Coronary Heart Disease

Comorbidity and Myocardial Dysfunction Are the Main Explanations for the Higher 1-Year Mortality in Acute Myocardial Infarction With Left Bundle-Branch Block

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Background—The purpose of this study was to assess the independent contribution of left bundle-branch block (LBBB) on cause-specific 1-year mortality in a large cohort with acute myocardial infarction (MI).

Methods and Results—We studied a prospective cohort of 88,026 cases of MI from the Register of Information and Knowledge about Swedish Heart Intensive care Admissions in 72 hospitals in 1995 to 2001. Long-term mortality was calculated by Cox regression analysis, adjusted for multiple covariates that affect mortality by calculation of a propensity score. LBBB was present in 9% (8041 of 88,026) of the MI admissions. Patients with LBBB were older and had a higher prevalence of comorbid conditions than patients with no LBBB. The unadjusted relative risk of death within 1 year was 2.16 (95% CI, 2.08 to 2.24; P < 0.001) for LBBB (42%, 3350 of 8041) compared with those with no LBBB (22%, 17,044 of 79,011). After adjustment for a propensity score that takes into account differences in risk factors and acute intervention, LBBB was associated with a relative risk of death of 1.19 (95% CI, 1.14 to 1.24; P < 0.001). In a subgroup of 11,812 patients for whom left ventricular ejection fraction was available and could be added to the analysis, the contributing relative risk of LBBB for death was only 1.08 (95% CI, 0.93 to 1.25; P = 0.33). The most common cause of death in both groups was ischemic heart disease.

Conclusions—MI patients with LBBB have more comorbid conditions and an increased unadjusted 1-year mortality. When adjusted for age, baseline characteristics, concomitant diseases, and left ventricular ejection fraction, LBBB does not appear to be an important independent predictor of 1-year mortality in MI. (Circulation. 2004;110:1896-1902.)

Key Words: bundle-branch block | mortality | myocardial infarction | patients | prognosis

Left bundle-branch block (LBBB) on ECG at presentation has been reported to occur in 1% to 15% of patients with myocardial infarction (MI).1-6 The significance of LBBB in the setting of MI has been studied in both the thrombolytic6-10 and prethrombolytic1-3,11,12 eras, demonstrating an association of LBBB with increased short- and long-term mortality. Previous studies have reported a wide range of 1-year mortality in patients with MI and LBBB, varying between 19% and 61%.3,4,6-13 However, although some studies suggest that LBBB is an independent predictor of short- and long-term mortality in patients with MI,6,7,9 others have found no effect.8 Some of these studies had small numbers of patients,1-3,5,6,8-10 and others were done in the prethrombolytic era.1-5,11-13 The survival benefit by reperfusion treatment in patients with MI and LBBB has been demonstrated previously.14,15 The recently published Multicenter Automatic Defibrillator Implantation Trial (MADIT) II study reported the largest survival benefit with implantable defibrillator therapy in patients with wide QRS complex (48% LBBB) in a population with previous MI and left ventricular dysfunction.16 Whether this larger benefit is related to the higher risk of death or to a specific effect because of conduction abnormality per se in LBBB population has not been elucidated.

The reasons for the poor prognosis in the LBBB patients with MI and the potential for specific effects of antiarrhythmic, reperfusion, or other treatments have not been well studied. The purpose of this study was to assess the independent contribution of LBBB compared with ST-segment elevation and non–ST-segment elevation on 1-year cause-specific mortality in a large cohort with MI.

Methods

The Register of Information and Knowledge about Swedish Heart Intensive care Admissions (RIKS-HIA) registers all patients admitted to the coronary care units of all participating hospitals. Information, including data on 100 variables, is reported on case record...
forms and has been described elsewhere.17 Briefly, the register includes information on age, sex, smoking status, hypertension, diabetes mellitus, hyperlipidemia, previous angina pectoris, previous MI, previous coronary revascularization, previous medications ("previ-
ous" means events occurring or medication started before the
current admission), symptoms, ECG at entry, biochemical markers,
oechocardiography, reperfusion treatment, pharmaceutical treat-
ment, interventional procedures, major complications, and outcomes
during the hospital stay; risk assessment with stress test, coronary
angiography, and revascularization procedures; and medications at
discharge. (The full protocol is available at http://www.riks-hia.se.)

Some data were continuously verified by comparison of the registry
information with the patient records of the hospital by an external
monitor.

One-year mortality data were obtained by merging the RIKS-HIA
database with the National Cause of Death Register, which includes
the vital status of all Swedish citizens in 1995 through 2002.
Previous history of stroke, dementia, renal failure, congestive heart
failure, chronic pulmonary disease, and cancer were obtained by
merging with the National Patient Register, which includes diag-
noses on all patients hospitalized in Sweden from 1987 and forward.
All patients for whom data were entered into RIKS-HIA were
informed of their participation in the registry (patients could request
to be excluded) and the long-term follow-up. The registry and the
merging with registries were approved by the National Board of
Health and Welfare and the Swedish Data Inspection Board.

We included all patients admitted with ST-segment elevation,
non–ST-segment elevation, or LBBB on the ECG at entry and with
acute MI as the final diagnosis. LBBB was diagnosed according to
standard definitions.18 Patients with agonal or pacemaker-induced
QRS complexes were excluded. The criteria for the diagnosis
of acute MI were standardized and identical for all participating
hospitals through the use of the World Health Organization criteria.19

The biochemical criterion was at least 1 measurement indicating
twice the upper limit of normal of an appropriate biochemical marker
(usually creatine kinase [CK]-MB protein concentration or troponin-
T). In the analyses, biochemical markers were divided into 4 groups:
(1) CK-MB ≤50 μg/L or troponin-T ≤1.0 μg/L, (2) CK-MB 51 to
150 μg/L or troponin-T 1.0 to 3.0 μg/L, (3) CK-MB >150 μg/L or
troponin-T >3.0 μg/L, and (4) missing values. ECG was classified
according to 3 variables: rhythm ([1] sinus, [2] atrial fibrillation or
wave, [5] other pathological QRS complex); and STT segment ([1]
pathological STT segment). Starting in a hierarchical order from
alternative 1 in each of the 3 variables, the first applicable alternative
that was correct for that part of the ECG was the coding for it. Left
ventricular ejection fraction (LVEF) was determined by echocardi-
ography before discharge and coded into RIKS-HIA in 6 groups: (1)
not performed, (2) performed (no information about LVEF), (3)
normal (LVEF >50%), (4) light dysfunction (LVEF 40% to 50%),
(5) moderate dysfunction (LVEF 30% to 39%), and (6) severe
dysfunction (LVEF <30%). Before 2001, LVEF was not part of
the mandatory protocol, and echocardiography was registered only
as performed or not performed. Hence, analyses including LVEF
were available in only a minority of patients.

Statistical Analysis

Different patient strata were compared by χ² tests for categorical
variables and by the t test for continuous variables. A propensity
score was calculated for each patient to estimate the probability of
being an LBBB patient (compared with a patient with no LBBB)
given the background characteristics and treatments received. Ad-
justing for the propensity score in the analysis was aimed at giving
a better estimate of the relative risk (RR) of death between groups.

Multiple logistic regression analysis was performed to calculate
the first propensity score (A), including 25 covariates: age, sex, previous
MI, history of diabetes mellitus, history of stroke, congestive heart
failure, renal failure, chronic pulmonary disease, dementia, cancer
within 3 years, history of hypertension, history of coronary artery
revascularization, medications before study entry (including ACE
inhibitors or angiotensin II receptor blockers, anticoagulants,
β-blockers, aspirin, or platelet inhibitors, calcium channel blockers,
digitalis, diuretics, lipid-lowering drugs, and long-acting nitrates),
circulatory arrest at arrival, presence of atrial fibrillation, signs of
congestive heart failure, and reperfusion therapy. Logistic regression
analyses were used to establish the relation between LBBB and
in-hospital complications. Cox proportional-hazards regression anal-
yses including the propensity scores were used to identify whether
LBBB by itself significantly influenced mortality.

To evaluate the influence of in-hospital therapy, coronary inter-
ventions, and discharge medication, a Cox proportional-hazards
regression analysis was also performed concerning the same out-
come in survivors at discharge and including a second propensity
score. The second propensity score (B) of the likelihood of LBBB on
ECG included the previous 25 covariates and an additional 13
covariates—heparin therapy, intravenous nitroglycerin, intravenous
β-blockers, coronary revascularization within 14 days, discharge
medication (including ACE inhibitor, oral anticoagulants, aspirin or
platelet inhibitors, β-blockers, calcium channel blockers, digitalis,
diuretics, lipid-lowering drugs, and long-acting nitrates)—for a total
of 38 covariates. In some Cox proportional-hazards regression
analyses, the ordinal variable, biochemical marker peak level group,
and the scale variable, Killip class, were included. In a subgroup for
which LVEF was available, the previously mentioned 4 groups of
LVEF were added as a scale variable to the Cox proportional-hazards
regression analysis of 1-year mortality, also including the 2 variables
of propensity score (A) and presence of LBBB on ECG. Statistical
analyses were performed with the statistical program R19 and SPSS
version 11.5 software (SPSS Inc).

Results

Data Validity

When 1972 computer forms from 38 hospitals containing 161 280 variables were reviewed specially by an external
monitor, there was 97% agreement between the registered
information and the source data in the patient records among
the 25 covariates included in logistic regression analysis A
and 95% agreement for the 38 variables in analysis B. With
regard to the ECG variable, in 0.6% of the cases, LBBB had
been miscoded as another type of QRS complex, and in 2.2%,
a QRS complex that really was not LBBB had been incor-
correctly coded as LBBB.

Patient Material and Baseline Characteristics

Nineteen hospitals participated in the registry in 1995, which
gradually increased to 72 of all 80 Swedish hospitals (90%) in
2001. During this period, a total of 88 026 admissions for MI
were recorded. Of these, 974 were excluded because of
pacemaker rhythm with pacemaker QRS complexes, and
45 265 with non–ST-segment elevation MI (NSTEMI),
33 746 with ST-segment elevation MI (STEMI), and 8041
with LBBB MI were included. Patients with STEMI or
NSTEMI were gathered into 1 group of no LBBB
MI were included. Patients with LBBB MI were divided into 3
age groups; <65, 65 to 74, and ≥75 years. Table

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shows baseline characteristics of patients with no LBBB or LBBB stratified by age. Even after age stratification, the differences in comorbid conditions, medications on admission, and previous coronary interventions between the LBBB and no-LBBB groups were significant. Killip class on admission was significantly (P<0.001) poorer in patients with LBBB compared with no-LBBB patients, revealing the following distribution: Killip class I, 44% versus 66%; class II, 26% versus 19%; class III, 15% versus 5%; and class IV, 15% versus 10%. When age stratification was performed, the differences in Killip class remained between the 2 ECG groups (data not shown).

In-Hospital Intervention and Long-Term Medical Treatment
Patients with LBBB were less likely to receive acute reperfusion therapy and to undergo cardiac catheterization and percutaneous coronary intervention (PCI) compared with no-LBBB patients (Table 2). A higher proportion of patients with LBBB received medication indicative of congestive heart failure (ACE inhibitors, diuretics, and digitalis) at discharge. In contrast, more no-LBBB patients were likely to receive β-blockade and antithrombotic agents compared with the LBBB population. However, in multiple logistic regression analyses, each adjusting for 25 covariates, the differences in long-term medical treatment at discharge were statistically significant only for ACE inhibitors (P<0.001) and digitalis (P=0.007). All other discharge medications had no statistical association with ECG appearance in these 2 MI groups.

In-Hospital Complications and Mortality
The 1-year mortality rates in relation to biochemical marker peak level (divided into 4 groups: [1] CK-MB ≤50
µg/L or troponin-T < 1.0 µg/L, [2] CK-MB 51 to 150 µg/L or troponin-T 1.0 to 3.0 µg/L, [3] CK-MB >150 µg/L or troponin-T >3.0 µg/L, and [4] missing values) were 38%, 42%, 45%, and 49% for the LBBB patients and 21%, 20%, 22%, and 26%, respectively, for the no-LBBB patients. The distributions of patients into the 4 biochemical marker groups were 44%, 23%, 20%, and 14% for LBBB compared with 37%, 23%, 25%, and 14% for no-LBBB patients. Patients with LBBB were at higher risk of developing new atrial fibrillation and clinical signs of heart failure in all age categories (Table 3). After adjustment for the 25 background covariates in a multiple logistic regression analysis, the difference remained statistically significant with regard to development of heart failure (P<0.001). Unadjusted 30-day and 1-year mortality rates were 21% (n=1682) and 42% (n=3350) for the LBBB group compared with 12% (n=9591) and 22% (n=17044) for the no-LBBB patients. One-year mortality was ~4 times as high for LBBB compared with no-LBBB patients among those <65 years of age. There was no statistically significant difference in cause of death, which was ischemic heart disease during the first year in no-LBBB patients in 74% (n=12670) compared with 76% of LBBB patients (n=2532) (P=0.13). The unadjusted RR of death within 1 year was 2.16 (95% CI, 2.08 to 2.24; P<0.001) for MI patients with LBBB compared with the no-LBBB group (Figure 1A). After adjustment for propensity score A (baseline characteristics and acute events), the

| TABLE 2. In-Hospital Intervention and Long-Term Medical Treatment in Acute MI Patients |
|---------------------------------|-----------------|-----------------|-----------------|
|                                 | LBBB on Admission ECG | Age ≤64 y     | Age 65–74 y    | Age ≥75 y      |
|                                 | (n=23 453)        | (n=23 612)     | (n=39 987)     |
|                                 | No   | Yes | No   | Yes | No   | Yes |
| IV β-blocker, %                 | 40†  | 35  | 33‡  | 27  | 27‡  | 22  |
| IV nitroglycerin, %             | 42   | 42  | 41   | 41  | 38   | 38  |
| Reperfusion therapy, %          | 46‡  | 32  | 35‡  | 21  | 25‡  | 12  |
| PCL, %                         | 22‡  | 12  | 13‡  | 7   | 5‡   | 2   |
| CAGB, %                        | 4.4  | 5.4 | 5.4‡ | 3.3 | 2.3‡ | 1.5 |
| Echocardiography, %             | 60‡  | 54  | 53‡  | 47  | 38‡  | 32  |
| Medical treatment at discharge, % |    |     |     |     |     |     |
| ACE inhibitor                   | 35‡  | 57  | 46‡  | 63  | 44‡  | 54  |
| Antiarrhythmics                 | 1†   | 5   | 2†   | 4   | 2†   | 4   |
| Anticoagulant/ASA               | 94‡  | 92  | 92‡  | 87  | 86‡  | 83  |
| Calcium channel inhibitor       | 11‡  | 16  | 15*  | 17  | 17‡  | 15  |
| β-Blocker                       | 87‡  | 81  | 81‡  | 76  | 71‡  | 64  |
| Digitals                       | 3‡   | 12  | 8‡   | 18  | 15‡  | 24  |
| Diuretics oral                  | 19‡  | 46  | 39‡  | 65  | 60‡  | 75  |
| Lipid lowering                  | 56   | 54  | 44   | 42  | 42‡  | 16  |
| Nitroglycerin                   | 28‡  | 42  | 40‡  | 46  | 48‡  | 53  |

IV indicates intravenous; ASA, acetylsalicylic acid. n=87 052.
*P<0.05, †P<0.01, ‡P<0.001 within age groups by χ².

| TABLE 3. In-Hospital and Long-Term Complications in Acute MI Patients |
|---------------------------------|-----------------|-----------------|-----------------|
|                                 | LBBB on Admission ECG | Age ≤64 y     | Age 65–74 y    | Age ≥75 y      |
|                                 | (n=23 453)        | (n=23 612)     | (n=39 987)     |
|                                 | No   | Yes | No   | Yes | No   | Yes |
| Hypotension, %                  | 7    | 13* | 9    | 14* | 12   | 15* |
| New atrial fibrillation, %      | 6    | 14* | 15   | 25* | 26   | 71* |
| Clinical signs of heart failure, % | 22  | 47* | 38   | 59* | 54   | 71* |
| Reinfarction, %                 | 3    | 4   | 4    | 4   | 5    | 4   |
| Mortality 30 d, %               | 3    | 12* | 9    | 16* | 20   | 24* |
| Mortality 1 y, %                | 6    | 22* | 16   | 30* | 35   | 48* |

n=87 052.
*P<0.001 within groups by χ².
large difference in relative mortality risk was reduced to 1.28 (95% CI, 1.23 to 1.33; \(P < 0.001\)) for LBBB. Further adjustment, including propensity score A, Killip class, and biochemical marker group, resulted in an additional reduction in RR to 1.19 (95% CI, 1.14 to 1.24; \(P < 0.001\)) for 1-year mortality for LBBB (Figure 1B). When later interventions also were included (propensity score B), there was still an increased risk of death associated with LBBB on ECG for MI patients (RR, 1.21; 95% CI, 1.15 to 1.27; \(P < 0.001\)).

**LVEF and Mortality**

Echocardiography was performed significantly less frequently in patients with LBBB (Table 2). In the 11,812 MI patients in whom it was performed, LVEF was worse in patients with LBBB. Among the LBBB patients, there were a significantly smaller proportion with normal LVEF (15% [n = 131] compared with 39% [n = 4,202]; \(P < 0.001\)), less with slight dysfunction (30% [n = 282] compared with 34% [n = 3,675]; \(P = 0.012\)), a larger proportion with moderate dysfunction (25% [n = 234] compared with 19% [n = 2,053]), and 4 times as high a proportion with severe dysfunction (LVEF <30%) among LBBB (32% [n = 299]) compared with (8% [n = 936]; \(P < 0.001\)) among no-LBBB patients. With decreased LVEF, the survival decreased for both ECG groups at the same time as the LBBB influence on mortality decreased. Patients with LVEF <30% revealed 1-year mortalities for the 3 age groups of 19%, 33%, and 47% for the no-LBBB group and 24%, 29%, and 50% for the LBBB group. When Cox proportional-hazards regression analysis that included the variables propensity score (A), Killip class, biochemical marker group, presence of LBBB on ECG, and LVEF group was performed in the 11,812 cases with LVEF available, LBBB did not have any significant contribution to the RR of 1-year mortality (RR, 1.08; 95% CI, 0.93 to 1.25; \(P = 0.33\); Figure 1C). When patients with normal to moderately decreased LVEF >30% were analyzed, unadjusted 1-year mortality was 23% (146 of 647) for LBBB and 10% (988 of 9,930) for no-LBBB patients. For patients with severely decreased LVEF <30%, the corresponding figures were 41% (123 of 299) for LBBB and 38% (353 of 936) for no-LBBB patients. After adjustment for propensity score A, Killip class, biochemical marker, and LVEF, there was a nonsignificant increase in RR of 1.20 (95% CI, 0.99 to 1.45; \(P = 0.066\)) associated with LBBB among those with normal to moderately decreased LVEF (Figure 2A), whereas among those with severely decreased LVEF, there was no statistically significantly higher risk for 1-mortality associated with LBBB (RR, 0.93; 95% CI, 0.74 to 1.17; \(P = 0.54\); Figure 2B).

**Discussion**

This study is the first to include a large enough population to allow an extensive multivariable statistical analysis to evaluate the risk contribution by LBBB per se, not only the associated risk. The conclusion that the extent of comorbidity substantially reduces the independent prognostic impact of LBBB in acute MI is new information of considerable importance for the management of these patients. Furthermore, in light of the ongoing animated debate about wide
QRS complex and implantable cardioverter-defibrillator therapy, we think this study has an important message. The most important finding in the present study is that after adjustment for differences in age, comorbidities, LVEF, and acute treatment, there is no significant difference in 1-year mortality in an MI population with LBBB compared with no LBBB. This finding might be due to the lack of identification of the peak levels in a substantial number of patients because of early deaths, lack of serial measurements, influence of different kinetics of the markers in reperfused and nonreperfused patients, and the use of different markers in different hospitals.

Reliability of Data
The method used by current RIKS-HIA was first used in 1991 and has become a reliable source of information on consecutive patients admitted to participating units. ECG had a high validity with 97% correct coding. The patient cohort in this study included unselected consecutive patients with MI from a large number of different hospital types. There were no exclusions resulting from the presence or absence of specific risk factors, comorbidities, anticipated adverse effects, participation in clinical trials, or contraindications to certain medications. The representativeness of the cohort was also strengthened by the inclusion of all patients with MI from the general population at the centers with different levels of care from 90% of the hospitals within an entire country.

In the present study, the prevalence of LBBB in a population of intensive cardiac care unit admissions for MI was 9%, consistent with the LBBB prevalence (7%) in the study reported by Newby et al. In the GUSTO-I trial, the prevalence of LBBB was as low as 0.5%, probably representing selection bias based on the entry criteria. Because the register covers background factors such as, age, risk factors, and previous diseases and medications, adjusting for differences in the composition of different population is possible.

Mortality and Left Ventricular Dysfunction
In the present study as in previous studies, LBBB patients were older, which could explain the higher mortality among MI patients with LBBB. Compared with the no-LBBB group, patients with LBBB on admission for MI had a higher prevalence of preexisting comorbid conditions such as previous MI, congestive heart failure, diabetes mellitus, hypertension, renal failure, chronic pulmonary disease, and history of stroke. Moreover, the LBBB population had more frequently undergone coronary intervention, further supporting the occurrence of more severe coronary artery disease. The increased use of ACE inhibitors, diuretics, and digitalis among LBBB patients on admission for MI had a higher prevalence of preexisting comorbid conditions such as previous MI, congestive heart failure, diabetes mellitus, hypertension, renal failure, chronic pulmonary disease, and history of stroke. Moreover, the LBBB population had more frequently undergone coronary intervention, further supporting the occurrence of more severe coronary artery disease. The increased use of ACE inhibitors, diuretics, and digitalis among LBBB patients on admission for MI had a higher prevalence of preexisting comorbid conditions such as previous MI, congestive heart failure, diabetes mellitus, hypertension, renal failure, chronic pulmonary disease, and history of stroke. Moreover, the LBBB population had more frequently undergone coronary intervention, further supporting the occurrence of more severe coronary artery disease. The increased use of ACE inhibitors, diuretics, and digitalis among LBBB patients on admission for MI had a higher prevalence of preexisting comorbid conditions such as previous MI, congestive heart failure, diabetes mellitus, hypertension, renal failure, chronic pulmonary disease, and history of stroke. Moreover, the LBBB population had more frequently undergone coronary intervention, further supporting the occurrence of more severe coronary artery disease. The increased use of ACE inhibitors, diuretics, and digitalis among LBBB patients on admission for MI had a higher prevalence of preexisting comorbid conditions such as previous MI, congestive heart failure, diabetes mellitus, hypertension, renal failure, chronic pulmonary disease, and history of stroke. Moreover, the LBBB population had more frequently undergone coronary intervention, further supporting the occurrence of more severe coronary artery disease.
Study Limitations
A limitation of this study was that LVEF was not evaluated by a core laboratory but was an on-site judgment during routine care by the physician performing the echocardiography. Another limitation was that LVEF was not available in most patients. Still, to the best of our knowledge, the subgroup of MI patients with LBBB and measured LVEF is the largest reported so far. In multiple regression analysis, 5% of the study population was excluded because of missing variables in the registry. However, when a sensitivity analysis was performed, there was no change in the main result. This study did not record any transient LBBB, nor could it differentiate between newly developed or old LBBB, so the conclusions should be applied primarily to persistent LBBB in patients with acute MI.

Clinical Implications
LBBB does not appear to be an important independent predictor of 1-year mortality in MI but mainly reflects higher age, comorbid conditions, and left ventricular dysfunction. Therefore, there seems to be no specific reasons and risks for death related to the conduction abnormality in the LBBB MI population. The recently published MADIT II study reported the largest survival benefit with implantable defibrillator therapy in patients with LBBB in a population with previous MI and left ventricular dysfunction.16 In our study, LBBB MI patients had a medical therapy on admission and discharge indicative of a relatively high prevalence of congestive heart failure; consequently, this population was fairly similar to the MADIT II patients with LBBB. Still, the adjusted mortality rate and the causes of death were similar in the LBBB MI and no-LBBB populations. Thus, the anticipated risk of death rather than a conduction abnormality should probably be used as a guideline for the selection of implantable defibrillator therapy and other effective treatments such as reperfusion therapy and early revascularization in post-MI patients.

References
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