CLINICAL RESEARCH
Acute coronary syndromes

High-grade atrioventricular block in acute coronary syndromes: insights from the Global Registry of Acute Coronary Events

Sheldon M. Singh[1], Gordon FitzGerald[2], Andrew T. Yan[3], David Brieger[4], Keith A.A. Fox[5], Jose López-Sendón[6], Raymond T. Yan[7], Kim A. Eagle[8], Ph. Gabriel Steg[9], Andrzej Budaj[10], and Shaun G. Goodman[3,11,12]*

[1]Division of Cardiology, Department of Medicine, Schulich Heart Centre, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Canada; [2]Center for Outcomes Research, University of Massachusetts Medical School, Worcester, MA, USA; [3]Terrence Donnelly Heart Centre, St Michael's Hospital, University of Toronto, Toronto, Canada; [4]Coronary Care Unit, Concord Hospital, Sydney, Australia; [5]Centre for Cardiovascular Science, The University of Edinburgh, Edinburgh, UK; [6]Hospital Universitario La Paz, Madrid, Spain; [7]University of Toronto, Toronto, Canada; [8]University of Michigan Medical Center, Ann Arbor, MI, USA; [9]Hôpital Bichat, Assistance Publique, Hôpitaux de Paris, Paris, France; [10]Grochowski Hospital, Warsaw, Poland; [11]Canadian Heart Research Centre, Toronto, Canada; and [12]Division of Cardiology, St Michael's Hospital, 30 Bond Street, Room 6-034 Queen, Toronto, Ontario, Canada M5B 1W8

Background	While prior work has suggested that a high-grade atrioventricular block (HAVB) in the setting of an acute coronary syndrome (ACS) is associated with in-hospital death, limited information is available on the incidence of, and death associated with, HAVB in ACS patients receiving contemporary management.
Methods and results	The incidence of HAVB was determined within The Global Registry of Acute Coronary Events (GRACE). The clinical characteristics, in-hospital therapies, and outcomes were compared between patients with and without HAVB. Factors associated with death in patients with HAVB were determined. A total of 59 229 patients with ACS between 1999 and 2007 were identified; 2.9% of patients had HAVB at any point during the index hospitalization; 22.7% of whom died in hospital [adjusted odds ratio (OR) = 4.2, 95% confidence interval (CI), 3.6–4.9, $P < 0.001$]. The association between HAVB and in-hospital death varied with type of ACS [OR: ST-segment elevation myocardial infarction (STEMI) = 3.0; non-STEMI = 6.4; unstable angina = 8.2, P for interaction < 0.001]. High-grade atrioventricular block present at the time of presentation to hospital (vs. occurring in-hospital) and early (<12 h) percutaneous coronary intervention or fibrinolysis (vs. >12 h or no intervention) were associated with improved in-hospital survival, whereas temporary pacemaker insertion was not. Patients with HAVB surviving to discharge had similar adjusted survival at 6 months compared with those without HAVB. A reduction in the rate of, but not in-hospital mortality associated with, HAVB was noted over the study period.
Conclusion	Although the incidence of HAVB is low and decreasing, this complication continues to have a high risk of in-hospital death.
Keywords	Acute coronary syndromes • Atrioventricular block • Artificial pacemaker • Percutaneous coronary intervention

Introduction

High-grade atrioventricular block (HAVB), defined as the presence of Mobitz type II second-degree or third-degree AV block, is a worrisome finding in patients with acute coronary syndromes (ACS). Prior studies have reported the incidence of HAVB in ACS between 3 and 14% with an associated three- to five-fold increased risk of in-hospital death.[1–12] These reports have been limited by the small numbers of patients studied, typically in ST segment myocardial infarction (STEMI) patients, and predominantly in patients receiving care in, or prior to, the 1990s.[1–12] Furthermore, the associations between clinical factors including in-hospital therapies received, and the risk of death within this group of patients is not well described. To address these limitations, we analysed data from

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* Corresponding author. Tel: +1 4168645722, Fax: +1 4168645407, Email: goodmans@smh.ca

a global population of ACS patients to determine: (i) the incidence of HAVB complicating ACS, (ii) the risk of death, and (iii) factors associated with death in patients with HAVB.

Methods

The design of the Global Registry of Acute Coronary Events (GRACE) study has previously been reported.[13] In brief, this prospective multi-national registry enrolled patients with ACS at 126 hospitals in 14 countries between 1999 and 2007. Eligible patients were $\geq$ 18 years of age with a presumptive diagnosis of ACS and $\geq$ 1 of the following findings: abnormal cardiac biomarkers, electrocardiography (ECG) changes consistent with ACS, or prior coronary artery disease. Patients were excluded if the ACS was precipitated by non-cardiovascular co-morbidities including trauma, gastrointestinal bleeding, or an operation or procedure. Local hospital ethics review board approval was obtained at each site and, where necessary, informed consent obtained from participating patients.

Standardized case report forms were completed by local study co-ordinators or physicians to document patient demographics, clinical history, presenting features, medication use (before and during hospitalization), in-hospital management (medical and invasive therapies), and in-hospital clinical events. Follow-up was also performed at 6 months to ascertain vital status and identify new clinical events.

ST-segment elevation myocardial infarction was defined as $\geq$ 1 mm ST-segment elevation in two contiguous leads or new left bundle branch block, accompanied by $\geq$ 1 positive cardiac biomarker confirming cardiac necrosis. Non-STEMI was diagnosed when $\geq$ 1 positive cardiac biomarker confirming cardiac necrosis was present without new ST-segment elevation. Unstable angina pectoris (UA) was diagnosed when cardiac biomarkers were within normal limits. The diagnosis of ACS was confirmed at the time of discharge.

ECGs were interpreted at the enrolling centre and not centrally adjudicated. High-grade atrioventricular block was defined in the GRACE as the presence of either Mobitz II second-degree AV block or third-degree AV block. High-grade atrioventricular block was categorized as occurring at presentation if HAVB was present on the index ECG and presumed to be of new onset. High-grade atrioventricular block was categorized as occurring in-hospital if HAVB was noted only on subsequent ECGs and not the index ECG. Patients with HAVB on both the index and subsequent in-hospital ECGs were categorized as HAVB at presentation.

Patients with ACS were categorized into one of two groups: those with HAVB and those without HAVB at any time during the ACS. Demographic, clinical features, and the use of in-hospital therapies were reported for each group. Continuous variables were reported as medians with 25th and 75th percentiles and categorical variables as percentages. Comparisons of the continuous and categorical variables were made with the Mann–Whitney U and χ^2 tests, respectively.

Multiple logistic regression analysis adjusting for the GRACE risk score, a validated predictor of in-hospital mortality[14,15] and the region in which the ACS occurred [(i) Europe; (ii) USA; (iii) Argentina/Brazil; (iv) Australia/New Zealand/Canada] was performed to assess the adjusted odds ratio (OR) and 95% confidence interval (CI) of in-hospital death associated with HAVB at any time during the admission for ACS. To assess the impact of the type of ACS, we repeated this analysis for each of STEMI, non-STEMI, and UA. Similar analyses were employed for 6-month outcomes.

Patients with HAVB were further evaluated according to the time HAVB was first noted (at presentation or in-hospital), and their vital status at hospital discharge. Univariate and multiple logistic regression analyses were performed to estimate the odds associated with various clinical factors and in-hospital death within this group of patients.

Linear temporal trend in rates was assessed by the Mantel–Cochran–Haenszel test. An alpha level of 0.05 was used in all significance testing.

All analysis was conducted using the SAS software package, version 9.2 (SAS Institute, Cary, NC, USA).

Results

A total of 59 229 patients with ACS hospitalized between 1999 and 2007 were included: 37% with STEMI, 33% with non-STEMI, and 30% with UA. Overall HAVB was present in 2.9% of the cohort; the incidence of HAVB with STEMI, non-STEMI, and UA was 5.0, 1.9, and 1.5%, respectively ($P < 0.001$) (*Figure 1*). High-grade atrioventricular block occurred at the time of presentation in 46% of patients, whereas 54% developed this complication during the index hospitalization.

Patients with HAVB presented with higher-risk features as evidenced by the higher GRACE risk score at the time of ACS presentation (*Table 1*). Cardiac catheterization was performed less frequently in patients with HAVB (58.2 vs. 62.7%) (*Table 2*). In-hospital complications such as heart failure (30.6 vs. 12.8%), shock (23.3 vs. 3.5%), and ventricular arrhythmias (14.0 vs. 2.7%) were more common in patients with HAVB. Of note, temporary pacemaker insertion was utilized in 35.0% of patients with HAVB compared with 1.5% without HAVB. The indication for temporary pacemaker insertion was not available in the GRACE.

Overall, 23% of patients with HAVB died prior to hospital discharge compared with 4.3% without HAVB ($P < 0.001$). After adjusting for the GRACE risk score and study region, this association remained statistically significant with an OR of in-hospital death of 4.2 (95% CI, 3.6–4.9; $P < 0.001$). The association between HAVB
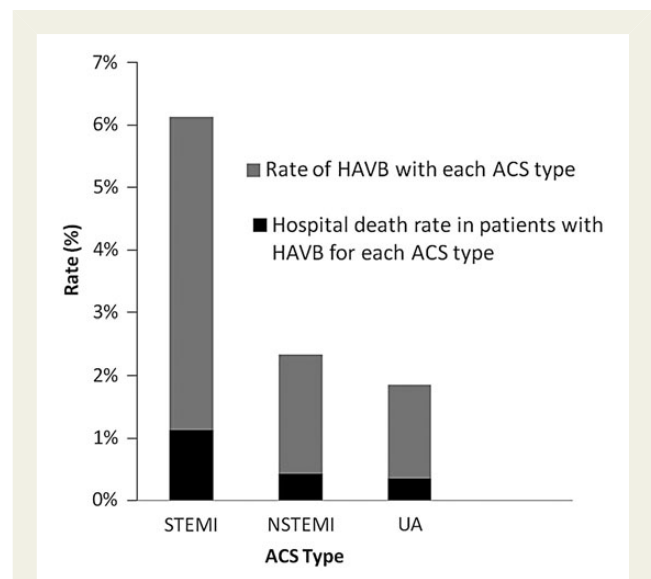

Figure 1 Rates of high-grade atrioventricular block (at presentation or later in-hospital) and associated in hospital mortality by acute coronary syndrome type. $P < 0.001$ for the interaction between high-grade atrioventricular block with acute coronary syndrome type (grey bars) and odds of death with each acute coronary syndrome type (see text for details).

Table 1 Baseline demographic, clinical features at presentation, in-hospital invasive therapies received, and clinical outcomes for patients with acute coronary syndrome according to the presence or absence of high-grade atrioventricular block

	HAVB (n = 1701)	No HAVB (n = 57 528)	P-value
Age (years)[a]	70 (60−79)	66 (56−76)	<0.001
Men (%)	1135 (66.6)	38 819 (67.3)	0.01
Medical history (%)			
Diabetes	496 (29.5)	14 348 (25.1)	<0.001
Hypertension	1019 (60.5)	35 637 (62.3)	0.14
Dyslipidaemia	641 (38.2)	27 965 (49.0)	<0.001
Peripheral vascular disease	176 (10.5)	5265 (9.2)	0.09
Transient ischaemic attack/stroke	155 (9.2)	4736 (8.3)	0.09
Myocardial infarction	441 (26.1)	17 182 (30.0)	0.001
Percutaneous coronary intervention	223 (13.2)	10 326 (18.0)	<0.001
Coronary artery bypass graft surgery	172 (10.2)	7110 (12.4)	0.01
Heart failure	215 (12.8)	5691 (10.0)	<0.001
Pre-hospital medication use			
Aspirin	526 (31.0)	23 050 (40.1)	<0.001
β-Blocker	426 (25.2)	18 961 (33.1)	<0.001
Statin	265 (15.7)	16 221 (28.4)	<0.001
Angiotensin-converting enzyme inhibitor	379 (22.5)	16 183 (28.3)	<0.001
Angiotensin receptor blocker	79 (4.7)	3546 (6.3)	0.01
Clinical presentation			
Systolic blood pressure (mmHg)[a]	126 (102−150)	140 (120−16)	<0.001
Heart rate (b.p.m.)[a]	66 (50−83)	77 (65−90)	<0.001
Killip class			
I	1212 (72.8)	47 048 (83.6)	<0.001
II	268 (16.1)	6621 (11.8)	
III or IV	184 (11.1)	2611 (4.6)	
Cardiac arrest	101 (6.0)	1102 (1.9)	<0.001
ST-segment deviation	1302 (76.5)	31 091 (54.0)	<0.001
ST-segment elevation	1075 (63.2)	20 872 (36.3)	<0.001
ST-segment depression	744 (43.7)	18 699 (32.5)	<0.001
Q-waves	433 (25.5)	12 233 (21.3)	<0.001
Left bundle branch block	104 (6.1)	2757 (4.8)	0.02
Positive initial cardiac biomarkers	921 (56.5)	26 669 (47.6)	<0.001
Ratio of maximum creatine kinase to upper limit of lab normal in first 24 h	4.8 (1.3−11.5)	1.7 (0.6−5.9)	<0.001
Ratio of maximum troponin to upper limit of lab normal in first 24 h	54.5 (10.7−231)	17.3 (2.0−100)	<0.001
Global Registry of Acute Coronary Events risk score[a]	151 (128−178)	128 (104−154)	<0.001

[a]Median (25−75th percentiles).

and in-hospital death varied with type of ACS (P for interaction < 0.001): 3.0 (95% CI, 2.5−3.7; P < 0.001) for STEMI, 6.4 (95% CI, 4.7−8.8, P < 0.001) for non-STEMI, and 8.2 (95% CI, 5.2−13, P < 0.001) for UA (Figure 1).

Of the patients surviving the initial hospitalization, follow-up at 6 months was obtained for 80%. Patients lost to follow-up had a similar rate of in-hospital HAVB (2.4 vs. 2.3%, P = 0.51), median age (66 vs. 66, P = 0.65), and GRACE risk score (127 vs. 128, P = 0.04) compared with those where follow-up was complete. No significant difference in post-discharge mortality between HAVB

and non-HAVB patients was observed at 6 months [7.2 vs. 4.2%; adjusted OR = 1.06 (95% CI = 0.80−1.4)].

The rate of HAVB in all ACS patients, temporary and permanent pacemaker implantation, and in-hospital mortality for patients with ACS (with and without HAVB) was determined for each year of the study (Figure 2). A significant linear decline was observed in the rate of HAVB in general (0.02%/year; P for trend < 0.001) including HAVB occurring at presentation (0.05%/year; P for trend = 0.02) and HAVB developing in-hospital (0.2%/year; P for trend <0.001), temporary (0.2%/year; P for trend<0.001), and permanent

Table 2 In-hospital procedures, clinical outcomes, and discharge medications for patients with acute coronary syndrome according to the presence or absence of high-grade atrioventricular block

	HAVB (n = 1701)	No HAVB (n = 57 528)	P-value
In-hospital procedures (%)			
Cardiac catheterization	981 (58.2)	35 808 (62.7)	<0.001
Percutaneous coronary intervention	720 (42.7)	22 421 (39.3)	0.005
Percutaneous coronary intervention <12 h	390 (24.8)	8213 (15.4)	<0.001
Coronary artery bypass graft surgery	81 (4.8)	2929 (5.2)	0.61
Fibrinolytics	413 (24.6)	7264 (12.8)	<0.001
Left ventricular ejection fraction assessment	837 (49.2)	27 295 (47.4)	0.15
Temporary pacemaker	593 (35.0)	879 (1.5)	<0.001
Permanent pacemaker	100 (5.9)	250 (0.04)	<0.001
Coronary anatomy: infarct territory[a] (%)			
Left main	20 (2.3)	743 (2.5)	0.74
Left anterior descending	173 (19.7)	12 717 (43.3)	<0.001
Circumflex	100 (11.4)	5646 (19.2)	<0.001
Right coronary artery	568 (64.7)	9200 (31.3)	<0.001
Saphenous vein graft bypass	17 (1.9)	1092 (3.7)	0.005
Coronary anatomy: >50% stenosis[a] (%)			
Left main	77 (4.9)	2597 (4.8)	0.86
Left anterior descending	580 (34.1)	23 855 (41.5)	<0.001
Circumflex	507 (29.8)	17 569 (30.5)	0.54
Right coronary artery	784 (46.1)	20 351 (35.4)	<0.001
Number of vessels with >50% stenosis[a] (%)			
0	43 (4.4)	3053 (8.5)	<0.001
1	298 (30.4)	12 679 (35.4)	
2	318 (32.4)	9943 (27.8)	
3 or more	322 (32.8)	10 133 (28.3)	
Left ventricular ejection fraction[b]			
Left ventricular ejection fraction (%, range)	48 (38–55)	50 (40–60)	<0.001
In-hospital clinical events (%)			
Myocardial re-infarction	50 (5.2)	823 (2.3)	<0.001
Congestive heart failure	514 (30.6)	7349 (12.8)	<0.001
Cardiogenic shock	393 (23.3)	2007 (3.5)	<0.001
Cardiac arrest	409 (24.5)	2322 (4.1)	<0.001
Sustained ventricular tachycardia	236 (14.0)	1574 (2.7)	<0.001
Atrial fibrillation/flutter	313 (18.6)	4235 (7.4)	<0.001
Acute renal failure	227 (13.5)	2095 (3.6)	<0.001
Stroke	29 (1.7)	397 (0.7)	<0.001
Death	386 (22.7)	2473 (4.3)	<0.001
Discharge medications[c]			
Aspirin	1018 (90.3)	44 431 (90.9)	0.46
β-Blocker	677 (60.4)	38 908 (79.9)	<0.001
Statin	722 (64.5)	35 397 (72.8)	<0.001
Angiotensin-converting enzyme inhibitor	723 (64.6)	30 819 (63.4)	0.45
Angiotensin receptor blocker	41 (3.7)	2653 (5.5)	0.01

[a]If had coronary angiography: performed in 981 with HAVB and 35 808 without HAVB.
[b]Left ventricular assessment performed in 837 with HAVB and 27 295 without HAVB.
[c]Thousand three hundred and fifteen with HAVB discharged alive and 55 638 without HAVB discharged alive.
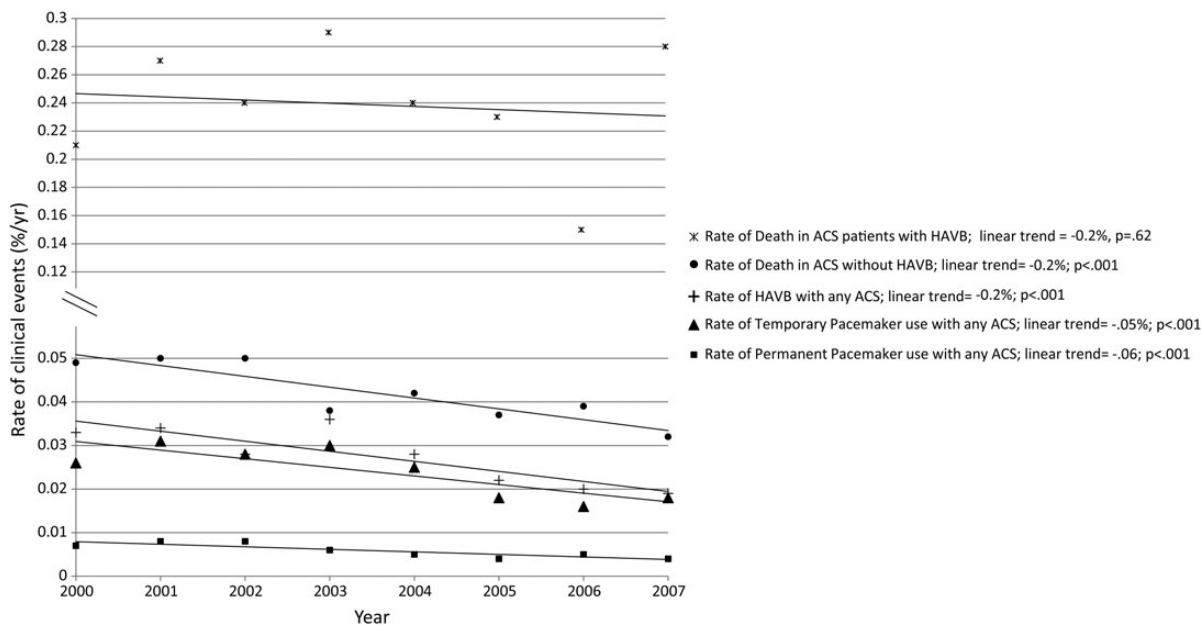
Figure 2 Temporal change in the rate of clinical events (death with acute coronary syndrome and high-grade atrioventricular block; death with acute coronary syndrome without high-grade atrioventricular block; high-grade atrioventricular block with any acute coronary syndrome; temporary pacemaker use; permanent pacemaker use) in patients with acute coronary syndrome between 2000 and 2007.

pacemaker use (0.06%/year; *P* for trend <0.001), and in-hospital mortality in patients with ACS without HAVB (0.2%/year; *P* for trend <0.001). A significant linear decline was not observed for in-hospital mortality associated with HAVB (*P* for trend = 0.62) regardless of the time HAVB occurred (at presentation; *P* for trend = 0.33 vs. in-hospital; *P* for trend = 0.58).

Patients with HAVB (*n* = 1701) were further analysed according to the time onset of HAVB (Supplementary material online, Appendix *Table S1*). When compared with patients with HAVB at the time of presentation, patients with HAVB that developed in-hospital had similar GRACE risk scores (152 vs. 151, *P* = 0.69), rates of percutaneous coronary interventions (PCI) (43 vs. 43%, *P* = 0.96), but had a larger number of coronary arteries with >50% stenosis (three or more coronaries: 21 vs. 16%. *P* = 0.02), left anterior descending territory infarctions (23 vs. 16%, *P* = 0.01), experienced a higher frequency of in-hospital complications including re-infarction (7.5 vs. 2.9%, *P* = 0.002), cardiogenic shock (29 vs. 17%, *P* < 0.001), and had a higher use of permanent pacemakers (7.3 vs. 4.2%, *P* = 0.01). In-hospital death was higher in patients with HAVB developing in-hospital compared with HAVB present at the time of presentation to the hospital [29 vs. 15%; adjusted OR = 2.9 (95% CI = 2.1–4.0)]. For patients surviving to hospital discharge, there was no associated increased risk of death at 6 months (adjusted OR = 0.92, 95% CI = 0.54–1.58).

Patients with HAVB were also analysed based on their vital status at the time of the hospital discharge (Supplementary material online, Appendix *Table S2*). Patients with HAVB who died in hospital were older (74 vs. 69 years, *P* < 0.001), had higher GRACE risk scores (180 vs. 145, *P* < 0.001), experienced more in-hospital

complications including myocardial re-infarction (15 vs. 2.7%, *P* < 0.001), congestive heart failure (53 vs. 24%, *P* < 0.001), cardiogenic shock (67 vs. 11%, *P* < 0.001), and ventricular arrhythmias (28 vs. 9.8%, *P* < 0.001). Temporary pacemaker use was higher in HAVB patients who died in hospital (52 vs. 30%, *P* < 0.001), whereas permanent pacemaker implantation was higher in survivors (7.1 vs. 1.8%, *P* < 0.001). After adjusting for all statistically significant variables present in the univariate analysis, associations between several variables and in-hospital death remained (*Table 3*). Specifically, HAVB at presentation, receipt of fibrinolysis or PCI within 12 h of hospitalization, and receipt of a permanent pacemaker were associated with a higher likelihood of in-hospital survival, whereas a prior history of heart or renal failure and the use of a temporary pacemaker were associated with higher risk of in-hospital death.

The positive association between permanent pacemaker implantation and in-hospital survival was further assessed by evaluating the association between permanent pacemaker implantation and survival after hospital discharge at 6 months. Patients with HAVB who survived the initial hospital admission and received a permanent pacemaker had an elevated odds of death at 6 months (adjusted OR = 2.4, 95% CI = 1.2–5.1).

Discussion

We described the clinical features and outcomes of HAVB in a global registry of patients with a broad spectrum of ACS. Although the incidence of HAVB in this cohort was lower than previously reported[1,3,5,7,9,10] and decreased throughout the study period, patients with this complication had an associated increased risk

Table 3 Among patients with high-grade atrioventricular block, adjusted associations for risk factors with in-hospital death

Risk factor	All patients with HAVB (n = 1300, 266 deaths[a])
HAVB at presentation vs. developing in hospital	0.35 (0.25–0.50)
Percutaneous coronary intervention <12 h and/or fibrinolytics	0.51 (0.36–0.71)
Temporary pacemaker	2.06 (1.49–2.84)
Permanent pacemaker	0.20 (0.08–0.50)
History of heart failure	1.49 (0.94–2.35)
History of renal failure	1.67 (1.00–2.81)

Results are reported as ORs and 95% CIs.
[a]With complete covariate information; results are also adjusted for the GRACE risk score for in-hospital mortality[14] and geographic region.

of in-hospital death. Moreover, despite advances in ACS care, in-hospital mortality associated with this complication did not decrease over the 9-year period of the registry, confirming the ongoing ominous nature of this complication. However, patients with HAVB who survived the initial hospitalization had similar long-term survival when compared with patients without HAVB.

Mechanism of high-grade atrioventricular block with acute coronary syndrome

Multiple mechanisms for HAVB have been proposed in the setting of ACS. Activation of parasympathetic afferent nerves in the inferior–posterior wall of the left ventricle may result in reflex bradycardia and AVB (Bezold–Jarisch reflex).[16–19] This phenomenon typically appears early, may reflect coronary reperfusion,[18,19] and is sensitive to atropine.[1,16,20] The AV node itself may become ischaemic if its blood supply is compromised.[16] While the AV nodal artery typically arises from the right coronary artery, collateral blood supply to the AV node is provided by the septal perforators of the left anterior descending artery and adjacent venous sinusoids, thereby providing this structure with some degree of protection.[21] Furthermore, this structure is resistant to transient ischaemia due to its high intracellular content of glycogen.[22] Despite this, prolonged ischaemia with extensive myocardial necrosis may result in irreversible AV nodal injury. Finally, extensive myocardial infarction involving the septum, typically in the setting of an anterior MI, may result in extensive bilateral bundle branch infarction.[23] It is likely that a combination of these mechanisms is in play during episodes of HAVB with the dominant mechanism of HAVB dictating the time course, duration, and clinical consequences associated with this complication. For example, our finding of a worse prognosis with UA or non-STEMI compared with STEMI, a finding not previously reported in the literature, may reflect the fact that patients with UA and non-STEMI typically have multi-vessel ischaemia with compromised primary and collateral blood flow to the AV node and the septum resulting in more severe conduction impairment, whereas STEMI patients

often have compromised, but frequently transient due to rapid reperfusion, flow to a single vessel resulting in less severe compromise to the conduction system.

Associations with in-hospital death in high-grade atrioventricular block patients

High-grade atrioventricular block developing in-hospital was associated with an increased risk of death when compared with HAVB observed at presentation to the hospital. This finding is not surprising as early HAVB may be related to increased vagal tone,[1,16–19] reversible AV nodal ischaemia, or the act of reperfusion itself,[17,18] whereas late HAVB may be associated with more complicated infarctions[2,24] as evidence by the higher rate of re-infarction and cardiogenic shock observed in patients with HAVB developing in-hospital. Our data are the first to demonstrate a positive association between reperfusion/early revascularization and survival in patients with HAVB complicating ACS. We speculate that the potential benefit of fibrinolysis or early PCI may be related to both the attenuation of the ischaemic insult to the conduction system, reduction in the risk of re-infarction, and a reduction in the overall infarct size, the latter of which has consistently been shown to be associated with improved overall survival.[25]

Temporary pacing, an intervention clearly indicated in this population,[26] was not associated with a reduction in in-hospital death but in fact associated with a two-fold increase in the risk of in-hospital death. While temporary pacemaker placement may be fraught with complications including ventricular fibrillation, cardiac perforation, and septicaemia,[27] the increased risk of death observed in this study likely reflects the fact that HAVB itself may not be responsible for a patient's death but rather be a reflection of the severity of the patient's ACS. Unlike temporary pacemaker insertion, a positive association between permanent pacemaker implantation and in-hospital survival was observed. While a true protective effect of permanent pacing cannot be excluded, it is quite possible that this finding may be related to survival bias—that is, patients receiving a permanent pacemaker would be required to survive to the time of pacemaker implantation which typically occurs later during hospitalization. The suggestion of increased odds of death at 6 months in patients with HAVB who received a permanent pacemaker compared with patients with HAVB who did not receive a pacemaker suggests that permanent pacemaker implantation may also be a marker of a higher-risk subgroup of patients with haemodynamically unstable HAVB and ACS. In this situation, patients with HAVB may survive the initial hospital admission thereby receiving a permanent pacemaker, but die shortly thereafter despite correction of the conduction abnormality due to the underlying severity of the ACS.

Implication

Our data suggest that the HAVB is associated with complicated ACS. Although pacing is warranted in this situation, this intervention in isolation may not improve survival in this patient population. Our findings suggest that reperfusion/early revascularization and potentially other interventions aimed at attenuating infarct size and minimizing additional complications associated with ACS could have an impact upon the incidence and possibly the outcomes associated with HAVB. Such interventions should be aggressively pursued as patients

who survive the initial hospitalization have a long-term survival comparable with those with ACS without HAVB. While long-term survival is not compromised in patients with HAVB surviving the acute hospital admission, one cannot exclude impaired quality of life in this subgroup of patients related to the detrimental effects of in-hospital complications. For example, patients with HAVB had a higher rate of stroke which may be a significant impact on long-term quality of life.

Limitations

Limitations of our work must be acknowledged. First, the insertion of temporary or permanent pacemakers was not randomized in this observational study. Patient and physician treatment preferences, availability of cardiac interventions, and other unmeasured confounders, likely exist and may not be accounted for in our analysis. It would be impossible to remove this bias outside the setting of a randomized controlled trial, which is likely not feasible. Second, patients not surviving the pre-hospital phase were not included in our registry which could lead to an under-estimation of the incidence of HAVB and the observed association between HAVB and death. Additionally, we assessed the association between in-hospital therapies such as early (within 12 h) PCI, temporary- and permanent-pacemaker insertion on death; however, our findings may be biased as almost one quarter of deaths in the GRACE registry occurred within the first 24 h of ACS admission[14] which could preclude receipt of these interventions. Third, in-hospital telemetry and frequent ECG monitoring were not mandated which may have decreased the ability to detect HAVB. This, as well as the absence of an ECG core lab, may have resulted in misclassification and potential under-estimation of the incidence of HAVB. Fourth, we were unable to distinguish HAVB due to a Mobitz type II second-degree from a third-degree AV block in the GRACE thereby preventing us from exploring the differential impact of each type of AVB on clinical outcomes. Finally, our analysis was of patients receiving care for ACS between 1999 and 2007, may not reflect current practice patterns. Despite these limitations, our analysis of the GRACE is unique, as it provides an opportunity to explore associations between HAVB and clinical events across a wide spectrum of ACS patients globally.

In conclusion, although the incidence of HAVB with ACS is low, in-hospital mortality with this condition remains high, and likely reflects the severity of the ACS. Aggressive supportive care in addition to pacing may be necessary to improve the outcome of patients with this serious complication.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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