A high HASBLED score identifies poor warfarin control in patients treated for non-valvular atrial fibrillation in Australia and Singapore

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ABSTRACT

Warfarin reduces stroke risk in atrial fibrillation (AF) patients. The quality of warfarin control, measured by time in therapeutic range (TTR), impacts outcomes and adverse events. One tool evaluating risk of adverse events and potential warfarin control would simplify risk-benefit assessment of warfarin. Recently HASBLED was demonstrated effective for this purpose, but this was in well-controlled patients with deep vein thrombosis. HASBLED as a predictor of warfarin control has not been validated in other populations including differing indications, warfarin control levels, and ethnicities. The aim of this study was to determine if HASBLED can predict warfarin control in patients with AF in Australia and Singapore.

Retrospective data was collected for patients receiving warfarin between January and June 2014 in Australia and Singapore. Patient data was used to calculate HASBLED at the start and end of the study period. TTR was calculated for each patient, and mean TTR used for analysis to stratified HASBLED scores.

Of the 4370 patients, there were 3199 in Australia and 1171 in Singapore with mean TTRs of 82% and 58% respectively. At the start of the study, a HASBLED score ≥3 predicted significantly lower TTR in Singapore, whilst at the end of the study, this score identified patients with poor control in both Australia and Singapore.

A HASBLED score ≥3 in patients treated with warfarin can differentiate significantly lower TTRs in Australian and Singapore patients with AF. HASBLED may assess bleed risk and warfarin control, identifying patients at high risk of poor warfarin outcomes requiring additional INR monitoring or alternative anticoagulation.
INTRODUCTION

Anticoagulant therapy such as warfarin can effectively reduce the risk of ischaemic stroke in patients with atrial fibrillation (AF).(1) Poor warfarin control is associated with complications including bleeds and thrombotic events.(2) The risk of these events is influenced by a number of patient factors including age, co-morbidities, and concurrent medications.(3) Some of these factors associated with an increased risk of adverse effects have been incorporated into risk predictor models. HASBLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history, Labile International Normalised Ratio or INR, Elderly>65years, Drugs/alcohol concomitantly) was proposed from the Euro Heart Survey population of patients with AF to assess the individual one year risk of major bleeding and assigns one point to each of the listed factors with the exception of abnormal renal/liver function and drugs/alcohol which may receive up to two points.(4) The calculated score ranges from 0 to 9 but patients are generally categorised as low-, intermediate-, or high-risk of bleeding based on scores of 0-1, 2, or ≥3 respectively.(5) HASBLED has been validated to provide accurate stratification of patients based on bleed risk and has the benefit of simplicity of application.(6, 7) Several international guidelines for patients with AF recommend HASBLED to conduct a formal assessment of bleed risk prior to the commencement of anticoagulant therapy.(8-10)

The HASBLED model assigns one point to labile INRs, a measure indicative of poor anticoagulant control in patients taking a vitamin K antagonist such as warfarin.(11) Percentage of INRs in range can predict adverse events such as bleeding but a more accurate measure of control and outcomes is time in therapeutic range (TTR).(12) A strong relationship exists between TTR and both bleeding and thromboembolic events.(13) Increased warfarin control or TTR improves the safety and efficacy of warfarin and patients may not benefit from warfarin unless a certain level of control is achieved.(14) In 2013, Apostolakis et al (15) proposed a model to predict control with vitamin K antagonists, namely SAMe-TT2R2 (Sex female, Age<60 years, Medical history [more than two co-morbidities], treatment [interacting drugs eg amiodarone], tobacco use, race). In this
model one point is assigned to each of the factors with the exception of race and tobacco which receive two points and an overall score of ≥2 identifies patients as requiring additional intervention to achieve acceptable warfarin control.(15) The SAMe-TT2R2 model specifically incorporates race as a factor known to influence warfarin control and it has been demonstrated to be a good predictor of control in both Caucasian (16, 17) and Asian (18, 19) patients with AF. The disadvantage to this model is the need to calculate an additional score to the already calculated bleed and stroke risk scores in patients with AF. Use of existing bleed risk scores such as HASBLED to predict warfarin control would simplify assessment of patients prior to commencement of anticoagulant therapy and potentially assist in selection of agents.

In 2017, Mueller et al (20) proposed that the existing HASBLED tool may be used to predict warfarin control and, specifically, patients with a HASBLED score ≥3 may be classified as high risk of poor warfarin control. However this study was in well controlled warfarin patients receiving warfarin for deep vein thrombosis in a predominantly Caucasian population.(20) It is unknown how effectively HASBLED can predict control outside this group, including in patients achieving poorer warfarin control, of differing ethnicity, and with different indications such as AF. Therefore, the aim of this study was to determine if HASBLED could be used to predict warfarin control in patients with non-valvular AF (NVAF) in both Caucasian and Asian populations, namely Australia and Singapore.

METHODS

Study Design

A retrospective analysis was conducted for patients treated with warfarin for NVAF for the period of January to June 2014 at two sites, one in Australia and one in Singapore. During the study period, data was collected in Australia for patients enrolled in the warfarin care program at Sullivan Nicolaides Pathology, Queensland, and in Singapore for patients dispensed warfarin at The National
Heart Centre Singapore. Data collected included INR test date and results, INR target ranges, age, gender, co-morbidities, and concurrent medications. Adverse bleeding events were recorded which had been reported to the clinics either via self-reporting from patients, e.g. nose bleeds, excessive bleeding from cuts, or from other health professionals, e.g. hospital admission due to bleed. Bleed events were defined as either major events i.e. requiring medical intervention, hospitalisation, or discontinuation of warfarin, and all other events such as self-limiting nose bleeds defined as minor. Patients with mitral stenosis, valve replacement and/or valve repair were excluded from the study. Patients were also excluded if they had received less than 30 days of warfarin treatment or had insufficient tests to calculate INR, i.e. less than two tests. Ethics approval was obtained from Griffith University (PHM/09/14/HREC and PHM/08/15/HREC) and SingHealth Centralised Institutional Review Board (CIRB 2015/2435).

Data and Statistical Analysis

TTR was calculated for each patient using Rosendaal’s linear interpolation algorithm with software downloaded from www.inrpro.com. The HASBLED risk score was calculated from patient characteristics as of the start of the study period, e.g. age as of 1 January 2014. Labile INRs were not included in this score but an additional HASBLED score was calculated at the end of the study period with a point assigned to labile INRs. Patients were categorised as low (0-1 points), moderate (2 points), or high risk (≥3 points) according to the total HASBLED score. Bleeding events were calculated as events per patient and applied to risk categories. Patient characteristics were reported as number and percentage for categorical data and mean±standard deviation for continuous data. Mean TTR was used for comparison across risk categories. Comparisons were made using ordinary analysis of variance through non-parametric methods, including Kruskal-Wallis test and Dunn’s multiple comparisons test. Data were analysed using GraphPad InStat version 3 and figures drawn using GraphPad Prism version 6.0. Significance was defined as* p<0.05, **p<0.01, and ***p<0.001.
RESULTS

A total of 4370 patients with NVAF were included in the study with 3199 patients in Australia and 1171 in Singapore following exclusions for valvular AF (276 Australia, 605 Singapore) or insufficient INR tests in study period (44 Australia, 259 Singapore). In total, there were 2380 (54.5%) male and 1990 (45.5%) female patients (Table 1). There were 3730 (85.4%) patients over 65 years with the mean age of patients 77.2 ± 9.1 years in Australia and 69.7 ± 10.0 years in Singapore.

The mean TTR was 82.3 ± 15.6% in Australia and 57.7 ± 34.2% in Singapore, which was significantly different (P<0.001). The mean number of tests per patient was significantly different between the two sites with 11.2 ± 5.6 Australia vs 5.6 ± 6.2 Singapore, p<0.0001. There were a total of 187 bleeding events reported across the two study sites with 147 (78.6%) classified as minor. The overall incidence of bleed events per patient was 0.043 in Australia and 0.041 in Singapore. According to HASBLED category the incidence of bleeds in the low-, moderate- and high-risk groups were 0.033, 0.051, and 0.054 respectively in Australia and 0.030, 0.053, and 0.039 respectively in Singapore (Figure 1). The incidence of major bleeds was 0.008 in Australia and 0.012 in Singapore with the incidence of major bleeds in the low-, moderate- and high-risk groups 0.003, 0.011, and 0.015 respectively in Australia, and 0.000, 0.018, and 0.021 respectively in Singapore.

The median HASBLED score at both sites was 1 at the start of the study. At this time, according to HASBLED score, 2323 (1624 Australia, 699 Singapore) patients were classified as low risk, 1560 (1159 Australia, 401 Singapore) moderate risk, and 487 (416 Australia, 71 Singapore) high risk. The mean TTR according to HASBLED category resulted in no significant differences at the Australian site between the low-, moderate-, or high-risk categories with all around 82% (Figure1). At the Singapore site the mean TTR according to low-, moderate-, and high-risk categories was 58.7 ± 34.6%, 58.0 ± 33.4%, and 45.9 ± 32.7% respectively, with significant differences in TTR found
between the low- and high-risk categories (p<0.01) and between the moderate- and high-risk categories (p<0.05).

<Insert Figure 1>

At the end of the study, the median HASBLED at both sites was 2 with 1873 (1442 Australia, 431 Singapore) patients classified as low risk, 1615 (1160 Australia, 455 Singapore) moderate risk, and 882 (597 Australia, 285 Singapore) high risk. Application of this HASBLED score to mean TTR resulted in significant differences (p<0.001) at both sites between all risk categories. At the Australian site the mean TTR for the low-, moderate- and high-risk categories was 86.4 ± 12.0%, 81.5 ± 16.2%, and 74.1 ± 18.5% respectively, whilst at the Singapore site the mean TTR for these categories was 75.8 ± 30.4%, 54.8 ± 33.3%, and 34.9 ± 24.8% respectively. The mean number of tests per patient according to low-, moderate- and high-risk HASBLED category differed significantly (p<0.001) between each category at both sites with 10.1 ± 4.5, 11.7 ± 6.1, and 13.1 ± 6.3 tests respectively in Australia and 4.1 ± 4.1, 5.9 ± 5.6, and 7.5 ± 8.9 tests respectively in Singapore.

DISCUSSION

The efficacy and safety of warfarin is highly dependent on the quality of warfarin control, commonly measured by TTR. Patients achieving high TTR are most suited to warfarin therapy and thus the ability to predict potential TTR would assist clinicians in determining a patient’s suitability to warfarin therapy. The use of existing risk models for this purpose would ease the burden of calculating additional scores when prescribing anticoagulant therapy for patients with AF. Recently, Mueller et al(20) proposed the use of the existing HASBLED tool as a predictor of warfarin control, with a score ≥3 predicting poor control as defined by a TTR <70%. However, this was in a largely Caucasian population of patients with deep vein thrombosis who had good warfarin control. Despite the fact HASBLED has been well validated to predict bleed risk in patients with AF, the potential for
this model to predict warfarin control in this population is yet to be tested. Furthermore, the ability of HASBLED to predict control in more diverse populations with differing levels of warfarin control has not been tested. Therefore the aim of this study was to determine if HASBLED could predict warfarin control in patients with NVAF in a largely Caucasian population in Australia and an Asian population in Singapore. This retrospective study found HASBLED calculated at the start of the study (i.e. without the inclusion of labile INRs) could not predict control in the Australian population but could predict poorer control in the Singapore population as patients with a HASBLED score ≥3 had significantly lower TTR than those in other categories. Recalculation of HASBLED at the end of the six month study period by including the measured parameter of labile INRs, was able to differentiate poorer warfarin control with a HASBLED score ≥3 for both the Australian and Singapore populations.

HASBLED is recommended by several international guidelines to assess bleed risk prior to anticoagulant therapy(8-10) and these guidelines also emphasise the need to optimise warfarin therapy by achieving a TTR over 65% (10) to 70%(8). The Australian site achieved above these targets with a mean overall TTR of 82%, whilst the Singapore site with a mean TTR of 58% did not. The overall mean TTRs for each site was similar to those found in an analysis by geographical region by Singer et al(21) where Australia had a TTR of 73% and Singapore a TTR of 64%. Similarly, Chiang et al(22) demonstrated that in the large comparative trials of warfarin and the newer oral anticoagulants, Asians consistently had a lower TTR of <60% compared to non-Asians. Suboptimal warfarin control in Asian populations compared to Caucasian populations has been associated with genetic polymorphisms but also differences in predominance of concomitant disease and medication.(23) Similar to this, our study found differences in patient demographics and concomitant disease with a higher incidence of hypertension and renal disease at the Singapore site, which may have influenced TTR. Further to this, Singer et al(21) concluded that patient clinical factors were only modest contributors of TTR, whilst regional variations in medical practices heavily influenced warfarin control and TTRs. The Australian site with a TTR around 80% conducted
significantly more tests per patient compared to the Singaporean site suggesting differences in
warfarin management practices. Further investigation is necessary to determine if the most
significant factors influencing the differing TTRs in our populations were ethnicity, patient
characteristics, or medical practices.

Rouaud et al(24) associated a high burden of patient co-morbidities with a low quality of warfarin
control and similar to this Menzin et al(25) suggested a lack of co-morbidities was a predictor of
good control as defined by 75% TTR. Given a number of concurrent conditions such as hypertension,
abnormal liver/kidney disease, and a history of stroke are assessed in the HASBLED model, it is
reasonable to assume this could be a predictor of warfarin control. In our study the HASBLED score
calculated at the beginning of the study did not predict poor control in Australia but patients in all
risk categories achieved TTRs over 80% and thus it could be argued that none of these patients fell
into a poorly controlled TTR. In contrast, in Singapore a HASBLED score ≥3 was associated with
significantly lower TTR (45%) than other categories (58%). Interestingly the mean TTR for patients in
the low- and moderate-risk HASBLED categories was consistent with the overall mean for that site so
the high HASBLED score could differentiate patients achieving TTR significantly below the mean for
that site. Thus in Asian populations that have difficulty in maintaining high TTRs, a high HASBLED
score may be more beneficial in identifying patients at particular risk of low quality warfarin control.

At the end of the study period, re-calculation of HASBLED with inclusion of labile INRs found a score
of ≥3 was associated with significantly poorer control at both sites, with a TTR of 74% in Australia
and below 35% in Singapore. This highlights the importance of continued assessment of patients as
within this six month period significant differences were found according to TTR and the recalculated
HASBLED score. International guidelines (8, 10) suggest patients at high risk according to HASBLED
score warrant caution and regular review including efforts to correct potentially reversible risk
factors for bleeding such as labile INRs. A trend of increasing number of tests per patient was found
according to increased HASBLED score, suggesting more regular follow-up of these patients. Despite
this the TTR significantly decreased according to HASBLED category so further investigation is necessary as to whether these patients could achieve higher TTRs with additional interventions, and the level of intervention required to achieve acceptable control.

The level of warfarin control is directly related to the efficacy and safety of warfarin. Connolly et al (27) have recommended a minimum TTR of 58-65% to ensure benefit of warfarin over antiplatelet therapy. In Australia the TTR was above this both overall and according to HASBLED category at the two time periods. In Singapore the overall mean TTR was at the minimum level of 58%, whilst the low- and moderate- risk categories had a mean TTR of 58% each at the start of the study but 75% and 54% respectively at the end of the study. Based on these results it would appear that application of the HASBLED score was not able to differentiate between good and poor control as defined by a minimum TTR threshold. At the end of the study, HASBLED was able to differentiate poor control at individual sites but this was compared to mean TTRs at each site and thus significantly different at our two study sites. Therefore, whilst HASBLED appears to differentiate poor warfarin control at individual sites, each country or health system would need to define their acceptable minimum level of warfarin control before applying HASBLED as a predictor of control.

In our study, the overall incidence of bleeds was similar in Australia and Singapore however the incidence of major bleeds was 1.5 times higher in Singapore compared to Australia. This is consistent with the overall difference in TTR between the countries, and similar to findings by Wan et al (12) who reported a TTR improvement of 6.9% reduced one major haemorrhagic event per 100 patient years. In both countries, HASBLED did not appear to be a good predictor of overall bleeds but the incidence of major bleed events increased according to HASBLED category. The retrospective nature of this study may explain this result as bleeds, particularly minor, were self-reported and patient recall of bleed events may have been higher in Australia due to the increased number of testing and hence reduced time between visits. The likelihood of adverse events increases with time outside therapeutic range, however bleeding complications can still occur in
patients with INR within normal range. Further investigation of the INR at the time of bleed events would assist in determining the most appropriate marker and possible predictor for clinical events.

The European guidelines suggest a high HASBLED score should not exclude patients from oral anticoagulation but where warfarin is used, efforts to improve the quality of control is needed. Our study suggests that regular use of HASBLED could be used to assist in identifying patients at risk of poor warfarin control and hence be more suited to alternate oral anticoagulant therapy. For example, the Australian site achieved a good mean TTR of 80% across all categories but after six months a HASBLED score ≥3 was associated with a TTR<75%. As mentioned previously, this is considered a good level of control and above recommended guidelines of 70% (8) thus all patients would be potential candidates for warfarin. In contrast, in the Singapore population a HASBLED score ≥3 was able to identify patients achieving TTR significantly below the mean 58% for that site both at the beginning of the study (TTR 45%) and after the six month period (35%). Given the low level of warfarin control achieved in these groups, it may be that these patients are not suitable candidates for warfarin and may be better suited to alternative anticoagulants. Further investigation would be required to test this hypothesis and consideration given to other patient factors, e.g. age and renal function, in deciding on the anticoagulant of choice.

In conclusion, HASBLED is commonly applied to patients with AF to assess bleed risk prior to the commencement of warfarin therapy. Consistent with Mueller et al (20), this study found a HASBLED score of ≥3 may also be a useful predictor of warfarin control and identify patients at high risk of poor warfarin control as measured by TTR, particularly in populations achieving poor overall control. HASBLED may serve a dual purpose of assessing bleed risk and warfarin control thus simplifying assessment of patients and enabling clinicians to identify patients at high risk of poor warfarin control who may require additional INR monitoring to achieve acceptable control, or who may benefit from alternate anticoagulants.
REFERENCES


Table 1 – Patient demographics, warfarin control, bleed events, and HASBLED scores at the Australian and Singapore sites.

<table>
<thead>
<tr>
<th>Country</th>
<th>Australia</th>
<th>Singapore</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>3199</td>
<td>1171</td>
</tr>
<tr>
<td>Male</td>
<td>1673 (52.3%)</td>
<td>707 (60.4%)</td>
</tr>
<tr>
<td>Female</td>
<td>1526 (47.7%)</td>
<td>464 (39.6%)</td>
</tr>
<tr>
<td>Age mean (SD) years</td>
<td>77.2 (9.1)</td>
<td>69.7 (10.0)</td>
</tr>
<tr>
<td>Age &gt;65 years</td>
<td>2912 (91.0%)</td>
<td>818 (69.9%)</td>
</tr>
<tr>
<td><strong>Medical History</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1185 (37.0%)</td>
<td>698 (59.6%)</td>
</tr>
<tr>
<td>Abnormal renal function</td>
<td>149 (4.7%)</td>
<td>164 (14.0%)</td>
</tr>
<tr>
<td>Abnormal liver function</td>
<td>11 (0.3%)</td>
<td>7 (0.6%)</td>
</tr>
<tr>
<td>Stroke/TIA history</td>
<td>487 (15.2%)</td>
<td>46 (3.9%)</td>
</tr>
<tr>
<td><strong>Warfarin control, mean (SD)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TTR</td>
<td>82.3 (15.6)</td>
<td>57.7 (34.2)</td>
</tr>
<tr>
<td>Number of test per patient</td>
<td>11.2 (5.6)</td>
<td>5.6 (6.2)</td>
</tr>
<tr>
<td><strong>Bleed events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td>113 (0.035)</td>
<td>34 (0.029)</td>
</tr>
<tr>
<td>Major</td>
<td>26 (0.008)</td>
<td>14 (0.012)</td>
</tr>
<tr>
<td>Total bleeds per patient</td>
<td>139 (0.043)</td>
<td>48 (0.041)</td>
</tr>
<tr>
<td><strong>HASBLED score Start of Study Period</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>1 (0-5)</td>
<td>1 (0-4)</td>
</tr>
<tr>
<td>0-1</td>
<td>1624 (50.8%)</td>
<td>699 (59.7%)</td>
</tr>
<tr>
<td>2</td>
<td>1159 (36.2%)</td>
<td>401 (34.2%)</td>
</tr>
<tr>
<td>≥3</td>
<td>416 (13.0%)</td>
<td>71 (6.1%)</td>
</tr>
<tr>
<td><strong>HASBLED score End of Study Period</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>1442 (45.1%)</td>
<td>431 (36.8%)</td>
</tr>
<tr>
<td>2</td>
<td>1160 (36.3%)</td>
<td>455 (38.9%)</td>
</tr>
<tr>
<td>≥3</td>
<td>597 (18.6%)</td>
<td>285 (24.3%)</td>
</tr>
</tbody>
</table>
HASBLED CATEGORY
START OF STUDY PERIOD

AUS TRALIA

HASBLED CATEGORY
END OF STUDY PERIOD

S I N GAPO RE

HASBLED CATEGORY
START OF STUDY PERIOD

HASBLED CATEGORY
END OF STUDY PERIOD
Figure 1 – TTR according to HASBLED Category at start and end of the six month study period for both sites, i.e. Australia and Singapore. TTR for each category is mean and standard deviation with statistical differences represented as * p<0.05, **p<0.01, and ***p<0.001. N=number of patients, T=mean number of tests per patient, B=number of bleed events per patient, and M=major bleed events per patient.