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原　著

Warfarin 在亞洲族群之治療目標準則

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摘　要

目的：透過文獻回顧及臨床實務經驗，建立適用亞洲人族群的 warfarin 使用準則，以提供臨床醫師與藥師在 warfarin 劑量調整的依據。

方法：依據文獻回顧彙整資料，經臨床專科醫師與藥師共同擬訂各適應症適當的 INR 治療範圍，以及依據 INR 檢測結果之 warfarin 劑量調整原則，並經過專家委員會同意後制訂。

結果：制訂適用於亞洲人族群之 warfarin 使用準則，內容涵蓋：一、其適應症之建議 INR 目標與治療期間；二、起始劑量的決定；三、門診與住院病人維持劑量的調整建議；四、INR 監測頻率建議；五、藥品交互作用的處置。

結論：本準則可提供國人 warfarin 使用的治療目標及劑量調整依據，但仍須前瞻性試驗評估其適切性。

關鍵詞：Warfarin，國際標準化凝血酶原時間比值 (INR)，劑量，亞洲族群

引言

Warfarin 是臨床上最常使用的抗凝血劑之一，廣泛地用於心房纖維顫動病人、心臟瓣膜置換病人栓塞的預防、深層靜脈栓塞與肺栓塞的治療等。Warfarin 的療效與血中濃度關聯不大，臨床上藉由監測國際標準化凝血酶原時間比值 (International Normalized Ratio, INR) 做為劑量調整的依據 [1]。研究顯示，當 INR 高於 1.8，即能顯著減少栓塞的併發症，但當 INR 高於 3.5，出血的風險將大幅增加 [2]。然而，warfarin 所須劑量受到多重因素影響，包括基因、疾病狀態、飲食、並用藥品、中草藥或健康食品等，臨床上劑量調整相當困難，即使嚴密監測，仍是最常造成不良反應與導致病人住院的藥品之一 [3]。亞洲人由於基因的變異，所需的 warfarin 劑量普遍比歐、美與非洲人低 [4]。許多研究顯示，在亞洲族群將 INR 維持在低於國外診療指引的範圍即可有效的預防栓塞並減少出血 [5-19]。臨床上的 warfarin 建議使用準則 (algorithm) 多為針對歐美族群所制定，用於亞洲族群的適切性仍有待討論。擬訂適用於國內族群的 warfarin 治療目標及劑量調整準則，可提供臨床醫師與藥師臨床劑量調整的依據，評估可能影響療效的因子，使病人獲得更好的治療。

方法

藉由 PubMed 資料庫，搜尋亞洲人使用 warfarin 之適當 INR 治療範圍相關研究。以關鍵字 “warfarin and INR and Asian”、“low-intensity warfarin” 或 “low intensity warfarin” 作搜尋。為避免遺漏，另針對東北亞各族群進行文獻搜尋，包括臺灣、日本、韓國、中國與港澳地區。僅納入研究族群大於 100 人、研究族群為東北亞人種、可取得全文文獻者，做為評估擬訂建議 INR 治

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療範圍之參考。經臨床藥師初擬治療目標及劑量調整準則草案，再經心臟內、外科、神經內科等醫師專家審查，透過專科醫師與臨床藥師組成之小組討論後，再提心臟血管小組討論，並經藥事委員會審查，通過後供全院臨床作業遵循。

結果

一、文獻回顧與 INR 治療目標之訂定

透過 PubMed 資料庫，以 “warfarin and INR and Asian” 搜尋取得 77 篇文章，以 “low-intensity warfarin” 搜尋取得 130 篇文章，以 “low intensity warfarin” 搜尋取得 236 篇文章。研究收納病人的 warfarin 適應症以心房纖維顫動或心臟瓣膜置換為主，符合收納病人數 100 人以上條件者共計 12 篇，其研究之適應症、國別、研究期間、型態、收納病人數及其年齡分布、及建議之 INR 目標值等資料彙整如 Table 1 [5-13, 16-17, 19]。

二、訂定 Warfarin 使用準則

準則之訂定主要參考文獻資料，初步擬訂之內容經心臟內、外科，神經內科等醫師專家審查，再經心臟血管用藥小組三次會議討論，整合各方意見及臨床實務作業，最終經藥事委員會作最後討論與決議，訂立全院遵循之準則。

臨床醫師及藥師在進行劑量調整前，仍應對於影響 INR 的因子先進行評估，包括並用藥品、食品、疾病狀態、酒精攝取量、及服藥之順從性等等。

（一）適應症、治療期間、建議 INR 目標值

依據文獻資料，彙整以亞洲人為對象之研究結果，歸納整理，針對各種適應症 warfarin 之建議治療期間及 INR 目標值，擬訂參考準則如 Table 2，除了擬訂適合亞洲族群之相關建議，並提供美國學會或歐、美國家訂定之準則以供參考。

（二）Warfarin 劑量調整準則

所有病人在開始使用 warfarin 前均應檢測 INR 基準值。曾經使用 warfarin 之病人，應先評估可能造成 INR 變化之因子，若無顯著變化，可參考先前之劑量，若有任何可能造成 INR 變化之因子介入，如並用藥品、食品、疾病狀態的改變等等，應重新檢測 INR，並依結果重新調整劑量。

1. 起始劑量

一般起始劑量為每日 2.5 至 5 毫克，但預期可能對 warfarin 敏感之病人，應給予較低的起始劑量，每日 1 至 2.5 毫克。可能對 warfarin 敏感之病人族群詳列如 Table 3 [20]。依據臺灣族群 warfarin 使用之回溯性分析，起始劑量之平均量為每日 3.4 ± 1.4 毫克 [15]。

門診病人依後續 INR 值進行 warfarin 劑量調整，依不同 INR 範圍，給予不同幅度之劑量調整，詳細準則彙整如 Table 4 [20]。建議於服用起始劑量 3 ~ 7 天內監測 INR 值。劑量調整同時可依據病人情況、合併用藥等一併考量，並與醫療團隊成員共同討論後修改。

住院病人同樣依 INR 值進行 warfarin 起始劑量調整，詳細準則彙整如 Table 5 [20]。但建議於服用起始劑量 1 ~ 3 天內監測 INR 值。劑量調整時另須依據病人情況、合併用藥等一併考量，並與醫療團隊成員共同討論後修改。

2. 維持劑量

初期使用 warfarin 之病人，當連續兩次 INR 介於治療目標且劑量穩定時，即可進入維持劑量。連續兩次定義為兩次 INR 數值至少間隔一至二週。維持劑量的調整幅度，不應超過每週或每日劑量的 5 ~ 20% 為原則，以避免 INR 變動幅度過大。對於 INR 數值穩定且介於治療範圍的病人，偶然一次 INR 數值過高或過低，若無法找出可能影響的原因，且變動幅度小於 0.5，可不須調整劑量，但須在一至二週重新監測。維持劑量的調整建議詳見 Table 6 [20]。調整建議可依據病人情況、合併用藥等一併考量，並與醫療團隊成員討論後修改。

（三）INR 監測頻率

使用 warfarin 的病人須定期監測 INR 做為劑量調整的依據，以避免 INR 過高或過低

Table 1. Comparison between studies regarding low-intensity INR in Asian groups [5-13,16,17,19]

Indication	Area	Authors	Study period	Study type	Study size	Age distribution	Suggested INR
Atrial fibrillation							
Atrial fibrillation	Hong Kong	Cheung *et al.* (2005)	2000/01 ~ 2002/06	Retrospective	555	NS	1.5 ~ 3.0
NVAF (≥ 70 years)	Japan	Naganuma *et al.* (2012)	2001/05 ~ 2006/12	Retrospective	845	74 [70,91]	1.5 ~ 2.5
NVAF (50-80 years)	China	Chen *et al.* (2012)	2002/11 ~ 2004/12	Prospective	786	S: 66.8 ± 6.9 L: 68.1 ± 7.0	1.6 ~ 2.5
NVAF with ischemic stroke or TIA (< 80 years)	Japan	Yamaguchi *et al.* (2000)	1994/04 ~ 1998/01	Prospective	115	S: 65.7 ± 6.8 L: 67.6 ± 6.1	1.5 ~ 2.1
NVAF with ischemic stroke (< 80 years)	Japan	Yasaka *et al.* (2001)	NA	Prospective	203	G1: 69.3 ± 7.7 G2: 66.7 ± 6.5	1.6 ~ 2.6
Valve replacement							
Valve replacement	China	Zhuang *et al.* (2004)	1996/07 ~ 1997/12	Retrospective	178	46.32 ± 7.48	1.4 ~ 2.0
Mechanical aortic or mitral valve replacement	Taiwan	Yu *et al.* (2005)	1996 ~ 2001	Retrospective	563	52.8 ± 13.8	INR < 2.0
Valve replacement	China	Liu *et al.* (2010)	2000 ~ 2008	Retrospective	845	46.97 ± 11.93	1.8 ~ 3.0
Valve replacement	China	Haibo *et al.* (2012)	1997 ~ 2002	Retrospective	1508	45.5 ± 12.0	Aortic valve: 1.3 ~ 1.8 Mitral valve, double valve: 1.8 ~ 2.3
Mechanical heart valve replacement	Korea	Yoon *et al.* (2013)	NA	Retrospective	818	NS	Aortic or mitral valve: 2.0 ~ 2.5 Aortic plus mitral valve: 2.1 ~ 2.6 Tricuspid valve: 2.3 ~ 2.8
VTE							
VTE	China	Yang *et al.* (2009)	NA	Prospective	180	NS	2.0 ~ 3.0; Age > 62 year: 2.0 ~ 2.5
Other indications							
Indications with INR target 2.0 ~ 3.0	Hong Kong	You *et al.* (2005)	1999/01-2001/06	Retrospective	491	65.8 ± 14.2	1.8 ~ 2.5

Data was expressed as mean ± standard deviation or median [range] unless specified.
G1, group 1 was the National Cardiovascular Center Non-Valvular Atrial Fibrillation Secondary Prevention study; G2, group 2 was the Japanese Non-Valvular Atrial Fibrillation-Embolism Secondary Prevention Cooperative study; L: low-intensity INR; NA: not available; NS: not specified; NVAF: non-valvular atrial fibrillation; S: standard INR or conventional INR; VTE: venous thromboembolism.

Table 2. Indications of warfarin use, treatment duration and suggested INR

Indication	Treatment duration	Target INR (in Asian)	Target INR (guidelines)
NVAF			
CHADS2[1] score ≥ 1 points	Life-time [23,30-31]	1.8 ~ 3.0	2.0 ~ 3.0 [23,30-31]
Ischemic stroke or TIA[2]	Life-time [23,30-31]	1.6 ~ 2.6	2.0 ~ 3.0 [23,30-31]
Valve replacement			
Mechanical valve			
Aortic valve replacement	Life-time [32-34]	1.5 ~ 3.0	2.0 ~ 3.0 (bileaflet) or 2.5 ~ 3.5[3] [32-34]
Mitral valve replacement	Life-time [32-34]	1.8 ~ 3.0	2.5 ~ 3.5 [32-34]
Aortic valve and mitral valve replacement	Life-time [32-34]	1.8 ~ 3.0	2.5 ~ 3.5 [32-34]
Bioprosthetic valve	3 months [32-34]	1.8 ~ 3.0	2.0 ~ 3.0[4] [32-34]
VTE			
VTE prophylaxis			
Hip or knee arthroplasty Hip fracture surgery	1 ~ 4 weeks, up to 5 weeks [27,35]	1.8 ~ 2.4	2.0 ~ 3.0 [27,35]
Unprovoked VTE			
First episode Transient risk factor	3 months [27,35]	1.8 ~ 2.4	2.0 ~ 3.0 [27,35]
Second episode Pulmonary embolism Proximal DVT without bleeding risk	Life-time [27,35]	1.8 ~ 2.4	2.0 ~ 3.0 [27,35]
VTE with cancer	Life-time or cancer resolved [27,35]	1.8 ~ 2.4	2.0 ~ 3.0 [27,35]

NVAF, non-valvular atrial fibrillation; VTE, venous thromboembolism
[1] CHADS2 risk score is used to stratify thromboembolism risk in patients with atrial fibrillation. However, CHA_2DS_2VASc risk score was recommended in latest guideline from American College of Cardiology / American Heart Association (ACC/AHA) and European Society of Cardiology (ESC).
[2] TIA stands for transient ischemic attack.
[3] According to ACC/AHA practice guideline, INR 2.0 ~ 3.0 was recommended for bileaflet mechanical or Medtronic Hall valves if there is no risk factor. According to American College of Chest Physicians (ACCP), 2.0 ~ 3.0 is recommended for all aortic valve replacement
[4] ACC/AHA: vitamin K antagonist for aortic valve replacement with risk and all mitral valve replacement. ACCP: mitral valve replacement.

Table 3. Patient characteristics for increased warfarin intensity [20]

Age > 75 year	CYP2C9 or VKORC1 polymorphism
Congestive heart failure	Post operation
Hyperthyroidism	Decreased oral intake or feeding
End stage renal disease	Malnutrition
Febrile	Hypoalbuminemia
Impaired liver function	Diarrhea
Malignancy	Drug-drug interactions
	Increased baseline INR

VKORC1: vitamin K oxide reductase complex.

Table 4. Initial dose of warfarin in outpatients [20]

Initial dose (mg/day)		Increased sensitivity to warfarin	General population
		1.0 ~ 2.5 mg	2.5 ~ 5.0 mg
Monitor INR after 3 ~ 7 days			
Target INR 1.8 ~ 2.4	Target INR 1.8 ~ 3.0		
< 1.3	< 1.3	Increase 20 ~ 50% dose	
1.3 ~ 1.7	1.3 ~ 1.7	Maintain current dose or increase 5 ~ 20%	
1.8 ~ 2.4	1.8 ~ 3.0	Maintain current dose or decrease 20 ~ 50%	
2.5 ~ 3.0	3.1 ~ 3.5	Decrease 20 ~ 50% dose	
> 3.0	> 3.5	Discontinue	

Table 5. Initial dose of warfarin in inpatients [20]

	Initial dose (mg/day)		Increased sensitivity to warfarin	General population
			1.0 ~ 2.5 mg	2.5 ~ 5.0 mg
	Monitor INR after 1 ~ 3 days			
	Target INR 1.8 ~ 2.4	Target INR 1.8 ~ 3.0		
Day 2	< 1.3	< 1.3	Maintain current dose	Maintain current dose
	1.3 ~ 1.7	1.3 ~ 1.7	Maintain current dose or decrease 20 ~ 50%	Maintain current dose or decrease 20 ~ 50%
	1.8 ~ 2.1	1.8 ~ 2.5	Decrease 50 ~ 75%	Decrease 20 ~ 50%
	> 2.1	> 2.5	Discontinue	Discontinue
Day 3	< 1.3	< 1.3	Maintain current dose or increase 20 ~ 50%	Maintain current dose or increase 20 ~ 50%
	1.3 ~ 1.7	1.3 ~ 1.7	Maintain current dose	Maintain current dose
	1.8 ~ 2.4	1.8 ~ 3.0	Maintain current dose or decrease 20 ~ 50%	Maintain current dose or decrease 5 ~ 20%
	2.5 ~ 3.0	3.1 ~ 3.5	Discontinue or decrease 50 ~ 75%	Discontinue or decrease 20 ~ 50%
	> 3.0	> 3.5	Discontinue	Discontinue
Day 4	< 1.3	< 1.3	Increase 20 ~ 50% dose	Increase 50 ~ 75% dose
	1.3 ~ 1.7	1.3 ~ 1.7	Maintain current dose or increase 5 ~ 20% dose	Maintain current dose or increase 5 ~ 20% dose
	1.8 ~ 2.4	1.8 ~ 3.0	Maintain current dose or decrease 5 ~ 20% dose	Maintain current dose or decrease 5 ~ 20% dose
	2.5 ~ 3.0	3.1 ~ 3.5	Decrease 20 ~ 50% dose	Decrease 20 ~ 50% dose
	> 3.0	> 3.5	Discontinue	Discontinue
Day 5	< 1.3	< 1.3	Increase 50 ~ 75% dose	Increase 50 ~ 100% dose
	1.3 ~ 1.7	1.3 ~ 1.7	Maintain current dose or increase 20 ~ 50% dose	Increase 20 ~ 50% dose
	1.8 ~ 2.4	1.8 ~ 3.0	Maintain current dose	Maintain current dose
	2.5 ~ 3.0	3.1 ~ 3.5	Decrease 5 ~ 20% dose	Decrease 5 ~ 20% dose
	> 3.0	> 3.5	Discontinue	Discontinue

Table 5. Initial dose of warfarin in inpatients [20] (continued)

≧ Day 6	< 1.3	< 1.3	Increase 75 ~ 100% dose	Increase 100% dose
	1.3 ~ 1.7	1.3 ~ 1.7	Increase 20 ~ 50% dose	Increase 50 ~ 100% dose
	1.8 ~ 2.4	1.8 ~ 3.0	Maintain current dose	Maintain current dose
	2.5 ~ 3.0	3.1 ~ 3.5	Decrease 5 ~ 20% dose	Decrease 5 ~ 20% dose
	> 3.0	> 3.5	Discontinue	Discontinue

Table 6. Maintenance dose of warfarin [20]

Target INR 1.8 ~ 2.4	Target INR 1.8 ~ 3.0	
< 1.3	< 1.3	Increase 10 ~ 20% of maintenance dose. Consider 1 additional maintenance dose.
1.3 ~ 1.5	1.3 ~ 1.5	Increase 5 ~ 15% of maintenance dose.
1.6 ~ 1.7	1.6 ~ 1.7	If the INR was therapeutic for 2 times before this test, unable to find the cause of sub-therapeutic INR, and under agreement with the primary physician, consider maintain current dose. If dose titration is considered, may increase 5 ~ 10% of maintenance dose.
1.8 ~ 2.4	1.8 ~ 3.0	Therapeutic INR
2.5 ~ 2.7	3 ~ 3.2	If the INR was therapeutic for 2 times before this test, unable to find the cause of supra-therapeutic INR, and under agreement with the primary physician, consider maintain current dose. If dose titration is considered, may decrease 5 ~ 10% of maintenance dose.
2.8 ~ 3.0	3.3 ~ 3.5	For patients with risk of bleeding, consider decrease 5 ~ 15% of maintenance dose.
3.0 ~ 3.5	3.5 ~ 4	Stop 1 ~ 3 maintenance doses. Reinitiate with 10 ~ 20% of dose reduction.
> 3.5	> 4	Stop warfarin. Follow up INR after 3 ~ 7 days (3 days is highly suggested). Reinitiate warfarin until the INR decreases to therapeutic range. Maintenance dose should be reduced. Reevaluate patient conditions including current medication, drug adherence, disease status, diet, and alcohol to determine new maintenance dose.

導致的合併症，增加 warfarin 使用的安全性。理想的 INR 監測頻率目前沒有定論，須依據病人 warfarin 使用的期間的長短 (初期使用或維持劑量)、順服性 (門診病人、醫療照護機構或住院病人)、warfarin 劑量調整幅度、疾病狀態、飲食習慣、並用藥品或保健食品以及先前 INR 穩定的程度評估 [20-21]。各診療指引對於 INR 監測頻率的建議有所不同。美國心臟學會 (American College of Caridology/American Heart Association, ACC/AHA) 建議初期使用 warfarin，應至少每週監測 INR，而在 INR 穩定之後，應至少每月監測 [22]。而美國胸腔醫學會 (American College of Chest Physicians, ACCP) 則建議 INR 穩定的病人，可將監測頻率延長至十二週。INR 穩定的定義為三個月內使用相同劑量而不須調整，且 INR 穩定的病人 [1]。本準則監測頻率的建議，依據門診與住院病人有所不同，詳列於 Table 7 [1,20,23]。住院病人若初期使用 warfarin，應密集監測 INR 直至穩定。若門診長期使用 warfarin，即使一向 INR 數值穩定，

住院期間可能因疾病、飲食或藥品使用的改變而導致 INR 變化，建議仍須評估基準值，此後每 3 至 7 天監測 INR。

（四）藥品交互作用的處置

複雜且眾多的藥品交互作用使得臨床上使用 warfarin 更加困難。藥品動力學 (pharmacokinetics) 交互作用是指並用藥品影響 warfarin 的吸收、分布、代謝與排除。Warfarin 有 S 與 R 兩種不同的旋光性 (chirality)，S-warfarin 的抗凝血作用較強，經 CYP2C9 代謝，R-warfarin 的抗凝血作用較弱，經 CYP3A4 代謝，並用可能誘導或抑制這些肝臟酵素的藥物，會影響 warfarin 在體內的濃度導致 INR 不穩，如 azole 類抗黴菌藥物、fluoroquinolone 類抗生素、抗癲癇藥 phenytoin 等。並用與白蛋白結合的比例偏高藥品，會導致 warfarin 被取代而活性增加，如抗癲癇藥 valproate sodium。藥品動態學 (pharmacodynamics) 交互作用指並用藥品具有協同或加成的抗凝血作用，導致 warfarin 的療效增加，如非類固醇類消炎止痛劑 (non-steroidal

Table 7. Frequency of INR testing [1,20,23]

	INR change	Frequency of INR testing
Outpatients		
Stable warfarin dose	Stable and therapeutic INR without dose adjustment for at least 3 months	Every 12 weeks
	Stable and therapeutic INR without dose adjustment for less than 3 months	Every 4 weeks
	Previous stable and therapeutic INR without dose adjustment. Current INR testing is out of range and the change is < 0.5.	No dose adjustment. Follow up in 1 ~ 2 weeks
Unstable warfarin dose	Previous unstable INR. Current INR testing is out of range.	Dose adjustment. Follow up in 1 ~ 2 weeks
	Any dose adjustment regardless of previous INR	Follow up in 1 ~ 2 weeks
Initiate or discontinue any medication, health supplements or herb with interactions with warfarin.		Dose adjustment if necessary. (Refer to Table 8).
Significant change in disease status or diet.		Follow up in 1 ~ 2 weeks or less. (Refer to Table 8).
Inpatients		
New starter		
Initiation dose	Before INR reaches therapeutic range	After the second or the third dose, monitor every day or every other day.
Stable warfarin dose	Two consecutive INR are at goal.	Every 3 ~ 5 days
	INR at goal for 1 week without dose adjustment	Every week
	INR at goal for 2 weeks without dose adjustment	Every 2 weeks
	INR at goal for 4 weeks without dose adjustment	Every 4 weeks
Long-term warfarin use		Baseline INR on admission.
Not initiate or discontinue any medication, health supplements or herb with interactions with warfarin.		Every 1 ~ 2 weeks
No significant change in disease status or diet.		Every 1 ~ 2 weeks
Initiate or discontinue any medication, health supplements or herb with interactions with warfarin.		Refer to inpatient with stable warfarin dose.
Significant change in disease status or diet.		Every 3 ~ 5 days then adjust according to the change of INR.

anti-inflammatory drugs, NSAID)、抗血小板製劑 aspirin、clopidogrel 等。抗生素可能影響腸道負責合成維生素 K 的菌叢，導致與 warfarin 的交互作用，但臨床上的影響因人而異。Table 8 整理 Micromedex 資料庫中文獻程度為良好以上 (good)、交互作用程度為主要 (major) 且臨床上較容易與 warfarin 並用之藥品 [24]。須注意每個病人對於藥品交互作用的反應不同，且臨床上仍存在文獻較少或交互作用機轉不明的藥品，因此對於藥品改變的病人，除須透過資料庫檢索是否存在可能的交互作用，還須擬定嚴謹的 INR 監測計畫以避免藥品治療的併發症。Table 9 整理 Micromedex 資料庫中文獻程度為良好以上 (good)、交互作用程度為主要 (major) 且臨床上較容易與 warfarin 並用之食品、中草藥與健康食品。食品方面，以固定量攝取為原則。中草藥與健康食品方面，不建議病人並用，若病人堅持，則以不超過文獻建議之成分含量為原則 [27]。

討論

近年來，隨著新一代口服抗凝血劑的上市，抗凝血劑的治療有了嶄新的契機。新一代抗凝血劑如 dabigatran、rivaroxaban 與 apixaban 作用精準，直接抑制凝血酶 (thrombin) 或第十凝血因子，預防栓塞的效果與 warfarin 相當，且顯著減少出血性中風的發生率。然而，新一代抗凝血劑的臨床使用有其限制，在特殊族群，如腎功能不全、心臟瓣膜置換病人等，warfarin 仍有其不可取代的地位 [23]。

Warfarin 的個體反應差異大，且治療範圍狹窄，臨床上劑量決定相當困難。此外，warfarin 須透過抑制肝臟第二、七、九、十凝血因子的合成，以達到抗凝血的作用，而各個凝血因子半衰期從 8 小時至 72 小時不等，因此達到穩定的抗凝血作用須 3 天到一個星期 [25]。若病人代謝 warfarin 的能力偏低，達到穩定效果的時間可能更長。最適切的 warfarin 劑量決定方式目前尚無定論。臨床上較常使用的方式是給予病人族群的平均維持劑量，而後依據 INR 調整。然而若病人所須的劑量偏離平均值甚遠，此方法會延長病人 INR 穩定所須的時間 [26]。針對某些須立即發揮抗凝血作用的病人，如深層靜脈栓塞或肺栓塞，因此須延長肝素的銜接治療的期間 [27]。給予病人 warfarin 速效劑量 (loading dose)，固然使較高比例的病人 INR 在第 5 天達到治療目標，但年長病人所須的劑量似乎偏低，且研究族群非亞洲人，5 毫克或 10 毫克的速效劑量未必適當 [28]。

基因是影響 warfarin 維持劑量的重要因素之一。與 warfarin 最相關連的基因變異是 CYP2C9 與 VKORC1 (vitamin K epoxide reductase complex subunit-1)。CYP2C9 的變異使 warfarin 代謝減緩，這個變異在亞洲人比例相當低。VKORC1 是 warfarin 作用的標的，負責體內將維生素 K 還原，使肝臟得以合成凝血因子。VKORC1 變異的患者對 warfarin 相當敏感，亞洲人百分之九十以上至少攜帶一個變異基因，也是亞洲族群需要較低 warfarin 劑量的原因 [26]。許多研究試圖利用回歸型分析建立藥品基因學的 warfarin 劑量預測模式。目前最大型的是 Kimmel et al. 於 2013 年發表，評估基因與臨床因子建立的 warfarin 劑量預測模式的成效，結果顯示兩者並無差異，然而此研究也非以亞洲族群為對象 [29]。針對亞洲族群的研究，人數較少，且沒有一定的結論。由於基因型的決定須要較長的時間，且對於劑量預測的效果沒有定論，因此目前的治療準則並沒有常規建議 [1]。

考慮給予病人平均的 warfarin 劑量，因缺乏疾病狀態的評估，可能延長病人達到理想抗凝血效果的時間，而基因型態的決定，在臨床上使用較不易普及，因此擬訂本準則做為病人治療目標及 warfarin 劑量調整的依據。本準則的建立，參照亞洲族群的文獻回顧，遵循國外診療指引，並彙集專家意見，以增加準則的可信度。然而，仍須前瞻性的研究以評估本準則的適用性。臨床上決定 warfarin 劑量時，藥師須評估並用藥品、食品、疾病狀態、酒精攝取量、及服藥之順從性等做為依據，以使病人達到更適切的治療。

Table 8. Drug interactions with warfarin [24]

Drug[1]		Warning	Severity/ Document	Onset	Mechanism	Management
Anti-platelet drug	Aspirin	↑ bleeding	M/E	Delayed	Antiplatelet agent	Avoid combination if possible. Decrease INR goal by 0.5 and closely monitor INR and bleeding.
NSAIDs	Naproxen	↑ bleeding	M/E	Delayed	Inhibit platelet aggregation	Monitor INR and gastrointestinal bleeding. Higher risk for non-COX selective NSAID.
	Celecoxib	↑ bleeding	M/G	5 ~ 7 days	CYP2C9 competition	Monitor INR, especially first few days.
Antiarrhythmic drugs	Amiodarone	↑ bleeding and hyperthyroidism	M/E	In 7 days[2]	↓ warfarin metabolism	Intensive INR monitoring for 12 weeks. Consider↓33 ~ 50% of warfarin dose. For long-term warfarin user, ↓35 ~ 65%.
	Dronedarone	↑ bleeding	M/G	In 7 days	Unknown	Monitor INR in 1 week after concurrent use or in 2 weeks after dose adjustment.
	Propafenone	↑ bleeding	M/G	Delayed	↓ warfarin clearance	Closely INR monitoring.
Drugs for dyslipidemia	Simvastatin	↑ bleeding and rhabdomyolysis	M/E	7 ~ 28 days	CYP3A4 competition	Closely INR monitoring.
	Fenofibrate	↑ bleeding	M/G	> 2 weeks	Unknown.	More frequently INR monitoring. ↓30% of warfarin dose.
Azole antifungal agents	Fluconazole	↑ bleeding	M/E	2 ~ 15 days	↓ warfarin metabolism	Closely INR monitoring.
	Voriconazole	↑ bleeding	M/G	Unspecified	CYP2C9 inhibition	Closely INR monitoring.
Quinolones	Levofloxacin	↑ bleeding	M/E	2 ~ 8 days	Unknown.	Monitor INR and bleeding.
	Moxifloxacin	↑ bleeding	M/E	1 ~ 7 days	Unknown.	Monitor INR and bleeding. Consider alternatives.
	Ciprofloxacin	↑ bleeding (high risk for elderly)	M/G	3 ~ 4 days	Unknown.	Closely INR monitoring.
Sulfa drugs	Sulfamethoxazole	↑ bleeding	M/E	2 ~ 15 days	↓ metabolism, protein displacement, change in gut flora	Closely INR monitoring. Consider↓10 ~ 20% of warfarin dose
	Metronidazole	↑ bleeding	M/G	Delayed	↓ warfarin metabolism	Closely INR monitoring, Monitor bleeding.
Anti-depressants	Escitazopram	↑ bleeding	M/G	Unspecified	Unknown.	Closely INR monitoring, Monitor bleeding.
	Fluoxetine	↑ bleeding	M/G	Delayed	CYP2C9 inhibition. Protein displacement	Closely INR monitoring, Monitor bleeding.
	Paroxetine	↑ bleeding	M/G	Delayed	Unknown.	Closely INR monitoring, Monitor bleeding.
	Sertraline	↑ bleeding	M/G	Delayed	Unknown.	Closely INR monitoring, Monitor bleeding.
	venlafaxine	↑ bleeding	M/G	Unspecified	Additive adverse effect	Closely INR monitoring, Monitor bleeding.

Table 8. Drug interactions with warfarin [24] (continued)

Drug[1]		Warning	Severity/ Document	Onset	Mechanism	Management
Anti-neoplastic drugs	Tamoxifen	↑ bleeding	C/G	3 ~ 14 days	Unknown. CYP2C9 inhibition	Lower dose. Consistent INR monitoring.
	5-FU	↑ bleeding	M/E	< 15 days	↓ CYP2C9 synthesis	Closely INR monitoring.
	capecitabine	↑ bleeding	M/E	Days to months	↓ CYP2C9 synthesis	Closely INR monitoring.
Others	Benzbromarone	↑ bleeding	Mo/E	Delayed	CYP2C9 inhibition.	Closely INR monitoring. ↓ 30% warfarin dose.

[1] Drug interactions with severity higher than "major" and documentation level higher than "excellent" are listed.
[2] The effect on INR recovers after 1 ~ 3 months of amiodarone discontinuation.
C: contraindicated; COX: cyclooxygenase; E: excellent: G: good; INR: international normalized ratio; NSAID: non-steroidal anti-inflammatory drugs; M: major; Mo: moderate.

Table 9. Drug food, drug herb or drug health supplements interactions with warfarin

	Warning	Severity/Document	Onset	Mechanism	Management
Cranberry juice	↑ bleeding	M/G	Delayed	Unknown	Conflicting data. Avoid drinking large amount of cranberry juice with warfarin.
Fish oil	↑ bleeding	M/G	Delayed	Inhibit platelet aggregation	Monitor INR and bleeding signs and symptoms after initiation or adjustment in fish oil. The dose of fish oil should not exceed 1gram per day.
Garlic (extract)	↑ bleeding	M/G	Delayed	Additive anticoagulant effect	Concurrent use is not recommended. Small amount of ingestion in food is not a concern. Monitor bleeding signs and symptoms.
Ginkgo	↑ bleeding	M/G	Delayed	Inhibit platelet aggregation	Avoid concurrent use.
Pomegranate	↑ bleeding	M/G	Not specified	Inhibit warfarin metabolism	Avoid concurrent use.
St. John's wort	↓ anticoagulant effectiveness	M/G	Delayed	Induce warfarin metabolism	Concurrent use is not recommended. Monitor decrease in anticoagulant efficacy.
Tan-Shen (丹參)	↑ bleeding	M/G	Delayed	Increase bioactivity of warfarin	Avoid concurrent use regardless of dosage form.
Vitamin K containing food	↓ anticoagulant effectiveness	Mo/E	Delayed	Altered absorption Direct antagonism of warfarin	Take warfarin consistently in relation to meals. Avoid large change in dietary consumption of foods containing high vitamin K.

E: excellent: G: good; INR: international normalized ratio; M: major; Mo: moderate.

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Warfarin Dosing Algorithm: Specific INR Goal for Asian Population

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ABSTRACT

Object: Several studies showed that in Asian population, low-intensity INR reduced the risk of bleeding whereas preserved the efficacy of preventing thromboembolism. The purpose of this study is to develop an Asian-specific warfarin dosing algorithm.

Methods: Previous reports concerning low-intensity INR were carefully reviewed to determine appropriate INR target for Asian population. Healthcare practitioners and clinical pharmacists with related expertise were enrolled to develop the dosing algorithm. The draft of algorithm was reviewed and approved by the Pharmacy and Therapeutic committee.

Results: The Asian-specific warfarin dosing algorithm was composed of (1) therapeutic INR target and duration of treatment per indication; (2) initiation dose for warfarin; (3) guides for dose adjustment in inpatient and outpatient; (4) recommended frequency of INR monitoring; and (5) management for drug-drug interaction.

Conclusions: The development of Asian-specific warfarin dosing algorithm can help increasing the efficacy and safety of warfarin utilization. Further prospective study is required to validate this algorithm.

Key words: Warfarin, INR, Dosing, Asian

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