Rivaroxaban新適應症:非瓣膜性心房顫動患者預防中風及全身性栓塞

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一、前言

抗凝血藥物rivaroxaban為高口服生體可用率高選擇性直接凝血因子Xa抑制劑(factor xa inhibitor)，我國健保局在2009年核可rivaroxaban 10mg tablet (xarelto)用於靜脈血栓高危險群(曾發生有症狀之靜脈血栓症)病患，以預防其於接受下肢重大骨科手術後之靜脈血栓栓塞症。隨著之後大型研究的進展，美國FDA在2011年11月4日通過核准rivaroxaban適用於非瓣膜性心房顫動患者中風之預防。我國健保局也自2013年2月1日起，給付rivaroxaban用於非瓣膜性心房顫動(non-valvular atrial fibrillation)且有下列至少一項風險因子(風險因子：心衰竭，高血壓，年齡大於等於75 歲，糖尿病，曾發生腦中風或短暫性腦缺血發作)的成人病患，預防中風及全身性栓塞(systemic embolism)。傳統上warfarin 是預防心房顫動病人發生缺血性中風的標準治療，但warfarin在使用上有諸多不便，例如眾多的食物藥物交互作用、個體基因體差異、病患順從性、需頻繁監測..等等，使得維持warfarin 在治療範圍內且避免出血成為一大挑戰，rivaroxaban此類不同機轉抗凝血劑的出現是否為心房顫動患者中風之預防帶來更多好處?本文將介紹rivaroxaban，及其用於非瓣膜性心房顫動患者中風之預防的討論。

二、Rivaroxaban藥物機轉與藥物動力學

凝血因子x經由內生性和外生性路徑活化成凝血因子Xa(Factor Xa)，並且在血液凝集的凝血連鎖反應扮演重要的角色，rivaroxaban可直接結合活化的凝血因子Xa以及凝血因子Xa和prothrombinase所形成的複合物，抑制其催化prothrombin(凝血因子Ⅱ)活化的功能截斷血液凝集的梯瀑式作用以達到抗凝血的效用。

rivaroxaban具有高生體可用率(80-100%)。口服錠劑後2~4小時，rivaroxaban可被迅速吸收而達到最高血中濃度，rivaroxaban 抑制凝血酶(thrombin)生成的作用具有濃度依賴性，在30mg的範圍內維持著強烈的線性抑制關係。血中蛋白結合率為92-95%。(1)

代謝與排除部分，大約三分之二的藥物經由肝臟代謝，其餘三分之一的藥物以原型化合物直接經由腎臟排泄在尿中。rivaroxaban會被CYP 3A4、CYP 2J2和非CYP之酵素代謝，再經由腎臟或糞便排除。原型的rivaroxaban為人體血漿中主要活性成分，在人體內無活性循環代謝物。藥物在健康年輕受試者的半衰期約5至9個小時，而健康老年受試者的半衰期約11至13個小時，年長病患的血漿濃度高於年輕病患，主要導因為整體及腎臟清除率降低所致。rivaroxaban在性別、種族(高加索人、美籍非洲人、西班牙人、日本人或中國病患)並無顯著差異，在極端體重(<50公斤與>120公斤)對rivaroxaban血漿濃度僅有些微影響(少於25%)。

rivaroxaban用於非瓣膜性心房顫動患者中風之預防劑量為每日一次15至20毫克，於中度腎功能不全（肌酸酐清除率30-50ml/min)的病患，建議劑量為每天一次15毫克。少數臨床資料顯示rivaroxaban在嚴重腎功能受損(CrCl：< 30 - 15 ml/min)或中度肝功能受損(Child pugh B) 族群中血漿濃度顯著增加，因此不建議使用rivaroxaban在嚴重腎功能受損或中度以上肝功能受損的病患。

三、交互作用

rivaroxaban經由肝臟cyp450代謝且為p-glycoprotein的受質，與同時具有強效CYP 3A4 和p-glycoprotein抑制劑併用，可能會同時降低肝臟和腎臟的清除率而顯著增加血中濃度。這類型的藥包含azole antimycotics 及HIV protease inhibitor(例如ketoconazole 或 ritonavir)，因此同時接受azole-antimycotics或HIV protease inhibitor全身性治療的病患，除了fluconazole 被認為對rivaroxaban的血中濃度影響較小，在緊密監控下可以合併使用，其餘皆不建議併用rivaroxaban。

在可能潛在影響凝血功能藥物或血小板抑制劑與rivaroxaban併用研究方面 (2) (3)，aspirin與NSAIDS類藥物並不會顯著影響rivaroxaban抑制凝血因子Xa的活性作用與延長PT、aPTT時間，但會延長出血時間，目前並無足夠證據證實併用可能潛在影響凝血功能藥物或血小板抑制劑是安全可行的，病患若併用此類藥物，應加強注意。

四、臨床研究

關於rivaroxaban用於非瓣膜性心房顫動中風預防的研究中(4)，在2011年在NEJM刊登了一篇雙盲、隨機的大型跨國研究rocket AF study(試驗設計見表一)，

收納14264名CHADS2 score ≥ 2心房顫動患者(CHADS2 score見表二)，結果顯示使用rivaroxaban 患者的中風或全身性栓塞的發生率不劣於 warfarin (1.7 versus 2.2 percent per year; hazard ratio:0.79, 95% CI 0.66-0.96 in the per-protocol as-treated analysis)。在整體出血率方面，Rivaroxaban 與 warfarin兩組並無顯著差異 (14.9 versus 14.5 percent per year, respectively)，但在發生顱內出血 (intracranial hemorrhage) 的比例 rivaroxaban 明顯低於 warfarin (0.5 versus 0.7 and 0.2 versus 0.5 events per 100 patient-years, respectively)。

五、討論

rivaroxaban 與 warfarin 相比，rivaroxaban在非瓣膜性心房顫動患者預防中風的效果並不劣於warfarin，rivaroxaban 在出血安全性的比較上，雖然總出血率並無顯著差異，但rivaroxaban優勢在於顱內出血發生率低於warfarin。另外rivaroxaban食物和藥物交互作用少，一日一次的頻次可增加患者順從性，血中濃度穩定不需定期作血中濃度監測等也為rivaroxaban之優點，但也因為缺乏可監測指標，無法精確地監測藥物療效，也沒有有效的拮抗藥物。此外藥物價格與健保給付條件亦為醫師臨床使用的考量。雖然rivaroxaban與warfarin相比有其優勢，但長期的療效和安全性仍需後續的上市後監測與研究。

表一:ROCKET AF study 試驗設計[4]	
試驗設計	Double-blind RCT
病人數	N =14236
試驗假設	Test the non-inferiority of Rivaroxaban compared with adjusted-dose warfarin
治療組	Rivaroxaban 20mg daily or 15 mg daily
對照組	Adjusted-dose warfarin：dose adjusted to a target INR of 2.5(治療區間2~3)
試驗期間	14~48個月
病人納入條件	CHADS2 score ≥ 2，平均年齡71歲，60%為男性，
主要評估指標	Primary efficacy end point:發生中風(ischemic or hemorrhagic)及全身性栓塞的比例 Priciple safety end point:發生主要及非主要臨床相關出血的比例
評估指標結果	

Table 2. Primary End Point of Stroke or Systemic Embolism.*

Study Population	Rivaroxaban			Warfarin			Hazard Ratio (95% CI)†	P Value	
	No. of Patients	No. of Events	Event Rate no./100 patient-yr	No. of Patients	No. of Events	Event Rate no./100 patient-yr		Noninferiority	Superiority
Per-protocol, as-treated population‡	6958	188	1.7	7004	241	2.2	0.79 (0.66–0.96)	<0.001	
Safety, as-treated population	7061	189	1.7	7082	243	2.2	0.79 (0.65–0.95)		0.02
Intention-to-treat population§	7081	269	2.1	7090	306	2.4	0.88 (0.75–1.03)	<0.001	0.12
During treatment		188	1.7		240	2.2	0.79 (0.66–0.96)		0.02
After discontinuation		81	4.7		66	4.3	1.10 (0.79–1.52)		0.58

* The median follow-up period was 590 days for the per-protocol, as-treated population during treatment; 590 days for the safety, as-treated population during treatment; and 707 days for the intention-to-treat population.
† Hazard ratios are for the rivaroxaban group as compared with the warfarin group.
‡ The primary analysis was performed in the as-treated, per-protocol population during treatment.
§ Follow-up in the intention-to-treat population continued until notification of study termination.

Table 3. Rates of Bleeding Events.*

Variable	Rivaroxaban (N=7111)		Warfarin (N=7125)		Hazard Ratio (95% CI)†	P Value‡
	Events no. (%)	Event Rate no./100 patient-yr	Events no. (%)	Event Rate no./100 patient-yr		
Principal safety end point: major and nonmajor clinically relevant bleeding§	1475 (20.7)	14.9	1449 (20.3)	14.5	1.03 (0.96–1.11)	0.44
Major bleeding						
Any	395 (5.6)	3.6	386 (5.4)	3.4	1.04 (0.90–1.20)	0.58
Decrease in hemoglobin ≥2 g/dl	305 (4.3)	2.8	254 (3.6)	2.3	1.22 (1.03–1.44)	0.02
Transfusion	183 (2.6)	1.6	149 (2.1)	1.3	1.25 (1.01–1.55)	0.04
Critical bleeding¶	91 (1.3)	0.8	133 (1.9)	1.2	0.69 (0.53–0.91)	0.007
Fatal bleeding	27 (0.4)	0.2	55 (0.8)	0.5	0.50 (0.31–0.79)	0.003
Intracranial hemorrhage	55 (0.8)	0.5	84 (1.2)	0.7	0.67 (0.47–0.93)	0.02
Nonmajor clinically relevant bleeding	1185 (16.7)	11.8	1151 (16.2)	11.4	1.04 (0.96–1.13)	0.35

* All analyses of rates of bleeding are based on the first event in the safety population during treatment.
† Hazard ratios are for the rivaroxaban group as compared with the warfarin group and were calculated with the use of Cox proportional-hazards models with the study group as a covariate.
‡ Two-sided P values are for superiority in the rivaroxaban group as compared with the warfarin group.
§ Minimal bleeding events were not included in the principal safety end point.
¶ Bleeding events were considered to be critical if they occurred in intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular (with compartment syndrome), or retroperitoneal sites.

表二: CHADS2 Index[9]

CHADS2 score, thromboembolic risk, and effect of warfarin anticoagulation

Clinical parameter	Points
Congestive heart failure (any history)	1
Hypertension (prior history)	1
Age ≥75 years	1
Diabetes mellitus	1
Secondary prevention in patients with a prior ischemic stroke or a transient ischemic attack; most experts also include patients with a systemic embolic event	2

CHADS2 score	Events per 100 person-years*		NNT
	Warfarin	No warfarin	
0	0.25	0.49	417
1	0.72	1.52	125
2	1.27	2.50	81
3	2.20	5.27	33
4	2.35	6.02	27
5 or 6	4.60	6.88	44

NNT: number needed to treat to prevent one stroke per year with warfarin.
* The CHADS2 score estimates the risk of stroke, which is defined as focal neurologic signs or symptoms that persist for more than 24 hours and that cannot be explained by hemorrhage, trauma, or other factors, or peripheral embolization, which is much less common. Transient ischemic attacks are not included. All differences between warfarin and no warfarin groups are statistically significant except for a trend with a CHADS2 score of 0. Patients are considered to be at low risk with a score of 0, at intermediate risk with a score of 1 or 2, and at high risk with a score ≥3. One exception is that most experts would consider patients with a prior ischemic stroke, transient ischemic attack, or systemic embolic event to be at high risk even if they had no other risk factors and therefore a score of 2. However, the great majority of these patients have some other risk factor and a score of at least 3.
Data from: Go AS, Hylek EM, Chang Y, et al. JAMA 2003; 290:2685; and CHADS2 score from Gage BF, Waterman AD, Shannon W. JAMA 2001; 285:2864.

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