Atrial fibrillation and CHADS$_2$ score as mortality predictors in young versus elderly patients undergoing coronary angiography

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Initially developed to predict stroke probability in patients with atrial fibrillation (AF),[1–3] CHADS$_2$ and CHA$_2$DS$_2$VASC scores are used to predict different outcomes in cardiac patients in both acute and chronic conditions.[4–5,8–12] The scores were also demonstrated to correlate with mortality.[4,6,7,11–15] AF also has been associated with mortality in different groups of patients, including elderly.[16–18] There is little information about the prognostic value of CHADS$_2$ score in elderly versus young patients, especially in mortality prediction (taking into consideration that age is a component of the score).

We hypothesized that both atrial fibrillation and the CHADS$_2$ score are independently associated with mortality in the young as well as elderly patients and that the CHADS$_2$ score can be a useful tool to predict mortality in patients undergoing coronary angiography in both young and elderly patients.

The study was approved by the institutional review board as a prospective registry. Nine hundred eighty six patients who underwent coronary angiography in Kaplan Medical Center (Jerusalem, Israel) were enrolled in this study. The hospital database and the Israeli population authority registry were used to collect the patients’ data.

The median follow up was 30 months. We divided the total cohort into two age groups: young group (< 75 years, $n = 666$) and the elderly group ($\geq 75$ years, $n = 320$). Baseline clinical characteristics, laboratory and procedural data and mortality were compared between patients in the two age groups. Then, we assessed mortality in the two age groups according to the CHADS$_2$ score. The chi-square test and Fisher’s exact test were used for dichotomous variables, and independent t test was used for continuous variables. Data are expressed as mean ± SD or frequency and/or percentage when appropriate.

Cumulative event proportions in the two age groups were calculated by Kaplan-Meier method, and outcome differences were assessed with the Log-Rank test. The multivariate analysis of the mortality predictors in the two age groups was done with Cox regression analysis. Receiver operating characteristic (ROC) curve was used to analyze C-statistics of the relevant CHADS$_2$ score. Comparison between ROC curves was done with DeLong method. A $P$ value $< 0.05$ was considered significant. Data were analyzed using SPSS statistical software version 21 and Medcalc 17.5.5.

During the follow up, 53 patients (8.0%) in the young age group and 75 (23.4%) in the elderly group died. The baseline demographic clinical and laboratory characteristics and the mortality in the two age groups are showed in Table 1. The distribution of the CHADS$_2$ score in the two age groups is described in Table 2. Due to the low number of patients with the score of 6, we combined patients with scores 5 and 6 into single category (5+).

Our data demonstrated that patients with CHADS$_2$ score of 0–1 in younger patients and score of 1–2 in the elderly patients had much lower mortality than patients with the higher scores in the relevant groups (Table 2). To further test the appropriate cutoff value for each group, we performed the ROC curve analysis for the total cohort and the two age groups and compared them using DeLong method (Figure 1). The C-statistics was optimal for CHADS$_2$ score of 2 in young group and 3 in the elderly group. On the basis of this data, we performed additional analysis using a cutoff value of $\geq 2$ in the young group and $\geq 3$ in the elderly group. Mortality was significantly higher in younger group (13.6% vs. 3.7, $P < 0.0001$) if CHADS$_2$ score was $\geq 2$; and in the elderly group (28.6% vs. 16.3%, $P = 0.01$) if CHADS$_2$ score was $\geq 3$. 

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Table 1. Baseline patient’s characteristics.

| Variable | Patients with age < 75 yrs | Patients aged ≥ 75 yrs | P value for difference |
|----------|-----------------------------|-------------------------|------------------------|
| Age, yrs | 62.1 ± 9.2                  | 80.26 ± 4.3             | < 0.00001              |
| CHADS2 score | 1.4 ± 1.0                   | 2.8 ± 1.0               | < 0.0001               |
| Creatinine, mg/dL | 1.15 ± 1.25                | 1.22 ± 0.77             | 0.313                  |
| HB, g/dL | 13.5 ± 1.6                  | 12.4 ± 1.5              | < 0.0001               |
| LVEF | 49.6% ± 9.6                  | 48.5% ± 10.7%             | 0.238                  |
| AF | 15.1%                      | 29.0%                   | < 0.00001              |
| Female | 25.5%                     | 40.0%                   | < 0.00001              |
| DM | 41.5%                      | 47.5%                   | 0.043                  |
| HTN | 69.7%                      | 88.1%                   | < 0.00001              |
| Previous MI | 21.4%                  | 24.1%                   | 0.187                  |
| Previous stroke | 8.9%                   | 11.5%                   | 0.125                  |
| PAD | 5.8%                       | 6.4%                    | 0.122                  |
| CHF | 12.1%                      | 18.6%                   | 0.005                  |
| CKD | 17.1%                      | 36.2%                   | < 0.0001               |
| ACS | 50.9%                      | 46.4%                   | 0.107                  |
| Obstructive CAD | 54.5%                 | 55.8%                   | 0.193                  |
| LVEF > 50% | 49.5%                 | 46.0%                   | 0.201                  |
| Mortality | 8.0%                       | 23.4%                   | < 0.0001               |

Data are expressed as mean ± SD or percent. ACS: acute coronary syndrome; AF: atrial fibrillation; CAD: cardiovascular disease; CHF: chronic heart failure; CKD: chronic kidney disease; DM: diabetes mellitus; HB: hemoglobin; HTN: hypertension; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PAD: peripheral arterial disease.

Table 2. Distribution of patients according to the CHADS2 score in the two age groups.

| CHADS2 score | N   | Percent | Cumulative percent | Mortality |
|--------------|-----|---------|---------------------|-----------|
| *Young age group* |     |         |                     |           |
| 0            | 142 | 21.3%   | 21.3%               | 4.2%      |
| 1            | 237 | 35.6%   | 56.9%               | 3.4%      |
| 2            | 202 | 30.3%   | 87.2%               | 10.4%     |
| 3            | 53  | 8.0%    | 95.2%               | 20.8%     |
| 4            | 29  | 4.4%    | 99.5%               | 17.2%     |
| 5+           | 3   | 0.5%    | 100%                | 66.7%     |
| Total        | 666 | 100%    | 100%                | 8%        |
| *The elderly group* |     |         |                     |           |
| 1            | 19% | 5.9%    | 5.9%                | 15.8%     |
| 2            | 116%| 36.3%   | 42.2%               | 16.4%     |
| 3            | 135%| 42.2%   | 84.4%               | 26.7%     |
| 4            | 25% | 7.8%    | 92.2%               | 40%       |
| 5+           | 25% | 7.8%    | 100%                | 28%       |
| Total        | 320%| 100%    | 100%                | 23.4%     |

*P value < 0.001 for any difference in mortality; **P = 0.068 for any difference in mortality.

Figure 1. ROC curve analysis of different CHADS2 cutoff values in the young and elderly groups. (A): ROC curve analysis of CHADS2 of 1, 2 and 3 for predictive probability of mortality in the younger group; and (B): ROC curve analysis of CHADS2 of 1, 2 and 3 for predictive probability of mortality in the elderly group. AUC: area under curve; ROC curve: receiver operating characteristic curve.
Univariate analysis of patients’ characteristics on mortality in the two age groups is showed in Table 3. Kaplan Meier analysis demonstrated a statistically significant correlation of CHADS2 ≥ 2 with mortality in the young group and CHADS2 ≥ 3 with mortality in the elderly group (Figure 2). AF was also associated with mortality in two age groups (Figure 3).

Table 3. Univariate analysis of effect on mortality.

| Variable          | Alive, n = 613 | Deceased, n = 53 | P Value |
|------------------|----------------|------------------|---------|
| Young age group  |                |                  |         |
| AF               | 6.6%           | 16.0%            | 0.003   |
| Female           | 7.7%           | 8.8%             | 0.367   |
| Previous MI      | 8.0%           | 7.9%             | 0.567   |
| CKD (creatinine > 1.1) | 5.9%     | 17.9%            | < 0.0001|
| ACS              | 6.7%           | 8.9%             | 0.186   |
| LVEF < 50%       | 8.2%           | 7.8%             | 0.214   |
| CHADS2 ≥ 2       | 3.7%           | 13.6%            | < 0.0001|
| Anemia (HB < 13) | 4.9%           | 14.6%            | < 0.0001|
| The elderly group|                |                  |         |
| AF               | 20.0%          | 32.6%            | 0.013   |
| Female           | 20.3%          | 28.1%            | 0.07    |
| Previous MI      | 23.0%          | 22.4%            | 0.522   |
| CKD (creatinine > 1.1) | 16.9%     | 34.2%            | < 0.0001|
| ACS              | 17.9%          | 28.6%            | 0.02    |
| Obstructive CAD  | 18.9%          | 27.4%            | 0.34    |
| EF < 50%         | 23.0%          | 32.2%            | 0.10    |
| CHADS2 ≥ 3       | 11.3%          | 28.6%            | < 0.011 |
| Anemia (HB < 13) | 17.1%          | 27.7%            | 0.038   |

ACS: acute coronary syndrome; AF: atrial fibrillation; CAD: cardiovascular disease; CKD: chronic kidney disease; EF: ejection fraction; HB: hemoglobin; LVEF: left ventricular ejection fraction; MI: myocardial infarction.

Multivariate analysis using Cox regression model which combined CHADS2 score, presence of AF, anemia (hemoglobin < 13 g/dL) and presence of renal insufficiency (creatinine > 1.1 mg/dL) demonstrated that CHADS2 ≥ 2 was independently associated with higher mortality in the younger group as was CHADS2 ≥ 3 in the elderly group. Presence of AF and renal failure were also independently associated with increased mortality in the two age groups. Anemia was independently associated with mortality only in the younger group (Table 4).

The major finding in our study is the independent association between increased CHADS2 score and mortality in patients undergoing coronary angiography in both young and elderly patients.

Older patients significantly differed from the younger patients by having much greater frequency of comorbidities, including, but not limited to hypertension, diabetes, history of stroke, congestive heart failure, lower hemoglobin levels, and chronic renal failure. Thus, the age component of the CHADS2 score reflects these comorbidities. Of note, LV systolic function, history of previous myocardial infarction, as well as presence of obstructive cardiovascular disease on the current angiography were not different between the two groups. By dividing patients into groups below and above 75 years of age, we nullified the effect of the age on the performance of the CHADS2 score as a mortality predictor.

Our data demonstrated that mortality in both age cohorts was similar in patients with no risk factors or one risk factor, and sharply increased with addition of one more risk factor in both age groups (from 4.3% and 3.4% to 10.4% in the younger age group and from 15.8% and 16.4% to 26.7% in the older age group).

Figure 2. Kaplan Meier survival analysis according to the CHADS2 score in young versus elderly groups. (A): Kaplan Meier survival analysis according to the CHADS2 Score 0–1 vs ≥ 2 and above in the younger age group; (B): Kaplan Meier survival analysis according to the CHADS2 Score 1–2 vs ≥ 3 in the older age group.
Table 4. Cox regression multivariate analysis of effect on mortality.

| Variable          | Hazard ratio | 95% CI      | P Value |
|-------------------|--------------|-------------|---------|
| **Young age group** |              |             |         |
| AF                | 2.06         | 1.11–3.82   | 0.021   |
| CKD               | 2.01         | 1.11–3.64   | 0.021   |
| HB < 13           | 2.07         | 1.15–3.73   | 0.03    |
| CHADS2 ≥ 2        | 2.4          | 1.26–4.57   | 0.008   |
| **The elderly group** |            |             |         |
| AF                | 1.76         | 1.09–2.82   | 0.021   |
| CKD               | 1.92         | 1.20–3.09   | 0.007   |
| CHADS2 ≥ 3        | 1.98         | 1.16–3.36   | 0.012   |

* HB < 13 g/dL was nonsignificant predictor of mortality in the multivariate analysis in the elderly group. AF: atrial fibrillation, CKD: chronic kidney disease; HB: hemoglobin.

Based on this data, we chose the CHADS2 ≥ 2 as a marker of high risk in younger patients and CHADS2 ≥ 3 in older patients. Additional analysis using C-statistics demonstrated that this cutoff was indeed optimal. Taking the cutoff lower provided less robust discrimination in both age groups and was even nonsignificant in the elderly group; while taking the cutoff value higher (i.e., three risk factors and more) did not improve the discrimination ability, but would miss a large number of patients with already increased mortality.

Kaplan Meier analysis demonstrated the ability of the pre-specified CHADS2 score value to reliably predict mortality in both age groups. The multivariate analysis done with Cox regression model demonstrated that the CHADS2 ≥ 2 in the younger group and ≥ 3 in the elderly group is significantly associated with mortality independently of renal function, anemia and presence of AF.

Thus, our study demonstrates that absence of any, or presence of one risk factor from CHADS2 score marks low risk patients in both age groups in patients undergoing coronary angiography. Presence of two risk factors, however, is associated with much higher mortality.

The performance of CHADS2 and/or CHA2DS2-VASC scores to predict cardiovascular outcomes, including mortality was studied previously.[4–15] Our study specifically demonstrated the impact of the CHADS2 score to predict mortality in both young and elderly groups. Moreover, this predictive ability was demonstrated to be independent from the presence of AF, anemia and renal failure, all of which are not only significantly associated with mortality, but also much more prevalent in the elderly patients.

The ROC curve analysis also supported the predictive utility of the CHADS2 score. The C-statistics in the young group was better than cited by Puurunen, et al.,[13] and similar to that of Chan, et al.[4] Elderly patients’ C-statistic was also valid, but more modest. This further validates the use of CHADS2 score for mortality prediction in both age groups.

Several scoring systems were developed to assess risk in cardiac patients, like those undergoing coronary angiography, i.e., GRACE score. However, the calculation of the GRACE score is complex. CHADS2 is a simple score with universal familiarity and ability to calculate it at the bedside. The simplicity of the CHADS2 score is its main advantage.

Our study, as others,[16–18] also demonstrated the independent association between AF and mortality. We demonstrated that this is true for both young and elderly patients.
Currently, there is a controversy about the ability of rhythm control (including catheter ablation) to influence negative outcomes associated with AF. Our study suggests that geriatric population should be specifically studied in this regard.

In conclusion, we found CHADS2 score can be used as a mortality predictor in patients undergoing coronary angiography. Its prediction is valid in both young and elderly patients, when presence of more than one risk factor is significantly associated with mortality.

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