relative risk increase in the rate of the primary efficacy endpoint with aspirin plus clopidogrel when compared with aspirin plus placebo (6.6 vs. 5.5%; *P* = 0.20) among the asymptomatic patients, and a significant reduction in the primary endpoint with a dual-antiplatelet strategy in the symptomatic cohort (6.9 vs. 7.9%; *P* = 0.046). Interactions with treatment and study inclusion category were assessed for the primary efficacy endpoint, overall death, and CV death in a Cox proportional hazards model using

Table 2 Concomitant medications

Medication	Original cohort		Primary vs. secondary		Primary prevention		<i>P</i> -value	
	Asymptomatic (<i>n</i> = 3284)	Symptomatic (<i>n</i> = 12153)	<i>P</i> -value	Primary (<i>n</i> = 2289)	Secondary (<i>n</i> = 13148)	<i>P</i> -value		ASA+Placebo (<i>n</i> = 1141)
Aspirin	99.6%	99.7%	ns	99.6%	99.7%	ns	99.6%	99.6%
Diuretics	58.6%	44.6%	<0.001	57.4%	45.8%	<0.001	55.6%	59.1%
Nitrates	16.3%	25.6%	<0.001	11.2%	25.8%	<0.001	10.8%	11.7%
Calcium channel antagonists	45.5%	34.5%	<0.001	44.8%	35.4%	<0.001	45.0%	44.6%
Beta-blockers	45.6%	58.0%	<0.001	38.6%	58.3%	<0.001	38.6%	38.6%
ACE-inhibitors	64.2%	59.5%	<0.001	63.7%	59.9%	0.001	64.1%	63.4%
Angiotensin II receptor blockers	36.1%	22.9%	<0.001	36.1%	23.9%	<0.001	34.8%	37.5%
Statins	72.1%	78.2%	<0.001	67.1%	78.6%	<0.001	68.1%	66.1%
Insulin	35.8%	12.3%	<0.001	37.7%	13.8%	<0.001	37.4%	37.9%
Thiazolidinediones	18.8%	5.1%	<0.001	19.0%	6.1%	<0.001	18.1%	19.9%
Other oral hypoglycaemics	68.1%	25.3%	<0.001	72.3%	27.8%	<0.001	72.2%	72.4%

Table 3 Unadjusted event rates

Endpoint	Symptomatic group			Asymptomatic group		
	ASA+Placebo (n = 6091)	ASA+Clopidogrel (n = 6062)	P-value	ASA+Placebo (n = 1625)	ASA+Clopidogrel (n = 1659)	P-value
CV death	3.1%	2.8%	0.34	2.2%	3.9%	0.01
Overall death	5.0%	4.6%	0.27	3.8%	5.4%	0.04
Myocardial infarction	2.7%	2.4%	0.27	2.0%	2.4%	0.45
Stroke	3.3%	2.8%	0.09	2.2%	2.1%	0.84
Hospitalization	13.2%	11.9%	0.03	9.0%	8.4%	0.55
CV death/MI/Stroke/Hospitalization	19.2%	17.6%	0.02	13.3%	13.5%	0.88
CV death/MI/Stroke	7.9%	6.9%	0.05	5.5%	6.6%	0.20
	Secondary prevention			Primary prevention		
Endpoint	ASA+Placebo (n = 6575)	ASA+Clopidogrel (n = 6573)	P-value	ASA+Placebo (n = 1141)	ASA+Clopidogrel (n = 1148)	P-value
CV death	3.1%	3.1%	0.81	1.8%	3.0%	0.07
Overall death	5.0%	4.8%	0.59	3.2%	4.4%	0.18
Myocardial infarction	2.8%	2.5%	0.42	1.5%	1.7%	0.76
Stroke	3.3%	2.6%	0.04	1.9%	2.4%	0.42
Hospitalization	13.3%	11.8%	0.01	6.5%	7.1%	0.54
CV death/MI/Stroke/Hospitalization	19.3%	17.6%	0.01	10.3%	11.5%	0.37
CV death/MI/Stroke	7.8%	7.0%	0.09	4.7%	5.7%	0.30

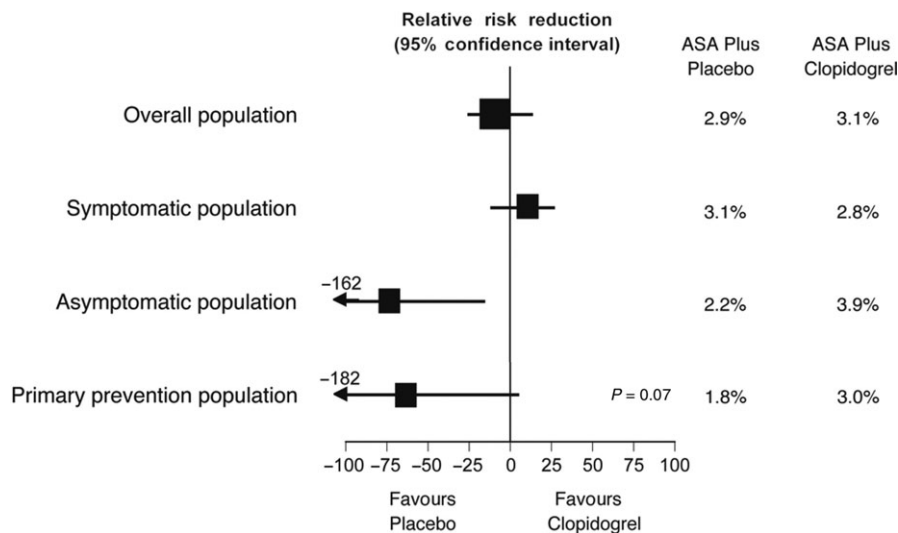


Figure 1 Cardiovascular mortality in the CHARISMA trial.

terms for the treatment, inclusion category, and their interaction. The interactions were significant for all three endpoints (primary efficacy endpoint, $P = 0.045$; overall death, $P = 0.02$; CV death, $P = 0.01$). After defining the primary prevention group, the interaction term is neither significant for overall death ($P = 0.15$) nor for CV death ($P = 0.07$, Figure 1). A time-to-death analysis is shown in Figure 2.

Multivariate analysis for CV death in the primary prevention patient population was performed and the results showed that aspirin plus clopidogrel was associated with an excess CV mortality with a hazard ratio of 1.72 and a confidence interval of 0.99–2.97, $P = 0.05$ (Table 4). Other independent predictors of increased mortality in the primary prevention population included age, elevated

systolic blood pressure, a history of congestive heart failure, and a history of AF. Caucasian ethnicity was relatively protective. The relative risk for CV mortality as seen in each subgroup is further delineated in Figure 1.

For the safety endpoints, an analysis of the original asymptomatic vs. symptomatic cohorts revealed no significant difference in GUSTO severe bleeding (1.6 vs. 1.5%, $P = 0.48$, Table 5). This finding was sustained when the comparison was made with the primary prevention and secondary groups (1.7 vs. 1.5%; $P = 0.41$). When rates of bleeding between aspirin plus placebo and aspirin plus clopidogrel were compared within the original cohorts, there was a significant increase in any bleed, minor/other bleed, and severe/moderate bleeding associated with aspirin plus clopidogrel in both the asymptomatic and symptomatic

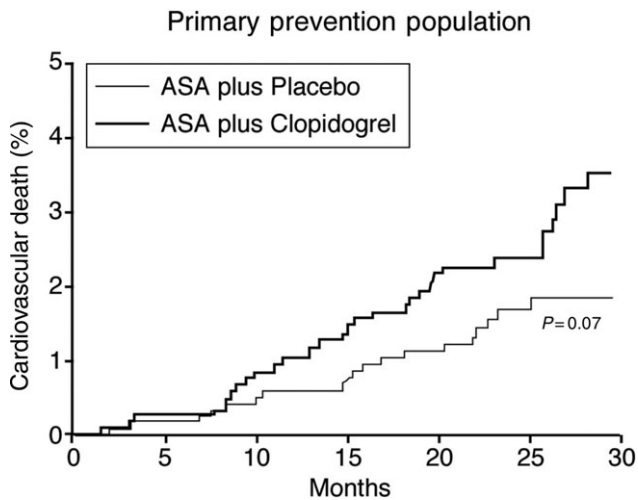


Figure 2 Time-to-death analysis.

Table 4 Cox model covariates for CV death in the Primary Prevention Group

Covariate	Hazard ratio	95% confidence interval	P-value
Clopidogrel	1.72	0.99–2.97	0.05
Age–10 year increase	1.68	1.23–2.29	0.001
Caucasian	0.55	0.32–0.96	0.03
History of CHF	2.50	1.07–5.85	0.04
Systolic blood pressure (5 mmHg increase)	1.09	1.02–1.18	0.01
Atrial fibrillation	4.21	1.81–9.79	0.001

groups (Table 5). In terms of moderate bleeding, there was a trend towards significance within the asymptomatic group ($P = 0.076$), whereas there was a significantly increased rate with dual-antiplatelet therapy in the symptomatic patients ($P = 0.001$). Finally, there was a non-significant increase associated with aspirin plus clopidogrel in the asymptomatic group for GUSTO severe bleeding not seen in the symptomatic group (Figure 3). There was no increase in severe bleeding within the primary prevention population ($P = 0.27$).

Finally, source documentation was reviewed in the Clinical Events Committee files to evaluate for post mortem data, but unfortunately none were available.

Discussion

Previous studies have demonstrated the utility of low-dose aspirin for primary prevention after appropriate risk stratification.^{2–4,12} The CHARISMA trial investigated the use of a dual-antiplatelet strategy in a broad spectrum of patients at risk for CV events. In the final analysis, there was a suggestion of benefit in patients with symptomatic atherothrombotic disease (relative risk, 0.88; 95% confidence interval, 0.77–0.998; $P = 0.046$), but also a suggestion of harm in patients with multiple risk factors who were asymptomatic with an increased rate of death from CV causes among those assigned to aspirin and clopidogrel vs. aspirin and placebo (3.9 vs. 2.2%, respectively; $P = 0.01$).¹⁰ This

excess mortality in the prespecified asymptomatic cohort was unexpected given the hypothesis that dual-antiplatelet therapy would be of overall benefit in this population. The current analysis was thus conducted to study the unanticipated mortality risk associated with dual-antiplatelet therapy in the asymptomatic population and, if possible, to understand its causes.

By removing patients who had prior events from the asymptomatic cohort, we attempted to define a primary prevention population. In this population, there was no significant harm seen with aspirin plus clopidogrel in terms of all-cause mortality but there was a trend for increased CV mortality ($P = 0.07$). The original asymptomatic cohort had a significant increase in death ($P = 0.038$) that was sustained and persisted for CV death ($P = 0.007$).

In terms of bleeding, the original asymptomatic cohort suggested an early and sustained risk of severe bleeding associated with aspirin and clopidogrel ($P = 0.065$) when compared with the symptomatic group ($P = 0.39$). However, this trend is not found within the primary prevention group ($P = 0.27$) and so it would be difficult to attribute any excess CV mortality to severe bleeding. Of note, there is a marked increase in minor or other bleeding associated with aspirin and clopidogrel. Whether this increase in minor bleeding could predispose to intra-plaque haemorrhage and rupture is unclear. Source documentation was reviewed in the Clinical Events Committee files in an effort to define whether the CV events were due to ruptured plaque, but unfortunately, post mortem data were not available.

The trend for increased mortality observed in the primary prevention population may be due to a number of factors. First, this analysis reveals that the asymptomatic and symptomatic populations were remarkably distinct groups with significant variance in most characteristics (Table 1). These differences held true between the primary and secondary prevention populations. Within the primary prevention group itself, patients were relatively well-matched except for a higher preponderance of diabetes in the dual-antiplatelet therapy arm. Similarly, as would be expected, patients were managed quite differently between the asymptomatic and symptomatic cohorts as well as between the primary and secondary prevention cohorts, but the treatment was well-matched within the primary prevention group itself.

The increased incidence of diabetes in the aspirin plus clopidogrel arm vs. the aspirin plus placebo arm of the primary prevention population may have contributed to the mortality difference as diabetes is known to have an increased incidence of inflammation, neovascularization, and intracoronary haemorrhage.¹³ Recent data have implicated intracoronary plaque haemorrhage as a critical factor in atherosclerotic disease and plaque destabilization,^{14,15} whereas pathologic studies have shown increased plaque haemorrhage at sites of vasa vasorum neovascularization^{16–19} which is associated with a hypercholesterolaemic diet²⁰ and diabetic atherosclerosis.¹³ This association, of course, cannot imply causality. In addition, because of the increased incidence of diabetes in this group, diabetic nephropathy may have contributed to the impaired clearance of clopidogrel. Decreased renal function and its associated effects on dual-antiplatelet therapy thus requires further investigation.

Table 5 Bleeding risk

Type of bleed	Original cohort			Primary vs. Secondary prevention		
	Asymptomatic (n = 3284)	Symptomatic (n = 12153)	P-value	Primary (n = 2289)	Secondary (n = 13148)	P-value
Severe	1.6%	1.5%	0.48	1.7%	1.5%	0.41
Fatal	0.3%	0.3%	0.49	0.3%	0.3%	0.79
Moderate	1.8%	1.7%	0.81	1.7%	1.7%	0.9
Severe/Moderate	3.4%	3.1%	0.33	3.5%	3.1%	0.37
Minor/Other bleed	27.2%	26.2%	0.29	26.0%	26.5%	0.57
Any bleed	29.2%	28.2%	0.29	28.0%	28.5%	0.65
	Asymptomatic group			Symptomatic group		
	ASA+Placebo (n = 1625)	ASA+Clopidogrel (n = 1659)	P-value	ASA+Placebo (n = 6091)	ASA+Clopidogrel (n = 6062)	P-value
Severe	1.2%	2.0%	0.065	1.4%	1.6%	0.39
Fatal	0.2%	0.4%	0.383	0.2%	0.3%	0.282
Moderate	1.4%	2.2%	0.076	1.3%	2.1%	0.001
Severe/Moderate	2.6%	4.2%	0.01	2.5%	3.6%	0.001
Minor/Other bleed	20.6%	33.6%	<0.001	18.6%	33.9%	<0.001
Any bleed	22.2%	36.0%	<0.001	20.3%	36.2%	<0.001
	Primary prevention			Secondary prevention		
	ASA+Placebo (n = 1141)	ASA+Clopidogrel (n = 1148)	P-value	ASA+Placebo (n = 6575)	ASA+Clopidogrel (n = 6573)	P-value
Severe	1.4%	2.0%	0.27	1.3%	1.6%	0.19
Fatal	0.3%	0.3%	0.71	0.2%	0.3%	0.18
Moderate	1.6%	1.9%	0.54	1.3%	2.2%	<0.001
Severe/Moderate	3.0%	3.9%	0.22	2.5%	3.7%	<0.001
Minor/Other bleed	18.9%	32.9%	<0.001	19.1%	34.0%	<0.001
Any bleed	20.8%	35.3%	<0.001	20.7%	36.3%	<0.001

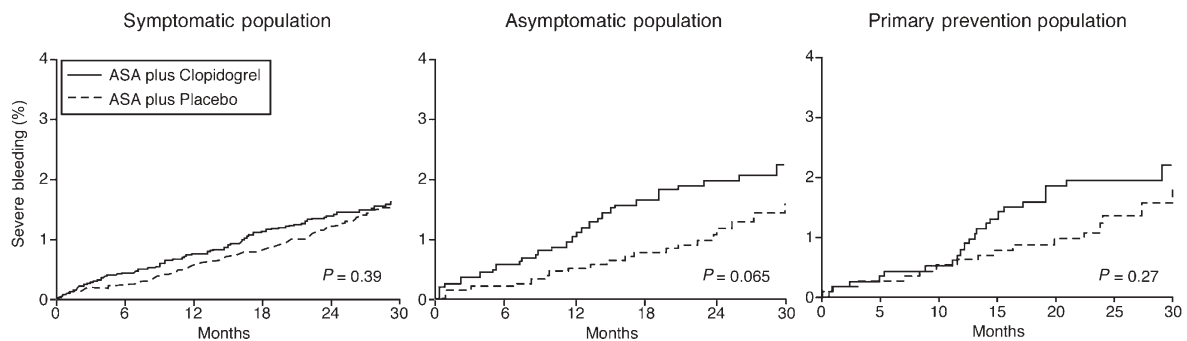


Figure 3 Severe bleeding risk.

Finally, strict compliance monitoring by measuring clopidogrel metabolites was not performed. Long-term therapy with clopidogrel has been shown to have less variance in the degree of platelet inhibition.²¹ Thus, it cannot be determined whether undetected non-compliance with study therapy may have contributed to platelet rebound activation and worsened outcomes.

The trend for increased CV mortality in the primary prevention group is also affected by the *post hoc* definition of the population. By defining the primary prevention population as a subset of the asymptomatic group, 995 patients were removed from the original 3284 asymptomatic patient group. While the original asymptomatic arm had a significant increase in all-cause mortality and CV mortality

for dual-antiplatelet therapy, the reduction in power may be responsible for the non-significant trend ($P = 0.07$) for increased CV mortality seen with dual-antiplatelet therapy in the primary prevention group. Conversely, because of the lack of a significant increase in hospitalization, myocardial infarction, or stroke in the primary prevention group with dual-antiplatelet therapy, the role of chance must be considered. For the secondary endpoint of CV death, MI, stroke, and hospitalization for ischaemic events no difference was seen in the asymptomatic group for aspirin and placebo vs. aspirin and clopidogrel.

The aetiology of the increased CV mortality associated with aspirin plus clopidogrel in a primary prevention population remains unclear. The role of diabetes and its role in

inflammation, plaque destabilization, renal dysfunction, and anti-platelet resistance must be further elucidated. Despite the lack of a clear pathophysiologic explanation in this analysis, however, primary prevention patients should not receive a dual-antiplatelet regimen.

Limitations

This study is limited by the *post hoc* retrospective nature of the analysis. In addition, the primary prevention population is defined to exclude the asymptomatic patients with a prior history of MI, PCI, CABG, CVA, TIA, carotid endarterectomy, and peripheral angioplasty or bypass to address the inclusion of patients with prior CV events in the prespecified asymptomatic arm of the CHARISMA trial. Another limiting factor was the lack of post mortem data to help define the mechanism of death better. Finally, strict compliance monitoring by measuring clopidogrel metabolites was not performed.

Conclusion

Dual-antiplatelet therapy with aspirin and clopidogrel in the primary prevention subgroup was associated with an increase in CV death. The cause of this apparent harm in this retrospective analysis is not elucidated, but requires further prospective evaluation.

Conflict of interest: D.L.B reports having received honoraria for consulting on scientific advisory boards from Astra Zeneca, Bristol-Myers Squibb, Cardax, Centocor, Daiichi-Sankyo, Eisai, Eli Lilly, Millennium, GlaxoSmithKline, Millennium, Otsuka, Paringenix, PDL, Sanofi-Aventis, Schering Plough, The Medicines Company, and TNS Healthcare. All such honoraria are currently donated to non-profit organizations; having received honoraria for lectures from Bristol-Myers Squibb, Sanofi-Aventis, and The Medicines Company in the past, and having provided expert testimony regarding clopidogrel (the compensation was donated to a non-profit organization). K.A.A.F reports having received consulting fees from Sanofi-Aventis; lecture fees from Sanofi-Aventis and Bristol-Myers Squibb; and grant support from Sanofi-Aventis. S.R.S reports having received consulting fees from Sanofi-Aventis, AstraZeneca, Eli Lilly, and the Medicines Company. D.M.B has no disclosures to report. W.H reports having received consulting and lecture fees from Sanofi-Aventis; lecture fees from Sanofi-Aventis and Bristol-Myers Squibb. K-H.M has no disclosures to report. T.A.P reports having received consulting fees from Sanofi-Aventis, Bristol-Myers Squibb, Bayer, Forbes Med-Tech, and Merck and lecture fees from Bristol-Myers Squibb, Abbott, AstraZeneca, Bayer, KOS Pharmaceuticals, Merck, Pfizer, and Merck/Schering-Plough. W.E.B reports having received consulting fees and lecture fees from Sanofi-Aventis, Bristol-Myers Squibb, KOS Pharmaceuticals, PDL BioPharma, and CV Therapeutics. P.G.S reports having received consulting fees from Sanofi-Aventis, AstraZeneca, Takeda, and GlaxoSmithKline and lecture fees from Sanofi-Aventis, Bristol-Myers Squibb, AstraZeneca, Servier, Merck, Novartis, Sankyo, Boehringer Ingelheim, Pfizer, and Nycomed. M.D.F reports having received consulting fees from Sanofi-Aventis, Bristol-Myers Squibb, GlaxoSmithKline, and Boehringer Ingelheim; lecture fees from Sanofi-Aventis, Bristol-Myers Squibb, GlaxoSmithKline, and Menarini; and grant support from Sanofi-Aventis, Bristol-Myers Squibb, GlaxoSmithKline, and Menarini. G.M reports having received consulting and lecture fees from Sanofi-Aventis and Bristol-Myers Squibb. E.J.T reports having served as a consultant to and having received lecture fees from Sanofi-Aventis and Bristol-Myers Squibb before 2005; grant support (P50 HL077101 and

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Clinical vignette

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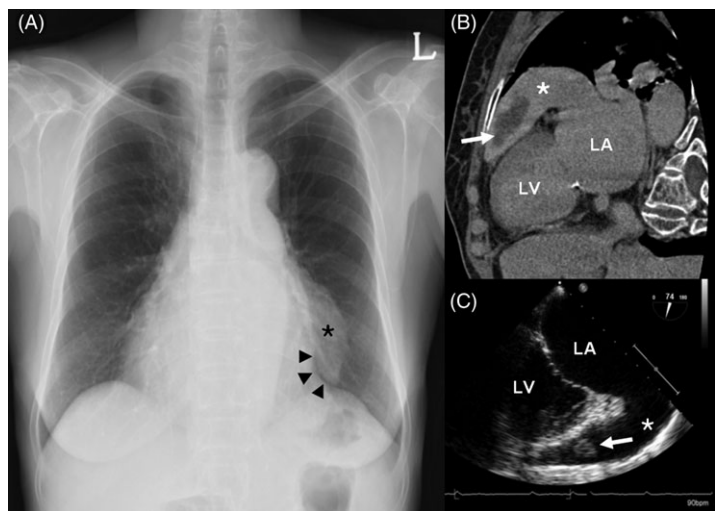
Giant left atrial appendage aneurysm

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A 67-year-old lady was referred to our hospital because of abnormal findings on a simple chest radiograph. The chest radiograph showed a markedly prominent left cardiac border (Panel A). Because a radiolucent cleft (Panel A, arrow heads) was observed in the lower medial side of the bulge, the bulging shadow rather looked like a longish mass (Panel A, asterisk). She had a complaint of atypical chest discomfort and a history of embolic stroke. Physical examination revealed no abnormalities except irregular pulse. The baseline ECG showed atrial fibrillation. Cardiac 64-slice multidetector computed tomography (MDCT) was undertaken, which demonstrated normal coronary arteries and a 4 × 6 × 8 cm-sized left atrial appendage aneurysm (LAAA) containing thrombus (Panel B). Transthoracic echocardiography was unremarkable, except a dilatation of the left atrial appendage. Transesophageal echocardiography clearly showed a huge aneurysm of the left atrial appendage and confirmed a mobile thrombus within it (Panel C). Because the patient strongly refused the surgery, she was discharged with oral anticoagulant therapy.



There are several conditions such as mediastinal mass, pericardial cyst, cardiac tumour, pericardial, or extracardiac fluid collection that can generate a prominent left cardiac border on the simple chest radiograph. If the prominent left cardiac border is incidentally found on the chest radiograph, and combined with atrial fibrillation and history of embolic stroke, a giant LAAA containing thrombus could be suspected, although it is extremely rare. Because the anomaly has a potential source and risk for systemic embolization and arrhythmia, surgical resection should be recommended even in asymptomatic patients.

Panel A. Simple postero-anterior chest radiograph shows a markedly prominent left cardiac border. Because there is a radiolucent cleft (arrow heads) indicating epicardial fat between the giant LAAA and the left ventricle, the bulging shadow looks like a longish mass (asterisk).

Panel B. Cardiac 64-slice MDCT. On 2 min delayed venous phase images, a 4 × 6 × 8 cm-sized left anterior mediastinal mass (asterisk) communicates with the left atrium and is opacified except a non-enhancing filling defect (arrow). These findings indicate a giant LAAA (asterisk) with a thrombus (arrow). LA, left atrium; LV, left ventricle.

Panel C. Transesophageal echocardiography demonstrates a giant LAAA (asterisk) and a mobile thrombus (arrow) within it. LA, left atrium; LV, left ventricle.