

Patients with prior coronary artery bypass grafting have a poor outcome after myocardial infarction: an analysis of the VALsartan in acute myocardial iNfarcTion trial (VALIANT)

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Aims

The number of patients presenting with an acute myocardial infarction (MI) and prior coronary artery bypass grafting (CABG) is increasing. We compared the baseline characteristics, treatment, and clinical outcomes of patients with and without prior CABG in the VALIANT trial.

Methods and results

Of the 14 703 patients with heart failure (HF), left ventricular systolic dysfunction, or both enrolled in VALIANT, 1026 (7%) had prior CABG. Prior CABG patients were older [mean age (SD): 67 (10) vs. 65 (12) years; $P < 0.0001$], had more comorbidity, and more frequent non-Q wave MI (66 vs. 30%; $P < 0.0001$). At hospital presentation, prior CABG patients received less aspirin (82 vs. 90%; $P < 0.0001$) and thrombolysis (21 vs. 36%; $P < 0.0001$), but had a similar rate of primary percutaneous coronary intervention (14 vs. 15%; $P = 0.2$). Prior CABG patients were more likely to experience the composite outcome of cardiovascular death, MI, HF, resuscitated cardiac arrest, or stroke; 3 year Kaplan–Meier rate, 64 vs. 39% (adjusted hazard ratio 1.29, 95% confidence interval 1.17–1.43; $P < 0.0001$).

Conclusion

Patients with prior CABG had a worse clinical profile and experienced more fatal and non-fatal outcomes. Greater recognition is necessary for these high-risk patients including optimization of evidence-based secondary preventive therapy.

Keywords

Coronary artery disease • Myocardial infarction • Coronary artery bypass graft • Prognosis

Introduction

The number of coronary artery bypass graft (CABG) operations performed globally peaked in the mid-1990s. More than 1.5 million patients had this surgery in the USA between 1990 and 1999,¹ and broadly similar activity rates occurred in Europe^{2,3} and Australia.⁴ However, it is known from angiographic studies that half of all vein grafts become diseased and one-quarter occluded

by 5 years,⁵ with an increasing risk of recurrent myocardial ischaemia and infarction in the longer term.^{5,6} As a result of these two trends, the number of patients admitted with an acute coronary syndrome (ACS) and a prior history of CABG has increased in recent years. In the United States National Registry of Myocardial Infarction, the proportion of patients with prior CABG has risen consistently every year from 10.6% in 1994 to 12.9% in 1999 ($P = 0.0001$),⁷ and the incidence of early complications in these patients has

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remained static. For example, the proportion of CABG patients presenting with cardiogenic shock did not change from 1995 (12.2%) to 2004 (11.8%).⁸ Furthermore, in the Global Registry of Acute Coronary Events (GRACE), which included 11 389 ACS patients enrolled between 1 April 1999 through 31 March 2001 in 14 countries from 18 geographic locations, a history of CABG was present in 12.6% of all patients and in 8.0% of all in-hospital deaths ($n = 509$).⁹ In patients who presented with myocardial infarction (MI) and survived to discharge, history of CABG was univariably associated with 6 month mortality.¹⁰ These data suggest that the global burden of unstable coronary artery disease in patients with prior CABG is rising.

There are few prospective controlled studies of the clinical characteristics, contemporary treatment, and, particularly, the long-term non-fatal and fatal cardiovascular outcomes in these patients. Therefore, we have carried out a detailed comparison of patients with and without prior CABG in the VALsartan In Acute myocardial iNfarcTion trial (VALIANT).

Methods

Trial design

The design of VALIANT has been reported in detail.^{11,12} Patients with an established diagnosis of acute MI were enrolled between 12 h and 10 days after symptom onset, had to have objective evidence of left ventricular (LV) systolic dysfunction [reduced LV ejection fraction (EF) $\leq 40\%$ on radionuclide ventriculography or $\leq 35\%$ on echocardiography or X-ray contrast angiography, or an echocardiographic wall motion index ≤ 1.2], clinical evidence of heart failure (HF) according to the criteria of the Acute Infarction Ramipril Efficacy trial (AIRE) investigators,¹³ or both. The main exclusion criteria were hypotension, shock, renal impairment, ongoing clinical instability (such as angina or arrhythmia), and intolerance or contraindication to use of an angiotensin-converting enzyme inhibitor. Patients were randomly assigned equally to receive captopril (target dose 50 mg three times daily), valsartan (target dose 160 mg twice daily), or the combination of the two (captopril 50 mg three times daily and valsartan 80 mg twice daily).

Data collected at baseline

The VALIANT case report forms collected data on the following: (i) basic demographic factors (age, sex, type and site of qualifying MI, etc.); (ii) medical history before the qualifying MI (including procedures and operations); (iii) treatments given for the qualifying MI (e.g., antiplatelet and reperfusion therapy); (iv) events occurring between the qualifying MI and randomization (such as development of post-infarction angina, arrhythmias, HF, or procedures); and (v) concomitant medications used within the 24 h before randomization (these baseline medications reflected a mixture of treatments prescribed at the time of admission and those begun after admission).

Trial endpoints

The primary endpoint of VALIANT was all-cause mortality.^{11,12} The secondary endpoints included cardiovascular mortality and a number of composites of cardiovascular mortality and non-fatal cardiovascular events including MI, hospitalization for HF, stroke, and resuscitation after cardiac arrest. All pre-specified endpoints were adjudicated by a clinical endpoints committee. Definitions of the endpoints have been previously published.¹¹

Statistical analysis

Patient characteristics, events, and treatments at baseline, at qualifying MI, and at randomization were compared between patients with prior CABG and those without a history of CABG. Categorical variables were summarized as percentages and differences between patients with prior CABG compared with no history of CABG were determined using the Pearson χ^2 test. Continuous variables were summarized as means and standard deviations or as medians with 25th and 75th percentiles (Q1, Q3). Patients with or without a history of CABG were compared on these characteristics using the non-parametric Wilcoxon rank sum test. The Kaplan–Meier method was used to estimate the probability of an event (e.g., death and treatment discontinuation) at or before a given time over the 3 year follow-up period. These estimates were stratified by history of CABG. With such a large sample size, statistical differences may occur when the clinical difference is not meaningful. Factors must be considered both clinically and statistically significant to be described as different in the text.

Cox proportional hazards regression modelling was used for the 3 year outcomes (mortality or cardiovascular death, and mortality plus morbidity including HF hospitalization, MI, stroke, or resuscitated cardiac arrest). Each analysis was adjusted for the pre-randomization patient characteristics from previously developed Cox proportional hazards models of each outcome. If not already present in a model, the CABG indicator was included. All analyses were performed using SAS software version 8.2 (SAS Institute, Inc., Cary, NC, USA).

Results

Of the 14 703 patients included in the intention to treat analysis of VALIANT, 1026 (7%) had a history of CABG.

Baseline characteristics and treatments

Baseline demographics and comorbidity

Compared with patients without previous CABG, patients with prior CABG were more often male, had more comorbidity (including congestive HF, previous MI and peripheral arterial disease, chronic renal insufficiency, and diabetes), and were randomly assigned approximately 10 h earlier ($P < 0.005$) (Table 1).

Qualifying myocardial infarction type, left ventricular function, and heart failure

Coronary artery bypass graft patients enrolled in VALIANT were significantly more likely than those without CABG to have had a non-Q wave MI (Table 2). Compared with patients without prior CABG, patients with prior CABG experienced an anterior MI less often and left bundle branch block more frequently. Left ventricular ejection fraction was lower in patients with prior CABG (Table 2).

Treatment for qualifying myocardial infarction

Prior CABG patients were less likely than patients without a history of CABG to have received aspirin, a beta-blocker, or thrombolytic therapy, but were more likely to have received glycoprotein IIb/IIIa inhibitor therapy (Table 2). Primary percutaneous coronary intervention (PCI) occurred with similar frequency in patients with or without prior CABG.

Table 1 Baseline demographics and comorbidity

	No CABG (n = 13 677)	Prior CABG (n = 1026)	P-value
Age, mean (SD), year	65 (12)	67 (10)	<0.0001
Male, %	68	79	<0.0001
Blood pressure, mean (SD), mm Hg			
Systolic	123 (17)	122 (17)	0.52
Diastolic	73 (11)	68 (11)	<0.0001
Heart rate, mean (SD), b.p.m.	76 (13)	74 (13)	<0.0001
BMI, median (25th, 75th), kg/m ²	27 (25, 30)	27 (25, 30)	0.16
Time from randomization, median (25th, 75th), h	117 (73, 172)	107 (68, 161)	0.01
Medical history, %			
MI	24	74	<0.0001
Angina pectoris	38	70	<0.0001
Unstable angina pectoris	19	47	<0.0001
PCI	5.3	34	<0.0001
Stroke	5.7	11	<0.0001
TIA	2.6	5.7	<0.0001
PAD	7.4	22	<0.0001
HF	13	37	<0.0001
Atrial fibrillation	6	14	<0.0001
Hypertension	55	64	<0.0001
Diabetes mellitus	22	38	<0.0001
Chronic renal insufficiency	1.5	6.1	<0.0001
COPD	8.2	13	<0.0001
Cigarette smoking, %			
Past	30	52	<0.0001
Current	33	21	<0.0001

Countries included in each geographic region: North America: USA and Canada; South America: Argentina, Brazil; East Europe: Czech Republic, Hungary, Poland, Russia, Slovakia; West Europe, Australasia and South Africa: Australia, Austria, Belgium, Denmark, France, Germany, Ireland, Italy, New Zealand, Norway and Spain, The Netherlands, South Africa, Sweden, UK. Of the 14 703 patients enrolled, 5056 (34.4%) were from North America, 848 (5.7%) were from South America, 4274 (29.1%) were from East Europe, and 4525 (30.8%) patients were from West Europe, Australia, and South Africa.

CABG, coronary artery bypass graft; SD, standard deviation; b.p.m., beats per minute; BMI, body mass index; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIA, transient ischaemic attack; PAD, peripheral arterial disease; HF, heart failure; COPD, chronic obstructive pulmonary disease.

Events and treatment between qualifying myocardial infarction and randomization

Prior CABG patients were more likely than patients without CABG to experience post-infarction angina and have cardiac catheterization, percutaneous coronary revascularization, intra-aortic balloon counterpulsation, and cardiac defibrillator therapy (Table 3). Coronary artery bypass grafting occurred with similar frequency in both groups.

Patients with a history of CABG were more likely to experience renal insufficiency, dyslipidaemia, and diabetes than patients without CABG. Congestive HF occurred with similar frequency in patients with or without prior CABG; however, ventricular fibrillation trended towards occurring less often in patients with prior CABG (Table 3).

Treatment within 24 h prior to randomization

There were several differences in the use of key treatments between patients with prior CABG and those without CABG,

notably in the use of beta-blockers and statins, which were used more frequently in patients with prior CABG (Table 4).

Early mortality

A total of 589 (4%) patients died by 30 days, and 47 (8%) of these patients had a history of CABG.

Long-term clinical outcomes

The median (Q1, Q3) duration of follow-up for survivors without a history of CABG [26 months (22, 31)] was similar to the median duration of follow-up in patients with prior CABG [27.5 months (22, 32)].

Mortality

Unadjusted all-cause mortality from randomization until the end of follow-up is shown in Figure 1. Patients with a history of CABG were more likely to die than patients without prior CABG. An identical pattern was seen for cardiovascular mortality (Figure 2). In a regression model, adjusting for over 25 significant pre-MI,

Table 2 Qualifying MI, HF, and LV function at baseline

	No CABG (n = 13 677)	Prior CABG (n = 1026)	P-value
Qualifying MI, %			
Q wave	69	30	<0.0001
Non-Q wave	30	66	<0.0001
Anterior site	61	35	<0.0001
LBBB	4.1	6.4	0.002
Killip class, %			
I	27	35	<0.0001
II	49	42	<0.0001
III	18	15	<0.0001
IV	6.3	7.2	<0.0001
Mean LVEF	0.36	0.33	<0.0001
Treatment for qualifying MI, %			
Aspirin	90	82	<0.0001
GP IIb/IIIa antagonist	13	19	<0.0001
Beta-blocker	60	56	0.03
Reperfusion therapy			
Thrombolysis	36	21	<0.0001
Primary PCI	15	14	0.2

CABG, coronary artery bypass graft; MI, myocardial infarction; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; GP, glycoprotein; PCI, percutaneous coronary intervention.

qualifying MI, and post-MI baseline variables, history of CABG was not an independent predictor of all-cause mortality (Table 5).

Composite mortality–morbidity outcomes

The unadjusted risks of the secondary composite outcomes of cardiovascular death or non-fatal hospitalizations, including MI, HF, stroke, and resuscitated cardiac arrest are shown in Supplementary material online, Figures S1A–C and the adjusted risks in Table 5. Prior CABG was an independent predictor of all the pre-specified cardiovascular mortality–morbidity composite outcomes.

Discussion

VALIANT, one of the largest contemporary trials of acute MI, is in a strong position to give a global perspective on the clinical characteristics, treatment, and outcomes of patients with prior CABG who experience an acute MI. This is by virtue of the large number of patients with prior CABG randomly assigned, detailed patient characterization at baseline, and multiple fatal and non-fatal events captured during long-term follow-up.

Clinical characteristics and treatment differences

Prior CABG patients differed in many important ways from patients without CABG. In keeping with earlier reports,^{10,14,15} CABG patients more often had a history of previous MI and

Table 3 Clinical events, investigations, and procedures between the qualifying MI and randomization

	No CABG (n = 13 677)	Prior CABG (n = 1026)	P-value
Ischaemic events, %			
Post-infarction angina	21	26	0.0002
Cardiac catheterization			
PCI	19	26	<0.0001
CABG	2.2	1.9	0.657
Arrhythmic events, %			
Atrial fibrillation	12	13	0.304
Sustained ventricular tachycardia	3.1	3.7	0.262
Ventricular fibrillation	4.0	2.8	0.0543
ICD implantation	0.3	1.2	0.0001
Pacemaker implantation	1.1	1.2	0.777
Intraaortic balloon pump	4	5	0.0454
Other clinical events, %			
Heart failure	58	58	0.979
Hypertension	35	38	0.0459
Diabetes mellitus	23	35	<0.0001
Dyslipidaemia	37	46	<0.0001
Renal insufficiency	4.0	9.4	<0.0001

CABG indicates coronary artery bypass graft; PCI, percutaneous coronary intervention; ICD, implantable cardioverter defibrillator.

presented more often with non-Q wave MI. Infarct size is typically less in prior CABG patients compared with MI patients without prior CABG,^{16,17} and the reasons for this include an increased likelihood of non-transmural MI and less jeopardized myocardium distal to the culprit vessel,¹⁷ which is usually a vein graft.^{16,18} Interestingly, patients with prior CABG presented less often with anterior MI suggesting protection by patent internal mammary artery-left anterior descending (LAD) artery conduits, which is the most common type of graft to the LAD.² Prior CABG patients more commonly had a history of treated congestive HF and a lower EF. Recurrent ischaemia and use of intraaortic balloon pump therapy were more common in the early post-infarct period in prior CABG patients, although the frequency of atrial or ventricular arrhythmias was similar in both groups. Patients with prior CABG were also older and had greater comorbidity, and prognostically important medical complications such as new diabetes and renal dysfunction occurred more often in these patients.

Patients with prior CABG received some evidence-based drug therapies less often. Underuse of beta-blockers probably reflects the higher prevalence of HF and chronic obstructive pulmonary disease. Underuse of aspirin may be related to the increased use

Table 4 Treatment at randomization

Treatment at randomization, %	No CABG (n = 13 677)	Prior CABG (n = 1026)	P-value
Secondary prevention			
Beta-blocker	70	75	0.002
HMG-CoA reductase inhibitor	32	57	<0.0001
Antiplatelet therapy			
Aspirin	91	90	0.08
Other antiplatelet	24	35	<0.0001
GP IIb/IIIa antagonist	6.3	11.3	<0.0001
Antithrombotic therapy			
Oral anticoagulant	9.1	13.5	<0.0001
Heparin	52	44	<0.0001
Antischemic therapy			
Calcium channel blocker	8	17	<0.0001
Nitrate	43	53	<0.0001
Antifailure therapy			
Diuretic	50	59	<0.0001
Digitalis glycoside	12	25	<0.0001
Potassium supplement	24	25	0.55
Potassium-sparing diuretic	8.9	11.4	0.01
Antidiabetic therapy			
Insulin	12	23	<0.0001
Oral hypoglycaemic	11	20	<0.0001
Antidepressant therapy			
SSRI	1.7	4.2	<0.0001
Other	2.9	6.0	<0.0001

CABG, coronary artery bypass graft; GP, glycoprotein; SSRI, selective serotonin reuptake inhibitor.

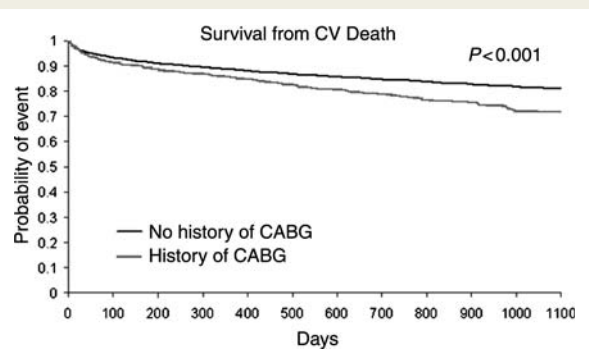


Figure 2 Kaplan–Meier curves for the unadjusted outcome of cardiovascular death.

Table 5 Adjusted risk of death and cardiovascular outcomes

Variable	Chi-square	HR	95% CI	P-value
All-cause mortality	1.978	1.101	0.963–1.259	0.160
CV death	0.176	1.031	0.895–1.187	0.675
CV death or HF	9.611	1.190	1.066–1.329	0.0019
CV death or MI	9.585	1.205	1.071–1.356	0.002
CV death, MI, or HF	24.746	1.290	1.167–1.427	<0.0001
CV death, MI, HF, RCA, stroke	24.244	1.294	1.168–1.434	<0.0001
Stroke	2.361	0.744	0.511–1.084	0.124

HR, hazard ratio; CI, confidence interval; CV, cardiovascular; HF, heart failure; MI, myocardial infarction; RCA, resuscitated cardiac arrest.

of warfarin in patients with prior CABG (Table 1.) The lower use of thrombolysis in patients with prior CABG presumably reflects a lower prevalence of ST segment elevation MI (inferred from the lower proportion of these patients with Q wave MI) and physician-preference for interventional management. However, by the time of randomization, the use of evidence-based secondary prevention therapy was greater in patients with prior CABG.

Outcomes

Previous clinical trials have shown that ACS patients with prior CABG have an increased risk of early mortality (Figure 3). In the GRACE registry,¹⁰ prior CABG was associated with increased in-hospital mortality⁹ and was a univariable, but not a multivariable, predictor of 6-month mortality.¹⁰ We have extended these observations to examine longer term outcomes and to describe non-fatal and fatal outcomes.

Prior CABG was an independent predictor of adverse cardiovascular outcomes, including the composite outcome of cardiovascular death, MI, and HF. Our multivariable findings extend those of an earlier Canadian cohort study in 410 MI patients with or without prior CABG in which a history of CABG was associated with a higher crude rate of ischaemic cardiac events at 5 years.¹⁹ Previous

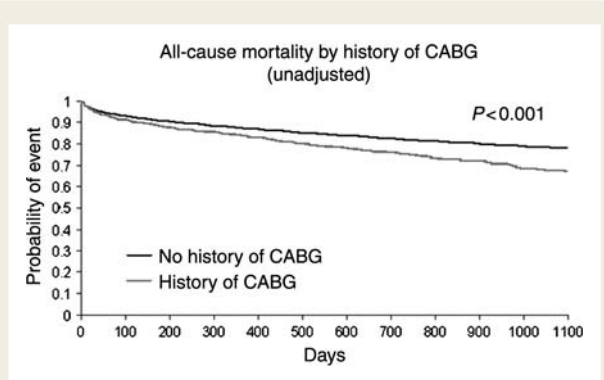


Figure 1 Kaplan–Meier curves for mortality from any cause according to history of prior coronary artery bypass graft in VALIANT (unadjusted rates).

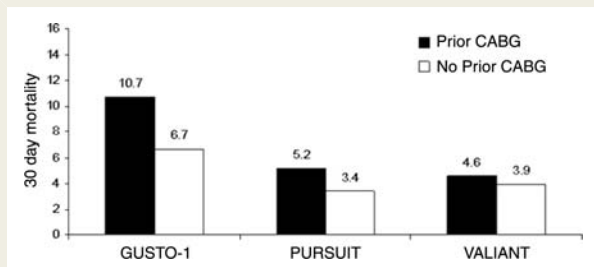


Figure 3 30 day mortality rates according to prior coronary artery bypass graft (CABG) status in two large clinical trials and in VALIANT. In the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-1) trial, 30 day mortality was 10.7% in patients with prior CABG ($n = 1784$) compared with 6.7% in patients without prior CABG ($n = 39,147$; $P < 0.001$).¹⁴ In the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial, the 30 day mortality rate in patients with a non-ST elevation ACS and prior CABG ($n = 1134$) was 5.2% compared with a rate of 3.4% in patients with no history of CABG ($n = 8321$).¹⁵ Prior CABG was an independent predictor of 30 day mortality (adjusted HR 1.45, 95% CI 1.06–1.98; $P = 0.019$).

studies have demonstrated that the risk of future ischaemic cardiac events after MI is linked to the extent of coronary atherosclerotic disease.^{19–21} Patients with prior CABG have more extensive native vessel CAD¹⁹ and their burden of atherosclerosis becomes more pronounced with vein graft disease. Therefore, the greater atherosclerotic burden in patients with prior CABG probably underlies their increased risk of ischaemic cardiac events post-MI, compared with patients without prior CABG. The higher prevalence of previous MI and LV dysfunction in patients with prior CABG, which we and others¹⁹ have shown, may explain the reduced capacity of these patients to withstand recurrent myocardial ischaemia or infarction and their increased risk of cardiac morbidity and mortality.

We also found that a history of prior CABG was a univariable but not a multivariable predictor of all-cause mortality. This result is consistent with similar results from the GRACE registry.¹⁰ These observations suggest that the adverse risk profile of patients with prior CABG, such as increased age, history of HF, and previous MI, explains the reduced survival rate of prior CABG patients compared to patients without prior CABG.

Clinical messages

Physicians are faced with increasing numbers of ACS patients with prior CABG and these patients are at high short- and long-term risk of poor outcome, even despite a higher rate of early invasive management. The reasons for the worse outcome of prior CABG patients are likely due to the higher risk profile of these patients (e.g., increased age, higher rates of cardiac, and non-cardiac morbidities), under-treatment with evidence-based therapies, and lack of an optimal initial reperfusion strategy in MI.

Lytic therapy has poor efficacy in thrombotic saphenous vein graft (SVG) occlusions.³⁰ On the other hand, primary PCI in a

culprit SVG is also much less likely to achieve normal antegrade flow compared with PCI in a native vessel, and failure to achieve adequate flow is an important determinant of subsequent mortality.¹⁸ No prospective randomized controlled trial has addressed this question adequately. In recent primary PCI trials, the absolute number of patients enrolled with prior CABG has been low (generally $<3\%$), limiting meaningful interpretation.^{22,23} Indeed, some trials of invasive vs. conservative management in ACS have excluded patients with prior CABG,^{24–26} and some of the trials that did include CABG patients have not reported outcomes in these patients.^{27,28} A prospective randomized trial of reperfusion strategies is merited in this high-risk group.

Under-treatment with some evidence-based drug therapies suggests these patients may benefit from more intensive management in order to reduce their risk of adverse cardiovascular events. Evidence-based pharmacological therapy is also important in this group with recent studies showing the importance of intensive lipid lowering therapy in CABG patients.²⁹ Consequently, our observations suggest that in acute MI, underuse of prognostically important medical therapies may be a complicating factor in patients with prior CABG who experience an acute MI.

Limitations

We focused on a subgroup within the VALIANT population, and VALIANT was not designed to prospectively investigate the outcomes of patients with prior CABG. We focused on CABG patients with clinical HF or a low EF, rather than CABG patients without these problems, in whom the outcomes are likely to be better. Our data do not permit an analysis based on the presence or absence of ST-elevation. Although our analyses are performed in a clinical trial population, there was no upper age limit for participation in VALIANT.

Supplementary material

Supplementary Material is available at *European Heart Journal* Online.

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