GASTROINTESTINAL BLEEDING RISK ASSESSMENT USING HAS-BLED IN ATRIAL FIBRILLATION PATIENTS WHO ARE RECEIVING WARFARIN IN HOSPITAL UNIVERSITI SAINS MALAYSIA

DR SRI SALWANI IDRIS

Dissertation Submitted In Partial Fulfillment Of The Requirement For The Degree Of Master Of Internal Medicine

UNIVERSITI SAINS MALAYSIA

2018

ACKNOWLEDGEMENT

I would like to begin by expressing my gratitude to Allah the Almighty for His guidance and blessing without which I would not be able to embark on this task of beginning and completing this dissertation. It would not have been possible to write this dissertation without the help and support of the kind people around me.

First and foremost, I am deeply grateful to my supervisor, Dr Amry bin Ab Rahim for his extremely valuable guidance, criticism and suggestion in the completion of this dissertation. He has always been there to guide me patiently and despite all my shortcomings, he still kept supporting and pushing me patiently to complete this dissertation. For this, I am forever grateful to his efforts and guidance.

I would like to thank Professor Dato Dr Zurkurnai Yusof, Head of Department of Internal Medicine, School of Medical Sciences, University Sains Malaysia (USM) for his support, suggestion, guidance and encouragement during the completion of this dissertation. Appreciation also forwarded to Assoc. Prof Wan Mohd Zahiruddin Wan Mohammad, Biostatistician from Department of Community Medicine for his invaluable guidance and opinion in this dissertation.

I would like to thank my husband, Mohd Hazim Suhaimi who have always being the pillar of my strength and been there to support me through thick and thin. Without his love and understanding, I would not be where I am now. To my daughters, Kauthar Amilin and Nisa Amalin, who have been the two angels of my heart, the reason for me to go on. Last but not least, thank you to my father, Hj Idris Ibrahim and my mother, Hjh Zainab Hj Dayan who were always there for me with their support and love.

SRI SALWANI IDRIS

TABLE OF CONTENTS

CONTENTS PAGE

LIST OF FIGURES

LIST OF TABLES

LIST OF APPENDIX

ABBREVIATION

ACS	Acute coronary syndrome
AF	Atrial Fibrillation
ATRIA	Anticoagulation and Risk Factors in Atrial Fibrillation
$CHADS_2$	Congestive heart failure, Hypertension (uncontrolled), Age (≥ 65 years), Diabetes Mellitus, Stroke (2 points)
CHA_2DS_2 VASc	Congestive heart failure, Hypertension (uncontrolled), Age (≥75 years) (2 points), Diabetes Mellitus, Stroke (2 points), Vascular disease, Age (65-74 years), Sex (Female)
ESC	European Society of Cardiology
FFP	Fresh Frozen Plasma
rFVIIa	Recombinant Activated Factor VII
GIB	Gastrointestinal bleeding
GI	Gastrointestinal
HAS-BLED	Hypertension, Abnormal Liver/Renal, Stroke, Bleeding tendency, Labile INR, Elderly (≥65 years), Drugs/Alcohol
$HEMORR_2HAGES$	Hepatic or renal disease, Ethanol abuse, Malignancy history, Older age (>75 years), Reduced platelet count/function/antiplatelet, Rebleeding risk, Hypertension (uncontrolled), Anaemia, Genetic factors, Excessive fall risk, Stroke history
ICH	Intracranial haemorrhage

INR	International Normalized Ratio
KRK	“Klinik Rawatan Keluarga”
NOACs	Non Vitamin K Antagonist Oral Anticoagulants
NSAIDs	Non-steroidal Anti Inflammatory Drugs
OGDS	Oesophagogastroduodenoscopy
SD	Standard Deviation
TIA	Transient Ischemic Attack
PCC	Prothrombin Complex Concentrates
USM	University Sains Malaysia
TTR	Time to Therapeutic Range
VKA	Vitamin K Antagonist
WARF	Wisconsin Alumni Research Foundation

PENILAIAN RISIKO PENDARAHAN GASTROINTESTINAL MENGGUNAKAN HAS-BLED DALAM PESAKIT FIBRILASI ATRIAL YANG MENERIMA WARFARIN DI HOSPITAL UNIVERSITI SAINS MALAYSIA

ABSTRAK

Terdapat peningkatan penggunaan antikoagulan dalam kalangan pesakit fibrilasi atrial di seluruh dunia. Warfarin menjadi antikoagulan yang paling lazim digunakan. Sejurus sebelum memulakan rawatan, risiko pendarahan perlu dinilai untuk meminimakan risiko pesakit mengalami pendarahan. HAS-BLED adalah ringkas dan selamat digunakan. Walaubagaimanapun, penggunaan HAS-BLED sejurus sebelum memulakan antikoagulan masih tidak diketahui.

Kajian ini telah diadakan untuk menilai penggunaan HAS-BLED dan kesannya ke atas kejadian pendarahan gastrointestinal (GI). Kajian retrospektif ini dijalankan dalam kalangan pesakit fibrilasi atrial yang menghadiri klinik pesakit luar INR atau KRK di antara Januari 2011 sehingga Disember 2017. 88 pesakit layak menjalani kajian ini dan HAS-BLED mereka telah dinilai. Pesakit berusia 18 tahun ke atas dengan fibrilasi atrial yang menerima warfarin dimasukkan dalam kajian ini. Kriteria penyisihan termasuk mereka yang mengambil warfarin untuk sebab selain daripada fibrilasi atrial. Kami menyasarkan untuk menentukan perkaitan di antara pendarahan GI dan AF dalam kalangan pesakit yang ada dan tiada HAS-BLED.

Di antara 88 pesakit yang dipilih, kadar kejadian pendarahan GI adalah 5.7 kes per 100 tahun pesakit. 44 (50%) pernah membuat penilaian HAS-BLED sejurus sebelum memulakan antikoagulan. Purata umur mereka yang menerima warfarin adalah 64 tahun

dengan jantina pembahagian jantina yang sama rata. 83 (94.1%) pesakit yang memulakan warfarin mempunyai skor CHA_2DS_2 VASc ≥2. Pendarahan GI berlaku dalam 11 (12.5%) daripada 88 pesakit. 6 (13.6%) pesakit mempunyai HAS-BLED dan 5 (11.4%) termasuk dalam kumpulan berisiko tinggi. Purata HAS-BLED di kalangan 44 pesakit adalah 1.92 (±0.936) dan purata HAS-BLED di kalangan 6 pesakit yang mengalami pendarahan gastrointestinal adalah lebih tinggi iaitu 2.83 (±0.98). Kadar pendarahan gastrointestinal bagi setiap 100 pesakit-tahun adalah 0.53 dan 2.63 bagi markah HAS-BLED 1 dan 3. Tiada perkaitan di antara pendarahan GI dan HAS-BLED nilai p=0.747). Terdapat perkaitan di antara pendarahan GI dan jangka masa pengambilan warfarin kurang daripada 30 hari (nilai p=<0.005).

Kesimpulannya, kadar penggunaan HAS-BLED masih rendah. Didapati tiada perkaitan di antara HAS-BLED dan pendarahan GI. Walaubagaimanapun, HAS-BLED adalah penting untuk menentukan faktor risiko boleh ubah sejurus sebelum memulakan warfarin untuk menurunkan pendarahan GI.

GASTROINTESTINAL BLEEDING RISK ASSESSMENT USING HAS-BLED IN ATRIAL FIBRILLATION PATIENTS WHO ARE RECEIVING WARFARIN IN HOSPITAL UNIVERSITI SAINS MALAYSIA

ABSTRACT

There has been an increase usage of anticoagulant among atrial fibrillation worldwide. Warfarin remains one of the commonest anticoagulant use. Prior to starting treatment, bleeding risk need to be assess in order to minimize patients' risk of bleeding. HAS-BLED is a simple and user friendly to use. Unfortunately, the utilization and usage of HAS-BLED prior to starting anticoagulant in HUSM was not known and not yet being studied.

This study had been done to assess utilization of HAS-BLED and its impact on the occurrence of gastrointestinal bleeding (GIB). This retrospective study was performed among atrial fibrillation (AF) patients who attended INR or KRK outpatient clinic between January 2011 to December 2017. 88 patients were eligible for this study and their HAS-BLED were assess. Patients above 18 years old with AF who received warfarin were included in this study. Exclusion criteria include those who were taking warfarin for other causes than atrial fibrillation. We aimed to determine the rate of GIB among AF patients who are on warfarin, assess GIB risk using HAS-BLED and determine the association between GIB in AF patients with and without HAS-BLED.

Among the selected 88 patients, the incidence rate of GIB is 5.7 cases per 100 patient-years. 44 (50%) had HAS-BLED assessment done prior to starting anticoagulant. The mean age of those who received warfarin was 64 years old with gender equally distributed. 83 (94.1%) patients who were started on warfarin had CHA_2DS_2 VASc score ≥2. GIB occurred in 11 (12.5%) out of 88 patients. Six (13.6%) patients were with HAS-BLED and 5 (11.4%) belong to the high risk group. The mean score for 44 patients with HAS-BLED was 1.92 (±0.936) and the mean score for 6 patients with GIB was much higher that was 2.83 (±0.98). The bleeding rate for every 100 patient-years was 0.53 and 2.63 for HAS-BLED score of 1 and 3 respectively. There was no association between GIB and HAS-BLED (p value= 0.747). There was association between GIB and duration of warfarin intake less than 30 days (p value <0.005).

In conclusion, the utilisation of HAS-BLED remains low. There is no association between HAS-BLED and GIB. However, HAS-BLED is important to determine modifiable risk factors prior to starting warfarin to reduce GIB.

CHAPTER 1: INTRODUCTION AND LITERATURE REVIEW

1.1 Atrial Fibrillation and Stroke

Atrial fibrillation (AF) is a supraventricular tachyarrhythmia commonly found in general population. It defined as irregularly irregular pattern with no distinct p waves recorded in the electrocardiographic (ECG) (Kapil Kumar MD, 2017). It caused mainly attributed to the single focus firing rapidly in the atria and the most common site is the pulmonary veins. Stretching of the atrial heart chamber increase the propensity for rapid firing as a result of stretch sensitive ion channels (Kalifa *et al.*, 2003).

According to Lim et al. prevalence of AF among Malaysian population is 0.54%. The prevalence rate are much higher in the US and UK which is 0.94% and 2.0% respectively (Lim *et al.*, 2016). In ECHOES trial, the prevalence for AF is higher in men (2.4%) compared to women (1.6%) (Davis *et al.*, 2012). This is comparable to Malaysian population conferring to REDISCOVER study where they found that prevalence among men is higher (58.5%) and women (41.5%) (Lim *et al.*, 2016). AF prevalence also increase with increasing age (Magnani *et al.*, 2011).

Clinical manifestation of AF varied from asymptomatic, palpitation, dyspnea, angina and infrequently, syncope. To highlight one of the most significant clinical features related to AF is stroke. AF is associated with 3 to 5-fold increase risk of stroke (Wolf *et al.*, 1991). When AF occurred, the dysrhythmia causing contractile dysfunction, stasis and blood clot formation that later increased the risk of thromboembolism or cardioembolic stroke (Kamel *et al.*, 2016). In addition, there are other systemic risk factors that increase the stroke risk via other mechanism outside the atrium such as in-situ small cerebral vessels occlusion and large artery atherosclerosis.

Stroke is the number 2 cause of death worldwide after ischemic heart disease (World Health Organization, 2017). Stroke patients with AF are at high risk of death both at the acute phase of stroke and during the subsequent year after the first acute stroke event. Mortality from cardiac diseases prevailed in the AF group during the acute phase of stroke (Kaarisalo *et al.*, 1997).

Stroke with AF also has worst prognosis than patients without AF (Steger *et al.*, 2004). Due to increase morbidity and mortality among AF patients, guidelines had been established to determine AF patients who are at risk of developing stroke. Guidelines has been made since 2 decades ago to determine AF patients who will benefit from oral anticoagulant. In 2001, Gage et al. had published a paper on validation of clinical classification schemes for predicting stroke in patients with atrial fibrillation; namely $CHADS_2$ (Gage *et al.*, 2004; Gage *et al.*, 2001). The risk stratification was being refined further in 2010 to include few other important risk factors, which is known as CHA_2DS_2 VASc (Lip *et al.*, 2010). With increasing risk factors, there is increased risk of having stroke. In recent European Society of Cardiology (ESC) guideline for the management of AF published in 2016, (Kirchhof *et al.*, 2016) anticoagulant should be considered in those with CHA_2DS_2 VASc score of ≥ 1 and obviously indicated if the score is ≥ 2.

1.2 Stroke Prevention Therapy In Atrial Fibrillation Patients

1.2.1 Warfarin or Vitamin K Antagonists

First found by L M Roderick in North Dakota in 1929, warfarin was created from mouldy silage made from sweet clover (*Melilotus alba* and *M. officinalis*). It showed that it contained a haemorrhagic factor that reduced the activity of prothrombin. However, it was not until 1940 that Karl Link and his student Harold Campbell in Wisconsin discovered that the anticoagulant in sweet clover was 3,3′-methylenebis (4-hydroxy

coumarin) (Kresge *et al.*, 2005). Further work by Link led in 1948 to the synthesis of warfarin, which was initially approved as a rodenticide in the USA in 1952, and then for human use in 1954. The name warfarin is derived from *WARF* (Wisconsin Alumni Research Foundation) and *–arin* from coumarin (Pirmohamed, 2006).

In this study, we chose to study warfarin because warfarin is the most widely used anticoagulant in the world. Warfarin is a highly effective treatment for the reduction of stroke in atrial fibrillation (AF) and its limitations are well studied. Despite the advent of non-vitamin K antagonist (VKA) oral anticoagulant drugs (NOACs), warfarin will always be the most relevant suitable drugs to be used since its introduction in 1954 due to various factors. It is easily available, cheaper, mechanism of action is well understood, reversal agents extensively accessible, and suitable to almost all patients. In the UK it has been estimated that at least 1% of the whole population and 8% of those aged over 80 years are taking warfarin (Wadelius and Pirmohamed, 2007).

Warfarin acts as an antagonist of vitamin K, inhibiting reductases involved in the synthesis of hydroquinone from epoxide, particularly epoxide-reductase (Figure 1). The inhibition of cyclic conversion of vitamin K induces the hepatic production and secretion of decarboxylated or partially carboxylated proteins that represent 10 to 40% of normal biological activity (Figure 1) which leads to reduced activation of several clotting factors.

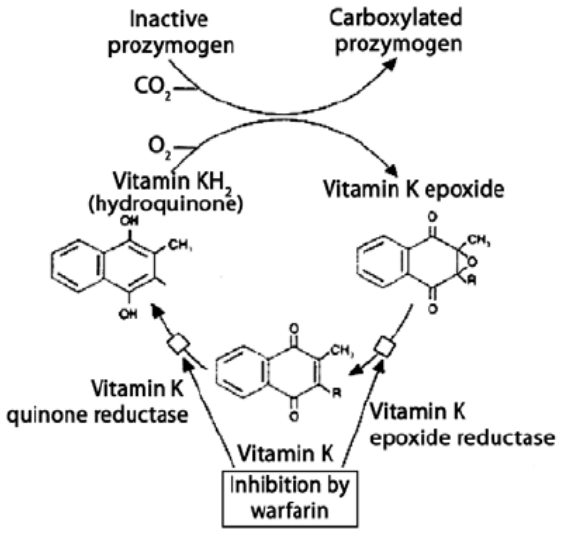

Figure 1: Cycle of Vitamin K and Its Inhibition by Warfarin

Source: Warfarin: pharmacological profile and drug interactions with antidepressant. Einstein 2012 (Souto Teles *et al.*, 2012).

The main adverse effect associated with warfarin is bleeding. Major and fatal bleeding events occur respectively at rates of 7.2 and 1.3 per 100 patient-years, according to a meta-analysis of 33 studies (Linkins *et al.*, 2003). The reported occurrence of intracranial hemorrhage (ICH), which represents the mostly feared bleeding complication of VKA therapy because of its high disability and/or fatality rate, is in the range of 0.2%-0.4% per year (Schulman *et al.*, 2008).

Warfarin is also number three on the list of drugs implicated in causing hospital admission through adverse effects (Pirmohamed *et al.*, 2004). Warfarin's narrow therapeutic index makes it difficult to maintain patients within a defined anticoagulation range. Due to difficulties to maintain INR within target range and frequency of follow up to out- patient clinic, it leads to the emergence of new oral anticoagulant drugs that can surpass these problems.

1.2.2 Non-Vitamin K Antagonist Oral Anticoagulant (NOAC) Drugs

In the last few years, emerging novel oral anticoagulants or NOACs (comprising apixaban (Eliquis®), edoxaban (Lixiana), rivaroxaban (Xarelto®) factor Xa inhibitors and dabigatran (Pradaxa®) direct thrombin inhibitor, have been used in patients with non-valvular atrial fibrillation as suitable alternatives to the perpetual warfarin and analogues (vitamin K antagonists or VKAs) to prevent stroke and venous thromboembolism (VTE). The major trials of NOACs in AF were: ARISTOTLE, ENGAGE-AF, Rocket-AF and RE-LY, respectively (Connolly *et al.*, 2009a; Giugliano *et al.*, 2013; Granger *et al.*, 2011; Patel *et al.*, 2011). NOACs are presently contraindicated in patients with mechanical heart valves, following several reports of valve thrombosis (Chu *et al.*, 2012; Kuwauchi *et al.*, 2013; Price *et al.*, 2012).

In a nationwide registry study to compare bleeding rates in patients with AF being prescribed oral anticoagulant, the author found out that risk of gastrointestinal bleeding was higher in rivaroxaban and dabigatran compared with warfarin (Figure 2).

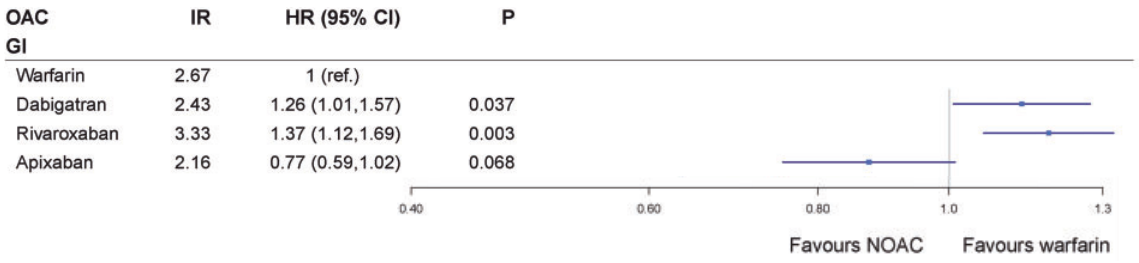

Figure 2: Forest plot showing the hazard ratios for first bleeding episode for dabigatran, rivaroxaban and apixaban compared with warfarin. Crude IR for first bleeding episode are given as events per 100 person-years. CI, confidence interval; GI, gastrointestinal; HR, adjusted hazard ratio; IR, incidence rate; OAC, oral anticoagulant.

Source: A Nationwide Registry Study To Compare Bleeding Rates in Patients With AF Being Prescribe Oral Anticoagulants. ESC 2017 (Halvorsen *et al.*, 2017).

The most common disadvantage of NOACs is the lack of an antidote to resolve major bleeding complications possibly associated with their ubiquitous use. Other than Idarucizumab (antidote for Dabigatran) (FDA Office of Hematology and Oncology Products, 2015), there are still no specific antidote available for other NOACs. Another major concern is the periprocedural management of patients on NOACs which is a common complex clinical problem and may pose a patient-specific concern. The third disadvantage is cost of each NOAC calculated as total daily cost and in comparison with warfarin. Furthermore, ensuring adherence to therapy is important to ensure patients get the greatest benefit by using NOACs. When using NOACs, there is no need for therapeutic monitoring. Although this is proven to be beneficial in those patients who have problems to come for regular follow up to the clinics, it is challenging for clinicians to ensure patient adherence. Poor adherence to therapy is a common problem, with typical adherence rates for prescribed medications to be approximately 50% (Nieuwlaat *et al.*, 2014). As NOACs have shorter half-lives than warfarin, close adherence to dosing regimens is needed to ensure the drug concentrations remains therapeutic. As a result, alternative measures of anticoagulation for assessing recent adherence are needed for the NOACs. Some drugs regimens for NOACs are bid dosing, and this may impact patient adherence, as in chronic patients, they generally adhere better to od compared with bid regimens, which might suggest a potential advantage of rivaroxaban compared with dabigatran and apixaban (Savelieva and Camm, 2014). Although INR monitoring during VKA therapy is a requirement and not an adherence tool, it does provide an indirect measure of adherence. Most NOACs are renal eliminated. It should be emphasized that there are no clinical data for the NOACs in patients on dialysis and the use of NOACs in this population is not recommended (Verma *et al.*, 2014). The Canadian Cardiovascular Society (CCS) guidelines for the management of AF recommend NOACs not be used

when creatinine clearance (CrCl) is <30ml/min (Turpie *et al.*, 2017). This recommendations is similar to FDA for patients with renal impairment, however the FDA has extrapolated the data from the clinical trials and approved a low dose dabigatran (75mg bid), apixaban (5mg bid or 2.5mg bid) and rivaroxaban (15mg od) for patients with AF and CrCl of 15-30ml/min (Turpie *et al.*, 2017).

1.2.3 Left Atrial Appendage Occlusion

Left atrial appendage (LAA) occlusion may also reduce stroke risk in patients with contraindications to oral anticoagulant. Only one device (Watchmanw) has been compared with vitamin K antagonist therapy in randomized trials [PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients With AF trial), and PREVAIL (Prospective Randomized Evaluation of the Watchman LAA Closure Device In Patients with AF Versus Long Term Warfarin Therapy trial)].In these data sets, LAA occlusion was non-inferior to VKA treatment for the prevention of stroke in AF patients with moderate stroke risk, with a possibility of lower bleeding rates in the patients who continued follow-up (Holmes Jr *et al.*, 2014). Surgical occlusion also may be considered during concomitant cardiac surgery.

1.3 Assessment prior to starting anticoagulant

1.3.1 Indications using CHA_2DS_2 VASc

Since $CHADS_2$ being introduced in 2001 and further redefined by Lip et al. in 2010, the usage of CHA_2DS_2 VASc score has been used to classify AF patients into stroke risk. It is a scoring system consists of clinical risk factor for stroke, introduced in the ESC guideline since 2010. It is used to guide clinicians in making initial decision to start oral anticoagulant in AF patients. It consists of: Congestive heart failure (defined as

signs/symptoms of heart failure or objective evidence of reduced left ventricular ejection fraction) (1 point), Hypertension (Resting blood pressure >140/90 mmHg on at least two occasions or current antihypertensive treatment) (1 point), Age 75 years or older (2 points), Diabetes mellitus (Fasting glucose >125 mg/dL (7 mmol/L) or treatment with oral hypoglycaemic agent and/or insulin (1 point), Previous stroke, transient ischaemic attack, or thromboembolism (2 points), Vascular disease, Previous myocardial infarction, peripheral artery disease, or aortic plaque (1point), Age 65–74 years (1 point), and Sex category (female) (1 point) (Kirchhof, 2016). Score of 1 should be considered for anticoagulant and score of ≥2 is indicated for anticoagulant in AF patients. If patient is contraindicated for anticoagulant, left atrial appendage occluding device may be considered (Kirchhof, 2016). Table 1 and 2 describe the CHA_2DS_2 VASc and adjusted stroke risk for patients with non-valvular AF.

Table 1: CHA_2DS_2 VASc risk factor score

Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes mellitus	1
Stroke/TIA/thromboembolism	2
Vascular disease- prior myocardial infarction, peripheral artery disease and aortic plaque	1
Age 65-74	1
Sex category- female	1
Maximum score	9

Table 2: Adjusted stroke rate according to CHA_2DS_2 VASc

CHA_2DS_2 VASc	**Patients (n=7329)**	**Adjusted stroke rate (%/year)**
0	1	0%
1	422	1.3%
2	1230	2.2%
3	1730	3.2%
4	1718	4.0%
5	1159	6.7%
6	679	9.8%
7	294	9.6%
8	82	6.7%
9	14	15.2%

Table 1 and 2 are adapted from Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC) (Camm *et al.*, 2010).

1.3.2 Bleeding risk assessment

1.3.2.1 HAS-BLED

From the time when the administration of warfarin as primary prevention for stroke has been implemented, usage of anticoagulant has dramatically increase. Practise of prescribing anticoagulant and looking at the impact and complications exclusively bleeding has already become 'the bread and butter' in medical care during the course of patient's treatment. Clinical decision on justification for the usage of anticoagulant is based on stroke risk using CHA_2DS_2 VASc score. Since stroke risk is also closely related to bleeding risk (Nieuwlaat *et al.*, 2006), thus HAS-BLED score has been created to assist in clinical decision making. Pister et al (2010) used the large population database from the prospective Euro Heart Survey on AF, with data collected between 2003 and 2004. 5333 patients were enrolled and 1 year follow up assessment were performed to determine survival and major adverse cardiovascular events, such as major bleeding. From this data, they create a novel friendly score name HAS-BLED by incorporating significant risk factors found in their derivation cohort as well as risk factor for major bleeding found in the literature from systematic reviews (Pisters *et al.*, 2010). The name used an acronym and each letter constitutes to 1 parameter which are included as a bleeding risk. Each component is given 1 mark each: Hypertension (uncontrolled; defined as systolic blood pressure persistently >160), Abnormal renal function (presence of chronic dialysis, renal transplantation, or serum creatinine ≥200 micromol/L), Abnormal liver function (chronic hepatic disease i.e. cirrhosis, biochemical evidence of significant hepatic derangement e.g bilirubin >2x upper limit normal in association with aspartate aminotransferase/ alanine aminotransferase/ alkaline phosphatase >3x upper limit normal and so forth), Stroke (previous history, particularly lacunar), Bleeding history or predisposition (anaemia),

Labile international normalized ratio (INR) (i.e therapeutic time in range <60%), Elderly (>65 years), Drugs/alcohol concomitantly (antiplatelet agents, NSAIDs, 1 point for drugs and 1 point for alcohol excess).

Those with score three or more are high risk of bleeding, score zero to two are classified into intermediate and low risk of bleeding (Kirchhof, 2016). Score of three and above had risk of 3.74 bleeds per 100 patient-years (Pisters *et al.*, 2010). The annual bleeding rate increased with the addition of risk factor from the derivation cohort. Table 3 and 4 showed HAS-BLED score and risk of major bleeding respectively.

Table 3 : Bleeding risk assessment- HAS-BLED

Letter	Clinical Characteristic	Points awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly	1
D	Drugs or alcohol (1 point each)	1 or 2

HAS-BLED = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (>65 years), Drugs/alcohol concomitantly; INR= international normalized ratio.

Table 4: The Risk Of Major Bleeding Within 1 Year In Patients With AF Enrolled In The Euro Heart Survey

Risk factor/Score	Number of patients	Number of bleeds	Risk of bleeds per 100 Patient-Years
0	798	9	1.13
1	1286	13	1.02
2	744	14	1.88
3	187	7	3.74
4	46	4	8.70
5	8	1	12.50
6	2	0	0.0
7	0	0	…
8	0	0	…
9	0	0	…
Any score	3071	48	1.56
P value for trend			0.007

Adapted from A Novel User-Friendly Score (HAS-BLED) To Assess 1-Year Risk Of Major Bleeding In Patients With Atrial Fibrillation : The Euro Heart Survey (Pisters *et al.*, 2010).

Using bleeding risk assessment is to ensure that administration of anticoagulant is justified and their bleeding risk assessed and addressed. The utmost important in managing patients with AF is to maximize appropriate antithrombotic therapy and minimize adverse events. HAS-BLED is a novel user-friendly score created in 2010. It is made to estimate 1-year risk of major bleeding (intracranial, hospitalization, hemoglobin decrease >2g/L, and/or transfusion). HAS-BLED is said to be more user-friendly for clinical application, all risk factors of HAS-BLED score are readily available from the medical history and routinely tested.

One of the important impact of using HAS-BLED is based on several studies. Konishi et al. used HAS-BLED score to assess long-term outcome after percutaneous coronary intervention (PCI) in patients taking dual antiplatelet therapy. From 1207 patients that had undergone PCI using drug eluting stent, they found that incidence of both death and major bleeding higher in the high HAS-BLED group (score ≥3) than in the low risk group (score 0-2) independent of the presence of AF (Konishi *et al.*, 2015).

In 2009, Connolly et al. investigate the hypothesis that addition of clopidogrel to aspirin would reduce the risk of stroke. A total of 7554 patients recruited who was deemed unsuitable for anticoagulant was given either clopidogrel or placebo, in addition to aspirin. In half (n=~3500) patients with high stroke risk, the most common applied classification was "unsuitable for oral anticoagulant", which was solely based on physician clinical judgement, without the presence of any predefined risk factor of bleeding or other objective risk scoring (Connolly *et al.*, 2009b). This reflects physicians' uncertainty about what to consider true risk factors of bleeding. With HAS-BLED, decision making will be more objective and fear of starting anticoagulant due to bleeding can be curtail. Chia et al. (2016) mentioned that anticoagulation management of AF patients among Singaporean population remains inadequate. From 62% AF patients who had CHA_2DS_2 VASc of ≥2, only 32% patients were given anticoagulant. Thus, their study recommended that objective assessment of bleeding risks should be performed before withholding anticoagulation.

HAS-BLED has been used in many clinical trials since 2011. The predictive performance of major bleeding using this score is better (Apostolakis *et al.*, 2012; Beltrame *et al.*, 2017; Gallego *et al.*, 2012; Guo *et al.*, 2016; Zhu *et al.*, 2015) leading to many clinical trials use HAS-BLED in assessing bleeding risk in their studies (Kirchhof, 2016; Li *et al.*, 2017). Wengen Zhu et al. and Apostolakis et al. concluded that HAS-

BLED score not only performs better than the other two scoring systems (HEMORR$_2$HAGES and ATRIA), it is also simple and easy to use. Although HAS-BLED has been validated in several population cohorts mainly from Europe, there are limited data in Asian cohorts (Guo *et al.*, 2013). As we know, bleeding risk among Asian population is differ from Europe. Asian population with AF may have different clinical profile related stroke risk that renders them to have higher bleeding risk especially intracranial haemorrhage (ICH) (Guo *et al.*, 2016). In Taiwanese cohort without anticoagulant therapy, the incidence of major bleeding events and ICH 4.5 per 100-person years and 0.87% per person-years respectively. These rates may be higher than reported rates from clinical trials or non-Asian population (Guo *et al.*, 2016). According to Laila et al., knowledge regarding oral anticoagulant among our population remains low (Matalqah *et al.*, 2013). Poor knowledge leads to reduce number of patients achieving time to therapeutic range (TTR; define as proportion of person-time within the target therapeutic range over the total person-time of follow up) >75%. With labile INR (define as TTR <75%), this further predispose them to bleeding. It is important to note that the prevalence of AF among stroke patients in Malaysia is 10.6% (Chee, 2014). Stroke patients with AF were observed to have a higher mortality rate and disability upon discharge. Although this is well known, Chia et al. found only 32.7% of AF patients with CHADS2 ≥2 were eventually prescribed warfarin (Chia *et al.*, 2016). Elderly women were less likely to be given warfarin, presumably because of perceived high bleeding risk. Therefore, this study is important to be done in our population in order see the practice of using HAS-BLED score as well as to look at objective evidence of gastrointestinal bleeding with respect to the HAS-BLED score.

Furthermore, those with high bleeding risk can be flagged up and follow up more closely and other modifiable risk factor can be addressed to reduce bleeding. Since we

know that stroke is one of the top ten causes of death worldwide (World Health Organization, 2017), prevention of stroke is noteworthy than omitting anticoagulant.

1.3.2.2 Other bleeding risk scoring system

1.3.2.2.1 HEMORR$_2$HAGES

This score was created in 2006. It comprise of: Hepatic or renal disease, ethanol abuse, malignancy, older age (>75 years), reduced platelet cound or function, hypertension (uncontrolled), anemia, genetic factors, excessive fall risk and stroke (Gage *et al.*, 2006). With each additional point, the rate of bleeding per 100 patient- years of warfarin increase: 1.9 for 0, 2.5 for 1, 5.3 for 2, 8.4 for 3, 10.4 for 4 and 12.3 for ≥5 points.

1.3.2.2. ATRIA

ATRIA stands for AnTicoagulation and Risk factors In Atrial fibrillation. The paper published in 2011 in Journal of American Cardiology. The components that being assessed in the score are: anemia (3 points), severe renal disease (e.g., glomerular filtration rate <30 ml/min or dialysis-dependent, 3 points), age ≥75 years (2 points), prior bleeding (1 point), and hypertension (1 point). Major hemorrhage rates were 0.8% for low risk (0 to 3 points), 2.6% for intermediate risk (4 points), and 5.8% for high risk (5 to 10 points) (Fang *et al.*, 2011). The differences between each risk prediction score is tabulated in Table 5.

Table 5: Risk Prediction Scores

Risk elements	**HAS-BLED**	**HEMORR$_2$HAGES**	**ATRIA**
Hypertension	1 point	1 point	1 point
Age	1 point (≥65 years)	1 point (≥75 years)	2 points (≥75 years)
Prior stroke/ TIA	1 point	1 point	
Chronic liver disease, cirrhosis	1 point	1 point	
Chronic renal insufficiency	1 point	1 point	3 points
Alcoholism	1 point	1 point	
Malignancy		1 point	
Thrombocytopenia/ antiplatelet use		1 point	
Prior bleeding event		2 points	1 point
Anemia		1 point	3 point
History of falls		1 point	
Genetic factors		1 point	
Prior bleeding events/ anemia	1 point		
Time to therapeutic range <60%	1 point		
Aspirin, clopidogrel, prasugrel, ticagrelor, NSAIDs	1 point		
Low risk	0	0-1	0-3
Intermediate risk	1-2	2-3	4
High risk	3+	4+	5-10

TIA, transient ischemic attack; NSAIDs, non-steroidal anti-inflammatory drugs

Adapted from Prevention of Gastrointestinal Bleeding in Patients Receiving Direct Oral Anticoagulants, AJGSup (Abraham, 2016).

1.4 Gastrointestinal Bleeding in Warfarin Anticoagulated Patients

1.4.1 Incidence

Upper gastrointestinal bleeding (GIB) is a major emergency situation. It is frequently encountered medical emergency with an incidence rate of 72 per 100,000 in Malaysia (Ministry of Health Malaysia, 2003). Over the past decade, there seems to have overall reduction in number of GIB event leading to hospitalisation with decreasing trend in upper GIB events. However, the number of lower GIB events is significantly increase (Lanas *et al.*, 2009). Despite advancement in medical amenities and resources leading to reduction in overall mortality of GIB, the in-hospital case fatality remains at around 10% (Ministry of Health Malaysia, 2003; Siau *et al.*, 2017). Mortality related to GIB are mainly contributed by advanced age, shock and coexisting illness (Kim *et al.*, 2016).

GIB not only contribute to increase number of hospitalisation, it is also associated with significant morbidity, 30 days mortality and health-care cost (Monteiro *et al.*, 2016). According to Cryer et al. in US, patients with upper GI bleeds experienced significantly higher 12-month health-resource utilization and costs than patients without upper GI bleeds (Cryer *et al.*, 2010). This is also supported by Campbell et al. where they estimated the average cost for in-hospital treatment for upper GIB is £2458 (~RM 13,151) per patient (Campbell *et al.*, 2015). This is a large burden to the government with inpatient stay, endoscopy and red blood cells transfusion as the main cost drivers.

One of the important risk factors that causing GIB is the usage of anticoagulant. Hreinsson et al. stated that aspirin, NSAIDs and warfarin remain the important role in acute upper GIB aetiology (Hreinsson *et al.*, 2013). Furthermore, GIB is one of the severe bleeding complications of warfarin anticoagulation and occurs in up to 12% of cases (Rubin *et al.*, 2003).

In large-scale epidemiological studies on patients receiving warfarin, the annual incidence of major bleeding complications ranged from 1.1% to 1.5%, gastrointestinal sites accounting for 30–60% of the total (Di Minno *et al.*, 2015).

Although the incidence of upper GIB among the north-Eastern (Terengganu and Kelantan) was said to be low due to low incidence of Helicobacter *pylori* infection (Ministry of Health Malaysia, 2003), Lee et al. stated that the absence of H. *pylori* infection may not reduce the risk of peptic ulcer bleeding in the presence of risk factors especially offending drugs and elderly (Lee *et al.*, 2014). AF patients were also known to have multiple comorbids and polypharmacy that further predispose to GIB. From Bashir et al. study, they found out that among Malaysian people who are on anticoagulant and developed clinically relevant bleeding events, the highest number of bleeding predominantly from the GIB (Beshir *et al.*, 2018).

1.4.2 Risk Factors

Most AF patients because of a history of coronary arterial disease (CAD) or cerebrovascular disease, low-dose aspirin and/or clopidogrel are often employed in older individuals. Especially when low-dose aspirin and/or clopidogrel are combined with warfarin, the capability of these drugs to act cumulatively as to the risk of GIB is well known (Hansen *et al.*, 2010). Other risk factors include concomitant usage of anti-depressant, NSAIDs, elderly age and other co-morbidities (Chen *et al.*, 2014; Hernandez-Diaz and Rodriguez, 2002; Kim *et al.*, 2014; Monteiro *et al.*, 2016). As expected, the annual incidence of GIB increased with an increased baseline of HAS-BLED score. Figure 3 showed the annual incidence of GIB requiring transfusion increased from 0.87%/year for those with baseline HAS-BLED score of ≤1 to 1.13%/year for those with

a baseline HAS-BLED score of 2, and to 1.13%/year for those with baseline HAS-BLED score of 3 (Chan *et al.*, 2015).

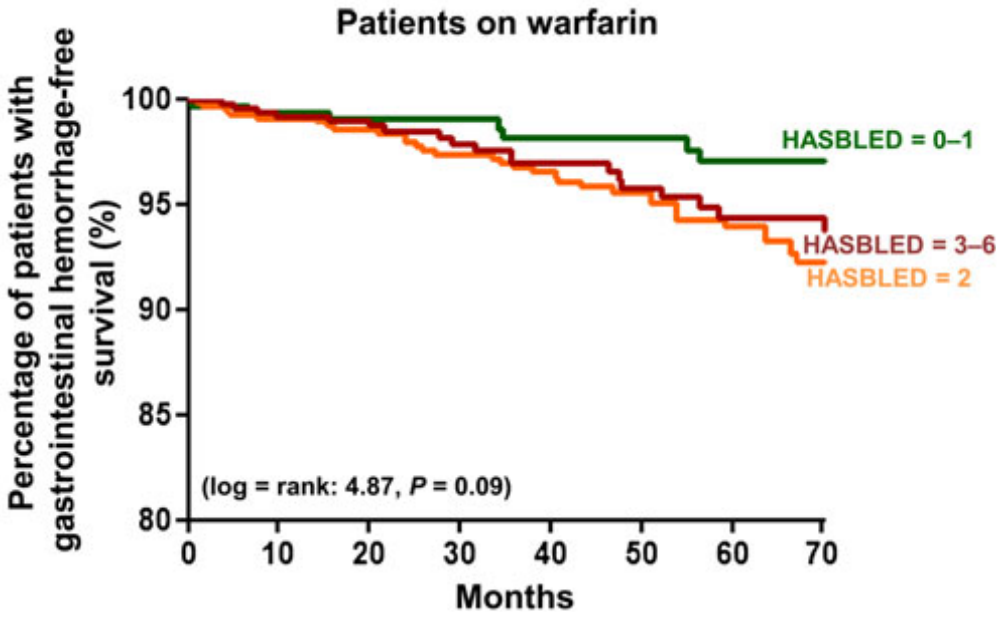

Figure 3: Kaplan-Meier estimates of gastrointestinal haemorrhage-free survival in AF patients receiving warfarin across different strata of the HAS-BLED score.

Adapted from Gastrointestinal haemorrhage in atrial fibrillation patients: impact of quality of anticoagulation control (Chan *et al.*, 2015).

1.4.3 Mechanism of warfarin related GIB

The GIB risk associated with warfarin appears to be related to its systemic anticoagulant effects via inhibition of key vitamin K–dependent clotting factors, and thus varies as a function of the international normalized ratio. Although the mechanism is unclear, the relative deficiency in vitamin K dependent clotting factors causing bleeding tendency as seen in cirrhotic patients may play a role (Chen *et al.*, 2014).

1.4.4 Management

Treatments can be divided into general and specific treatments. Acute treatment when patients presented to casualty includes resuscitation, administration of blood products and IV pantoprazole infusion. Treatment for reversal of vitamin K antagonist is also warranted by either transfusion of fresh frozen plasma (FFP), prothrombin complex concentrates (PCC), administration of recombinant activated factor VIIa (rFVIIa) or/and administration of vitamin K (Figure 4) to antagonize the VKA anticoagulation effect. Vitamin K can be given orally or intravenously, with the parenteral route having the advantage of a more rapid onset of action (Crowther *et al.*, 2002).

After intravenous administration of vitamin K, the INR will start to drop within 2 hours and will be normalized within 12-16 hours (Lubetsky *et al.*, 2003), whereas after oral administration it will take up to 24 hours to normalize the INR. While low (1-2.5 mg) to moderate (2.5-5 mg) doses of vitamin K given orally are indicated for the management of non-emergency bleeding, slow intravenous infusion of 10 mg vitamin K should be given in emergency situations (Radaelli *et al.*, 2015). Higher doses of vitamin K are equally effective but may induce resistance to VKAs for more than 1 week, and are therefore not recommended (Rubboli *et al.*, 2011).

Specific treatment includes endoscopic treatment in order to locate the site of bleeding and stop the bleeding. Early endoscopy (within 24 hours) for evaluation and therapy in patients with active GIB is both warranted and safe (Abraham and Castillo, 2013). The most common etiologies for upper GI blood loss in these patients are peptic ulcer disease and erosive diseases of the esophagus, stomach, and duodenum. Diverticular bleeding is the most common cause of lower GI bleeding (Acosta *et al.*, 2016).

Considering the recognized benefits of early endoscopy in acute upper GI bleeding, various authors have recommended that endoscopy should not be postponed to correct coagulopathy in patients with an INR ≤2.5 (Barkun *et al.*, 2010). Rockall score assessment can be used to identify 15% of all cases with acute upper gastrointestinal haemorrhage at the time of presentation and 26% of cases after endoscopy who are at low risk of rebleeding and negligible risk of death who might therefore be considered for early discharge or outpatient treatment with consequent resource savings (Rockall *et al.*, 1996).

In those with chronic liver disease, administration of infusion octreotide or somatostatin are also important. In patients whose bleeding cannot be stop by endoscopic intervention, they might require emergency surgery, or catheter angiography with embolization by intervention radiologist. Colonoscopy is recommended for patients with hematochezia and a negative upper endoscopy unless other source of bleeding have been identified (John R Saltzman, 2018).

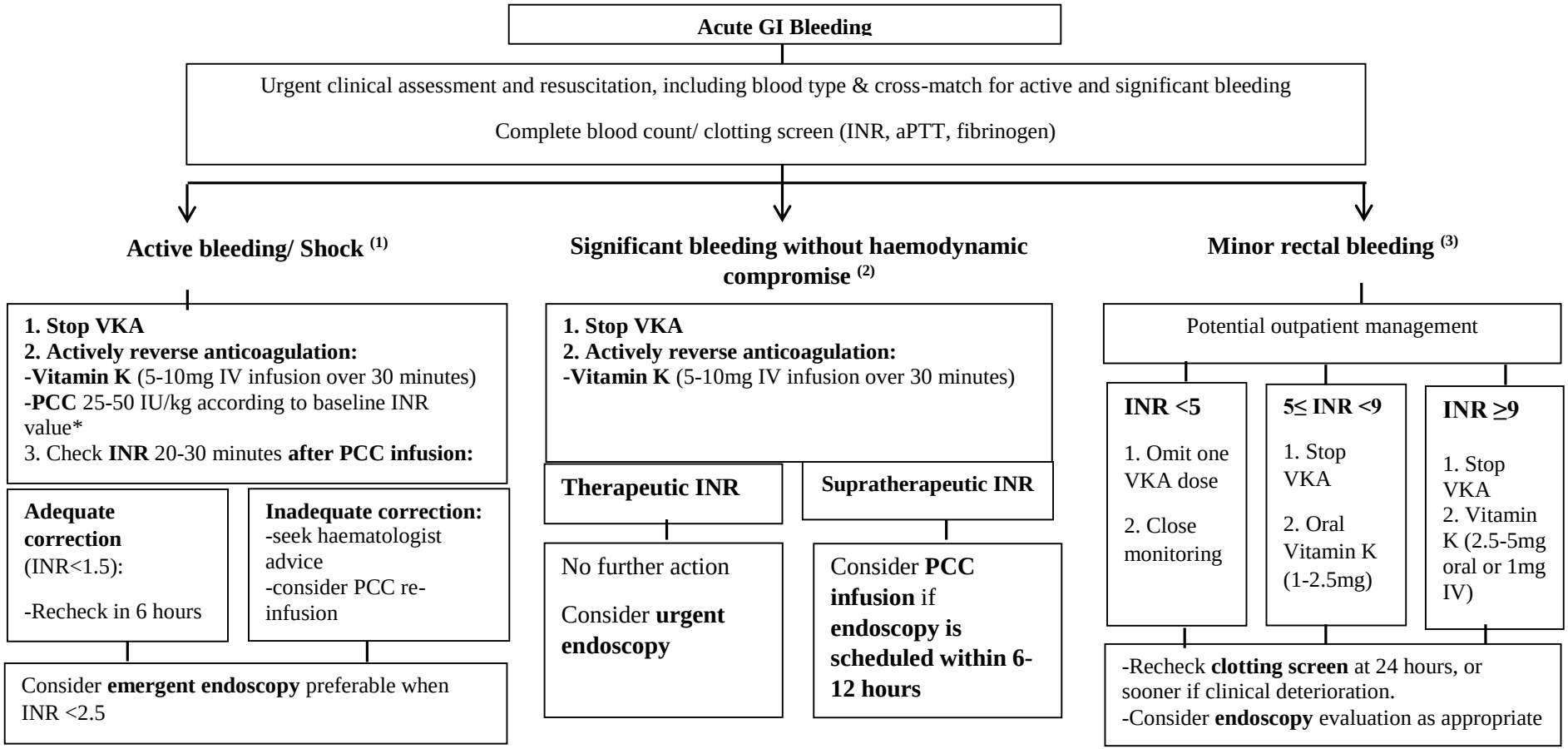

Figure 4: Management algorithm for acute GIB on vitamin K antagonists aPTT, activated partial thromboplastin time; PCC, prothombin complex concentrate; INR, international normalized ratio; IU, international unit. *Administer 15 mL/kg FFP only if PPC is unavailable. (1) Overt acute GI bleeding (haematemesis, maelena, haematochezia), with shock or persistent/intermittent haemodynamic instability. (2) Overt acute GI bleeding but no haemodynamic compromise. (3) Scanty, self-limited haematochezia, with neither anaemia nor haemodynamic compromise.
Adapted from Management of anticoagulation in patients with acute GIB, Digestive and Liver Disease (2015) (Radaelli *et al.*, 2015).

1.4.5 Outcome Following Gastrointestinal Bleeding In Patients Taking Oral Anticoagulants

In Pourafkari et al. (2017), patients with AF on anticoagulant had hospital mortality of 9.8% with upper GIB. Older age and previous history of peptic ulcer disease were the predictors of upper GIB in patients with excessive warfarin anticoagulation. (Pourafkari *et al.*, 2017) According to Manatsathit et al., mortality rates are much lower, 3.8% with mean INR level of 2.54 was (±0.3) (Manatsathit *et al.*, 2014). Mortality rates are higher in patients with recurrent GIB and supratherapeutic INR level (≥4.0) (Rubin *et al.*, 2003).

In those AF patients with GIB and restarted on warfarin, the outcomes were stratified by duration of warfarin interruption, restarting warfarin after 7 days was not associated with increased risk of GIB but was associated with decreased risk of mortality and thromboembolism compared with resuming after 30 days of interruption. Decision to restart warfarin after an episode of major GIB is associated with improved survival and decreased thromboembolism without increased risk of GIB after 7 days of interruption (Qureshi *et al.*, 2014). Anticoagulation is often stopped after the acute bleeding event, but restarting anticoagulation at discharge after the index event was associated with fewer thromboembolic events without a significantly increased risk of recurrent gastrointestinal haemorrhage at 90 days (Sengupta *et al.*, 2015).

1.4.6 Resuming anticoagulant following GIB

The main parameters to take into consideration when restarting anticoagulant are the risk of recurrent bleeding and the thromboembolic disease of the underlying disease for which anticoagulant was prescribed before the bleeding event. In fact, American Society for Gastrointestinal Endoscopy (ASGE) proposed the re-initiation of

anticoagulant if the thromboembolic risk exceed the risk of recurrent bleeding. This means that every case should be individualised and a common decision among the gastroenterologist and cardiologist should be reached, based on the history and indications for each particular patient (Anderson *et al.*, 2009).

The risk of recurrent bleeding could not be predicted with accuracy. If endoscopy findings of peptic ulcers with clean based, the risk can be as low as less than 5% as compared to those with signs of recent haemorrhage stigmata, recurrence may be as high as 55% (Elmunzer *et al.*, 2008). Several scoring system has been proposed to calculate the gastrointestinal re-bleeding risk (e.g Blatchford, Rockall and Baylor College). According Laursen et al. they found that Glasgow Blatchford Score (GBS) accurately identifies patients with upper GIB most likely to need hospital-based intervention and also best suited for outpatient care. No scoring system seems to accurately predict patients' 30-day mortality or rebleeding (Laursen *et al.*, 2012). Both GBS and Rockall score are illustrated in table 6 and 7.

Apart from that, the decision to resume anticoagulant also depends on patients' thrombotic risk as a result of anticoagulant discontinuation. Based on CHA_2DS_2 VASc score the stroke risk is as high as >9% in those with score of ≥6. According to Chatree et al., the thromboembolic event occurred in 9.9% of those who resume warfarin compared to 16.4% who did not. Recurrent GIB occurred in 10.1% resuming warfarin compared to 5.5% who did not. Resumption of warfarin leads to significant reduction in mortality (Chai-Adisaksopha *et al.*, 2015).