台灣中風醫誌

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台灣中風醫誌

目　錄

第1卷 第1期 2019年6月

創刊號主編

鄭建興

指 引

綜 說

原著論文

個案報告

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Contents

主 編 的 話

台灣腦中風學會自1994年5月起持續有學會的會訊出刊，提供會員一個很好抒發個人的研究興趣、觀點、感想、經驗與意見等的交流平台，累積了許多精彩、務實的中風相關文章。近10年在林慧娟醫師的主持帶領下，加上幾位年輕熱忱的醫師編輯共同努力，會訊一直能保持很好的水準，還引介了不少篇臨床研究方法學的基本功及相關課題。

為了進一步提升本學會的學術與教育目的、能更好的保存文章，並增加能見度與被引用的機會，將會訊轉型為雜誌與電子期刊是有需要的，鄰近的日、韓、大陸都已經有自己本土與國際腦中風雜誌雙軌進行，台灣腦中風學會確實需要調整與趕上。期刊名稱經本會理監事認可為「Formosan Journal of Stroke台灣中風醫誌」，預計1年4期編輯，第1期於2019年6月出刊。期刊保留原先會訊的精神，與中風醫學相關之學術論著：包括指引、綜論、原著、病例報告、專題報導或其他報告，均歡迎來稿刊載，特別是期待年輕醫師磨練投稿。醫誌由本人為主編，邀請林慧娟、陳志弘、李怡慧等醫師為副主編，執行編輯包括陳右緯、宋昇峰、蔡力凱、謝鎮陽、周中興、陳柏霖、湯頌君、鍾芷萍、宋碧姍、李孟等醫師，學會的理監事們為編委會。

要經營好醫學期刊並不容易，在尚無SCI或PubMed光環加持下更是不易吸引原著論文，除了每期刊載的中風指引，希望能多提供綜論與病例報告，期待對於中風預防、治療、研究有興趣的醫界同好們共同努力耕耘。

主編 鄭建興

2019年6月

指 引

2019台灣腦中風學會急性缺血中風靜脈血栓溶解治療指引

陳志弘[1]、謝函潔[1]、宋昇峯[2]、謝鎮陽[3]、陳柏霖[4]、蔡力凱[5]、黃虹瑜[6]、鄭建興[5]、急性缺血中風靜脈血栓溶解治療指引共識小組

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[2]嘉義基督教醫院神經內科
[3]台南新樓醫院神經內科
[4]台中榮總神經科
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1. 前　　言

缺血性腦中風是目前台灣最常見的腦中風型態，此源於腦部血管的阻塞，最常見的原因包括於心臟中產生栓子、或頭頸部或腦部的血管硬化造成阻塞。腦組織在急性缺血情形之下，很快即受破壞而死亡，由於缺乏有效治療方法，早期只能著重於預防腦中風再發生；直至血栓溶解藥品(例如 recombinant tissue-type plasminogen activator; rt-PA)被成功開發，且經過美國國家神經及中風疾病研究院(NINDS)臨床試驗[1]發現(Class I; Level of Evidence A)，在急性缺血性腦中風發生3小時內，沒有禁忌情況之下，予以靜脈注射血栓溶解劑rt-PA，可有效提升腦中風患者神經功能之恢復率。雖然接受rt-PA治療之患者發生腦出血的比例稍多，但死亡率並無明顯增加。此研究結果大幅度改變這些年來急性缺血性腦中風的治療方式，然而，由於此治療伴隨著腦出血增加的風險，許多國家也根據相關的研究訂定指引(包含符合條件和排除條件)。此藥物於1996年和2002年被美國食品暨藥物管理局與歐盟正式核准上市，可使用在發生於3小時內的缺血性腦中風患者，我國亦於2002年核准使用，台灣腦中風學會於2008年初次訂定此藥物之使用指引。隨著後續許多關於rt-PA之研究發表，包含探討腦中風發作3至4.5小時內以及年齡大於80歲之患者是否適合接受治療，歐盟之治療指引已經隨之修正，台灣腦中風學會於2013年針對這兩項議題，修訂了治療指引。

由於靜脈注射血栓溶解劑治療有其風險，各國主管機關針對此藥物之仿單，皆條列眾多之禁忌症，然而在仿單所列之藥物使用禁忌症中，部分並未具備實證醫學之證據[2]，因此導致臨床實際治療患者時之困境。血栓溶解劑的禁忌症，基本上是根據臨床試驗的排除條件所制定[1]，當時認為這些禁忌症可能會增加症狀性腦出血之風險，而違反某些治療準則的確與症狀性腦出血的增加相關，例如治療前過高之血壓[3]。但是，並非所有的禁忌症在實際臨床經驗中皆會導致症狀性腦出血風險的增加。在國外一些針對仿單核准適應症外使用血栓溶解劑之觀察性研究當中，並未發現這一群病患發生症狀性腦出血風險有明顯增加[4-8]，而針對華人的觀察性研究，也並未發現這群患者有明顯增加症狀性腦出血風險[9, 10]。當然這些研究的結果並不表示所有的禁忌症都可以一視同仁，根據最新一項觀察性研究顯示，這些禁忌症是否會增

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加症狀性腦出血之風險，會因為症狀性腦出血之定義不同而有不同的結果[11]。除此之外，還必須考慮在某些患者可能有合併兩種以上之禁忌症，這種情況是否對腦出血風險有加成之作用，目前並不確定[12]。

美國食品暨藥物管理局於2015年修訂了血栓溶解劑之藥物仿單[13]，所根據之理由，並非基於藥物治療之新發現或新事證[14]，而是為了讓血栓溶解劑之藥物仿單上所呈現之資訊，能符合該國仿單標示之規範[15]，以提供清楚而簡潔之內容供臨床人員參考。在此新的仿單中，將血栓溶解劑之禁忌症與警示清楚的呈現，所謂禁忌症指的是現有證據清楚指出治療的風險高於益處，而警示指的是有合理的證據顯示使用本藥物可能與藥物不良事件有關。不過，在此新的仿單中，靜脈注射血栓溶解劑仍僅限使用於腦中風發作3小時內之患者[13]。歐盟的藥物仿單雖然已放寬治療時間至腦中風發作4.5小時內，但是對於年齡大於80歲之患者，仍屬於禁忌症[16]。

由於現存仿單與治療指引對於適應症與禁忌症之載明有所出入，導致許多臨床人員在治療急性缺血性腦中風患者時，為了遵循仿單規範之禁忌症，採取了適應症範圍較為限縮的治療策略，以致於有部分腦中風患者並未接受靜脈注射血栓溶解劑。根據一項最新的研究[17]，若是將美國仿單中關於時間的限制放寬至4.5小時，或是將歐盟仿單中關於年齡大於80歲之限制取消，與採用現行仿單之規範來比較的話，除了可接受治療之患者數目增加之外，治療一樣能顯著增加患者恢復到功能幾乎正常之機會，同時在中風後90天時之存活率也是相當的。

靜脈注射血栓溶解劑在我國已核准使用多年，雖然藥物仿單於民國107年有小幅度之修訂，但仿單上之禁忌症，相較於美國與歐盟之規範仍較為嚴格，因此與目前國外及本國之治療指引有相當明顯之出入。根據2002年當時我國衛生署之衛署醫字第0910014830號函，藥物於仿單核准適應症外使用時，必須基於治療疾病的需要以及符合醫學原理及臨床藥理。治療時應據實告知患者，且不得違反藥品使用當時已知的、具公信力的醫學文獻。因此，為了使國內醫師於治療缺血性腦中風患者時有所依循，同時基於醫療人權和社會倫理，台灣腦中風學會召集專家群，一同研討與撰寫更新版本之指引，作為臨床應用上的參考。

2. 中風發作超過3小時急性缺血中風靜脈注射rt-PA治療

2013至2018年間，針對發作3至4.5小時急性缺血性腦中風患者靜脈注射rt-PA治療，雖無新的隨機分配、安慰劑控制之臨床試驗結果發表，但有數篇高品質之統合分析研究，以及歐洲、美國大規模的登錄研究報告，可以提供臨床證據之更新。

首先，是STT (Stroke Thrombolysis Trialists' collaborative group)團隊整理過去全球9個靜脈注射rt-PA臨床試驗，共6,756筆個別患者資料的統合分析[21]，其中有2,812位患者是發作3-4.5小時(1,375位被分到rt-PA組，1,437位被分到控制組)，分析顯示rt-PA組復原良好至modified Rankin Scale (mRS) 0-1分的比例較高(35.3%比30.1%；OR [95% CI]：1.26 [1.05-1.51])。進一步分析顯示[22]，與發作3小時內的患者相較，發作3-4.5小時的患者使用rt-PA，並不會增加SICH的風險(SITS-MOST定義之SICH；發作3小時內較控制組增加之機率 [95% CI]：3.1% [1.7-5.2]；發作3-4.5小時較控制組增加之機率 [95% CI]：3.0% [1.6-5.0])。

根據2013年之美國心臟學會與美國中風學會指引[23]，針對發作3-4.5小時的急性缺血性腦中風患者靜脈注射rt-PA，是依照ECASS-III的收案條件，排除年齡大於80歲、使用口服抗凝血劑、起始NIHSS分數大於25分、影像學檢查顯示中風範圍超過1/3以上的中大腦動脈灌流區域、或先前已有中風及糖尿病病史之患者[24]；

而歐洲腦中風學會的指引[25]，針對發作3-4.5小時患者，則沒有大於80歲的年齡限制。在藥政主管機關的處方建議方面，美國食品暨藥物管理局迄今仍未開放rt-PA於發作3-4.5小時使用[26]，歐盟則於2012年開放rt-PA於發作3-4.5小時使用，惟仍限80歲以下患者[16]。

針對美國、歐盟兩地藥品仿單資訊的差異[16, 26]，STT團隊再度使用上述個別患者資料做統合分析[27]，結果顯示若美國仿單放寬至時間限制到4.5小時，或是歐盟仿單放寬80歲的年齡限制，SICH的風險均沒有增加，復原良好(mRS 0-1分)的勝算比與遵照原美國或歐盟仿單條件的患者族群相比，結果沒有統計上顯著的差異。

除了統合分析，另有幾個大型的中風登錄資料研究結果可供參考。首先是美國GWTG-Stroke資料庫中[28]，共有65,384位接受靜脈注射rt-PA的患者，其中11,559位患者是發作3-4.5小時內接受治療，與發作3小時內使用的患者相比，經校正年齡、中風嚴重度等許多變項之後，發作3-4.5小時內這組患者，其出院時復原良好(mRS 0-1分)的比例較低，SICH與住院中死亡的風險較高。另一個在歐洲的SITS-ISTR資料庫中[29]，有14,240位年齡大於80歲的急性缺血性腦中風患者，在發作4.5小時內接受rt-PA的治療，若針對其中8,353位完全符合年齡以外其他歐盟仿單條件的患者再進行分析(6,278位是發作3小時內，2,075位是發作3-4.5小時)，經校正重要干擾因子後，3-4.5小時組的三個月後復原良好(mRS 0-1分)比例仍較低(OR [95% CI]：0.79 [0.68-0.92])，SICH風險較高(SITS-MOST定義之SICH，OR [95% CI]：1.62 [1.12-2.34])，但三個月內死亡的風險無統計上之顯著差異(OR [95% CI]：1.10 [0.95-1.28])。

2013年台灣腦中風學會修訂血栓溶解治療指引時，對於發作3-4.5小時患者，亦建議參考ECASS III的收案條件；而2014年另一篇GWTG-Stroke資料庫的研究顯示，在4,910位發作3-4.5小時並接受rt-PA治療的患者當中，有31.5%違反了ECASS III的收案條件，但其SICH與住院期間死亡等不良結果的風險並未增加[30]。因此，2018年美國心臟學會與中風學會指引亦作出修正，針對發作3-4.5小時的患者，若又有年齡大於80歲、過去有腦中風合併糖尿病史、過去有使用warfarin但INR ≤ 1.7，其治療建議等級有較正向提高，但對於NIHSS > 25分者，仍需審慎評估治療風險效益後，再決定是否施打[19]。

台灣在2018年有一個針對發作3-4.5小時的rt-PA臨床試驗，由16家醫院提供過去10年的個案，共374名接受發作3-4.5小時的rt-PA治療病人，與對照組比較，三個月後復原良好(mRS 0-1分)比例明顯較多(OR [95% CI]：1.75 [1.27-2.42])，SICH風險稍高些(NINDS定義之SICH，OR [95% CI]：1.96 [0.93-4.13])，三個月內死亡的風險無統計上之顯著差異(OR [95% CI]：1.04 [0.61-1.78])[31]。目前我國食品藥物管理署正在考慮放寬rt-PA於急性缺血性腦中風發作3-4.5小時使用之適應症[32]。

另考量最近急性腦中風治療理念，已逐漸由time-based移到tissue-based[19]，針對發作3-4.5小時之族群，符合適應症者可使用靜脈注射rt-PA，若因有排除條件而未能符合適應症者(例如：NIHSS > 25分)，亦可考慮參與其他事先使用影像篩選之血栓溶解藥物臨床試驗[33]，或是考慮跳過靜脈血栓溶解，直接進入動脈內取栓，特別是那些經灌流顯影掃描檢查後，仍有存活腦組織的大血管阻塞之患者。2018年發表的WAKE-UP試驗，針對254位中風發生時間不確定病人，以MRI的DWI已經有高強度信號但FLAIR尚無高強度信號，可能代表中風發生時間尚在4.5小時內，rt-PA治療組較對照組，三個月後復原良好(mRS 0-1分)比例明顯較多(OR [95% CI]：1.62 [1.17-2.23])，SICH風險稍高些(2%比0.4%，OR [95% CI]：4.95 [0.57-42.87])[34]。

最新發表的EXTEND (EXtending the time for Thrombolysis in Emergency Neurological

Deficits)試驗是針對急性腦缺血中風發生後4.5-9小時(若病人是醒來時發現中風則加上最後正常入睡時間至清醒時間的1/2)內給予靜脈注射rt-PA，病人以CT或MRI影灌流影像評估是否納入，若符合還有相當範圍的腦組織是缺血而尚未壞死，以RAPID影像分析軟體自動判讀，包括缺血對壞死區域比值>1.2、缺血較壞死區域>10毫升、壞死區域<70毫升。共225位病人參與試驗， rt-PA治療組較對照組，三個月後復原良好(mRS 0-1分)比例明顯較多(OR [95% CI]：1.44 [1.01-2.06]，P=0.04)，SICH風險稍高些(6.2%比0.9%，OR [95% CI]：7.22 [0.97-53.5]，P=0.05)[35]。這試驗可能對於未來急性腦缺血中風使用靜脈注射rt-PA有很大影響，經過適當的灌流顯影選擇合適的病人，可以將治療時間窗明顯延長。

建議：

1. 急性缺血性腦中風的患者符合靜脈注射rt-PA治療規範，且年齡≦80歲、未使用口服抗凝血劑、NIHSS分數≦25分、影像學檢查未顯示中風範圍超過中大腦動脈灌流區域1/3以上、未同時有先前中風及糖尿病病史者，可考慮於發生3-4.5小時內接受rt-PA治療(Class I，Level of Evidence B-R)。
2. 急性缺血性腦中風的患者符合靜脈注射rt-PA治療規範，若年齡>80歲、或正使用口服抗凝血劑warfarin而INR<1.7、或同時有先前中風及糖尿病病史者，可考慮於發生3-4.5小時內接受rt-PA治療(Class IIa, Level of Evidence B-NR)。
3. 急性缺血性腦中風的患者符合靜脈注射rt-PA治療規範，若符合灌流影像有相當多的腦組織缺血但尚未壞死，可考慮於發生4.5-9小時內接受rt-PA治療(Class IIb, Level of Evidence B-R)。

3. 年齡大於80歲之急性缺血中風患者靜脈注射rt-PA治療

最近5年，針對年齡大於80歲急性缺血性腦中風患者靜脈注射rt-PA治療，雖無新的隨機分配、安慰劑控制之臨床試驗結果發表，但有幾篇高品質之統合分析研究報告，可提供臨床證據之更新。

首先，是實證醫學權威機構：Cochrane系統回顧與統合分析報告[36]，該報告顯示，年齡大於80歲或18-80歲的急性缺血性腦中風患者，在3小時內靜脈注射rt-PA，其治療效果相當。而STT團隊使用個別患者資料(individual patient data)之統合分析研究亦顯示，年齡大於80歲與否，並不會改變在急性缺血性腦中風患者靜脈注射rt-PA的效益(mRS 0-1；大於80歲，OR [95% CI]：1.56 [1.17-2.08]； 18-80歲，OR [95% CI]：1.25 [1.10-1.42])[21]；而且使用於年齡大於80歲的患者，也不會增加施打之後症狀性腦出血的風險(SITS-MOST定義之SICH；大於80歲，SICH較控制組增加之機率[95% CI]：3.1% [1.7%-5.3%]；18-80歲，增加機率[95% CI]：3.3 [1.8-5.6])[22]。儘管年齡大於80歲是預後不良的因素，和年齡18-80歲間接受rt-PA的患者相較，有較高的死亡率、症狀性腦出血的發生率和預後不良的比例，但是和同樣大於80歲的患者相比，有無使用rt-PA並不會顯著增加患者風險[22]。

根據2018年美國心臟學會與中風學會指引[19]，急性缺血性腦中風患者靜脈注射rt-PA並無80歲之年齡上限，歐洲[25]、日本[20]與澳洲[37]之中風學會指引則強調在80歲以上患者，須謹慎使用。而在藥政主管機關的處方建議方面，美國食品暨藥物管理局並無80歲之年齡限制[26]，日本提到針對年齡81歲以上患者須謹慎給藥[20]，歐盟則未核准80歲以上患者使用rt-PA[16]。我國食品藥物管理署亦在2016年將「年齡超過八十歲」從「禁忌症」改為「警語」[38]，而藥品仿單也因此於2017年10月修改，將「年齡超過八十歲」從禁忌症中刪除[33]。在食品藥物管理署修正相關治療規定之後，「年齡大於80歲」應不該再被視為rt-PA治療的單一排除因素，實

務上還需整體考量其他的臨床條件，包含到院治療時間、患者的健康狀態、家屬或患者接受治療之意願強度、以及其他排除條件(例如其他任何可能會增加出血風險的狀況...等)。

關於rt-PA的劑量問題，根據Taiwan Thrombolytic Therapy for Acute Ischemic Stroke study (TTT-AIS)的觀察性研究，在我國年長患者使用標準劑量(0.9 mg/kg)之rt-PA可能會增加症狀性腦出血風險[39]；進一步研究發現，71-80歲以上病患使用較低劑量(0.6 mg/kg) rt-PA，預後可能比較好[40]。隨後ENCHANTED臨床試驗發現，低劑量(0.6 mg/kg) rt-PA在≥65歲或<65歲均無法達到不劣性試驗終點(non-inferiority trial endpoint)[41]；而ENCHANTED進一步的次分析所使用的rt-PA劑量(0.6 mg/kg或0.9 mg/kg)並不影響不同年齡層患者之治療成效[42]。總結目前針對此劑量議題尚未達到共識，仍存有許多爭議，需要更多的研究來解答；而根據目前我國食品藥物管理署的最新建議，rt-PA仍維持標準劑量(0.9 mg/kg)，但在仿單中註明上述TTT-AIS與ENCHANTED的研究結果，供臨床使用時參考[33]。

建議：

1. 使用靜脈注射rt-PA於年齡18-80歲或大於80歲之急性缺血性腦中風患者，均提供在三個月後神經功能改善之可能性；「年齡大於80歲」不應單獨成為排除rt-PA治療的指標，而應綜合其他指標做整體評估後，謹慎使用(Class I, Level of Evidence A)。

   註：上述之其他指標包含到院治療時間、患者的健康狀態、家屬或患者接受治療之意願強度、以及其他排除條件(例如其他任何可能會增加出血風險的狀況...等)。

4. 輕微或迅速改善之急性缺血中風患者靜脈注射rt-PA治療

雖然NIHSS被廣泛接受為評估中風嚴重度的標準量表，但NINDS靜脈溶栓治療試驗的收案標準是患者必須有清楚的發作時間及可以NIHSS測得的神經學缺失[(1)]，例如語言障礙、運動功能不良、眼睛運動障礙或視野缺失等，就可以納入試驗，而不是僅以NIHSS總分為判斷是否執行靜脈血栓溶解治療的唯一標準；雖然排除條件包含所謂的輕微或迅速改善的腦中風，但當時操作手冊所定義的輕微中風是指只有感覺異常、或僅有共濟失調(ataxia)的症狀，或NIHSS中的肢體運動總分為1分者，而不是普遍認定的NIHSS < 4。2005年美國食品暨藥物管理局核定的alteplase仿單不建議該藥物使用於輕微或迅速改善的患者，此點成為患者被排除於靜脈血栓溶解劑治療的最常見原因之一[43, 44]，研究發現大約有三分之一的急性缺血性腦中風患者因被判定為輕度或快速改善而沒有接受靜脈血栓溶解劑治療[43, 45]，但其中NIHSS≤4分的患者，約15-35%出院時無法獨立移動或回家[43, 46]，且因症狀輕微或迅速改善而沒有接受靜脈血栓溶解劑的急性缺血性腦中風患者，在第3個月時約有15-29%的患者出現顯著失能[43, 47]，因此輕微或迅速改善的急性缺血性腦中風仍有惡化或失能的風險，而且除了運動功能障礙外，輕微或迅速改善的腦中風也可能導致認知障礙或憂鬱[48]，而這些認知徵候是無法以NIHSS分數呈現的。

過去針對輕微或迅速改善的急性缺血性腦中風的靜脈血栓溶解劑的研究結果分歧，部分研究顯示靜脈血栓溶解劑治療無法改善這些患者的預後[49, 50]，但也有研究分析指出，接受靜脈血栓溶解劑治療的患者有較好的預後[51, 52]，因此如何挑選可能受益於靜脈血栓溶解治療的患者是很重要的，NINDS試驗研究團隊曾針對5種失能定義下的輕微急性缺血性腦中風患者進行事後分析[53]，發現靜脈血栓溶解治療可以顯著改善預後，於第3個月有良好預後的勝算為沒有接受靜脈血栓溶解治療者的2倍；澳洲的一項登錄研究也顯示[54]，輕微急性缺血性腦中風(NIHSS ≤ 5)的患者如接受靜脈血栓溶解劑治

療，相較於沒有接受治療的患者，有1.5倍的機會預後良好。法國的一項登錄研究顯示[55]，接受靜脈血栓溶解劑治療的輕微急性缺血性腦中風(NIHSS≤4)的患者中，約有40%合併有該區腦灌流大動脈阻塞；另有神經影像學的研究指出[56]，輕微或迅速改善的急性缺血性腦中風患者如合併有該區腦灌流大動脈阻塞，會有較高的惡化風險。反之，輕微急性缺血性腦中風患者的腦部影像如合併有半影區(penumbra)[57]，則靜脈血栓溶解劑治療可顯著改善預後；中國的一項登錄研究也指出[58]，輕微急性缺血性腦中風(NIHSS≤5)分類為大血管粥狀硬化分型的患者，靜脈血栓溶解劑治療可顯著改善預後。而且輕微急性缺血性腦中風相較於重度缺血性腦中風的患者，接受靜脈血栓溶解劑後發生症狀性腦出血的機會較低，大約0-2%[12, 59]。2018年美國心臟學會與中風學會的治療指引則指出急性缺血性腦中風不論年紀或中風嚴重度，只要有失能的患者，如無其他禁忌症，應該於發病後3小時內施打靜脈血栓溶解劑(Class I; Level of Evidence A)[19]；迅速改善的腦中風患者有可能持續惡化並且導致失能[60, 61]，NINDS試驗排除迅速改善的腦中風是為了避免於暫時性腦缺血的患者使用靜脈血栓溶解劑[62]，因此患者只要有NIHSS可以測得的神經學缺失，且未改善至無失能的狀況，就是NINDS試驗的受試者，因此迅速改善的腦中風患者如仍有可能導致失能的症狀，仍然可以考慮靜脈血栓溶解劑治療；The Re-Examining Acute Eligibility for Thrombolysis (TREAT) Task Force建議以下情況應視為失能：(1)視野偏盲，(2)失語症，(3)忽視症狀，(4)肢體力量無法抵抗重力，(5) NIHSS > 5分，(6)或醫師認為中風症狀可能導致失能[62]。至於迅速改善至輕微且沒有失能情況、或沒有腦灌流大動脈阻塞的急性缺血性腦中風患者，則必須由醫師針對患者的個別情況衡量好處與壞處，決定是否需施打靜脈血栓溶解劑。至於發作3-4.5小時之間的輕微急性缺血性腦中風患者是否可施打靜脈血栓溶解劑？ECASS III試驗的次分析顯示[63]，NIHSS在0-9分之間的患者，雖然3個月的良好預後並不顯著(OR [95% CI]：1.28 [0.84-1.96])，但與較高NIHSS的組別相較，組間良好預後機會的差異並不顯著；在GWTG登錄研究也顯示[64]，NIHSS≤5的患者於中風發作3-4.5小時之間接受靜脈血栓溶解劑的效果與安全性與於發作3小時內接受靜脈血栓溶解劑的患者沒有差別，因此發作3-4.5小時之間的輕微急性缺血性腦中風接受靜脈血栓溶解劑，可能仍有好處。最近剛發表的PRISMS試驗，針對313位輕微急性缺血性腦中風患者(NIHSS≦5)，且判斷無明確失能症狀，在中風發作3小內接受靜脈血栓溶解劑治療，相對以aspirin治療的病人，未能顯著增加3個月的良好功能比例(RD [95% CI]：-1.1% [-9.4%-7.3%])，且SICH較多(RD [95% CI]：3.3% [0.8%-7.4%])[65]。

建議

1. 輕微或迅速改善的急性缺血性腦中風患者，經診治醫師判斷合併有失能狀況，且無禁忌症時，可考慮於腦中風發作3小時內施打靜脈血栓溶解劑(Class IIa; Level of Evidence A)。
2. 輕微或迅速改善的急性缺血性腦中風患者，如未合併有失能狀況，是否施打靜脈血栓溶解劑可由診治醫師衡量整體益處與風險後，再做決定(Class IIb; Level of Evidence C-LD)。

5. 使用抗凝血劑之急性缺血中風患者靜脈注射rt-PA治療

接受抗凝血劑治療的患者，一旦發生急性缺血性腦中風，靜脈注射血栓溶解劑理論上會增加腦出血或全身性出血的機會，因此過去幾個血栓溶解治療的大型臨床試驗為了研究的單純性，皆將接受抗凝血劑治療的患者排除[1, 66]。然而臨床上，這些正接受抗凝血劑治療的患者，常常也正是缺血性腦中風的高危險群(如心房顫動的患者)因此，針對這些患者要如何使用血栓溶解劑，是臨床上常見的重要問題。以下

將分別就傳統口服抗凝血劑(warfarin)、針劑型抗凝血劑(heparin/ low molecular weight heparin)及非維生素K拮抗劑口服抗凝血劑(non-vitamin K antagonist oral anticoagulant; NOAC)的使用患者，其接受腦中風靜脈血栓溶解治療的建議。

5.1 傳統口服抗凝血劑(warfarin)

對於正在使用warfarin的患者，若腦中風發作於3小時內，目前美國心臟學會與中風學會的治療指引建議，當患者的INR ≤ 1.7或PT值低於15秒時，仍可進行靜脈血栓溶解治療[23]。而歐洲腦中風學會的治療指引亦建議患者的INR ≤ 1.7時，可接受靜脈血栓溶解治療[4]。美國GWTG中風登錄資料庫分析，在23,437位接受靜脈血栓溶解治療的患者，1,802名有使用warfarin且INR ≤ 1.7，和未使用warfarin的患者相比，發生症狀性腦出血的風險無統計差異(OR [95% CI]：1.01 [0.82-1.25])[67]，此結果支持目前的治療指引。個別研究多顯示在有使用warfarin的情形下、INR不高時，不會顯著增加症狀性腦出血的風險，但統合分析顯示warfarin的使用仍會增加症狀性腦出血的機會(OR [95% CI]：2.31 [1.15-4.62])[68]。代表若患者正在使用warfarin，即使INR ≤ 1.7，經靜脈施打血栓溶解劑仍需謹慎評估及充分解釋。而針對INR > 1.7的病人，一小型研究顯示，於26位病人施打4因子凝血酶複合濃縮物(4-factor prothrombin complex concentrate)後立即給予rt-PA治療，結果並無任何病患發生症狀性腦出血[69]，此治療策略未來於臨床的應用尚待後續研究確認。

腦中風發作3-4.5小時之間，有使用任何口服抗凝血劑者，則排除於ECASS III臨床試驗[66]，因此目前臨床指引多不建議有使用warfarin之急性缺血性腦中風患者，在發作3-4.5小時內給予血栓溶解治療[23, 67]。但根據美國中風登錄資料庫分析顯示[30]，於2,311位使用warfarin並且接受了經靜脈血栓溶解治療的患者，治療的時間於發作3-4.5小時與3小時之內者相比較，發生症狀性腦出血的比例相近(5.7%比6.8%；p=0.49)。因此，美國中風學會近年有專家提出將腦中風發作3-4.5小時並正使用warfarin的患者之處置建議，調整為若其INR ≤ 1.7時仍可考慮進行經靜脈血栓溶解治療[14]，然而此族群的患者是否的確可使用血栓溶解劑，尚待未來更多研究結果給予建議。

5.2 針劑型抗凝血劑(heparin/low molecular weight heparin)

美國心臟學會與中風學會建議，若中風發作前48小時內患者曾使用heparin，且目前aPTT數值高於正常值上限，則不應施打血栓溶解劑[(23)]；若中風發作前24小時內患者曾使用低分子量肝素(low molecular weight heparin, LMWH)，則不應進行血栓溶解治療[19]。分析使用LMWH對血栓溶解治療影響的研究[70]，於24小時內若有使用LMWH (21名；86%在12-24小時)，和未使用抗凝血劑的患者相較(1,384名)，發生症狀性腦出血的比例顯著較高(14.3%比2.3%；p<0.001)，且死亡率亦較高(8.42倍)。由於LMWH的半衰期約為3-6小時[71]，考量藥物經過4個半衰期後，血液中殘存藥物濃度僅約餘原濃度之5%，因此以24小時內LMWH的使用作為是否進行血栓溶解治療的原則應屬合理。若是為了預防深部靜脈栓塞使用低劑量的LMWH，則不會明顯增加症狀性腦出血風險，SITS-ISTR分析2003至2017年109,291位接受血栓溶解治療病人，1,047 (1.3%)位有使用低劑量的LMWH預防深部靜脈栓塞，症狀性腦出血與死亡風險未增加，3個月良好功能比例也與其他病人相當[72]。

5.3 非維生素K拮抗劑口服抗凝血劑(non-vitamin K antagonist oral anticoagulant; NOAC)

近年來使用NOAC的患者愈來愈多(包括dabigatran、rivaroxaban、apixaban及edoxaban)，一旦這些患者發生急性缺血性腦中風，歐洲中風學會建議[73]，若患者於24 (至

48)小時內有服用NOAC，則不應直接經靜脈施打血栓溶解劑，而應考慮進行動脈內取栓術治療。而美國心臟學會與中風學會亦建議[19]，使用NOAC治療的患者不應接受靜脈血栓溶解治療，除非於過去48小時內並未服用NOAC，或是血液檢查顯示正常的相關凝血指標(如PT/ aPTT/ thrombin time/ factor Xa activity等)。然而使用常規的PT或aPTT來評估NOAC的藥效，偽陰性(false negative)的機會非常高，只有患者在使用dabigatran時，使用thrombin time比較能準確的評估藥效[74]，但thrombin time檢查多無法非常快速的得到結果。而以美國中風登錄資料庫分析顯示[75]，有使用NOAC (n=251)和未使用NOAC的患者相比，於施打血栓溶解劑後，發生症狀性腦出血的相對風險並未較高(OR [95% CI]：0.79 [0.36-1.72])。此外，一個綜合評論分析了過去發表的31位使用NOAC並直接接受靜脈血栓溶解治療的患者[76]，發現症狀性腦出血發生機會為6.5%，雖然此比例和過去大型試驗(6.4%)相較並不算高[1]，但一方面此分析為集合許多個案報告的結果，因而結果可能有所偏差；此外仍然有治療後因嚴重腦內出血而死亡的案例，因此是否未來有機會在慎選患者後，於使用NOAC患者直接進行經靜脈血栓溶解治療，仍需更多經驗來驗證。另外，若患者使用抗凝血劑時接受了動脈內取栓術治療，和無使用抗凝血劑的患者相比，症狀性腦出血(16.7%比8.3%；p=0.13)或3個月死亡率(6.7%比19%；p=0.08)皆無顯著差異[77]，因此若患者因使用了抗凝血劑而不適合接受經靜脈血栓溶解治療，可考慮進行動脈內取栓術治療。

目前dabigatran已有專屬的反轉劑idarucizumab，可在施打5分鐘後即拮抗dabigatran的作用[78]，在大型臨床試驗亦顯示，在使用dabigatran的患者若出現嚴重出血或需進行緊急高風險治療，給予idarucizumab後98%以上的患者可有效反轉dabigatran的作用[79]。於德國的19位案例顯示，使用dabigatran的缺血性腦中風患者，在接受idarucizumab後進行血栓溶解治療，之後完全沒有症狀性出血的案例[80]，而過去包含了48位病患的統合報告亦發現此治療策略是安全的，只有二位患者出現症狀性腦出血[81]。於台灣已有10位病患在接受idarucizumab後進行血栓溶解治療，除了一位病人發生症狀性腦出血外，整體之神經學表現有顯著進步[82, 83]。因此有歐洲專家建議，於使用dabigatran的中風患者，在接受idarucizumab後可考慮經靜脈施行血栓溶解治療[84, 85]。而日本治療指引建議，由於此治療模式的證據目前僅有個案經驗，因此於大血管阻塞的腦梗塞患者，應考慮以執行經動脈血栓移除術為優先考量[81]。

建議：

1. 急性缺血性腦中風發作3小時內，有使用warfarin之患者，若INR ≤ 1.7，可考慮施打血栓溶解劑(Class IIb; Level of Evidence B-NR)。
2. 急性缺血性腦中風發生前48小時內使用heparin之患者，且aPTT高於正常值上限，不建議施打血栓溶解劑(Class III; Level of Evidence C-EO)。
3. 急性缺血性腦中風發生前24小時內使用低分子量肝素(low molecular weight heparin)之患者，不建議施打血栓溶解劑(Class III; Level of Evidence B-NR)。
4. 於急性缺血性腦中風患者，若中風發生前48小時內曾服用非維生素K拮抗劑口服抗凝血劑(NOAC: dabigatran, rivaroxaban, apixaban, edoxaban)，不建議施打血栓溶解劑(Class III; Level of Evidence C-EO)，而此類患者若懷疑有顱內大血管阻塞，可考慮進行動脈內取栓術(Class IIb; Level of Evidence B-NR)。至於針對服用dabigatran的急性缺血性腦中風患者，可考慮使用反轉劑idarucizumab後再施打血栓溶解劑(Class IIb; Level of Evidence C-EO)。

6. 可能或即將進行動脈內取栓術之急性缺血中風患者接受靜脈血栓溶解治療(橋接治療)

自2015年以來，全球發表數篇針對大血管阻塞中風患者的隨機分組臨床試驗，證實橋接治療(動脈內取栓前接受靜脈血栓溶解劑治療，bridging thrombectomy；即靜脈血栓溶解劑rt-PA合併經腦動脈內取栓術Intra-arterial thrombectomy)臨床療效優於單純使用靜脈血栓溶解劑[86-93]。最新2018年美國心臟學會與中風學會建議近端大血管阻塞之腦中風患者，若發病時間於6小時內、NIHSS≧6、腦部電腦斷層分數(Alberta Stroke Program Early CT Score; ASPECTS)≧6，建議可啟動動脈內取栓術治療[19]。

然而進行動脈內取栓術之急性缺血性腦中風患者，目前並無隨機分組臨床試驗證明跳過靜脈血栓溶解劑治療而直接進入動脈內取栓術治療之臨床療效是否更好。靜脈血栓溶解劑治療優點在於可快速啟動再灌流治療，可能在動脈內取栓前打通血管(5-10%)，可能使動脈內取栓術更加容易，或即使動脈內取栓術未能成功打通血管也能持續再灌流治療；然而靜脈注射血栓溶解劑理論上可能增加動脈內取栓術之腦出血風險，並可能延遲轉院或影像到鼠蹊部穿刺時間等缺點。動脈內取栓術雖能有效打通血管與改善預後，但能夠施行動脈內取栓術的醫院較少，同時需要多科人力整合，且準備時間較長，並且仍有可能無法打通血管[94, 95]。美國心臟學會與中風學會目前建議對於大血管阻塞之腦中風患者，若符合靜脈血栓溶解劑治療條件，應該先施打靜脈血栓溶解劑，且不需等待與觀察血栓溶解劑的療效，並可盡早啟動與準備動脈內取栓術治療[19]。

一篇回溯性研究之統合分析顯示[96]，接受橋接治療者，相較於直接進行動脈內取栓治療（未接受靜脈施打血栓溶解劑）者，在發生腦中風三個月後神經功能預後顯著較好(3個月mRS 0-2的OR [95% CI]：1.27 [1.02-1.55])、死亡率較低(OR [95% CI]：0.71 [0.55-0.91])、較少的取栓器械通過次數(OR [95% CI]：2.06 [1.37-3.10])、打通率較高(OR [95% CI]：1.46 [1.09-1.96])，且症狀性腦出血比率並無差異(OR [95% CI]：1.11 [0.69-1.77])。但此篇研究當中直接進行動脈內取栓治療者多為不適合靜脈施打血栓溶解劑的患者，並且存在許多選擇偏差。後續有三篇回溯性研究針對符合靜脈施打血栓溶解劑條件的患者[97-99]，直接進行動脈內取栓術可顯著縮短影像到鼠蹊部穿刺時間，且功能預後、死亡率與出血率相當，並且可能降低內頸動脈阻塞中風的死亡率，但因為決定患者直接取栓的條件並無特定規則，仍具有顯著的選擇偏差。

腦中風患者的神經功能預後和越早開始再灌流治療(包含靜脈血栓溶解劑與動脈內取栓術)有顯著相關。即使是大血管阻塞的病人，及早給予靜脈血栓溶解劑仍明顯有效，包含7個試驗的HERMES (Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials)聯合分析，在601位大血管阻塞的病人僅接受靜脈血栓溶解劑治療，每增加60分鐘時間則mRS為0-2分的機會降低45% (OR [95% CI]：0.55 [0.37-0.81])[100]。然而直接進行動脈內取栓術是否優於橋接治療，尚待未來更多研究結果給予建議。

建議：

1. 疑似或確診大血管阻塞之急性缺血性腦中風患者，可能或將進行動脈內取栓術前，若符合靜脈施打血栓溶解劑條件，可先施打靜脈血栓溶解劑治療(Class IIa; Level of Evidence A)。
2. 疑似或確診大血管阻塞之急性缺血性腦中風患者，開始接受靜脈血栓溶解劑治療時，宜盡快啟動動脈內取栓術之評估與後續治療，不需等待或觀察靜脈血栓溶解劑的療效(Class

IIa; Level of Evidence B-R)。

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附 I：簡寫註解

簡寫	正式名稱
AHA/ASA	American Heart Association/American Stroke Association
BI	Barthel index
CI	confidence interval
ECASS-III	European Cooperative Acute Stroke Study III
ESO	European Stroke Organization
GOS	Glasgow outcome scale
IST	International Stroke Trial
mRS	modified Rankin Scale
NIHSS	National Institutes of Health stroke scale
NINDS	National Institute of Neurological Disorders and Stroke
OR	odds ratio
RD	risk difference
rt-PA	recombinant tissue plasminogen activator
sICH	symptomatic intracerebral hemorrhage
SITS-ISTR	Safe Implementation of Treatments in Stroke- International Stroke Thrombolysis Registry
STT	Stroke Thrombolysis Trialists’ collaborative group
TTT-AIS	Taiwan Thrombolytic Therapy for Acute Ischemic Stroke study

表1　台灣、歐盟、美國與日本仿單禁忌症及美國、日本兩國治療指引之比較

	仿單				治療指引	
準則	台灣	歐洲[16]	美國[13]	日本[18]	美國[19]	日本[20]
症狀發作時間	3 小時*	4.5 小時	3 小時	4.5 小時	4.5 小時	4.5 小時
小於18歲或大於80歲	V (<18歲) W (>80歲)	V	W (高齡)	W (>75歲)	<18	W (≥81歲)
症狀已迅速改善或症狀輕微	V	V	X	X	X	W
臨床評估為嚴重之中風(例如NIHSS > 25)	V	V	X	W (NIHSS >23)	X	W (NIHSS ≥26)
患者正接受口服抗凝血劑，如warfarin sodium	V	V	W	V (INR >1.7)	V (INR >1.7)	V (INR >1.7)
中風發作時併發癲癇	V	V	X	V	X	W
最近 3個月內有中風病史	V	V	X	V	V	V (最近1個月內有中風，不包括暫時性腦缺血)
血糖＜50或＞400 mg/dL	V	V	X	V	X	V
過去曾中風且合併糖尿病	V	V	X	X	X	W
最近3個月內曾患胃腸道潰瘍或食道靜脈曲張出血	V	V	W (近期胃腸道或泌尿道出血)	V (21日內胃腸道或泌尿道出血)	V (21日內胃腸道出血)	V (21日內胃腸道或泌尿道出血)
中樞神經系統損害之病史(腫瘤、血管瘤、顱內或脊柱的手術)	V	V	W (最近3個月內有顱內或脊柱內手術、或嚴重頭部創傷)	V (3個月內)	V (最近3個月內)	V (最近3個月內有嚴重顱內或脊柱創傷或手術)
顱內出血病史	V	V	W (近期顱內出血)	V	V	V (非外傷性顱內出血)

V：禁忌症；W：警示；X：非禁忌症

*：納入條件為症狀發作時間3小時內，但排除條件為症狀發作時間>4.5小時。

表2　AHA/ASA (美國心臟學會與中風學會)證據等級及建議強度認定標準

COR (Class of Recommendation)	Strength
Class I: Strong	Benefit >>> Risk
Class IIa: Moderate	Benefit >> Risk
Class IIb: Weak	Benefit ≧ Risk
Class III: No benefit (Moderate)	Benefit = Risk
Class III: No benefit (Strong)	Risk > Benefit

LOE (Level of evidence)	Quality
Level A	
Level B-R	Randomized
Level B-NR	Nonrandomized
Level C-LD	Limited data
Level C-EO	Expert opinion

表3　施行靜脈血栓溶解治療前的檢核表

	是	否
納入條件(必須均為是)		
年齡≧18歲	□	□
中風發生至施打alteplase藥物時間＜4.5小時	□	□
無顱內出血	□	□
有NIHSS評估	□	□
簽署同意書	□	□
排除條件(必須均為否)		
自發性顱內出血病史	□	□
臨床評估為嚴重中風(例如NIHSS＞25)	□	□
臨床評估為輕微中風(例如NIHSS＜4)，且無合併失能情況	□	□
CT顯示超過1/3中大腦動脈區域腦梗塞	□	□
血壓經治療仍超過185/110 mmHg	□	□
最近3個月有腦梗塞中風	□	□
最近3個月有顱內或脊柱的手術	□	□
最近3個月有嚴重頭部外傷	□	□
最近21天有胃腸道潰瘍或食道靜脈曲張出血	□	□
顱內腫瘤、血管瘤	□	□
心內膜炎	□	□
主動脈剝離	□	□
正接受口服抗凝血劑warfarin，且INR≧1.7	□	□
中風發生前48小時內使用heparin，且aPTT高於正常值上限	□	□
中風發生前24小時內使用低分子量肝素(low molecular weight heparin)	□	□
中風發生前48小時內曾服用非維生素K拮抗劑口服抗凝血劑	□	□
正使用Glycoprotein IIb/IIIa receptor inhibitor	□	□
凝血指數異常，包括血小板＜$10^5/mm^3$、INR＞1.7、aPTT＞40秒、PT＞15秒	□	□
血糖＜50或＞400 mg/dL	□	□
對alteplase過敏	□	□

2019 Taiwan Stroke Society Guideline for Intravenous Thrombolysis in Acute Ischemic Stroke Patients

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ABSTRACT

Intravenous thrombolysis is still one of the most effective therapies for patients with acute ischemic stroke. Recombinant tissue-type plasminogen activator (rt-PA) has been approved for clinical use since 2002 in Taiwan. Previously, Taiwan Stroke Society has published the guidelines of intravenous thrombolysis for acute ischemic stroke patients in 2008 and 2013, respectively. Enhanced effort to increase intravenous rt-PA treatment for acute ischemic stroke patients in Taiwan can be observed, and the rate of treatment reached to 4-5% in recent years. However, the indication and treatment time of intravenous thrombolysis have been expanded recently. To provide the evidence-based recommendations, and standardize intravenous thrombolysis for acute ischemic stroke, the Taiwan Stroke Society Guideline Consensus Group revised the guideline. The guideline contains 5 issues, including intravenous rt-PA treatment for onset to needle time more than 3 hours, age over 80 years, mild or rapidly improving symptoms, pre-stroke use of anticoagulants, and probably endovascular thrombectomy for patients with large vessel occlusion.

Keywords: acute ischemic stroke, guideline, thrombolysis, thrombectomy

綜 說

來源不明之栓塞型中風? ESUS的診斷及處理

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Embolic Stroke of Undetermined Source (ESUS)的定義和診斷

目前廣為使用的缺血性腦中風分類方法，TOAST Classification[1]，是在1993年提出來的，根據病因分類成五種中風亞型，包含：(1) 小動脈疾病，或是lacune，約佔25%；(2) 大動脈粥樣硬化，約佔25%；(3) 原因不明的中風(cryptogenic stroke)，約佔25%；(4) 常見主要風險(major-risk)的心因性栓塞(cardioembolism)，例如來自心房震顫(atrial fibrillation, AF)，約佔20%；(5) 其它少見的特定病因，例如動脈剝離，約佔5%。後來2014年Hart等人[2] 提出一個新分類的名詞，來源不明之栓塞性中風ESUS，類似於原因不明的中風cryptogenic stroke，但強調要有一個更明確的診斷定義。Hart等人[2] 將cryptogenic stroke當中經過標準評估後真正不明病因的部分定義為更清楚的一種中風亞型ESUS，要排除沒有完整評估的中風或者有兩個以上的病因而無法得到結論者(圖1)。ESUS的定義可以方便記為“三不一沒有”，包括(1) 不是小血管堵塞、(2) 不是超過50%的大動脈粥樣狹窄、(3) 不是常見的心因性栓塞(即圖1附註*主要風險的心臟栓塞來源major-risk cardioembolic sources)、以及(4)沒有其他特定少見的病因。Hart等人[2] 建議ESUS需要一套最基本的診斷評估(圖2)，可記為包括“HEAD”的：(1) Head imaging：電腦斷層或是核磁共振來排除小間隙梗塞、(2) EKG：12導程心電圖和24小時連續心電圖，和Echocardiography，經胸壁心臟超音波是首選來排除心因性栓塞，而經食道心臟超音波並非必要選項、(3) Arterial imaging：進行頸部動脈超音波以及穿顱都卜勒超音波，或是磁振血管攝影，電腦斷層血管攝影，或是導管血管攝影來排除顱內外的大動脈粥樣硬化、(4) Differential diagnosis：排除其它特定病因的中風，例如高凝血狀態的疾病等[3]。鑑別診斷其它特定病因的中風需要進一步評估，包含動脈剝離、感染相關的血管炎、毛毛樣血管疾病(Moyamoya disease)、自體免疫疾病、偏頭痛、血管痙攣、遺傳性的顯性大腦動脈病變合併皮質下中風與腦白質病變(Cerebral autosomal dominant arteriopathy with subcortical infarct and leukoencephalopathy, CADASIL)和法布瑞氏症等[4]。高凝血狀態則有動脈栓塞及靜脈栓塞等等(圖3)。更進階的檢驗例如血液標誌物或是遺傳基因檢測等，雖然不是診斷ESUS的必要要求，但是了解病人的病因永遠都是精準治療的前提[3]。

來源不明之栓塞性中風ESUS的可能潛在的栓塞來源包含心臟、異常來源和大血管來源(詳見後述)[2]。心臟來源[5] 包含隱蔽未被發現的陣發型心房震顫(covert paroxysmal AF)，或是心臟結構的缺陷例如卵圓孔閉鎖不全patent foramen ovale，或者心房中隔缺損，當病人的

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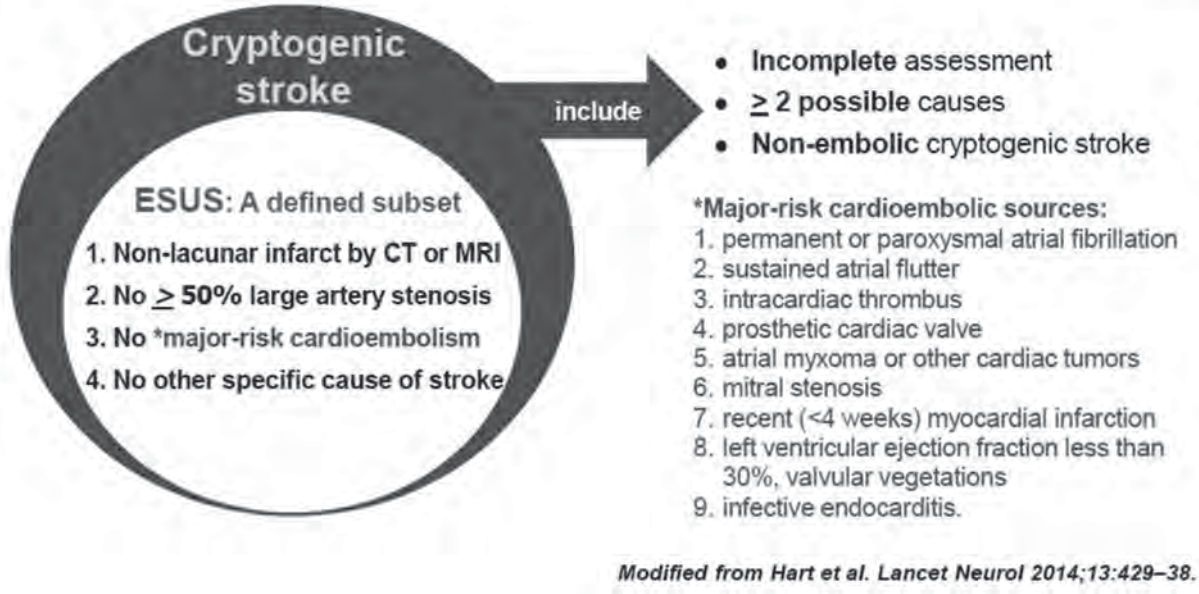
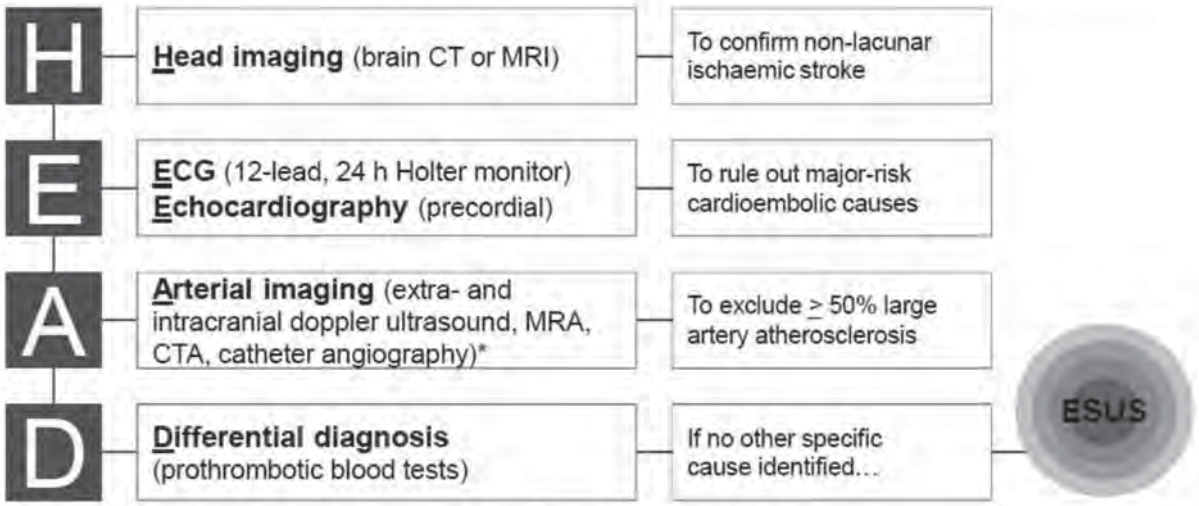
DOI: 10.6318/FJS.201906_1(1).0002

圖1、ESUS的定義



Modified from Hart et al. Lancet Neurol 2014;13:429–38.

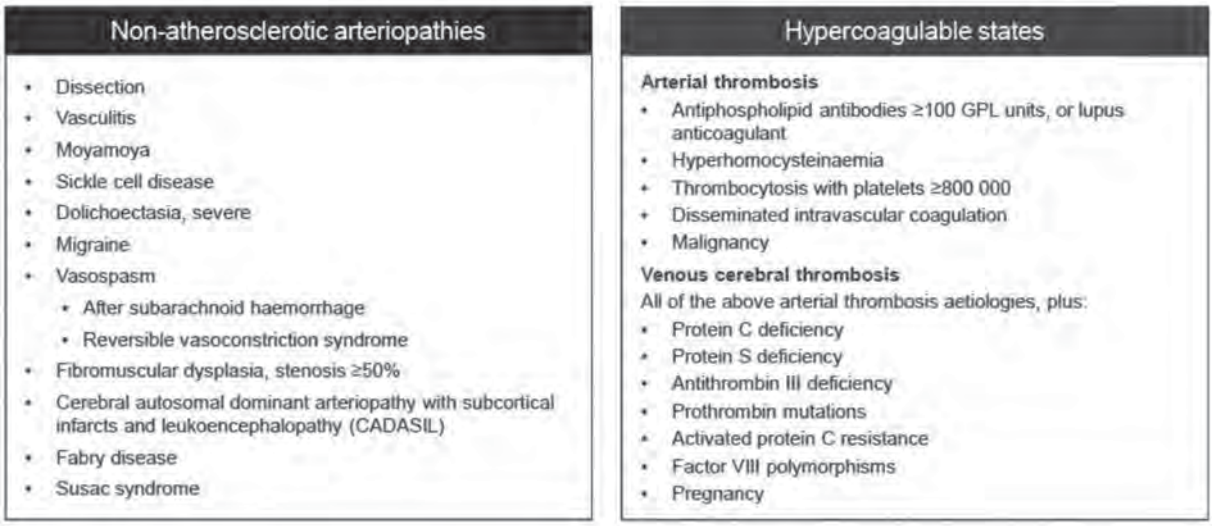
圖2、ESUS需要基本的診斷標準



Imaging of aortic arch or transoesophageal echocardiogram (TEE) is not required

Modified from Hart et al. Lancet Neurol 2014;13:429–38.

圖3、鑑別診斷其他特定病因的中風 (但進階評估非診斷ESUS的必要條件)



Adapted from Saver. N Engl J Med 2016;374:2065–74 Suppl.

下肢靜脈栓塞流回心臟後，發生從右到左分流的異常栓塞paradoxical embolism造成腦中風。還有較少見次要風險的心因性栓塞(minor-risk cardioembolism詳見後述)。大血管來源[6]則是頭頸部大動脈小於50%的不穩定潰瘍斑塊剝落，或是不容易評估的主動脈弓粥樣斑塊aortic arch atheroma剝落等。

ESUS的流行病學研究

Hart等人[7]在2017年整理了來源不明之栓塞性中風ESUS的系統分析，發現8個ESUS研究的2,045位病患年齡多在60歲以上，ESUS發生率約佔缺血性腦中風9-25% (平均17%)，六個病人中約有一個發生ESUS。這些病患的特徵是較其他中風亞型的年齡輕(平均65歲)，中風症狀較輕微(栓塞小，發病時NIHSS平均分數為5分)，長期的死亡率低但復發率高(平均每年復發率為4.5%)。因此，ESUS的辨識和預防是很重要的，尤其是60歲以上越年長，潛在的心因性栓塞也越是增加，例如隱蔽的陣發型心房震顫。多數(86%)病人是以抗血小板劑(antiplatelets)預防治療，少數則使用抗凝劑(anticoagulants)治療。這篇分析的每年中風復發率為2-8%；如果綜合死亡和其它血管性死亡，年發病率甚至高達9%。

另一個令人印象深刻的是Ntaios等人長期追蹤雅典登錄的中風復發[8, 9]，該研究將患者分類為不同缺血性中風亞型並追蹤約3-5年，總共追蹤了2,731名患者，其中10%為ESUS患者(275名)。發現中風復發的機率最高的兩個亞型是ESUS和心因性栓塞中風，兩者的累積中風復發率29%和26.8%類似，顯著高於其它非心因性的中風亞型，像是小間隙梗塞(lacunar)或大動脈粥樣硬化性梗塞。但是ESUS死亡率遠低於心因性栓塞中風。在275名ESUS患者中，高達44%患者後來發現有隱蔽的心房震顫極可能是潛在病因。Ntaios等人[10]為了預測哪些病人較容易中風復發，拿評估心房顫動的CHA2DS2-VASc分數來預測沒有心房顫動的中風病人，發現當閾值設定為2分並將患者分為低風險0分和高風險大於等於2分時，與0分組相比，大於等於2分那組的5年累積中風復發率高出3倍且具有統計意義，暗示沒有心房顫動的病人也可能利用CHA_2DS_2-VASc大於等於2分高風險來預測中風復發的機會較高。

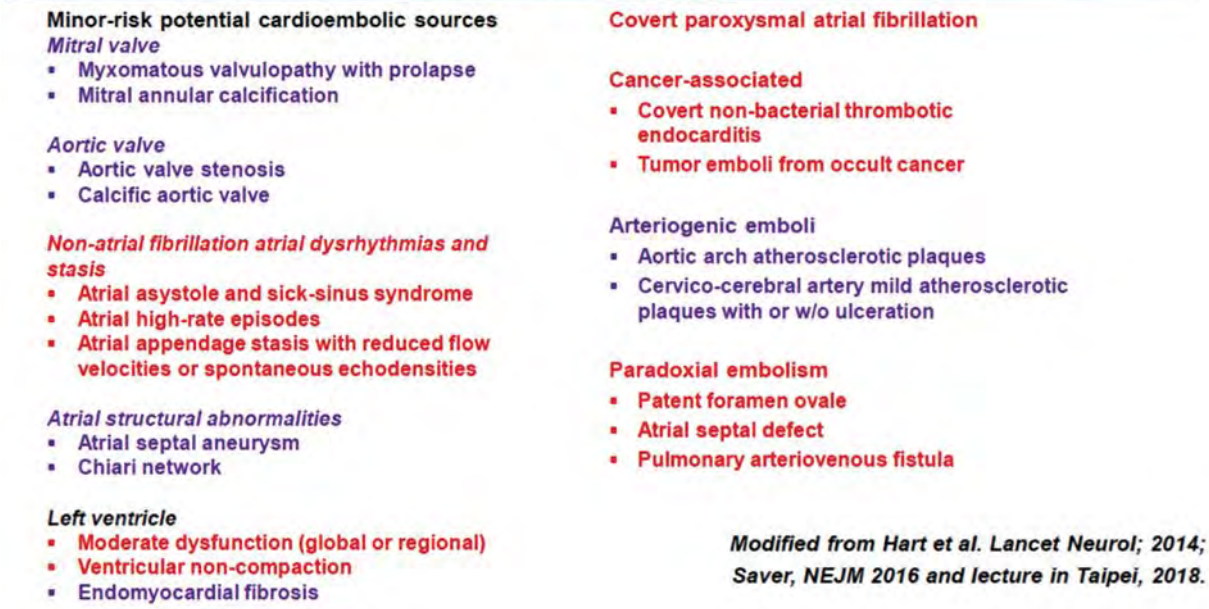
來源不明之栓塞性中風ESUS常見在晚發型中風，但在年輕早發型(16-55歲)中風的發生率則較少研究報導。臺北榮民總醫院中風登錄(TVGH stroke registry)於2009年到2017年，年輕早發型(16-55歲)的中風病人有1,321人佔此期間所有中風人數7,809的17%，其中出血性中風(52%)比缺血性中風(48%)略多一些。出血性中風的前三大病因分類為：高血壓性腦出血、蜘蛛膜下腔出血(subarachnoid hemorrhage, SAH)及不明原因腦出血。而缺血性中風的前三大病因分類為：大動脈疾病、其它特定病因、及原因不明的中風(cryptogenic stroke) (佔缺血性中風20%，其中包含急性期死亡無法查明病因、和來源不明之栓塞性中風ESUS)[11]。其它特定病因的缺血性中風包含動脈剝離、自體免疫疾病(抗磷脂綜合徵、全身性紅斑狼瘡)以及Moyamoya disease、遺傳性的顯性大腦動脈病變合併皮質下中風與腦白質病變(Cerebral autosomal dominant arteriopathy with subcortical infarct and leukoencephalopathy, CADASIL)、粒線體異常引發之肌腦病變、乳酸中毒、中風症候群(mitochondrial myopathy, encephalopathy, lactic acidosis, strokes syndrome; MELAS)、以及Fabry's disease等。所以，在早發型中風的ESUS比例可能不亞於晚發型中風的ESUS，但早發型ESUS潛在的病因更為多樣化。

ESUS的處理指引

2008年ESO指引[12]中建議24小時連續心電圖足以診斷ESUS，持續至少30秒的AF是診斷AF的標準[13]，這也是現行的ESUS診斷要求。但是越長時間或者植入式的心律監測可能偵測到越多沒有症狀的心房顫動AF，而將中風歸因於更多心因性栓塞中風。CRYSTAL-AF試驗[14]納入≥40歲且24小時連續心電圖監測期間沒有AF的不明原因中風(cryptogenic stroke)患者，在中風(index event)發生後90天內進行隨機分派。比較使用植入式心臟監測器(insertable cardiac monitor, ICM)的連續監測組和標準監測組，發現連續監測組隨著觀察的時間越長，監測到越多的無症狀的AF。到3年時，連續監測組有高達30%的患者被偵測到有無症狀的AF。另外FIND-AF試驗[15]納入了年齡≥60歲的急性缺血性中風、竇性心律且無AF病史的患者，隨機分派至延長監測(即基線使用10天連續心電圖監測，以及第3個月和第6個月的追蹤監測)或是標準監測組(即至少24小時的節律監測)。結果發現，大多數AF在急性中風的前10天連續心電圖被偵測到，所以急性期開始延長10天監測相較於標準24小時監測會發現更多的AF。臨床上在哪些狀況下會建議病人接受超過24小時更長時間或者植入式的心律監測呢？2014年美國心臟學會AHA / ASA指引[16]建議在原因不明的中風(cryptogenic stroke)發生6個月內進行長時間監測(7至30天)是合理的處置(證據等級為IIa類；C級)。2019年AHA/ACC的指引更新[17]更進一步指出植入式心率監測器(loop recorder)較體外心率監測器更能全時間避免遺漏地偵測到無症狀的AF (證據等級為IIa類；B級)，能提供臨床助益。但是CRYSTAL-AF和[14]和FIND-AF試驗[15]主要研究長期監測發現無症狀的AF的機率，不是改變治療或者比較療效，因此患者的存活或是中風復發沒有組間的差異，所以2018年的AHA指引[18]提到，長時間的心率監測還沒有證據顯示改善中風的預後或者復發(證據等級IIb類)。

目前來源不明之栓塞性中風ESUS預防治療首選是抗血小板劑(詳見本期蔡力凱醫師的撰文)。從2008年ACCP (American College of Chest Physicians)指引[19]就建議，預防ESUS須使用抗血小板劑。對於其它非心因性栓塞性中風，如小間隙性和大動脈粥樣硬化，抗血小板劑也是首選。而心房顫動心因性栓塞的中風(除了中重度的二尖瓣狹窄或者機械性心臟瓣膜)，預防首選則是新型口服抗凝劑(專對第IIa和第Xa凝血因子的拮抗劑)[12, 16, 18-20]。ESUS的可能栓塞來自於常見主要風險的心因性栓塞(covert paroxysmal AF)、較少見次要風險的心因性栓塞

圖4、釐清ESUS的潛在病因轉為ESPS (possible),可以有助於對症下藥選擇抗血小板劑(紫字)或者抗凝血劑(紅字)



(minor-risk cardioembolism)、大動脈粥樣斑塊以及異常栓塞(圖4)。未來治療的發展，是進階診斷中一旦發現潛在病因，患者將被再分類至其它可能病因，即診斷從ESUS改變成為ESPS (Embolic stroke of Possible source)，則可以對症下藥選用最佳藥物治療是抗血小板劑或抗凝劑(圖4中分別以紫色和紅色字分別標記)。除了藥物治療外，還有其它治療選項如卵圓孔閉鎖不全(patent foramen ovale, PFO)的關閉器。在2017年的3項隨機對照試驗，Gore REDUCE、CLOSE以及RESPECT，建議嚴格選擇高風險患者(大的PFO分流和有心房間隔動脈瘤)、排除小間隙性(lacune)和其它原因引起的中風、使用較新的卵圓孔關閉器可以提供長期預防中風的優勢，效果優於對照組使用抗血小板劑或是併用抗凝劑[21]。

結　論

- ESUS是來源不明之栓塞型中風，需要經過基本的診斷評估來排除不完全診斷或者其他中風原因。
- ESUS的診斷定義是排除小間隙性腦梗塞、排除近端大動脈≥50%狹窄、排除常見的心因性栓塞中風、以及沒有其他特定病因的中風。
- ESUS的預防復發目前仍建議採用抗血小板劑。建議進一步釐清可能的潛在病因，針對中風病因機制來選擇抗凝劑或抗血小板劑治療及其他治療方法。

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What is ESUS? Diagnosis and Management

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ABSTRACT

Embolic stroke of undetermined source (ESUS) is an embolic subtype of cryptogenic stroke requiring a minimum diagnostic assessment to exclude those with incomplete assessments or other stroke etiologies. The diagnostic definition of ESUS includes (1) non-lacunar infarction, (2) no > 50% severe atherosclerotic stenosis in large arteries supplying the ischemic area, (3) no major-risk cardioembolic sources, and (4) no other specific causes of stroke. Potential embolic sources of ESUS include minor-risk cardiac sources, paradoxical embolism from veins, and non-occlusive (<50%) atherosclerotic plaques in the aortic arch or cervical cerebral arteries. The frequencies of ESUS range from 9 to 25% (average 17%) of ischemic stroke and patient characteristics include mild symptoms but high recurrent rates. Hence, the identification and preventive strategies of ESUS are important. The risk of stroke recurrence and death in ESUS patients can be stratified and predicted using CHA2DS2-VASc scores. Although antiplatelets are recommended for secondary prevention of ESUS, optimal treatments, including antiplatelets, anticoagulants or nonpharmacological interventional therapies, are based on elucidation of most possible pathophysiologies, i.e. turning ESUS into ESPS (embolic stroke of possible source).

Keywords: ESUS, Stroke Classification, Embolism, Anticoagulants, Antiplatelets

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綜 說

ESUS治療之過去、現在及未來

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來源不明之栓塞型中風Embolic stroke of undetermined source (ESUS)是於2014年予以定義且漸被重視的缺血性腦中風亞型[1]，在NOAC (non-vitamin K antagonist oral anticoagulant)的相對安全性被證實，而研究又發現ESUS病患可能有約30%為陣發性心房顫動病人後[2]，目前已有二篇大型跨國第三期ESUS臨床試驗已發表結果[3, 4]。針對ESUS病人後續之腦中風預防性治療，本文以過去研究證據、目前發表的試驗結果和未來展望進行回顧和分析。

ESUS治療之過去相關研究

非心因性缺血性腦中風之抗凝血預防性治療

於90年代針對心因性栓塞型中風(尤其是心房顫動)，多個大型臨床試驗已證實了口服抗凝血劑的預防性角色[5]。而對於非心因性缺血性中風患者，2001年WARSS研究對2,206位病人進行warfarin和aspirin預防性療效的比較，結果顯示主要療效指標(復發性缺血性中風或死亡)及重大出血事件於二組皆無顯著差異，但warfarin組的輕微出血事件顯著較多[6]。2007年ESPRIT研究針對1,068位大動脈來源的輕度腦缺血患者進行了warfarin和aspirin的療效比較，結果兩組的主要指標(非致命性中風/心肌梗塞、大出血及血管性死亡)相似，而重大出血事件於warfarin組顯著較高(2.56倍)[7]。

Cochrane後續於2012年對大動脈來源的輕度梗塞或暫時性缺血患者進行了臨床試驗之統合分析，比較warfarin與抗血小板藥物(主要是aspirin)對後續預後的結果。其發現任何warfarin的劑量對腦中風之復發都無法優於抗血小板藥物，且中度(international normalized ratio [INR] 2-3)或強度(INR 3-4.5)的warfarin治療皆會顯著增加出血併發症的機會[8]。因此目前無論是美國腦中風學會[9]或是台灣腦中風學會[10]治療指引，對於非心因性缺血性腦中風的次級中風預防，均建議長期使用抗血小板藥物，而非口服抗凝血劑。至於原因不明的腦中風類型(cryptogenic stroke)，由於過去定義較不一致，故較無特定試驗進行研究，於治療指引中建議比照非心因性缺血性腦中風的處置原則，即使用抗血小板藥物進行腦中風的預防。

於ESUS使用抗凝血劑的理論基礎

上述WARSS臨床試驗之後續次群組分析(subgroup analysis)發現，若病人屬於cryptogenic stroke的分組，則warfarin在一些特定情況的腦中風預防效果較aspirin佳，包括患者無高血壓、低NIHSS、小腦/後大腦動脈中風等，這些狀況似乎暗示了栓塞性中風(embolic stroke)的可能性，亦即於栓塞型之cryptogenic stroke，使用抗凝血劑可能有機會較aspirin要好[11]。Boeckh-Behrens等人分析了145個經動脈取栓術

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所取出的血栓，其發現心因性栓塞和不明原因的血栓成分相似，代表多數的cryptogenic stroke有可能亦為心因性栓塞所致[12]。而Crystal-AF試驗顯示，cryptogenic stroke的病患若接受植入型長期心律檢測，在1年及3年後分別有12.4%及30%的病患可偵測到暫時性心房顫動(時間大於30秒)[2]，然而此種暫時性心房顫動於臨床的意義仍需後續研究釐清。綜合以上結果可知，原因不明的缺血性腦中風和心因性栓塞息息相關，而口服抗凝血劑在此族群可能有腦中風預防之角色。

為了對cryptogenic stroke進行後續治療性試驗，Hart等人於2014年提出ESUS的概念[1]，建議診斷此類患者一般需要進行的相關檢查，使臨床診斷及未來研究有較一致的原則，此概念即於過去cryptogenic stroke的診斷中排除掉檢查不全和病人具有多種病因的情形。而若分析ESUS潛在的常見可能病因，可發現其中雖然於主動脈弓粥樣斑塊(aortic atheroma)和頸動脈非狹窄性斑塊，目前多建議應使用抗血小板藥物治療，但有許多其它可能病因的中風預防的確可考慮使用口服抗凝血劑，如陣發性心房顫動、癌症相關性中風、卵圓孔未閉合(PFO, patent foramen ovale)合併paradoxical栓塞及一些輕微風險性心血管疾病(如非心房顫動型心律不整等)。尤其是最近研究已發現NOAC和warfarin相較，NOAC可顯著下降發生嚴重出血的機會[13]，近年來因此也衍生出幾個跨國性第三期大型臨床試驗的進行，針對ESUS病患比較NOAC和aspirin於未來腦中風之次級預防的效益性。

ESUS之兩篇大型臨床試驗結果

NAVIGATE ESUS臨床試驗

NAVIGATE ESUS為跨國性第三期隨機對照試驗，結果已於2018年發表[3]。其納入ESUS發生7天至6個月內且為50歲以上的患者，比較rivaroxaban (每日15毫克)與aspirin (每日100毫克)的療效和安全性。主要療效指標為缺血性或出血性中風或是全身性栓塞；而主要安全性指標為重大出血事件的發生。本試驗於期中分析時發現rivaroxaban組的出血機會顯著較aspirin組高而提早終止。

研究兩組皆約有3,600名病患，兩組間的基本特色皆類似，平均年齡為約67歲，隨機分組時的NIHSS中位數都為1。結果顯示，兩組間的主要療效指標相似，rivaroxaban組每年中風復發及全身性栓塞發生率為5.1%，而aspirin組為4.8%，p值=0.52，次要療效指標之缺血性中風發生率，兩組皆為4.7%。而主要安全性指標於rivaroxaban組顯著地高於aspirin組(每年重大出血發生率分別為1.8%及0.7%，HR=2.72，p<0.001)，其他安全性指標方面，無論是致命性出血、非重大出血或症狀性顱內出血之發生率，均在rivaroxaban組中顯著地升高(p<0.01)。在次群組分析中，aspirin組在年齡<60歲、亞洲人及腎功能良好(eGFR > 80 mL/min)的族群中均相對具有優勢。總結而言，於ESUS病人的長期藥物使用，rivaroxaban對中風復發及全身性栓塞的發生並未優於aspirin，且rivaroxaban之重大出血發生機會顯著較aspirin高，因此rivaroxaban並無法取代aspirin於ESUS的次級中風預防。

RE-SPECT ESUS臨床試驗

RE-SPECT ESUS亦為跨國性第三期隨機對照試驗[4]，其納入ESUS發生0至6個月內且為18歲以上的患者，比較dabigatran (150或110毫克，每日2次)與aspirin (每日100毫克)的療效和安全性，其中，當病患75歲以上或肌酸酐廓清率(creatinine clearance, Ccr)為30-50 mL/min時則使用110 mg劑量。主要療效指標為任何中風發生率，而主要安全性指標為重大出血的發生率。

研究兩組各有2,695名病患，基本特色於兩組間皆類似，平均年齡為約64歲，追蹤時間的中位數為19個月。結果顯示，兩組的主要療

效指標無顯著差異，dabigatran組每年中風復發率為4.1%，而aspirin組為4.8%，HR=0.85，p值=0.1，次要療效指標之缺血性中風發生率分別為4.0%及4.7%，HR=0.84 (95%信賴區間為0.68-1.03)。而主要安全性指標於兩組亦相似(每年重大出血發生率分別為1.7%及1.4%，HR=1.19，95%信賴區間為0.85-1.66)，僅於臨床有意義的非嚴重性出血發生率在dabigatran組顯著較高(1.6%及0.9%，HR=1.73，95%信賴區間為1.17-2.54)。在次群組分析中，dabigatran組在老年人(75歲以上)、低藥物劑量(110毫克)、使用氫離子幫浦阻斷劑及腎功能相對不良(Ccr=50-79 mL/min)族群的表現優於aspirin組。總結而言，針對ESUS病人，dabigatran在預防復發性中風方面並無顯著優於aspirin，雖然dabigatran的使用亦無顯著增加重大出血的風險，但該試驗仍無法支持以dabigatran取代aspirin於ESUS的次級中風預防。此兩大試驗的結果比較如表1。

ESUS治療之未來展望

進行中之NOAC臨床試驗

ATTICUS臨床試驗是一個多中心隨機雙盲開放式的第三期試驗，納入約500名ESUS患者，以比較apixaban與aspirin的療效與安全性。其受試者之納入條件除ESUS外，需加上以下至少一項特色，包括左心房大小>45 mm、spontaneous echo contrast in the left atrium appendage (LAA)、LAA內流速≤0.2 m/sec、心房心搏過速發作、CHA_2DS_2-VASc分數≥4分、及PFO。這個試驗執行時間從2015-2019年，主要療效指標為第12個月時經腦部核磁共振(MRI的FLAIR與DWI影像)診斷是否有新發生之缺血性病變[14]。

ARCADIA試驗亦為多中心隨機雙盲的第三期臨床試驗，預估將收錄1,100名ESUS受試者，且病患需合併有心房病變(atrial

表1　RE-SPECT ESUS和NAVIGATE ESUS臨床試驗之比較

	RE-SPECT (n = 5390) Follow up 19 months			**NAVIGATE (n = 7372) Follow up 11 months**		
	Dabigatran	Aspirin	HR (95% CI)	Rivaroxaban	Aspirin	HR (95% CI)
Age (year)	64.5 ± 11	63.9 ± 11		66.9 ± 9.8	66.9 ± 9.8	
Prior stroke/TIA	18%	19%		17%	18%	
Stroke to randomization (day)	46	43		38	36	
Monitor > 48 h	18%	16%		34%	34%	
NOAC / aspirin dose	150/110 bid	100 mg qd		15 mg qd	100 mg qd	
Recurrent stroke / (SE)	4.1%	4.8%	0.85 (0.69-1.03)	5.1%	4.8%	1.07 (0.87-1.33)
Ischemic stroke	4.0%	4.7%	0.84 (0.68-1.03)	4.7%	4.7%	1.01 (0.81-1.26)
Major bleeding	1.7%	1.4%	1.19 (0.85-1.66)	1.8%	0.7%	2.72 (1.68-4.39)
ICH	0.7%	0.7%	0.98 (0.60-1.60)	0.6%	0.1%	4.02 (1.51-10.7)
Death	1.2%	1.3%	0.96 (0.66-1.38)	1.9%	1.5%	1.26 (0.87-1.81)

CI代表confidence interval; ICH, intracranial hemorrhage; HR, hazer ratio; NOAC, non-vitamin K antagonist oral anticoagulant; SE, systemic embolism; TIA, transient ischemic attack.

cardiopathy)。試驗目的為驗證於合併心房病變之ESUS病患的腦中風預防，是否apixaban (5或2.5毫克，每日2次)優於aspirin (每日81毫克)，其中劑量部分，若病患在下列三項指標中出現2項，包括年齡80歲以上、體重60公斤以下及creatinine ≥1.5 mg/dl，則使用2.5毫克的apixaban。每位病患將追蹤1.5至4年，主要療效指標為中風復發率，而主要安全性指標為有症狀的顱內出血和重大出血，試驗預計執行時間從2018-2022年[15]。此兩試驗和NAVIGATE ESUS及RE-SPECT ESUS試驗不同之處，為以上兩進行中試驗皆嘗試在ESUS診斷下，以其它臨床特色來篩選提高心因性中風的可能性，以增加NOAC於預防腦中風的角色。

Embolic Stroke of Possible Source

在兩個大型ESUS臨床試驗結果不如預期後，ESUS診斷的合宜性應需重新予以檢視。美國神經學專家Saver JL於2018年11月受台灣腦中風學會邀請來台演講時，提出了以ESPS (embolic stroke of possible source)取代ESUS，亦即盡量於臨床資訊中嘗試將腦中風病因作可能的分類，以提升藥物選擇的準確度。而以上兩個進行中的ESUS試驗精神便類似此原則。

在ESPS的概念下，如何在ESUS中找到陣發性心房顫動的患者亦是重要的方向。Crystal-AF試驗的後續研究發現，若將符合ESUS定義(以NAVIGATE ESUS及RE-SPECT ESUS的試驗標準)的病患重新進行分析，可發現有34-36%的病人於3年追蹤下可偵測到陣發性心房顫動，而若病患的CHADS2分數≥4分，則此比率可更增加到47-50%[16]，其代表高CHADS2分數的ESUS病患，具有陣發性心房顫動的較高可能性。此外，近年來針對陣發性心房顫動診斷的長期偵測儀器越見多元[17]，由7天、14天甚至3年(植入型)的長期偵測已漸入臨床。其中，在台灣腦中風學會的主導下，將進行台灣多中心的心房顫動偵測臨床試驗，期待未來能獲得重要的成果。

於NAVIGATE ESUS臨床試驗之次群組分析顯示，在7.4%具有PFO的534位ESUS患者中，使用rivaroxaban比aspirin有較低發生缺血性中風復發的趨勢(2.6和4.8/100人年)，但統計未達顯著。而若加上過去相關研究進行整合分析，可發現使用口服抗凝血劑比抗血小板藥物可於PFO病人顯著下降腦中風的復發(OR=0.48，95% CI=0.24-0.96)[18]。因此在合併有PFO的ESUS患者，嘗試使用抗凝劑治療是值得後續研究的方向。

結　論

心因性及大動脈狹窄性缺血性腦中風於過去廣泛研究下，次級中風預防的藥物使用策略已多了解，然而ESUS或cryptogenic stroke領域多年來卻是長期被忽略，不過近年於ESUS的診斷、預後和次級預防性治療的研究漸受重視。雖然兩個大型臨床試驗(NAVIGATE ESUS和RE-SPECT ESUS)顯示NOAC於ESUS的治療角色不如預期，但該兩試驗結果卻也提供了未來研究的方向，即 (1) 以ESPS取代ESUS的概念及 (2) 積極尋求確切診斷的重要性。在此原則下，目前已有二個針對合併ESUS及心房病變的NOAC大型臨床試驗在進行中，而且對於陣發性心房顫動的長期偵測亦被高度研究中。至於當前臨床實際的ESUS藥物選擇上，抗血小板藥物原則上仍是ESUS患者的標準治療方法，但未來的ESUS試驗次群組分析和新的大型臨床試驗將帶來重要的治療方向。

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Treatment for ESUS: Past, Present, and Future

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ABSTRACT

Previous clinical trials have demonstrated that warfarin was not better than antiplatelet agents for secondary stroke prevention in patients with non-cardiogenic ischemic stroke, including embolic stroke of undetermined source (ESUS). However, anticoagulants may be effective for stroke prevention in some major causes of ESUS such as paroxysmal atrial fibrillation (AF), minor-risk cardioembolic source, paradoxical embolism, and cancer-related stroke. Notably, paroxysmal AF was detected in about 30% patients with cryptogenic stroke or ESUS using a long-term cardiac recorder. Therefore, two recent large clinical trials compared the effectiveness and safety of non-vitamin K antagonist oral anticoagulants than aspirin for patients with ESUS. The NAVIGATE trial showed that rivaroxaban had similar effect in stroke prevention but higher risk of major bleeding in comparison with aspirin. The RE-SPECT ESUS trial demonstrated that dabigatran and aspirin had similar risk in stroke and major bleeding. With the essentially negative results of both trials, the concept of ESUS might be modified to be ESPS (embolic stroke of possible source) in the future. Various devices for cardiac monitoring may be helpful to increase the AF detection rate. The results of ongoing trials comparing apixaban and aspirin in patients with both ESUS and atrial cardiopathy are anticipated.

Keywords: Anticoagulants, antiplatelets, embolism, ESUS, Stroke

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綜 說

急性腦梗塞與暫時性腦缺血之抗血小板藥物選擇：及早掌握機會、快速勝利得分

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1. 前　　言

身為第一線面對急性中風的臨床醫師，應該常會遇到以下的情境，60歲男性，約6小時前突發一側肢體輕微無力，NIHSS是3分，已超過可以施打靜脈血栓溶解劑的適應症，又缺乏大血管阻塞的證據，這時急診科醫師請教您，是否就處方一顆aspirin、生理食鹽水滴注、等待住院即可？你的回答會是什麼呢？根據什麼理由呢？

雖然使用抗血小板藥物(例如：aspirin)來預防缺血性腦中風再發生，幾乎是所有臨床醫師的反射動作，但該用哪種藥、針對哪些病人、以及該用多久卻又是更深一層的學問，對於每日大量處理腦中風的神經科醫師來說特別需要了解。本文特別要討論的是那些發生「輕度急性腦梗塞」(常見定義為NIHSS分數≤3分)或「暫時性腦缺血」(transient ischemic attack, TIA)的病人，因為他們可能並不符合接受急性溶栓治療的條件(無論是靜脈注射血栓溶解劑rt-PA、或者血管內取栓術)，但根據文獻指出，這些病人其實在3個月內再中風的危險機會高達10-15%[1, 2]，而且最好發於前2至7天之間，因此這些病人的早期用藥其實至為重要，有時光是一顆aspirin的保護效果可能不夠，還得考慮併用兩種抗血小板藥物才行，但用太強、或合併使用太久又怕有出血等副作用，也因此需要有大型臨床試驗來回答這些問題。所幸相關研究於這十年內陸續發表，以下就針對急性腦梗塞與暫時性腦缺血的抗血小板藥物臨床試驗做一系列回顧。

2. 臨床研究實證

2-1. 早期Aspirin研究

在急性腦梗塞時馬上使用口服抗血小板藥物，在現在的臨床醫師看來已成共識。但在20年前，其實這答案還未定論，當時甚至有一派說法覺得在急性時可以使用抗凝血劑(例如：heparin)來有效抑制血栓，而對於aspirin應用在急性腦梗塞上的效果是否能如同在急性冠心症上，也還不確定。因此當時同時進行了兩項大型隨機、非盲、介入性研究，分別是由英國主導、在歐美亞非各國收案的International Stroke Trial (IST)[3]，以及由中國進行的Chinese Acute Stroke Trial (CAST)[4]，都同樣收案將近兩萬人，並且都在腦中風發病後48小時內給予aspirin，在IST中aspirin劑量為每日300毫克、CAST則為每日160毫克。兩研究的設計方法雖有不同，但結論同樣看到使用aspirin者相較安慰劑，可減少病患發病後2至4週內的腦梗塞復發率(IST：

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兩週內為2.8%比3.9%，P<0.01；CAST：4週內為1.6%比2.1%，P=0.01)、並些微降低死亡率(IST：9.0%比9.4%；CAST：3.3%比3.9%，P=0.04)，同時並不會增加出血性腦中風(IST：0.9%比0.8%；CAST：1.1%比0.9%)。

在整合上述CAST及IST的一個統合分析顯示(這兩個試驗佔了98%收納人數)[5]，早期(<14天內)使用aspirin，可以顯著降低死亡與殘障5% (number need to benefit = 79)，下降23%的腦梗塞復發(number need to benefit = 140)，但換來的代價是的卻是會增加23%的症狀性腦出血(number need to harm = 574)。若把缺血及出血性腦中風綜合起來計算的話，則aspirin整體來說可以下降12%的再中風機會(number need to benefit = 200)。幾點值得注意：(1)早期的研究沒有要求一定要在收案前做過腦部電腦斷層(IST 33%、CAST 12%沒做)，因此是否可能誤收治了腦出血的病人其實不得而知；(2)早期研究沒有區分是否為心因性中風，也因此有事後分析發現，在這兩大試驗裡的非心房顫動的病患中，使用aspirin可有效降低中風(P=0.0003)，但在已知心房顫動的病患中，使用aspirin與否則沒明顯差異[6]。

無論如何，早年的這兩個研究已為急性腦中風病患使用aspirin奠下明確的實證基礎，而且自2000年以降，靜脈注射血栓溶解劑(rt-PA)成了急性治療的顯學，因此有好一段時間沒有其他大規模的急性抗血小板藥物研究。但觀念仍繼續演變，從一藥通殺的作法進展到「客製化」的研究假說，特別是針對那些較不符合傳統上急性溶栓(施打rt-PA或動脈內取栓)適應症的輕度腦梗塞或暫時性腦缺血的病患，去看哪些藥物對這類型病患族群會更有益。

2-2. 愈早、愈快(FASTER and EARLY)!

追隨著冠狀動脈治療成功的腳步，急性腦梗塞研究也試著想使用雙抗血小板藥物(dual anti-platelet therapy)來治療，其中較有名的研究應該是發表於2004年的MATCH試驗[7]，其比較連續使用18個月的aspirin 75毫克加上clopidogrel 75毫克、與單用clopidogrel 75毫克兩組的效果，但發現雙抗血小板藥物組並沒有在主要試驗終點(降低腦梗塞、心肌梗塞、血管因子死亡等)明顯優於單一抗血小板藥物組，反倒造成統計上顯著較多的腦出血。此研究最大敗筆可以歸因於「太晚給藥」了，腦中風後復發或惡化之高危險期是在一週之內，但該試驗病人從指標中風事件之後到收案時間之平均時間竟然是26天！也難怪這研究看不到好處，反倒可能因為雙重用藥時間拉長而增加了出血的危險。

有了這樣的「後見之明」，接下來的試驗就著重在「早期給藥」以及「慎選病人」之上(參見表1及表2)。在2007年發表、於加拿大和美國收案進行的Fast Assessment of Stroke and Transient ischaemic attack to prevent Early Recurrence (FASTER)試驗[8]，主要收納40歲以上發生輕度腦梗塞(NIHSS≦3)或暫時性腦缺血(≧5分鐘)者，且須在症狀發生起24小時內接受治療，介入組藥物為每日75毫克之clopidogrel加上81毫克之aspirin，對照組則為每日81毫克之aspirin，同樣使用90天、且同樣在第一日都使用起始劑量(clopidogrel 300毫克、aspirin 162毫克)。本研究一共收納392位病患，平均給藥時間為8小時左右，結果顯示使用雙抗血小板藥物比單一組稍微降低90天內之所有中風(風險比為0.7，95%信賴區間0.3–1.2，P=0.19)，顱內出血的風險稍高1% (P=0.5)，而整體症狀性出血的風險則顯著增加3% (P=0.03)。本研究雖然沒有直接顯示使用雙重抗血小板藥的優勝之處，但至少證明愈早開始、且短期內使用並不會增加腦出血風險，也為之後的更大試驗鋪下道路。

另一項研究則是在2010年發表、於德國46家醫學中心進行的Early treatment with aspirin plus extended-release dipyridamole for transient ischaemic attack or ischaemic stroke within 24 h of symptom onset (EARLY)試驗[9]，研究概念是將一

表1　急性腦梗塞或短暫腦缺血的抗血小板藥物試驗特點比較

	FASTER	CHANCE	POINT	EARLY	TARDIS	SOCRATES
地區	加拿大、美國	中國	北美、歐洲、澳洲、紐西蘭	德國	英國、丹麥、喬治亞、紐西蘭	33國
人數	392	5,170	4,881	543	3,096	13,199
納入條件						
年齡	≧40歲	≧40歲	≧18歲	≧18歲	≧50歲	≧40歲
症狀發生至開始治療	<24小時	<24小時	<12小時	<24小時	<48小時	<24小時
急性腦梗塞或短暫腦缺血	腦梗塞：NIHSS≦3 短暫腦缺血：≧5分鐘	腦梗塞：NIHSS≦3 短暫腦缺血：ABCD^2≧4	腦梗塞：NIHSS≦3 短暫腦缺血：ABCD^2≧4	腦梗塞：NIHSS≦20	腦梗塞：NIHSS不限 短暫腦缺血：≧10分鐘	腦梗塞：NIHSS≦5 短暫腦缺血：ABCD^2≧4
男性	52.8%	66.2%	55.0%	62.4%	62.8%	50.9%
平均年齡(歲)	68.1 (13.1)	介入組63 (55-72) 對照組62 (54-71)	介入組65 (37-96) 對照組65 (56-74)	介入組68 (27-95) 對照組69 (24-90)	介入組69.1 (9.9) 對照組68.9 (10.3)	介入組65.8 (11.2) 對照組65.9 (11.4)
症狀發生至開始治療時間	中位數 8.2-9.1小時	平均 13小時	平均 7小時	--	中位數29.3 (21.8-39.6)小時	<12小時：36.5%
急性腦梗塞或短暫腦缺血比例	--	急性腦梗塞：72.1% 短暫腦缺血：27.9%	急性腦梗塞：56.8% 短暫腦缺血：43.2%	--	急性腦梗塞：71.7% 短暫腦缺血：27.1%	急性腦梗塞：73.2% 短暫腦缺血：26.8%
腦梗塞初始NIHSS	中位數1	--	中位數2	中位數3	平均4.0	NIHSS>3: 32.1%
介入組藥物	Clopidogrel第1日300毫克，第2-90日75毫克 Aspirin第1日162毫克，第2-90日81毫克	Clopidogrel第1日300毫克，第2-90日75毫克 Aspirin第1日75-300毫克，第2-21日75毫克	Clopidogrel第1日600毫克，第2-90日75毫克 Aspirin第1-90日50-325毫克(建議第1-5日162毫克，接著每日81毫克)	Aspirin 25毫克+Dipyridamole長效型200毫克每日2次，第1-90日	Clopidogrel第1日300毫克，第2-90日75毫克 Dipyridamole長效型200毫克每日2次，一般型100毫克每日3-4次 Aspirin第1日300毫克，第2-90日75毫克	Ticagrelor第1日180毫克，第2-90日90毫克每日2次
對照組藥物	Aspirin第1日162毫克，第2-90日81毫克	Aspirin第1日75-300毫克，第2-90日75毫克	Aspirin第1-90日50-325毫克(建議第1-5日162毫克，接著每日81毫克)	Aspirin第1-7日100毫克，第8-90日Aspirin 25毫克+Dipyridamole長效型200毫克每日2次	選擇Clopidogrel或Aspirin+Dipyridamole(用法同上)	Aspirin第1日300毫克，第2-90日100毫克
主要試驗終點	90日內所有中風	90日內所有中風	90日內所有中風、心肌梗塞、死亡	90日的modified Rankin Scale	90日內所有中風、短暫腦缺血	90日內所有中風、心肌梗塞、死亡
參考文獻	[8]	[10]	[11]	[9]	[13]	[15]

表2　急性腦梗塞或短暫腦缺血的抗血小板藥物試驗結果比較

	FASTER	CHANCE	POINT	EARLY	TARDIS	SOCRATES
主要試驗終點	所有中風的風險：0.70 (P=0.19)	所有中風的風險：0.68 (P<0.001)	所有中風、心肌梗塞、死亡的風險：0.75 (P=0.02)	90日的modified Rankin Scale為0-1之差距：4.1% (P=0.45)	所有中風、短暫腦缺血的風險：0.90 (P=0.47)	所有中風、心肌梗塞、死亡：0.89 (P=0.07)
次要試驗終點	所有中風、心肌梗塞、心血管死亡的風險：0.70 (P=0.28)	所有中風、心肌梗塞、心血管死亡的風險：0.69 (P<0.001)	所有中風的風險：0.74 (P=0.01)	所有中風、心肌梗塞、主要出血、死亡的風險：0.73 (P=0.20)	所有中風的風險：1.05 (P=0.79)	所有中風的風險：0.86 (P=0.03)
		腦梗塞中風的風險：0.67 (P<0.001)	腦梗塞中風的風險：0.72 (P=0.01)		腦梗塞中風的風險：0.89 (P=0.56)	腦梗塞中風的風險：0.87 (P=0.046)
		心肌梗塞的風險：0.97 (P=0.94)	心肌梗塞的風險：1.44 (P=0.46)		死亡的風險：0.89 (P=0.69)	心肌梗塞的風險：1.20 (P=0.55)
		死亡的風險：0.69 (P<0.001)	血管疾病死亡的風險：0.74 (P=0.01)			血管疾病死亡的風險：1.18 (P=0.48)
出血事件	顱內出血增加1% (P=0.5)	腦出血的風險：1.01 (P=0.98)	腦出血的風險：1.68 (P=0.47)		顱內出血的風險：3.14 (P=0.026)	顱內出血的風險0.68 (P=0.30)
	症狀性出血增加3% (P=0.03)	嚴重出血風險：0.94 (P=0.94)	嚴重出血風險：2.32 (P=0.02)		嚴重出血風險：2.23 (P=0.0063)	嚴重出血風險：0.84 (P=0.70)

組分為早期組、前24小時內就直接使用雙抗血小板藥物(每日25毫克aspirin與每日兩次200毫克緩釋型dipyridamole 200毫克)，與晚期組、前7天先單用每日100毫克aspirin、第8天再改成上述雙抗血小板藥物，同樣使用90天之後，看臨床上有較佳預後者之比例。其收納條件較寬，只要是中風嚴重程度在NIHSS≦20分者皆可納入，但最終收案之平均NIHSS僅為3分。此研究結果發現早期組比晚期組多4.1%的較佳預後(56.4%比52.4%，P=0.45)，在綜合終點(所有中風、心肌梗塞、主要出血、死亡等)上，早期組相較晚期組的風險比為0.73 (P=0.20)，但兩組在一周之後發生事件曲線就明顯拉開，暗示早期用藥組在一周之後的長期好處較為明顯。不過早期用藥組換來的代價是副作用較多，特別是前一周發生的頭痛，這也和臨床上我們給病人使用經驗上頗像，只要能夠忍受過前幾天的副作用，之後長期吃即尚可適應。

總的來說，這兩試驗主要終點雖然沒達到顯著，但都顯示出早期使用雙抗血小板的安全性。而且一項把EARLY與FASTER合起來的統合分析顯示，雙抗血小板比起單用aspirin，在綜合終點上都有保護作用(風險比0.68，P=0.01)，雖然主要效果是由FASTER試驗所貢獻的[9]。

2-3. 抓住大好機會(CHANCE)

如上所述，到底aspirin與clopidogrel併用能否在急性中風帶來好處仍未得到強而有力的證據，也因此於2013年發表的Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE)試驗的成功[10]，就帶給臨床工作者一劑強心針。但CHANCE之所以會成功，並非只是"by chance"，而是有精心調配後的概念，也值得臨床工作者仔細參考。

CHANCE試驗是由中國主導進行的多中心臨床試驗，招募40歲以上發生輕度腦梗塞(NIHSS≦3)或暫時性腦缺血(ABCD^{2}分數≧4)者，且須在症狀發生起24小時內接受治療，介入組藥物為前21日使用每日75毫克之clopidogrel加上75毫克之aspirin、第22至90天單用每日75毫克之clopidogrel，對照組則為每日均使用75毫克之aspirin共90日，兩組都在第一日使用起始劑量(clopidogrel 300毫克、aspirin 75至300毫克之間)。試驗終點為90日內所有新發生中風事件(缺血及出血)。本研究共收納5,170人，有28%是因暫時性腦缺血而收案，而平均給藥時間為症狀發生後13小時。在結果面來看，雙抗血小板組可顯著下降32%的中風復發(8.2%比11.7%，number need to treat = 29)，而且並不會增加腦出血(0.3%比0.3%)或嚴重出血(0.2%比0.2%)的風險。

本研究有幾點特別值得注意。首先，本研究掌握了「早期給藥」以及「慎選病人」的兩大原則，在指標事件發生後24小時內馬上速效給藥，也因此中風復發在兩試驗組中差異最明顯的時期就是前幾天(first few days)，之後兩組就保持穩定差距了，而且在次分析上，平均給藥時間>12小時組，在數據上仍比<12小時組有稍高之再中風率(雖未達統計上顯著)，這些暗示著就算在輕微腦梗塞或暫時性腦缺血的病人，前幾天、甚至前幾小時乃是動脈硬化斑塊最不穩定、最容易在製造出血栓的時期，因此及早投藥仍是有好處的。此外在慎選病人上，此試驗收納的都是症狀較輕者，故比較不會發生腦梗塞後出血性變化，這點也是和之前一些研究的不同之處。再者，本研究試驗組真正使用雙抗血小板用藥的時期只有21天，不像之前動輒連續3個月、甚至一年半載，因此沒有增加出血風險，這點或許可以和下面的POINT試驗相比較。

2-4. 是否來到決勝點(POINT)?

雖然有了CHANCE試驗振奮人心的結果，但畢竟實務考量上，這研究完全在中國境內執行，其中風照顧體系、以及中風危險因子的控制程度與西方國家不盡相同，此外，CYP2C19

是讓clopidogrel此一前驅藥轉換成活性成分的酵素，而由於基因多型性之故，東亞人相較西方人有較高比率其CYP2C19功能較差，進而降低其抑制血小板的能力。因此學者們就會對此試驗的外推性存疑，需等待更大規模的跨國研究來相呼應，而在2018年發表的Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT)試驗就可作為重要的比較[11]。

POINT是由北美、歐洲、紐澳等地進行的多中心臨床試驗，招募18歲以上發生輕度腦梗塞(NIHSS≦3)或暫時性腦缺血(ABCD^{2}分數≧4)者，且須在症狀發生起12小時內接受治療，共服藥90日，介入組藥物為每日使用75毫克之clopidogrel (首日起始劑量600毫克)、加上50–325毫克(建議前1–5日162毫克、6–90日為81毫克)之aspirin，對照組則為每日均單用aspirin (與介入組建議劑量相同)。試驗終點為90日內所有重大缺血事件(腦梗塞、心肌梗塞和死亡)。本研究共收納4,881人，有43%是因暫時性腦缺血而收案，而平均給藥時間為症狀發生後7小時。在結果面來看，雙抗血小板組可顯著下降25%的重大缺血事件(5.0%比6.5%，風險比0.75，P=0.02)，但卻付出了超過兩倍的重大出血風險(0.9%比0.4%，風險比2.32，P=0.02)。

雖然表面上看來這研究有利有弊互相抵銷，很難證明雙抗血小板用藥的好處，但解讀上卻需要仔細留意。首先，在好處上，絕大多數被預防的事件都是腦梗塞，這也是神經科醫師最關注的重點，因此可視為有臨床上重要好處。另一方面，雖然安全事件定義為重大出血，但其中大多數為全身性出血而非顱內出血，真正的腦出血在兩組之間並無顯著差異(0.2%比0.1%，P=0.47)。再者，經分析後也發現，雙抗用藥的好處在前7天內、或前30天內更為明顯，但出血風險則是在8–90天才比較明顯。這點可以拿來和上述的CHANCE作比較，很可能因為CHANCE只有合併用藥21天，因此並無增加出血的風險。POINT雖有較高的clopidogrel起始劑量(600毫克)，但根據文中表示出血是在後期比較明顯，則可推測可能是因為雙抗用藥合併使用較長(POINT 90天、CHANCE 21天)，才導致出血風險較高。

之前有人質疑的CYP2C19帶因比率不同導致的藥物代謝差異，在先前CHANCE試驗的事後分析發現，不管是否loss-of-function不會影響合併用藥對於出血的風險[12]，而在本POINT試驗裡並無預先設定好了CYP2C19次族群，只能從種族之次族群分析中並無明顯交互作用稍微推論，或許這並不是明顯的影響因子。另外，POINT試驗裡有將近一半病患收案指標事件是暫時性腦缺血，而且整個試驗的終點事件發生率(5~6%)比之前CHANCE (8~11%)較低，因此也要小心或許有一部份收案病患並沒有實際發生腦缺血，而是stroke mimic。整體來說，POINT試驗仍提供了很有價值的資料，讓臨床醫師能更針對病患作個別化醫療，慎選病人、小心用藥。

2-5. TARDIS能否突破時空?

TARDIS這字詞對台灣人或許比較陌生，但這其實是英國長青科幻電視劇「Doctor Who」裡的時間機器和太空飛行器，能將乘客輸送到任何時間中宇宙裡的任何一處，因此也成了該電視劇的經典象徵之一。或許這正是為何英國研究者以此命名本臨床試驗(Triple Antiplatelets for Reducing Dependency after Ischaemic Stroke, TARDIS)：如果雙抗血小板用藥有效，那三種合併(aspirin、dipyridamole、clopidogrel)能否更強而有力地突破限制、預防中風呢？

TARDIS是由英國、丹麥、喬治亞及紐西蘭等地進行的多中心臨床試驗[13]，納入40歲以上發生腦梗塞(不限制NIHSS)或暫時性腦缺血(症狀超過10分鐘)者，在症狀發生起48小時內接受治療，共服藥30日(介於CHANCE與POINT之間)，介入組藥物為每日使用75毫克之clopidogrel (首日起始劑量300毫克)、400毫

克之dipyridamole以及75毫克(首日起始劑量300毫克)之aspirin；對照組則根據規範，單用clopidogrel、或者aspirin合併dipyridamole，簡單概念就是三重用藥對上標準療法。試驗終點為90日內任何中風(出血及缺血)以及暫時性腦缺血事件。本研究共收納3,096人，有27%是因腦梗塞而收案，而平均給藥時間為症狀發生後29小時、比前面幾個試驗都來的長，而且本試驗可以納入施打過rt-PA的病患。在結果面來看，三重用藥組並沒有比標準療法明顯降低再中風(6%比7%，勝算比為0.90，P=0.47)，但卻顯著增加了兩倍致命或嚴重出血(3%比1%，風險比2.23，P=0.006)以及三倍腦出血的風險(1%比<1%，風險比3.14，P=0.03)，最後若把再中風和致病或嚴重出血綜合起來當作終點的話，則兩組就沒有明顯差異(6%比5%，風險比1.24，P=0.19)。

簡單來說，這個試驗顯示三重用藥並不能有效降低再中風、反倒會增加出血風險，因此不建議常規使用。本研究有幾點特別值得注意。首先，本研究並不符合上述成功試驗的「慎選病人」，反倒有11%病人有較嚴重的腦梗塞(NIHSS>6)、也有10%病人接受過血栓溶解劑，這都是可能造成腦出血的危險因子，而且本研究中也發現施打rt-PA與出血事件有明顯交互作用，再度證實這點，沒有慎選病人可能是導致此研究失敗的最大原因。另一點就是本研究也不算「及早用藥」，畢竟有將近70%病患是在24–48小時內才投藥，這段期間是中風後、血腦屏障最不穩定的時期，此時投予高劑量且多種抗血小板藥物，無啻更易導致出血，這點也可從兩組之間出血風險是從剛開始投藥、至前14天之間最明顯一事得證。在進一步的探索分析中發現，若是在24小時內用藥者，三重用藥組可比標準用藥組顯著降低在中風風險，但若是超過24小時才用藥者則沒有此保護效應，這樣的觀察再度呼應CHANCE及POINT試驗的「及早用藥」原則[14]。總之很可惜地，TARDIS並沒有辦法突破限制、顯現出合併三重用藥在急性中風的益處。

2-6. 蘇格拉底的審判(SOCRATES)

以上各試驗幾乎都是在比較合併多種抗血小板藥物與單用aspirin的差別，但是否有考慮直接換另外一種、非aspirin機轉的抗血小板藥物呢? 特別是前文提到，clopidogrel因為是前驅藥物(prodrug)、需要經體內代謝轉換成有活性藥物，因此在每個人體內實際藥效可能差異頗大。此時，另一種可逆性血小板P2Y12受體抑制劑ticagrelor就提供了替代選項。Acute Stroke Or Transient IsChaemic Attack TReated with Aspirin or Ticagrelor and Patient OutcomES] (SOCRATES)試驗就嘗試回答這問題。只不過，若用搜尋網站輸入“SOCRATES trial”時，反倒會出現一整面的關於蘇格拉底的審判(Trial of Socrates)事件，倒也頗有趣味。

SOCRATES是由藥廠發起、於全球33國多中心進行之臨床試驗[15]，納入50歲以上發生腦梗塞(NIHSS≦5)或暫時性腦缺血($ABCD^2$ 分數≧4、或有症狀性顱內外大血管狹窄)者，在症狀發生起24小時內接受治療，共服藥90日，介入組藥物為每日使用180毫克之ticagrelor，對照組藥物則為每日使用100毫克之aspirin (首日起始劑量300毫克)。試驗終點為90日內所有中風、心肌梗塞和死亡事件。本研究收納13,199人，有73%是因腦梗塞而收案、其中三分之一病患之NIHSS>3，另外有32%病患在收案前已經在吃aspirin。在結果面來看有點可惜，ticagrelor組只能稍微、但沒達統計上顯著地降低主要終點事件(6.8%比7.5%，風險比0.89，P=0.07)，不過若單看預防所有再中風(6.0%比6.8%，風險比0.86，P=0.03)或腦梗塞(5.9%比6.6%，風險比0.87，P=0.04)則都能達到統計上顯著，且並不會增加顱內出血(0.2%比0.3%，P=0.30)或嚴重出血的風險(0.5比0.6%，P=0.45)。在副作用上，雖然ticagrelor不會增加嚴重出血，但呼吸不順(dyspnea)以及任何小出血卻是使病患無法耐受的主要原因，也使得

ticagrelor組停藥比率稍高(17.5%比14.7%)。

本研究因為收案人數很多、又有許多事先設定好的次族群分析，因此以下幾點仍值得注意：(1) 本研究中有近1/3受試者之前即有在常規服用aspirin，這群人若納入ticagrelor組之後，能比繼續使用aspirin來的更有保護效果(6.5%比8.3%，風險比0.76，P=0.02)[16]，這些人或許因為體內之前有常規維持的aspirin濃度，在急性中風且收案後幾天內達到了某種程度的雙抗血小板藥效，因而達到好處。(2) 本研究中的亞洲族群(佔29%受試者)相較於歐美族群，竟有高達兩倍風險發生再中風等終點事件(10.6%比5.7%，P<0.01)! 但若單看亞洲族群裡，使用ticagrelor者的保護效果亦比aspirin來的有效(9.7%比11.6%，風險比0.81，P=0.04)[17]，但這不確定是真的因為亞洲人生理上較有效，或只是因為發生比率高而檢力較強、或甚至是因為亞洲人平常危險因子控制較差之故。(3) 本研究中屬於動脈硬化致因者(atherosclerotic origin，包括同側顱內或顱外大血管狹窄、有主動脈血栓或斑塊)，使用ticagrelor明顯比aspirin來的有效(6.7%比9.6%，風險比0.68，P=0.003)，但若是小血管疾病者(small vessel disease)則沒有差別[18]，因此再度呼籲要為腦梗塞病人作詳細檢查找出病因、才更能對症下藥。不過話說回來，本研究一開始即是設定分層式檢定(hierarchical testing)，也就是只要主要試驗終點沒達到顯著，其他次要終點及次族群分析都只能當作參考用而已。

總結來說，SOCRATES試驗無法顯示出單用ticagrelor比aspirin用在輕微中風病人上的優勝處，但至少是一樣安全，不過也有可能歸咎於其設定的主要終點包含太廣之故、又或者要使用到合併雙抗血小板用藥才更有效，因此「蘇格拉底的審判」一如其最終下場，無法宣告成功(保住性命)。這正是目前還在進行當中的THALES (Acute STroke or Transient IscHaemic Attack Treated With TicAgreLor and ASA for PrEvention of Stroke and Death)試驗想回答的問題，此試驗將比較合併ticagrelor與aspirin是否能優於單用aspirin、在30天內降低再中風及死亡的風險。

3. 臨床應用

回到文章一開頭所提及的個案，根據上述文獻回顧之後，讀者會選用什麼藥物治療方式呢? 在此之前，可先參考一下國內外的抗血小板藥物指引，特別著重在急性預防部分。在台灣腦中風學會2016年出版的「缺血性腦中風的抗血小板藥物治療指引」[19]當中指出：(1) 在急性腦中風發作48小時內，如無禁忌症則建議考慮使用aspirin (160至300毫克)來預防復發。(2) 暫時性腦缺血(ABCD^{2}分數≥4)或急性輕微缺血性腦中風(NIHSS≤3，可合併使用aspirin及clopidogrel三週，並考慮續用clopidogrel至90日。(3) 無法使用aspirin或aspirin治療無效的病人可考慮使用clopidogrel。在美國心臟學會與腦中風學會出版的「2018年急性缺血性腦中風早期治療指引」[20]當中也提到：(1) 除了施打血栓溶解劑病患以外，建議可在發作24至48小時內給予aspirin (160至300毫克)。(2) 在輕度中風病患，發作24小時內開始給予雙重抗血小板藥物(clopidogrel及aspirin)至21天。(3) 在輕度中風病患不建議使用ticagrelor。以上兩篇文章都是在POINT試驗尚未發表前出版的，因此只以CHANCE試驗作主要參考提出建議。

最近有一篇統合分析來討論合併clopidogrel與aspirin與單用aspirin在輕度急性腦梗塞或暫時性腦缺血的效果，經過篩選之後其收納的文章就是FASTER、CHANCE與POINT試驗，共10,447位病患[21]。整體來說，在症狀發生24小時內就合併用藥可以降低近三成的再中風風險(4.4%比6.3%，絕對差異為1.9%，number need to benefit＝53，風險比0.70，95%信賴區間0.61–0.80)，同時不會增加死亡率(0.6%比0.5%，風險比1.27，95%信賴區間0.73–2.23)或非致命性出血(0.5%比0.3%，風險比1.71，95%信賴區間

0.92–3.20)，另外可以稍微改善以改良式Rankin量表評估之臨床功能障礙(相對風險0.90，95%信賴區間0.81–1.01)、並提升生活品質(相對風險0.81，95%信賴區間0.66–1.01)。另一篇統合分析研究[22]，納入10個隨機試驗的15,434位病人，探討短期(≦1個月)、中期(≦3個月)與長期(>3個月)使用雙抗血小板藥物(clopidogrel與aspirin)與單用aspirin的比較，結果是長期使用不會明顯減少缺血中風發生但增加出血事件，中期使用可減少缺血中風發生但還是增加出血事件，短期使用減少缺血中風發生且不增加出血事件，因此最佳策略為短期(≦1個月)使用雙抗血小板藥物。

要記得的是，這三篇文章只有CHANCE是合併使用21天、其他兩個都是使用90天，但在臨床效益之上，兩組病患從第1天開始再中風發生率就顯著拉開，到第10天後則發生曲線就變成平行、兩組差距不再改變。相較來說，出血風險雖然統計上沒有達顯著差異，但卻是從第1天開始、雙抗血小板藥組一直比單方組較高且逐漸拉開，一直到試驗結束的第90天。在數據上來看，這一萬多人當中90天內所有再發生之腦梗塞事件有786件、腦出血則只有23件，因此就絕對數字標準來說，使用雙抗血小板藥在臨床上還是利大於弊。

另外，藥物動力學及基因多型性的影響也須納入考量，特別是亞洲族群裡有較高比率者帶有功能不強的CYP2C19，會對clopidogrel反應較差。雖然臨床規範並不建議常規檢測，但在亞洲人或許可以視情況檢測此基因多型性、站在個人化醫療角度來選擇較佳之抗血小板用藥，比如針對loss-of-function者給予更高劑量的clopidogrel、或是換成ticagrelor。當然這種做法的效果、可行性及成本效益仍需經由嚴謹的臨床試驗才可得知[14]。

從以上各篇文獻以及統合分析可以得知，合併使用雙抗血小板藥物因為其容易出血的危險性，因此要小心衡量利弊之後，慎選病人、及早用藥、並勿使用太久。以下彙整出文獻證據並供臨床使用參考(圖1)。

給誰用？非心因性輕度腦梗塞(通常指NIHSS≦3)或高危險群(通常指ABCD^2≧4)之暫時性腦缺血病患。

用甚麼藥？clopidogrel首日起始劑量300毫克、維持劑量每日75毫克；aspirin每日75至325毫克之間皆可。

何時開始？理想狀況在症狀發生24小時內、且有影像證據支持之下(排除腦出血)即可

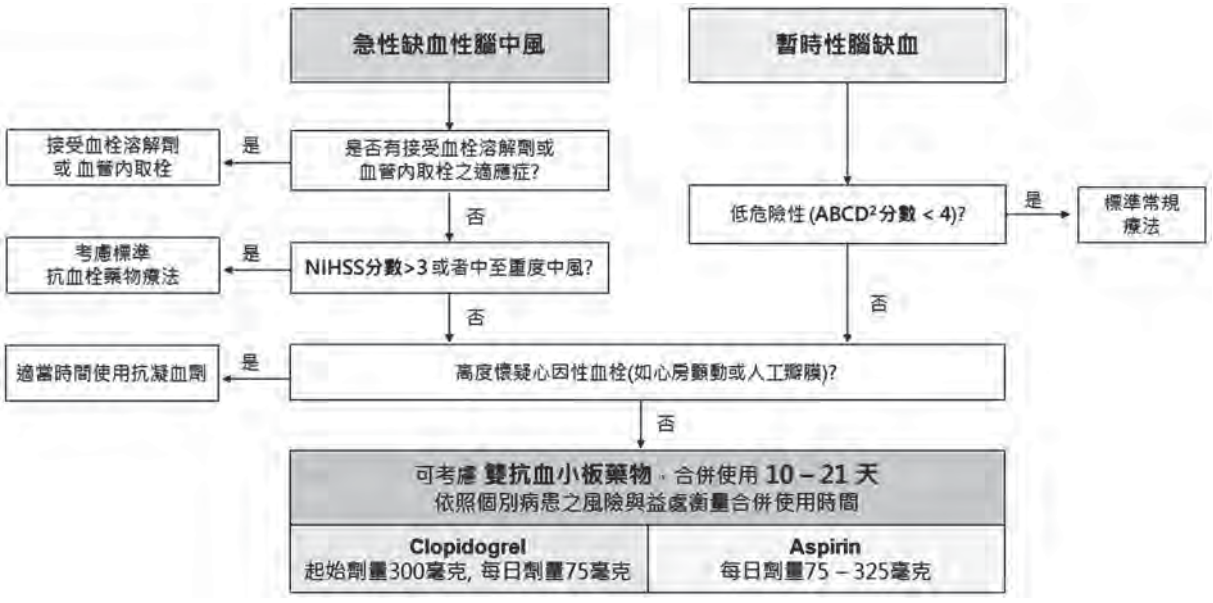

圖1　使用高強度雙抗血小板藥物之建議評估流程圖

使用。

用多久？兩者合併使用21天，之後換回單方(可考慮以clopidogrel為主)。若擔心出血風險，甚至可考慮只要合併使用10天即可。

當然，還有許多問題無法依照目前的文獻回答，例如有一定要嚴格限定NIHSS≦3分嗎？畢竟左右半球、甚至前後循環之中風在NIHSS上的比重都不盡相同，若是擔心出血，是否可以納入MRI中風大小來當參數決定呢？又或者，若單用clopidogrel是否也能達到跟雙抗用藥同樣的好處？使用ticagrelor與aspirin的效果又如何？對於同時有顱內血管狹窄的病患，是否可以在急性期開始後持續使用更久(一如SAMMPRIS試驗[23])呢？對於腦部有較多小血管病變及微出血的病患，使用雙抗用藥是否較容易出血?如此林林總總的不確定，實證醫學文獻能回答的範圍畢竟有限，臨床上很大一部分還是要靠醫療團隊與病患溝通討論後、斟酌選擇出最適合的藥物，使用方式也會因人時地而異，如此才能朝向精準醫療的方向邁進。

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Beyond Aspirin: EARLY CHANCE, FASTER Winning POINT!

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ABSTRACT

In the era of reperfusion therapy, timely and proper antithrombotic agents can still protect acute ischemic stroke patients from early recurrent events, especially in those who are initially "too good" for thrombolysis or thrombectomy. Aspirin monotherapy, although commonly used, can only provide limited benefit for secondary prevention. More intensive antiplatelet regimens, such as short-term dual antiplatelet therapy, has been proved to be effective in selective patient group. The results of FASTER, CHANCE and POINT trials demonstrated that early administration (within 24 hours) of short-term clopidogrel and aspirin can prevent at least 30% recurrent stroke in patients with minor ischemic stroke (NIHSS≤3) or high risk transient ischemic attack, while that prolonged combination use of antiplatelet therapy beyond 21 days may bring up unwanted risk of hemorrhage. Other antiplatelet agents, such as dipyridamole and ticagrelor need to prove their clear benefits in early secondary stroke prevention. Clinicians should be aware of these possible therapeutic choices and tailor their management according to individual's condition to achieve maximum benefit over risk.

Keywords: acute ischemic stroke, transient ischemic attack, antithrombotic, antiplatelet

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原著論文

Secular Trends of Stroke Subtypes in Taiwan ~ National Taiwan University Hospital Stroke Registry, 1995~2018

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ABSTRACT

Background and Purpose: Stroke registries can provide important information on risk factors, pathogenesis, treatment and prognosis over time. Here, we report the secular trends of stroke subtypes between 1995 and 2018 from a hospital-based stoke registry in Taiwan.

Methods: The National Taiwan University Hospital (NTUH) Stroke Registry began in January 1995, recruiting all patients with stroke onset within 10 days of hospital arrival or stroke occurrence during hospitalization. The 24-year period until 2018 was divided into 1995-1999, 2000-2004, 2005-2009, 2010-2014 and 2015-2018. We analyzed the secular changes in stroke subtypes, risk factors and etiologies.

Results: There were 27,743 patients with 31,975 admissions to NTUH for stroke during the study period. Of these patients, 22,803 (male, 57.9%; mean age, 64.5 ± 15.5 years) had first-ever stroke. The percentage of cerebral infarcts increased slightly from 70.5% in 1995-2009 to 72.9% in 2010-2018, but the percentage of intracerebral hemorrhage decreased (23.9% to 21.3%). In patients with cerebral infarct, cardioembolism significantly increased from 19.9% in 1995-1999 to 28.5% in 2015-2018, as did atrial fibrillation (from 17.6% in 1995-1999 to 25.7% in 2015-2018, $p < 0.001$). The percentage of those receiving intravenous or intra-arterial reperfusion therapies increased significantly from 2005, reaching 12.4% in 2015-2018. In patients with intracerebral hemorrhage, the percentage of those with cerebral amyloid angiopathy and medication-related hemorrhage increased significantly (10.2% to 12.9% and 3% to 5.5%, respectively, both $p < 0.001$), but the percentage of those with hypertensive angiopathy decreased significantly (57.7% to 50.8%, $p = 0.008$) over time.

Conclusions: Over 24 years, rates of cardioembolism in cerebral infarct and cerebral amyloid angiopathy in intracerebral hemorrhage among first-ever acute stroke patients increased.

Keywords: intracerebral hemorrhage, ischemic stroke, secular change, stroke epidemiology, subarachnoid hemorrhage.

Introduction

In 2017, stroke was the second leading cause of mortality among non-communicative diseases, causing 6.17 million deaths, about 11% globally.[1] The global lifetime stroke risk from age 25 years onward among both men and women is 24.9%, with the highest risk in East Asia, 38.8%.[2] Over the past decades, similar with other developing countries, Taiwan has experienced a significant

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transition in the epidemiology of stroke, especially after the development of acute reperfusion therapies, and the identification of risk factors and their associated treatment.[3-5] Therefore, it is important for clinicians in Taiwan to have a general impression of the secular trends of distribution of stroke subtypes and risk factors, to enable them to make optimal decisions on diagnosis and therapy for individual patients.

A stroke data bank or stroke registry can record important information about the risk factors, pathogenesis, treatment and prognosis related to different types of stroke. In addition, a stroke registry can monitor and improve the quality of stroke care and can be used for a wide range of research studies.[6-10] The National Taiwan University Hospital (NTUH) Stroke Registry is a prospective hospital-based registry initiated in January 1995 with a high quality of data integrity and scientific results.[11-14] The aim of this study was to explore the epidemiological transition in stroke types, risk factors and etiologies of patients with first-ever strokes during the period of 1995 to 2018 from The NTUH Stroke Registry.

Methods

The NTUH Stroke Registry is a hospital-based registry initiated in January 1995. The NTUH Stroke Registry was developed to facilitate the study of the etiological factors, clinical course, prognosis and complications of stroke.[11-13] All patients who had stroke onset within 10 days of hospital admission or during hospitalization were included. We prospectively captured all cases of stroke in our hospital by daily screening all patients receiving head computed tomography (CT) or with a diagnosis of stroke at the emergency department or during hospitalization, as well as screening for a diagnosis at discharge, using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 430 to 437, excluding 432 (subdural hemorrhage) and 435 (transient ischemic attack). Since 2016, the diagnostic screening has been updated to the International Statistical Classification of Disease and Related Health Problems, Tenth Revision, Clinical Modification (ICD-10-CM) codes I60 to I68. Studies using The NTUH Stroke Registry have been approved by the Institutional Ethics Committee.

A detailed medical record, including medical history, stroke type, clinical course and outcome, was reviewed in each patient. Also included for each patient was the history of potential vascular risk factors, including hypertension, diabetes mellitus, hyperlipidemia, cardiac disease, ischemic heart disease, valvular heart disease, atrial fibrillation (AF), previous transient ischemic attack, malignancy, smoking and drinking habits and conditions assumed to be associated with stroke. Most patients received at least one brain CT and/or magnetic resonance imaging (MRI), and were classified as cerebral infarct (CI), intracerebral hemorrhage (ICH) or subarachnoid hemorrhage (SAH). Patients with CI were further classified into five categories in accordance with key clinical features: large artery atherosclerosis (LAA), lacunar stroke, cardioembolism, other determined etiologies and undetermined etiology, categories adopted from the Trial of Org 10172 in Acute Treatment (TOAST) classification system.[15]

Patients with traumatic ICH or primary subdural/epidural were excluded. The etiologies of ICH patients were further classified, by means of the SMASH-U classification method, as structural lesions, systemic disease-related, medication-related, cerebral amyloid angiopathy (CAA),

hypertensive angiopathy (HA) or undetermined etiology.[16, 17]

Statistical analysis

We used frequencies with percentages to describe discrete variables, and means ± standard deviations (SD) or medians (interquartile range) to describe continuous variables. For continuous variables, we used the independent sample Student's *t*-test and the Mann-Whitney U-test, as appropriate. Either chi-squared test or one-way analysis of variance (ANOVA) was used for categorical variables. We divided the 24-year period into five segments of 1995-1999, 2000-2004, 2005-2009, 2010-2014 and 2015-2018. A chi-square test for linear trend was used to calculate the changes in types of stroke, and the subtypes of CI and ICH across the period 1995-2018. A logistic regression analysis was used to adjust for factors related to the diagnosis of cardioembolism of cerebral infarct, and included age, sex, important risk factors and the different periods of time in the model. A P-value <0.05 was considered to indicate statistical significance. Statistical analysis was performed using SPSS Statistics for Windows, Version 17.0 (SPSS Inc., Chicago, IL).

Results

Between 1995 and 2018, there were 27,743 patients with 31,975 admissions to NTUH for stroke. Of these patients, 22,803 (male, 57.9%; mean age, 64.5 ± 15.5 years) had first-ever stroke, including 16,361 with CI, 4,971 with ICH and 1,471 with SAH. Table 1 shows the demographics of the overall study population and by each type of first-ever stroke from The NTUH Stroke Registry. In Table 2, there was a significant secular trend in age, but not gender, across the time period. The mean age increased from 62.9 ± 15.3 to 63.7 ± 15.6, 64.3 ± 15.7, 65.5 ± 15.5 and 65.8 ± 15.4 years in 1995-1999, 2000-2004, 2005-2009, 2010-2015 and 2015-2018, respectively. The percent of

Table 1. Demographics of Study Population

	All (n = 22803)	Cerebral infarct (n = 16361)	Intracerebral hemorrhage (n = 4971)	Subarachnoid hemorrhage (n = 1471)
Mean age, y	64.5 ± 15.5	66.8 ± 14.4	59.0 ± 17.1	57.1 ± 15.2
Male sex	13,210 (57.9)	9,513 (58.1)	3,140 (63.2)	557 (37.9)
Hypertension	13,974 (70.1)	11,526 (70.4)	3,718 (74.8)	730 (49.6)
Diabetes mellitus	6,868 (30.1)	5,732 (35.0)	955 (19.2)	181 (12.3)
Hyperlipidemia	7,944 (34.8)	6,629 (40.5)	1,159 (23.3)	156 (10.6)
Cardiac disease	7,343 (32.2)	6,338 (38.1)	831 (16.7)	174 (11.8)
Ischemic heart disease	3,199 (14.0)	2,702 (16.5)	411 (8.3)	86 (5.8)
Atrial fibrillation	3,983 (17.5)	3,621 (22.1)	315 (6.3)	47 (3.2)
Malignancy	3,266 (14.3)	2,441 (14.9)	709 (14.3)	116 (7.9)
Smoking habit	6,036 (26.5)	4,609 (28.2)	1,213 (24.4)	214 (14.5)
Alcohol drinking	3,349 (14.7)	2,334 (14.3)	868 (17.5)	147 (10.0)
1-month mortality	2,399 (10.5)	1,054 (6.4)	968 (19.5)	377 (25.6)

Values are mean ± standard deviation, or number (percentage).

Table 2. Secular Trend of Age, Sex, and Stroke Types in 1st-ever Stroke Patients

	1995-99 (n = 4150)	2000-04 (n = 4967)	2005-09 (n = 4558)	2010-14 (n = 4887)	2015-18 (n = 4241)	P-value
Mean age, year	62.9 ± 15.3	63.7 ± 15.6	64.3 ± 15.7	65.5 ± 15.5	65.8 ± 15.4	<0.001
Age ≦45 year	522 (12.6)	583 (11.7)	532 (11.7)	500 (10.2)	425 (10.0)	<0.001
Male sex	2,401 (57.9)	2,837 (57.1)	2,610 (57.3)	2,895 (59.2)	2,467 (58.2)	0.221
Stroke types						
Infarct	2,909 (70.1)	3,522 (70.9)	3,215 (70.5)	3,623 (74.1)	3,092 (72.9)	<0.001
ICH	992 (23.9)	1,075 (21.6)	1,028 (22.6)	972 (19.9)	904 (21.3)	<0.001
SAH	249 (6.0)	370 (7.4)	315 (6.9)	292 (6.0)	245 (5.8)	0.003

Values are mean ± standard deviation, or median (interquartile range), or number (percentage).
ICH indicates intracerebral hemorrhage; SAH, subarachnoid hemorrhage.

those who were young stroke patients (onset ≦45 years) decreased significantly over the period, from 12.6% in 1995-1999 to 11.7% in 2000-2009, 10.2% in 2010-2014, and 10.0% in 2015-2018. Recent years showed no evidence of greater occurrence of young stroke. In terms of stroke types, the percentage of CI did not change obviously between the first three periods encompassing 1995 to 2009 (70.1%, 70.9% and 70.5%, respectively), but it then increased significantly to 74.1% in 2010-2014 and 72.9% in 2015-2018 (p for trend <0.001). On the other hand, the percentage of ICH decreased during the study period, from 23.9% in 1995-99 to 21.3% in 2015-2018 (p for trend <0.001).

Table 3 shows the secular trends of major risk factors and subtypes in first-ever CI patients. The age at onset and rates of hypertension, diabetes, atrial fibrillation and malignancy all increased significantly over time (all p<0.001). By contrast, the percentage of those with smoking, alcohol drinking and previous transient ischemic attack tended to decrease (all p<0.001). Notably, the percentage of hyperlipidemia seems decreased in early year and increased in recent years (p<0.01). Furthermore, the percentage of AF had the most significant increase among the vascular risk factors in CI patients, from 17.6% in 1995-1999 to 25.7% in 2015-2018 (p for trend <0.001). In terms of the distribution of CI subtypes, the percentage of cardioembolism increased most significantly (19.9% to 28.5%, p<0.001) and that of small vessel occlusion decreased most significantly (32.5% to 21.7%, p<0.001) over time. Importantly, the trend of reperfusion therapies for CI patients, either by intravenous thrombolysis, intra-arterial thrombolysis or thrombectomy, increased significantly over time (p for trends, both <0.001), particularly since 2005 for intravenous thrombolysis and since 2015 for intra-arterial thrombolysis and thrombectomy.

Table 4 shows the logistic regression model for factors determining the diagnosis of cardioembolism in first-ever CI patients. The cardioembolism diagnosis, most from AF, was significantly related to older age, female sex and ischemic heart disease. After adjustment of these factors, we still found a significant period effect of greater likelihood of cardioembolism diagnosis, increasing 63-70% in 2010-2018 compared to 1995-1999.

Table 5 shows the secular trend in risk factors and subtypes in first-ever ICH patients. Similar to CI patients, over time the percentages of those with hypertension, diabetes and AF increased

Table 3. Secular Trend of Risk Factors and Subtypes in Patients with First-ever Cerebral Infarct

	1995-99 (n = 2909)	2000-04 (n = 3522)	2005-09 (n = 3215)	2010-14 (n = 3623)	2015-18 (n = 3092)	P-value
Age, year	65.1 ± 14.1	66.5 ± 14.0	66.7 ± 14.7	67.5 ± 14.6	68.0 ± 14.4	<0.001
Male sex	1,658 (57.0)	2,025 (57.5)	1,869 (58.1)	2,136 (59.0)	1,825 (59.0)	0.386
Risk Factors						
Hypertension	1,868 (64.2)	2,330 (66.2)	2,347 (73.0)	2,713 (74.9)	2,268 (73.4)	<0.001
Diabetes	925 (31.8)	1,223 (34.7)	1,146 (35.6)	1,270 (35.1)	1,168 (37.8)	<0.001
Hyperlipidemia	1,305 (44.9)	1,476 (41.9)	1,010 (31.4)	1,419 (39.2)	1,419 (45.9)	<0.001
Ischemic heart disease	705 (24.2)	600 (17.0)	471 (14.7)	469 (12.9)	457 (14.8)	<0.001
Atrial fibrillation	512 (17.6)	867 (18.9)	718 (22.3)	929 (25.7)	795 (25.7)	<0.001
Valvular heart disease	162 (5.6)	128 (3.6)	95 (3.0)	101 (2.8)	126 (4.1)	<0.001
Smoking habit	987 (33.9)	917 (26.0)	951 (29.6)	1,009 (27.8)	745 (24.1)	<0.001
Alcohol drinking	610 (21.0)	499 (14.2)	484 (15.1)	454 (12.5)	287 (9.3)	<0.001
Malignancy	368 (12.7)	507 (14.4)	421 (13.1)	558 (15.4)	587 (19.0)	<0.001
Previous TIA	114 (3.9)	182 (5.2)	132 (4.1)	130 (3.6)	91 (2.9)	<0.001
Infarct subtypes						
LAA	405 (13.9)	633 (17.5)	637 (19.8)	554 (15.3)	448 (14.5)	<0.001
SAO	945 (32.5)	1,041 (29.6)	939 (29.2)	909 (25.1)	671(21.7)	<0.001
Cardioembolism	578 (19.9)	695 (19.7)	735 (22.9)	1,003 (27.7)	882 (28.5)	<0.001
Other determined	168 (5.8)	194 (5.5)	187 (5.8)	226 (6.2)	217 (7.0)	0.099
Undetermined	813 (27.9)	959 (27.2)	717 (22.3)	931 (25.7)	874 (28.3)	<0.001
NIHSS	--	--	4 (2-10)	5 (2-11)	5 (2-12)	<0.001
GCS	--	--	15 (14-15)	15 (14-15)	15 (13-15)	<0.001
In-hospital stroke	170 (5.8)	280 (8.0)	255 (7.9)	269 (7.4)	390 (12.6)	<0.001
1-month mortality	162 (5.6)	222 (6.3)	196 (6.1)	233 (6.4)	241 (7.8)	0.008
IV thrombolysis	1 (0.03)	22 (0.62)	78 (2.42)	276 (7.61)	259 (8.37)	<0.001
IA thrombolysis or thrombectomy	0	11 (0.31)	32 (0.99)	27 (0.74)	195 (6.30)	<0.001
Reperfusion therapy	1 (0.03)	32 (0.90)	99 (3.07)	297 (8.19)	383 (12.38)	<0.001

Values are mean ± standard deviation, or median (interquartile range), or number (percentage).
GCS indicates Glasgow coma scale; IA, intra-arterial; IV, intravenous; LAA, large artery atherosclerosis; NIHSS indicates National Institute of Health Stroke Scale; SAO, small artery occlusion; TIA, transient ischemic attack.

significantly (p for trend, all <0.001), and the percentages of those with hyperlipidemia, smoking habit and alcohol drinking decreased significantly (p for trend, all <0.001). Most importantly, regarding the etiologies, the percentages of CAA and of medication-related ICH increased significantly (10.2% to 12.9% and 3% to 5.5%, respectively, both p<0.001), but the percentage of hypertension-related ICH decreased significantly (57.7% to 50.8%, p=0.008) over time.

Table 4. Factors Determining the Diagnosis of Cardioembolism in Patients with First-ever Cerebral Infract.

Variable	ß	Odds ratio	95% Confidence intervals	P-value
Age <45 y	--	1.00	--	
45-64 y	-0.034	0.97	0.81-1.15	0.697
≧65 y	0.531	1.70	1.44-2.00	<0.001
Female sex	0.290	1.34	1.23-1.45	<0.001
Hypertension	-0.232	0.79	0.73-0.87	<0.001
Diabetes mellitus	-0.387	0.68	0.62-0.74	<0.001
Ischemic heart disease	1.134	3.11	2.83-3.41	<0.001
Hyperlipidemia	-0.541	0.58	0.54-0.63	<0.001
Smoking Habit	-0.258	0.77	0.70-0.85	<0.001
Period 1995-1999	--	1.00		
2000-2004	0.059	1.06	0.93-1.21	0.371
2005-2009	0.256	1.29	1.14-1.47	<0.001
2010-2014	0.611	1.84	1.63-2.09	<0.001
2015-2018	0.658	1.93	1.70-2.19	<0.001

Discussion

This study comprehensively demonstrated the secular changes in stroke types, CI and ICH subtypes, risk factors and other related parameters in the NTUH Stroke Registry between 1995 and 2018. Apparently, stroke epidemiology changed significantly in our hospital during this 24 year-period, including not only the percentages of ischemic or hemorrhagic strokes, but also their subgroup characteristics. Whether this finding reflects the epidemiological trends of the whole population of Taiwan awaits further investigation. Nevertheless, the results of our study do provide information important to clinicians, especially for those who work in hospital settings similar to the NTUH in Taiwan.

Although significant, the distribution of ischemic and hemorrhagic stroke in The NTUH Stroke Registry did not change materially over time. These results were in contrast to those from a study of a hospital-based stroke registry in Peking during 2006-2015, which showed a significantly increasing proportion of CI and a decreasing proportion of ICH and SAH.[18] In the Japan Public Health Center-based prospective study, between 1995-1999 and 2005-2009, the proportion of ICH decreased for men, while the proportion of CI (among all types of stroke) and embolic infarction (among CI) increased for both men and women.[19] However, some stroke subtypes and risk factors did have remarkable secular trends, such as increased AF or malignancy-related CI and medication- or CAA-related ICH,[17, 20] and in turn reduced small vessel disease in CI and hypertensive ICH. Our study had similar results in terms of CI subtypes as those from the Korean Stroke Registry, which showed increased frequency of cardioembolism, decreased frequency of small vessel occlusion and a relatively steady frequency of large artery atherosclerosis.[21] Furthermore, the data showed a constantly increasing use of reperfusion therapy, whether intravenous or intra-arterial, in patients with acute CI, reflecting the rapid progress of the

Table 5. Secular Trend of Risk Factors and Subtypes in Patients with First-ever Intracerebral Hemorrhage

	1995-99 (n = 992)	2000-04 (n = 1075)	2005-09 (n = 1028)	2010-14 (n = 972)	2015-18 (n = 904)	P-value
Age, year	58.3 ± 16.8	57.6 ± 17.6	59.3 ± 17.2	59.9 ± 16.8	60.0 ± 16.7	0.005
Male sex	641 (64.6)	682 (63.4)	617 (60.0)	641 (65.9)	559 (61.8)	0.056
Risk Factors						
Hypertension	734 (74.0)	778 (72.4)	754 (73.3)	757 (77.9)	695 (76.9)	0.019
Diabetes	160 (16.1)	186 (17.3)	182 (17.7)	222 (22.8)	205 (22.7)	<0.001
Hyperlipidemia	308 (31.0)	263 (24.5)	154 (15.0)	211 (21.7)	223 (24.7)	<0.001
Cardiac disease	224 (22.6)	128 (11.9)	163 (15.9)	154 (15.8)	162 (17.9)	<0.001
Atrial fibrillation	52 (5.2)	40 (3.7)	73 (7.1)	71 (7.3)	79 (8.7)	<0.001
Smoking habit	297 (29.9)	241 (22.4)	206 (20.0)	266 (27.4)	203 (22.5)	<0.001
Alcohol drinking	233 (23.5)	174 (16.2)	151 (14.7)	183 (18.8)	127 (14.0)	<0.001
ICH subtypes						
Structure lesion	52 (5.2)	89 (18.3)	76 (7.4)	71 (7.3)	68 (7.5)	0.103
Systemic diseases	137 (13.8)	153 (14.2)	132 (12.8)	113 (11.6)	112 (12.4)	0.429
Medication-related	30 (3.0)	18 (1.7)	41 (4.0)	39 (4.0)	50 (5.5)	<0.001
CAA	101 (10.2)	109 (10.1)	145 (14.1)	150 (15.4)	117 (12.9)	<0.001
HA	572 (57.7)	604 (56.2)	534 (51.9)	510 (52.5)	460 (50.9)	0.008
Undetermined	100 (10.1)	102 (9.5)	100 (9.7)	89 (9.7)	97 (10.7)	0.816
NIHSS	--	--	12 (5-21)	12 (4-24)	14 (4-25)	0.280
GCS	--	13 (7-15)	13 (8-15)	14 (9-15)	13 (9-15)	0.241
In-hospital stroke	71 (7.2)	90 (8.4)	78 (7.6)	38 (3.9)	83 (9.2)	<0.001
1-month mortality	240 (24.2)	199 (18.5)	201 (19.5)	170 (17.5)	158 (17.5)	0.001

Values are mean ± standard deviation, or median (interquartile range), or number (percentage).
CAA indicates cerebral amyloid angiopathy; GCS, Glasgow coma scale; HA, hypertensive angiopathy; ICH, intracerebral hemorrhage; NIHSS indicates National Institute of Health Stroke Scale.

concept and employment of team-based care in acute stroke management over the past decade.[22]

Generally speaking, several major factors should be considered as affecting the secular trends of stroke epidemiology. Besides the changes in lifestyle and certain environmental factors, the promotion of aggressive risk factor control, especially hypertension, may lower the incidence of hemorrhagic stroke and small vessel occlusion in ischemic stroke over time. The empirical use of advanced imaging tools may increase the detection of large artery stenosis or occlusion. Recently, the identification of AF with prolonged electrocardiographic monitoring has been the critical factor for the increasing percentage of cardioembolisms. Furthermore, the aging of the population may also increase the occurrence some age-related risk factors, such as AF and, consequently, increase the number of cardioembolic stroke cases. Most importantly, various updated stroke guidelines and hospital accreditations have emphasized the performance of the aforementioned strategies for primary or secondary stroke prevention and management. In a database of consecutive patients with acute ischemic stroke or transient ischemic attack (TIA)

admitted to the Royal Melbourne Hospital stroke unit between 2004 and 2015, the prevalence of AF increased 1.4 times over 12 years.[23] In another hospital-based registry in Ontario, the proportion of cardioembolic stroke increased from 26% in 2002 to 56% in 2012, but AF increased only from 7% to 11%.[24] In the Athens Stroke Registry, between 1993 and 2012, the rate of newly-diagnosed AF increased significantly, as did the proportion of AF patients on proper antithrombotic treatment.[25]

Previously, similar studies of longitudinal stoke epidemiology had different results, which may be influenced by ethnicity, region, lifestyle, medical system and other factors.[26, 27] Therefore, results from local data in Taiwan are unique and irreplaceable. The greatest advantage of this study is the data generated from a prospectively gathered stroke registry with high quality. However, the NTUH is a tertiary referral center which may be biased toward selecting more serious patients. To minimize selection bias, we recruited acute stroke cases not only from the neurological ward, but also from any patient who had a stroke or TIA before being brought to our emergency room, as well as from all in-hospital stroke patients. Another study limitation would be that the interpretation of stroke etiology may be restricted to our hospital, and the changes in etiology may also be influenced by patients' tendency to seek medical care and changes in the natural population over time.

In conclusion, there were secular trends of an increasing percentage of ischemic stroke, especially AF-related, and a decreasing percentage of ICH, especially hypertension-related, among first-ever acute stroke patients over the past 20+ years in The NTUH Stroke Registry. Further studies with multi-center or population-based designs are needed to determine the changes over time in stroke subtypes and the stroke risk factors in Taiwan.

Disclosures of conflicts of interest

The authors report no conflicts of interest. All authors have seen and approved the final version of this manuscript, had full access to all of the data in the study, and take responsibility for the integrity of the findings and the accuracy of analyses.

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中風類型的年代變遷：1995-2018年臺大醫院中風登錄研究

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臺大醫院神經部暨腦中風中心

摘　要

背景與目的：中風登錄可提供相關風險因子、機轉、治療和預後的重要資訊。本研究探討1995至2018年的臺大醫院中風登錄的中風亞型的年代變遷長期趨勢。

方法：臺大醫院中風登錄於1995年1月開始，所有到院前10日或住院中發生中風均納入，至2018年將24年期間分為5個時期：1995-1999、2000-2004、2005-2009、2010-2014和2015-2018。分析了缺血中風、腦出血中風與蜘蛛膜下腔出血、及中風亞型及危險因子的長期年代變化。

結果：24年期間的初發中風共有22,803例(男性57.9%；平均年齡64.5 ± 15.5歲)。腦梗塞的百分比從1995-2009年的70.5%輕微增加到2010-2018年的72.9% (72.9%)，而腦出血的百分比則相對下降(23.9%至21.3%)。腦梗塞的心因性栓塞從1995-1999年的19.9%顯著增加到2015-2018年的28.5%，伴隨著心房顫動也明顯增加(1995-1999年為17.6%，2015-2018年為25.7%，$p < 0.001$)。2005年之後，靜脈或動脈內再灌注治療的百分比顯著增加，並在2015-2018年達到12.4%。腦出血的腦澱粉樣血管病變和藥物相關性出血顯著增加(分別為10.2%至12.9%和3.0%至5.5%，$p < 0.001$)，但高血壓性血管病顯著下降(57.7%至50.8%，$p = 0.008$)。

結論：1995至2018年間，初發中風患者的心因性腦栓塞和澱粉樣血管病變的腦出血顯著逐漸增加。

關鍵詞：腦出血、缺血中風、蜘蛛膜下腔出血、中風流行病學、年代變遷

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Editorial

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Tang *et al*. wrote a research paper using National Taiwan University Hospital (NTUH) Stroke Registry to explore the secular change of stroke subtype, risk factors, and etiologies from 1995 to 2018.[1] They found cardioembolism and atrial fibrillation increased significantly over this period. Using the entire population in Taiwan by National Health Insurance Research Database also obtain similar result of increase of atrial fibrillation.[2] The higher percentage of atrial fibrillation in NTUH registry than in nationwide data (25% vs 10%) probably because NTUH is a tertiary referral hospital which likely to receive more serious patients and many of them may be caused by atrial fibrillation.

There was misunderstanding that frequency of young stroke was increasing and the result of this study rebutted such myth. Since smoking is a major risk factor for young stroke, decreasing frequency of smoking habit may contribute, at least partially, to lower frequency of young stroke.

Although frequency of hypertension increased over time in both ischemic and hemorrhagic stroke, the percentage of hypertensive-related intracerebral hemorrhage and lacunar stroke, also hypertension related, decreased. Increase of hypertension frequency may be explained by increased awareness of the importance of hypertension resulting in more frequent rendering and recall of diagnosis. Even the frequency of hypertension increased, baseline blood pressure might decrease steadily over time period, as shown in a previous study,[3] which may explain the decease of lacunar stroke and hypertensive-related intracerebral hemorrhage. However, baseline blood pressure was not available in this study.

This study provide overview of ischemic and hemorrhagic stroke over 24-year period in a tertiary hospital and such information is helpful for both clinical practice and future stroke research in Taiwan.

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個案報告

Recurrent Embolic Strokes of Undetermined Source in A Patient with A Remote History of Endometrial Cancer : A Case Report

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ABSTRACT

Objective: Cerebral infarction is relatively common in patients with active cancer. However, evaluation and management of cryptogenic stroke in patients with a remote history of cancer are challenging.

Case report: We present the case of a 58-year-old woman with a history of endometrial cancer in complete remission who experienced two episodes of embolic stroke of undetermined source. Warfarin was prescribed for stroke prevention. Three months later she presented to the emergency department with left chest pain, and a moderate pleural effusion was found. Multiple masses were discovered in the left pleura, and pleural fluid cytology revealed malignant cells. Recurrence of endometrial cancer with distant metastasis was suspected. Blood tests indicated elevated D-dimer. During hospitalization, there was acute infarction of the thalamus bilaterally. Recombinant tissue plasminogen activator was administered with improvement of neurological deficits. Recurrent multifocal cerebral infarctions and hemorrhage occurred afterwards, however, and the patient eventually died.

Conclusion: In patients with a remote history of cancer, unexplained embolic stroke and elevated D-dimer level should raise suspicion of cancer recurrence even when imaging study and tumor marker results are negative. In cancer-associated stroke patients, an elevated D-dimer level also implies poor survival.

Keywords: D-dimer, endometrial cancer, cryptogenic stroke, embolic stroke of undetermined source.

Introduction

For cancer patients, cerebral infarction is relatively common with an occurrence rate as high as 15%.[1] Several mechanisms causing cancer-related ischemic stroke have been reported, including conventional pathway, direct tumor effects, cancer complications such as coagulopathy and infections, and therapeutic and diagnostic interventions.[2] Among them, hypercoagulopathy is the most common cause of ischemic stroke in cancer patients. In active cancer patients, strokes are often categorized as "of undetermined etiology" or as "other determined etiology" using the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) classification system.[3] In cryptogenic

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stroke, patients with cancer often have high D-dimer levels and multiple lesion patterns in several vascular territories,[4, 5] as reflected in the reduced survival rates. Consequently, these patients need specific consideration and individualized treatment.

In this paper, we describe the case of a 58-year-old woman with a remote history of endometrioid adenocarcinoma in complete remission who experienced two episodes of embolic stroke of undetermined source followed by recurrent multifocal cerebral infarctions and hemorrhages.

Case Report

A 58-year-old woman presented to the emergency department with left chest pain of 3-day duration which radiated to the back. She had a history of endometrioid adenocarcinoma (Stage IA by FIGO staging system; pT1aN0M0 by TNM classification) and received a total abdominal hysterectomy with bilateral salpingo-oophorectomy as well as complete radiotherapy 3 years previously. She underwent regular examinations following the initial treatments, and the most recent abdominal and pelvic computed tomography (CT) scans performed 8 months before her first embolic stroke showed no evidence of cancer recurrence.

The patient had been hospitalized twice due to embolic stroke 8 and 3 months prior to the current admission, respectively. The first time, she had infarcts of the right corona radiata, insula, parietal and temporal lobes, as well as left occipital and frontal lobes (Figure 1). Her

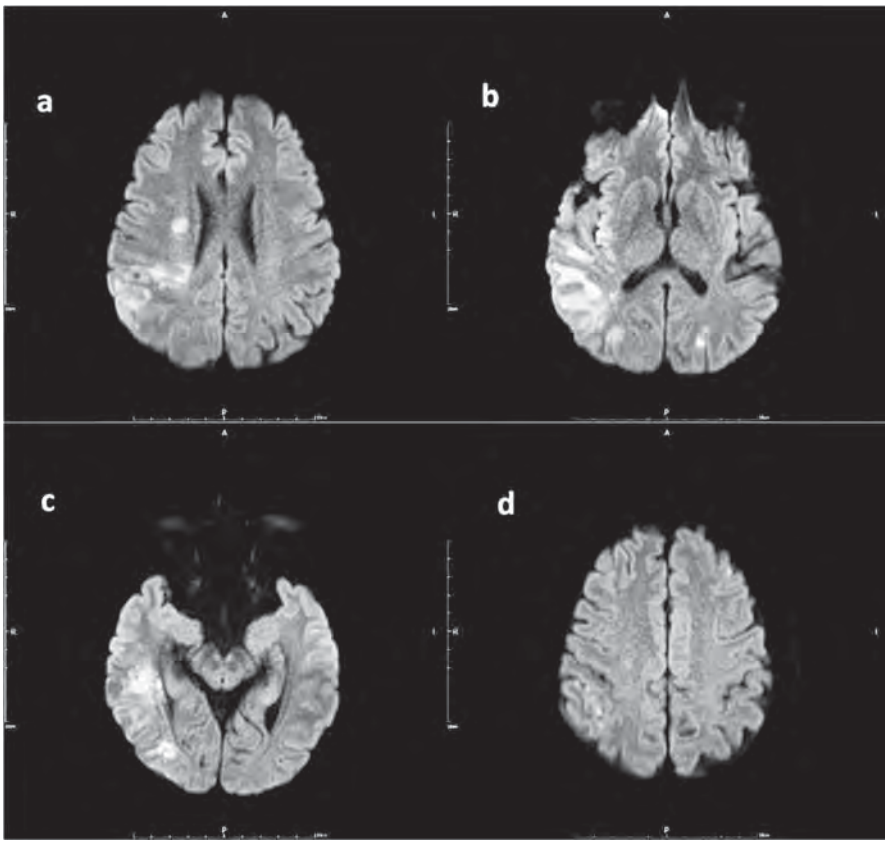

Figure 1. Diffusion-weighted images show multiple areas of restricted water diffusion in the (a) right corona radiata and parietal lobe, (b, c) right insula, temporal lobe, and left occipital lobe, and (d) right parietal and left frontal lobes, findings consistent with embolic infarcts.

National Institutes of Health Stroke Scale (NIHSS) score was 3 and Modified Rankin Scale (MRS) was 2 after discharge. No remarkable etiologies were found after detailed examinations for cardioembolism, tumor markers, autoimmune disease, and hematologic disorders. Chest X-ray imaging and abdomen and pelvis CT with contrast showed no remarkable findings. Ticlopidine 100 mg three times a day was prescribed initially; this was later switched to Dabigatran 150 mg two times a day under the impression of embolic stroke of undetermined source (ESUS). However, a second ischemic stroke occurred 5 months later with infarcts in the left occipital lobe, right frontal lobe, and bilateral cerebellum (Figure 2). NIHSS and MRS were unchanged from the first discharge. No specific etiologies were noted after surveys including transesophageal echocardiography. Consequently, the two episodes of ischemic strokes were classified as "of undetermined etiology" by TOAST classification. The D-dimer level was mildly elevated (0.93 mg/L; normal range: <0.55 mg/L). Warfarin 3.5 mg per day was prescribed for stroke prevention thereafter.

On arrival, her vital signs were stable, and crackles were heard on left chest auscultation. Chest X-ray revealed a moderate left-sided pleural effusion. Chest CT showed multiple masses in the left pleura with effusion and atelectasis of her lung, suggestive of metastases. Blood tests revealed markedly elevated D-dimer (18.36 mg/L) and tumor markers (CA-125: >200 U/ml, normal range: <35 U/ml; CA153 >150 U/ml, normal range: <30 U/ml). Recurrence of endometrial cancer with distant metastasis was suspected.

After withholding warfarin for 4 days to

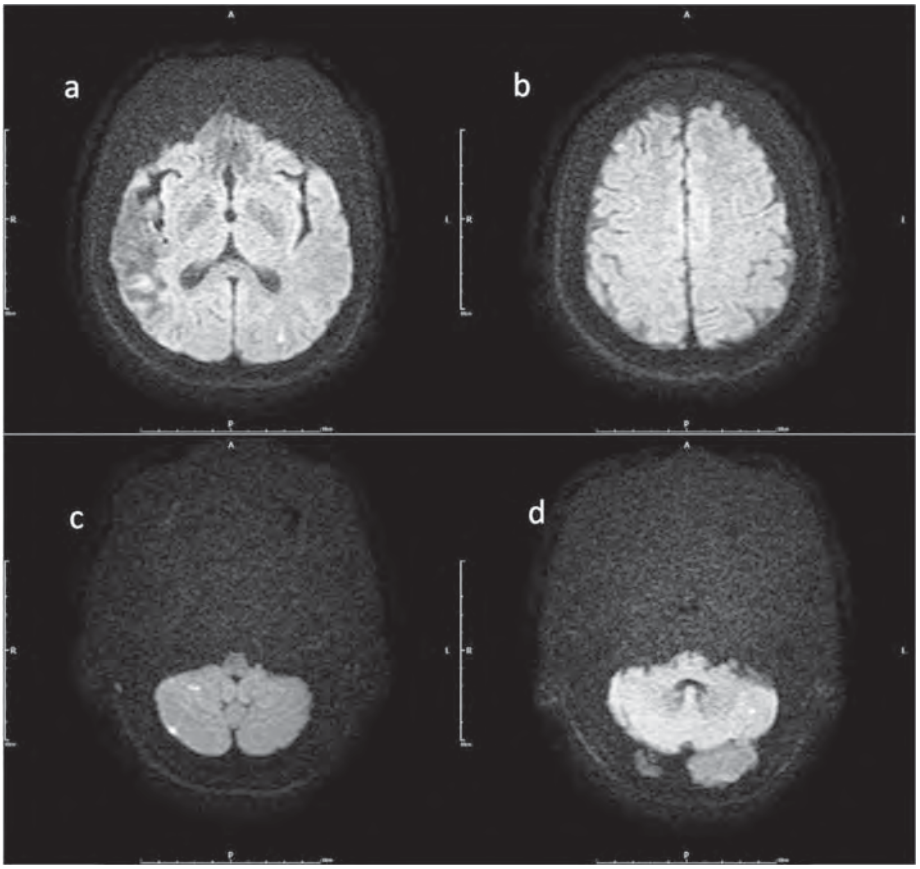

Figure 2. Diffusion-weighted images show multiple embolic infarcts involving (a) left occipital lobe, (b) right frontal lobe, and (c, d) bilateral cerebellum.

prepare for surgery, the INR level decreased from 2.6 to 1.3, and she experienced a sudden onset of consciousness change [Glasgow Coma Scale (GCS) was E1V1M2]. Acute infarcts in the bilateral ventral thalami were found (Figure 3). Recombinant tissue plasminogen activator (rt-PA: 0.7 mg/kg) was administered immediately. The NIHSS score dropped from 22 to 8, and the GCS was 15 one day later. Nonetheless, 8 days after rt-PA treatment her consciousness deteriorated (GCS was E2V1M4) again, and brain CT revealed an acute hematoma (2.1×1.9 cm^2) in the right frontal lobe (Figure 4). Thoracocentesis of a left pleural effusion was dark-red in color, and fluid cytology revealed abnormal cells with hyperchromatic nuclei and high nuclear-cytoplasmic ratio, suggestive of malignant cell morphology. Persistently high D-dimer level (> 35 mg/L) was then noted. Two weeks after rt-PA treatment, brain CT revealed a newly developed infarct in the right cerebellum and left parietal lobe with hemorrhagic transformation. Her consciousness level progressively declined from stupor to coma. The patient subsequently died due to respiratory failure.

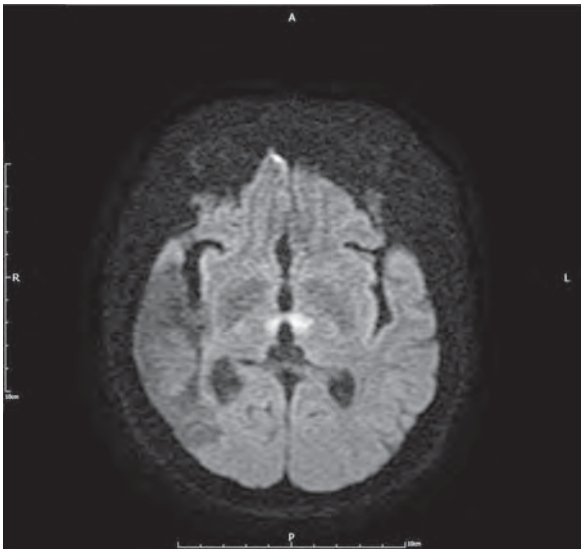

Figure 3. Diffusion-weighted image reveals water diffusion restriction in the ventral thalami bilaterally, suggesting acute infarcts.

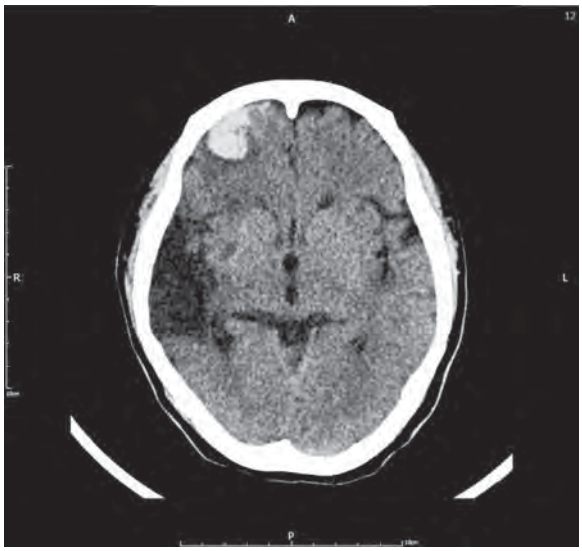

Figure 4. Without-contrast CT image shows a 2.1×1.9 cm^2 hyperdense lesion in the right anterior frontal lobe as well as a surrounding hypodense area, indicating acute intracranial hematoma with perifocal edema.

Discussion

Direct tumor effects, coagulopathy, cancer-related therapies, invasive procedures and infections are probable pathways leading to a cancer-associated stroke.[2] Hypercoagulability is common in patients with cancer and is the main factor in mechanisms of stroke. In addition, thrombotic events may precede the diagnosis of malignancy.[6]

The D-dimer is a degradation product of crosslinked fibrin protein, thus elevated D-dimer levels imply activation of the coagulation system and a hypercoagulable state.[7-9] An elevated D-dimer level and presence of multifocal vascular lesions are independent factors related to the presence of active cancer in cryptogenic stroke patients.[10] D-dimer also can serve as a predictor of early neurologic deterioration and survival rate in the patient with cryptogenic stroke and active cancer.[11, 12]

Endometrial cancer is the most common gynecological malignancy in developed countries. Most of these cancers are diagnosed at an early stage (FIGO I-II) and are associated with a good prognosis following the treatment.[13] However, the recurrence rate was approximately 10-15%, and the majority (80-90%) of recurrences takes place within three years.[14] Age, FIGO grade, nuclear grade, time to recurrence, and response to treatment were found to be independent and significant prognostic factors for overall survival rate.[15]

In this case, the recurrent multifocal ischemic and hemorrhagic strokes during admission were likely due to cancer-associated hypercoagulation, and the rapid surge in the D-dimer level reflected the patient's poor prognosis. The first two episodes of embolic strokes in this patient were designated as ESUS after standard diagnostic evaluation. Although ESUS refers to non-lacunar infarct with unknown origin, it is usually caused by relatively smaller emboli from valvular and arterial sources rather than larger emboli originating in the cardiac chambers.[16] Cancer–associated coagulopathy and embolism is one of other potential causes of ESUS. In patients with ESUS and remote history of cancers, the risk of cancer recurrence should be carefully evaluated even when imaging and tumor marker studies are all negative. Close imaging follow-up with CT, the mainstay modality for surveillance is recommended, and more comprehensive studies to survey for malignancy, such as positron emission tomography (PET), may be taken into consideration.

The choice of antithrombotic agents remains challenging for stroke prevention in cancer patients. Low molecular weight heparin may be the first choice for secondary prevention of cancer-associated stroke.[2] Among patients with cancer-associated stroke, the recurrence rate is possibly lower for enoxaparin than warfarin.[7] Tissue factor pathway inhibitor released by heparin can inactivate tissue factor which triggers thromboembolic events in cancer patients and explains its superiority.[7] There are also many ongoing clinical trials comparing the benefits and risks of each antithrombotic agent, including new oral anticoagulants, aspirin and warfarin. Long-term subcutaneous heparin therapy may lower the recurrence of cancer-associated stroke.[17] However, deterioration of cancer, physical and mental stress associated with injections, and hemorrhagic complications are the main reasons for discontinuation of or declining treatment with subcutaneous heparin therapy.[17] Precise enoxaparin doses and treatment periods with the lowest hemorrhagic complications or clinical deterioration remain to be established for prevention of stroke.

In conclusion, tumor recurrence should be considered in patients with unexplained embolic strokes and a remote history of cancer. D-dimer levels and detailed imaging studies for risk stratification of recurrent thromboembolic events are included in acute inpatient stroke evaluations. Early recognition and management may improve prognosis and clinical outcome.

Conflicts of Interest Statement

none

Acknowledgments

none

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子宮內膜癌病史個案反覆發生不明原因之栓塞性中風：一病例報告

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摘　要

背景：針對有癌症病史但尚無證據證明其癌症復發的個案若發生不明原因中風，處置仍具相當挑戰性。在具癌症病史發生不明原因中風的病人當中，高D-雙合蛋白血中濃度及多發性與多血管性病灶可能反映出癌症的存在或復發。

病例報告：58歲女性先前有子宮內膜癌及兩次不明原因栓塞性中風之病史。當時使用warfarin作為預防中風的主軸藥物。此次因胸痛、惡性肋膜積水及血中D-雙合蛋白濃度上升住院治療。在住院期間，發生兩側丘腦梗塞故施打靜脈血栓溶解劑。然而，數次多發性栓塞性腦部缺血性梗塞及出血卻接踵發生，最後這名病人病逝。

結論：儘管規則腫瘤追蹤皆為正常，包含電腦斷層掃描及腫瘤指數，但兩次無法解釋之栓塞性中風及D-雙合蛋白輕微上升都可能暗示一個潛藏癌症之存在。更全面性的腫瘤檢查如正子掃描應及早考慮。在癌症相關之中風個案中，高D-雙合蛋白也反映出預後不佳。低分子量肝素或許為目前二度預防癌症相關之中風的首選藥物。

關鍵詞：D-雙合蛋白、子宮內膜癌、原因不明中風、來源不明之栓塞型中風

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個案報告

Endovascular Thrombectomy for Acute MCA Occlusion Caused by Tumor Embolus of Rhabdomyosarcoma: A Case Report

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ABSTRACT

Background: Cerebral tumor embolism is a rare stroke etiology among cancer patients with cancer-related thrombosis. Here, we reported one case with rhabdomyosarcoma, who presented with acute right middle cerebral artery (MCA) occlusion caused by tumor emboli and treated successfully with suction thrombectomy.

Case Report: A 32-year-old woman, with epitheloid rhabdomyosarcoma of the left thigh and multiple lung metastases, presented with acute onset left upper limb weakness and disorganized speech. Brain CT angiography showed partial occlusion of the right distal M1 segment of the MCA and suspected brain metastases at the right temporo-parietal lobe. Intravenous thrombolysis was not indicated for intra-axial brain tumor. Endovascular thrombectomy was not performed initially due to possible brain tumor related seizure and low NIHSS score. However, her symptoms progressed (NIHSS from 6 to 12) 2 hours 45 minutes after symptoms onset and suction thrombectomy was performed in the right M1 with TICI 2b immediately. The retrieved embolus reported metastatic epitheloid rhabdomyosarcoma pathologically. Her neurological status improved in 3 days with mild anomic aphasia. (NIHSS = 1) However, the patient died 1 week after the stroke onset due to acute respiratory failure.

Conclusion: Hitherto, acute large cerebral arterial occlusion caused by tumor embolus by epitheloid rhabdomyosarcoma has not been reported. Although there is a high risk of recurrent systemic tumor embolization and poor survival outcome, endovascular thrombectomy is effective in achieving revascularization and improving ischemic neurological deficit.

Keywords: cancer, ischemic stroke, rhabdomyosarcoma, tumor embolism.

Background

Cerebral tumor embolism is a rare stroke etiology among cancer patients with cancer-related thrombosis. In an early review, among 256 cancer patients with large artery occlusion, only 2 cases are caused by tumor emboli.[1] Primary or metastatic lung tumor with left atrial or pulmonary venous invasion, cardiac metastases or surgical intervention for lung tumors has been reported to be risk factors for cerebral tumor embolism. Here, we reported one case with rhabdomyosarcoma and systemic metastases, who presented with right middle cerebral artery (MCA) occlusion caused by

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tumor emboli and treated successfully with suction thrombectomy.

Case Report

A 32-year-old woman was diagnosed as epitheloid rhabdomyosarcoma of the left thigh with systemic metastases to bilateral lungs, liver and spleen since 9 months ago (Figure 1a). She was presented with acute onset left limb weakness and disorganized speech. Her initial NIHSS was 6, including impaired fluency, left side hemianopia and left central type facial palsy. Brain CT angiography showed partial occlusion of the right distal M1 segment of the MCA, together with a 5.7 cm enhancing mass at the right temporo-parietal lobe, suspected brain metastases (Figure 1b,c). Intravenous thrombolysis was not indicated for

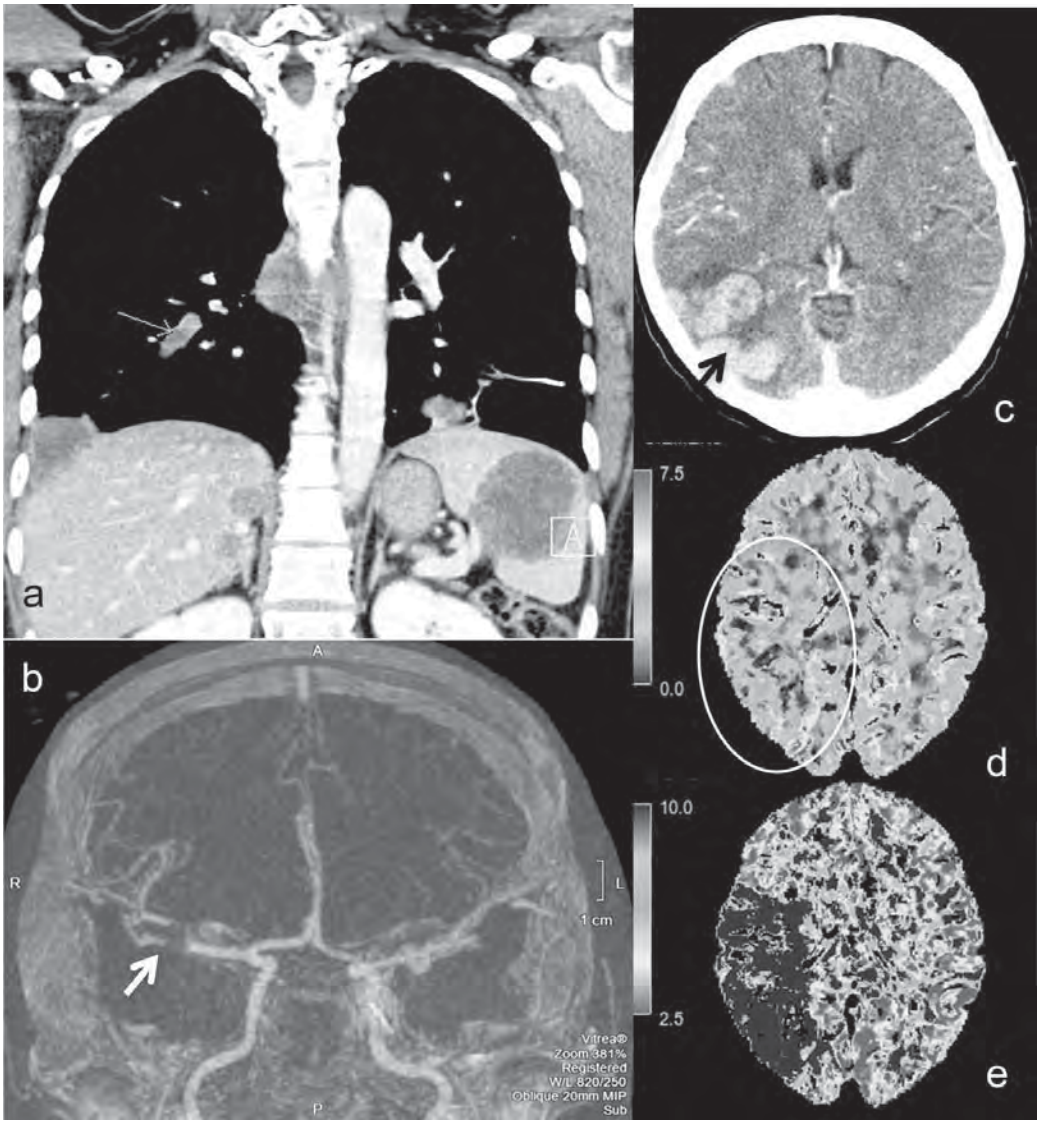

Figure 1. (a) Follow-up whole body CT with contrast, 3 weeks prior to stroke onset, reveals multiple metastases over bilateral lungs, spleen, mediastinal lymph node, together with thromboembolism in the right lower lung. (arrow) (b) CT angiography shows a clot (arrow) in the distal M1 segment of the right MCA with partial occlusion. (c) Brain CT with contrast shows a 5.7 cm lobulated enhancing mass at the right temporo-parieto-occipital lobe (arrow), indicating brain metastases. (d-e) CT perfusion shows prolonged mean transit time at the right fronto-parieto-temporal lobe with preserved cerebral blood volume. (as indicated of the white-circled region)

intra-axial brain tumor. Though with penumbrae (Figure 1d,e), endovascular thrombectomy was not performed initially due to possible brain tumor related seizure and relatively low NIHSS score. However, her symptoms progressed (NIHSS = 12) 2 hours and 45 minutes after symptoms onset. Suction thrombectomy was performed 3 hours and 10 mins after stroke onset. The occluded right MCA M1 segment was recanalized with TICI 2b in 7 minutes from the puncture time and in 32 minutes from onset time of worsening symptoms (Figure 2a,b). Two fragments of thrombi with reddish yellow and elastic, 1.0 × 0.1 × 0.1 cm in size was retrieved (Figure 2c).

The retrieved thrombi were analyzed pathologically. High-grade epithelioid to pleomorphic spindle cells arranged in sheets with geographical necrosis admixed with blood clots were seen. Immunochemical staining shows positive for desmin, and focally positive for myogenin. Considering her clinical history, a metastatic epithelioid rhabdomyosarcoma was

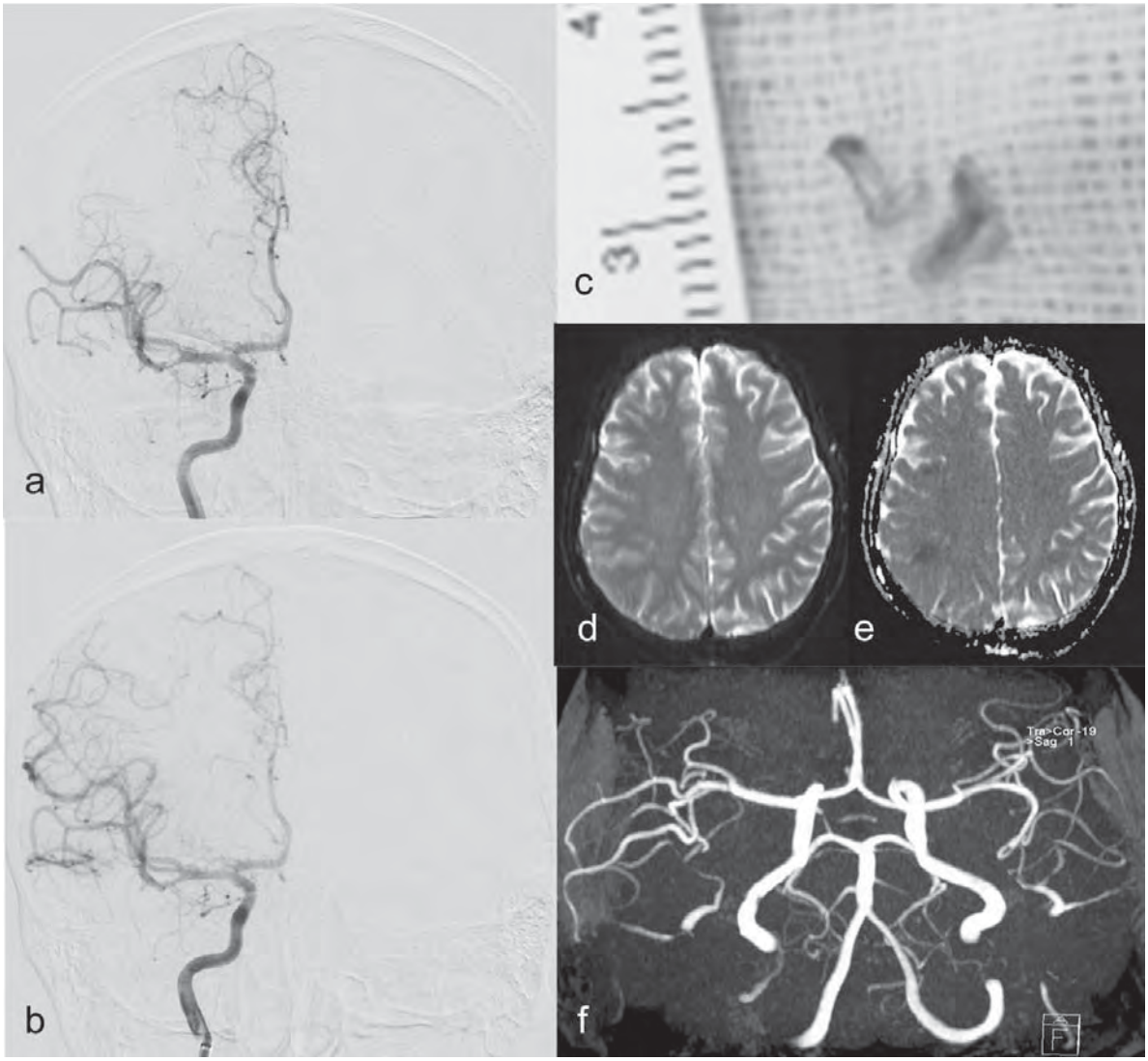

Figure 2. (a) Diagnostic angiography shows a clot causing partial occlusion of the distal M1 segment of the right MCA. (b) Recanalization of the right MCA after suction thrombectomy of the right M1 clot, TICI 2b obtained in 7 minutes from puncture time. (c) Two fragments of thrombi, reddish yellow and elastic, 1.0 × 0.1 × 0.1 cm in size. (d-e) DWI and ADC showed scattered foci of diffusion restriction in the right cerebrum. (f) MRA shows no significant abnormality of intracranial vessels.

diagnosed.

Her neurological status improved significantly with only mild reading and naming difficulties (NIHSS = 1) on the third day. The D-dimer level was slightly elevated (2.26 μg/mL) and the HbA1C and lipid profiles were within normal limits. No atrial fibrillation was detected by 12-lead electrocardiogram. Follow-up brain MRI showed scattered foci of diffusion restriction in the right cerebrum and no significant large intracranial arterial stenosis was revealed by contrast enhanced MRA (Figure 2d-f). Echocardiogram and whole body CT were arranged for survey of tumor emboli and cancer status. However, before the imaging study, acute respiratory failure developed rapidly and she died 7 days after stroke onset.

Discussion

Hitherto, acute large cerebral arterial occlusion caused by tumor embolus in epitheloid rhabdomyosarcoma has not been described before. Lung malignancies, other type of soft tissue sarcoma and cardiac myxoma were once reported with major cerebral infarction from tumor embolus.[2-7] In previous case report, cerebral tumor embolism is most commonly seen in cancer patients with pulmonary and cardiac involvement, which included pulmonary venous invasion or left atrial invasion caused by primary or metastatic malignant lung tumor or direct cardiac metastases.[2-7] Several reported cases experienced acute stroke during lung surgery, which may be caused by spontaneous tumor embolization or release of tumor thrombi after surgical manipulation.[2] Concurrent systemic embolization, including splenic artery, renal artery or the artery of four extremities may also be presented in cases with cerebral tumor embolism.[8]

In our case, no classic stroke risk factors, including hypertension, diabetes, dyslipidemia, smoking or atrial fibrillation were found. Though seizure was considered initially due to newly found brain metastases with fluctuated clinical presentation, cancer-related thrombosis was still the first possible etiology to be considered. Advanced cancer stage, recent exposure of chemotherapy and use of the anti-angiogenic agents have been reported to be related with increased risk of cancer-associated thrombosis,[9] as our case, who had advanced sarcoma and just received chemotherapy with bevacizumab 3 weeks before stroke onset. However, the slightly elevated serum D-dimer level, which usually presented with higher level in cancer-related stroke,[10] does not support the cancer-related thrombosis. The gross appearance of the retrieved thrombus may be both yellowish/elastic in tumor embolus and cancer-related thrombosis.[3, 4, 11] Not until the confirmation of pathology with immunochemical staining could we make the diagnosis of cerebral tumor embolism. Considering her previous history of tumor thromboembolism over right lower lung with multiple lung and systemic metastases, our patient is at high risk of systemic tumor embolism.

During the clinical practice in our hospital, retrieved thrombus was always sent to pathological examination, which may provide the information for clarifying the stroke etiology, including hypercoagulability in cancer patient or cerebral tumor embolism. Once the diagnosis of tumor embolism confirmed, immediate survey for emboli source and systemic organ involvement from tumor emboli should be considered. However, the echocardiogram and whole body imaging are not readily to be performed before the clinical condition deterioration. Though the patient was in advanced stage of cancer with poor prognosis, her

functional outcome before the stroke episode still remained independent and the clinical deterioration after stroke stabilized was also unexpected. Together with timely diagnosis and short onset to puncture time, intra-arterial thrombectomy was still considered a cost-effective intervention for this patient.

In conclusion, cerebral tumor embolism is a rare cause among cancer patients presented with acute ischemic stroke. Suction thrombectomy is an effective treatment in large arterial occlusion caused by tumor emboli. Once the pathology of thrombus confirmed the diagnosis, pulmonary and cardiac survey are suggested for risk assessment of recurrent stroke and systemic tumor embolization. Although the patient is at advanced cancer stage with high risk of recurrent systemic tumor embolization and poor survival outcome, endovascular thrombectomy is effective in achieving revascularization and improving ischemic neurological deficit.

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動脈取栓術於橫紋肌肉瘤的瘤栓致急性中大腦動脈栓塞：一病例報告

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摘　要

背景：在癌症合併急性缺血性中風，腫瘤栓子致急性大腦動脈栓塞十分罕見。此病例報告將呈現因瘤栓引起右中大腦動脈栓塞後，成功接受經動脈取栓術的橫紋肌肉瘤個案。

病例報告：32歲女性被診斷左大腿之上皮樣橫紋肌肉瘤併多處肺部轉移，呈現突發左上肢無力及語言表達困難，腦部電腦斷層血管攝影顯示右側中大腦動脈第一段血管阻塞，同時新發現一右側顳-頂葉處的轉移性腦瘤。軸內腦瘤為血栓溶解治療禁忌故未施打。因無法排除腦腫瘤引起之癲癇及相對輕微的臨床症狀，未在第一時間考慮動脈取栓術。然而，病人因初始症狀2小時45分鐘後症狀惡化，美國國家衛生院腦中風量表分數由6分進展至12分，因此施予抽吸取栓術，於取栓術開始起算7分鐘內移除右中大腦動脈之血栓，重新開通血管(TICI 2b)，取出血栓的病理報告為轉移性橫紋肌肉瘤。3天後，病人的神經功能缺損進步至只有輕微命名困難。然而，病人因急性呼吸衰竭惡化，於中風1週後病逝。

結論：迄今，尚未有病例報告過上皮樣橫紋肌肉瘤之瘤栓引起的急性腦部大動脈栓塞。雖然病人因癌症末期預後不佳及具全身多處血管栓塞之風險，經動脈取栓術在瘤栓引起之大血管急性腦中風仍為一有效開通血管及改善神經學症狀的治療方式。

關鍵詞：癌症、缺血中風、腫瘤栓子、橫紋肌肉瘤

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7. 附表，每一表格需有一簡短標題，內容儘可能使用中文必要時得中、英文並列；表格中勿用縱線，橫線也盡可能避免。圖片請盡量提供電子檔，解析度至少為 300 像素（dpi），圖片格式為 JPG 檔。圖說明以中文為限，儘量簡潔。
8. 引用他人之表格或圖示須徵得著作權所有人同意，否則該圖表不予刊登。若使用已發表的圖片表達概念者，作者需重新製作附圖且避免侵犯版權，必要時作者必須簽結必要文件，以負完全法律責任。
9. 封面頁資料：包括論文屬性、標題、作者姓名、任職單位，及投稿者與通訊作者之聯絡電話（含手機）、通訊地址、電子郵件信箱等資料，以方便聯絡。
10. 參考文獻：文中引用參考文獻按先後順序，以阿拉伯數字採右上標示法；引用相連篇數 3 篇（含）以上，其號數以連號連之，如 1, 3-5。參考文獻書寫方式請參照Index Medicus，雜誌－著者姓（全）名（縮）：題目。雜誌名、年份、卷、起迄頁數。著者 6 人（含）以下，所有著者全列；著者 7 人以上，則列出前 3 人，後面加“*et al*”或“等”表示之。範例如下：
    (1) Hsieh FI, Lien LM, Chen ST, *et al*. AHA/ASA Get With The Guidelines – stroke performance indicators: surveillance of stroke care in the Taiwan Stroke Registry. *Circulation* 2010;122:1116-1123. doi: 10.1161/CIRCULATIONAHA.110.936526.
    (2) Tsai HH, Pasi M, Tsai LK, *et al*. Distribution of lacunar Infarcts in Asians with intracerebral hemorrhage: an MRI and amyloid PET study. *Stroke* 2018;49:1515-1517. doi: 10.1161/STROKEAHA.118.021539.
    (3) Chung CP. Types of stroke and their differential diagnosis. In: Caplan LR, Biller J, Leary MC, Lo EH, Thomas AJ, Yenari M, Zhang JH, eds. Primer on Cerebrovasculasr Diseases, 2nd ed. London, United Kingdom, Academic Press, 2017:372-376.
    (4) 湯頌君、鄭建興、廖漢文、高明見：急性缺血性腦中風治療的最新發展。台灣醫界 2017;60:178-181。
11. 來稿一經刊載，版權屬本會所有，未經書面同意，不得以任何方式轉載。校對由著者負責初校，校對時請避免在原稿中追加字句或大幅修改。

「台灣中風醫誌」投稿聲明書

一、本人（等）擬以下列題目（請勾選一項）：□指引、□綜論、□原著、□病例報告、□專題報導、□其他報告，申請投稿於「台灣中風醫誌」。

題目：_____

作者：_____、_____、_____、_____、_____、_____、_____、_____、_____、_____

二、本文稿過去未曾發表於國內外其他期刊雜誌，且本人（等）同意本文稿在貴刊接受審查期間及刊登於貴刊後，不投刊其他期刊雜誌；同時接受貴刊投稿之稿約規定。

三、本文稿所有列名之作者皆擔保本文稿係原創性著作，並擔保本文稿未含有誹謗或不法之內容，且未侵害他人智慧財產權。若因審稿、校稿因素導致著作名稱變動，同意視為相關著作，不影響本同意書之效力。

四、本文稿所有列名之作者皆同意文稿之所有內容，並同意投稿於貴期刊。本文稿所有列名之作者皆為實際參與研究及撰述，並均能擔負修改及答覆審查者之意見。

五、如經貴編輯委員會同意刊登於「台灣中風醫誌」，本文稿所有列名之作者皆同意本文稿之著作權溯及投稿時移轉予台灣中風學會所有；除商得台灣中風學會同意外，不得轉載於其他雜誌。惟作者仍保有集結出版、教學及個人網站等無償使用之權利。

通訊作者代表所有作者簽名：_____

西元_____年_____月_____日

健康樂活 告別中風 — A Stroll A Day Keeps Stroke Away

台灣腦中風學會2019學術研討會

2019 Annual Meeting of Taiwan Stroke Society

22 - 24 Nov 2019 | 嘉義 Chiayi

會議主題

急性腦梗塞治療：動脈血栓移除治療、靜脈溶栓治療 | 急性中風緊急醫療、遠距中風醫療、檢傷、中風團隊 | 中風急性後期照護、長期照護 | 血管性失智症、小血管疾病 | 腦內出血、蜘蛛膜下腔出血、外科治療 | 急性中風影像 | 心房顫動偵測與治療 | 開放性卵圓窗偵測與治療 | 仿似中風與中風之不典型表現 | 人工智慧在醫學上之應用 | 神經超音波工作坊 | 其他

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Acute stroke therapy：endovascular thrombectomy, intravenous thrombolysis | Emergency medical service, telestroke, triage, stroke team | Post-acute care, long-term care | Vascular dementia, small vessel disease | Intracerebral hemorrhage, subarachnoid hemorrhage, neurosurgery | Imaging of acute stroke | Atrial fibrillation: detection and treatment of atrial fibrillation | Patent foramen ovale: detection and treatment | Stroke mimics and chameleons | Artificial intelligence in medicine | Neurosonology workshop | Others

嘉義是台灣越來越夯的城市之一，位於著名景點阿里山腳下，這個城市有著豐富的文化與歷史淵源。近來，嘉義令人垂涎的美食也受到國際矚目，在 Netflix 的街頭美食紀錄片中備受推崇。您可以在嘉義街頭悠閒地徜徉，由檜意生活村，沿著鐵道文化園區，一路漫步至文化路夜市。這個輕旅行必定能讓您五感滿足。

Chiayi is one of Taiwan's most up-and-coming cities. Nestled under the island's popular attraction — Alishan, it is a city of rich cultural and historical background. Recently, Chiayi's mouthwatering cuisines earned global recognition, being featured in *Street Food*, Netflix's documentary series . Take a stroll through the laid-back streets: starting from the Hinoki Village, passing by the Railroad Arts District, then wrapping up your day at the Wenhua Road night market. It will definitely be a journey that delights all your five senses.

108年度「獎勵提供心血管疾病病人戒菸服務」競賽

一、前言

國際知名醫學期刊The Lancet於2010年及2015年分析主要健康風險因子，其中菸害(含吸菸及二手菸)皆列為造成男性健康失能或死亡的第一位與第二位高風險因子。由菸害所造成的健康損失中，又以心血管疾病，例如腦中風和心肌梗塞，導致的失能或死亡比例最高。

菸品至少含有7,000種以上的物質，其中一氧化碳(CO)與血紅素的結合力遠大於氧氣，因此吸菸會造成一氧化碳進入血液中，減少我們身體的氧氣攜帶率。與一氧化碳結合的血紅素濃度在正常人體內為0.5-2%，但在吸菸者體內濃度可以高達5%，甚至可以高達10%。

這些對身體的影響可能造成紅血球質量的增加、或是血液黏滯度增高，進而影響到一些血栓事件的發生，像是腦中風和心肌梗塞。尼古丁會增加心搏量、心跳速率、血壓；除了對動脈粥狀硬化有一些影響外，尼古丁更會對動脈血管造成收縮。

吸菸也增加了身體的自由基，造成氧化壓力升高，影響動脈粥狀硬化並增加心血管疾病的機會。其實，不管是吸菸者本身或暴露於二手菸者，都造成輕重不一的傷害。據統計，和非吸菸者比較,吸菸者其冠狀動脈心臟病會多出80%的機會，二手菸的接觸者也多出30%的機會。

學會致力推動心血管疾病病人戒菸服務，期能藉此競賽降低國人動脈粥狀硬化疾病，以維護心臟血管健康。

二、主旨：

提高心血管疾病相關科醫師對心血管疾病病人戒菸治療的重視，並投入戒菸服務。

三、活動辦法及報名：

(一) 有意參與本方案之醫學中心或區域醫院，應於108年6月28日(五)前於指定網站報名，報名時應提供下列資料：該院所有參加戒菸競賽的心臟內科、神經內科及復健科專任主治醫師之姓名和身分證字號，報名表請參考台灣腦中風學會網站。

(二) 參與本方案者，應鼓勵該院心臟內科、神經內科、復健科醫師接受本學會於108年6月 22日(台北場)、6月23日(台中場)及6月23日(高雄場)辦理之戒菸治療訓練課程，獲得證書後和國民健康署簽訂合約。

(三) 參與本方案者，應辨識所有病人吸菸情形，對於吸菸個案，應直接提供戒菸服務或轉介給院內戒菸服務提供單位，並持續追蹤個案後續回診及戒菸成功情形，並至國民健康署醫事機構戒菸服務系統(VPN)填報轉介、提供戒菸服務、追蹤等相關資料。

四、參與對象：

醫學中心與區域醫院心臟內科、神經內科、復健科有簽訂戒菸服務合約之主治醫師。

五、評價指標及獎項：

(一) 戒菸轉介王：心臟內科、神經內科、復健科轉介至其他科成功收案人數。

1. 指標定義：108年7月1日至108年11月30日間，該院上述科別醫所轉介個案到其他科戒菸，其他科別成功收案總人數。(有關轉介人數規定，醫學中心須超過100例以上，區域醫院須超過60例以上，始進入評比)

2. 競賽組別分成兩組：

第一組 心臟內科醫師。

第二組 神經內科醫師+復健科醫師。

3. 獎項：醫學中心及區域醫院每組轉介成功總人數最高的前三名，各得2萬元、1萬5仟元、1萬元。

4. 備註：

(1) 其他科別係指該院主要執行戒菸服務之科別如家醫科、胸腔科等。

(2) 成功收案指個案於最後一次獲轉介後，應在7天(含)之內於其他科別接受戒菸服務(治療或衛教都計)。

(3) 轉介量以人數計，但醫院可多次進行轉介。

(4) 應至國民健康署VPN系統填報轉介個案基本資料，俾進行分析統計。數據將以108年11月30日前(含)填報的資料為準。

(二) 戒菸成功王：治療個案3個月點戒菸成功率。(有關成功王的規定，各競賽組別戒菸服務治療總人數，須超過30人，始進入評比)

1. 指標定義：

$$\frac{\text{各組3個月點戒菸成功人數}}{\text{各組戒菸治療服務總人數*}}$$

2. 競賽組別分成兩組：

第一組 心臟內科醫師。

第二組 神經內科醫師＋復健科醫師。

3. 獎項：參與本方案之醫院(不分醫學中心及區域醫院)，戒菸服務個案3個月點戒菸成功率，每組最高的前三名，各得2萬元、1萬5仟元、1萬元。

4. 備註：

(1) 考量方案期程，僅計算108年7月1日至8月31日間起始治療療程者之3個月點戒菸成功率。

(2) 服務人數及成功人數皆以登錄於國民健康署醫事機構戒菸服務系統(VPN)數據為準，因此請記得依限追蹤個案戒菸情形並登錄(以107年11月30日作為統計截止日，也就是8月31日為最後收案日，且要完成3個月VPN追蹤填報才會計入)。

(三) 戒菸服務王：醫師戒菸治療服務量

1. 指標定義：於競賽期間參與本方案醫院之合約醫師(不分科別)，個人戒菸治療服務人數。

2. 獎項：醫學中心與區域醫院各取前三名，分別可獲得 2萬元、1萬5仟元、1萬元。(若戒菸病人數相同，以醫師年齡大者為勝)

3. 備註：服務人數以108年11月30日前(含)填報於國民健康署醫事機構戒菸服務系統(VPN)數據為準。

六、頒獎：

預訂在 108年12月21日於中華民國血脂及動脈硬化學會及台灣腦中風學會合辦之戒菸研討會頒發各獎項。

七、其他：

本方案主辦單位為中華民國血脂及動脈硬化學會，指導單位為衛生福利部國民健康署，協辦單位為台灣腦中風學會。本方案因故無法進行時，主辦單位保有修改、變更或暫停本活動之權利，如有未盡事宜，悉依主辦單位相關規定或解釋辦理，並得隨時補充公告之。

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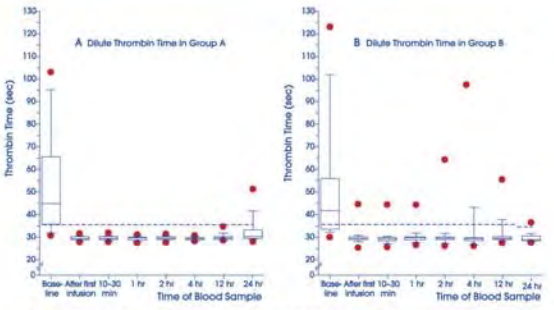
【僅限醫藥專業人員參考：處方藥物請參考衛生福利部核准仿單說明書】【使用前請詳閱說明書警語及注意事項】



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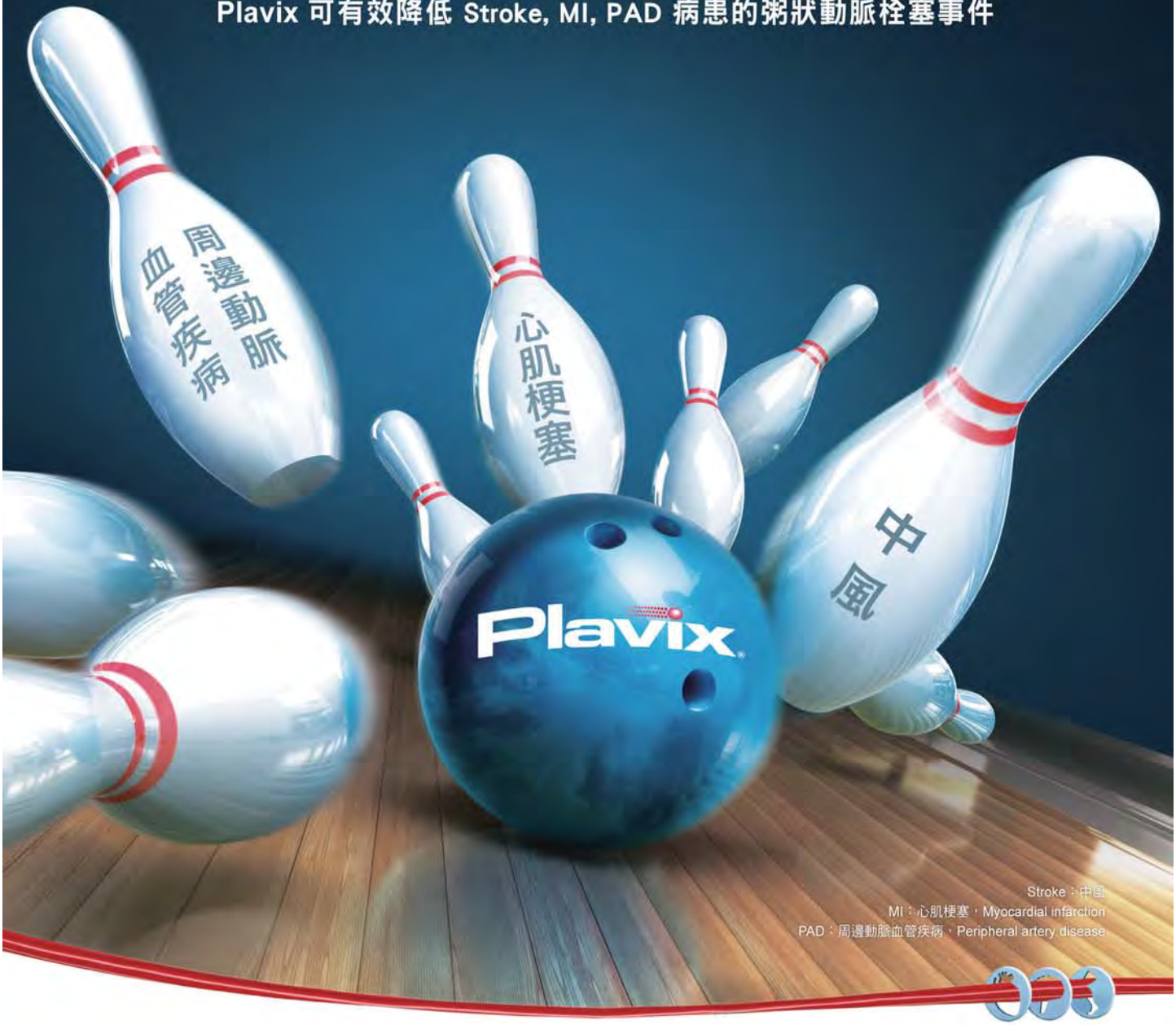

Stroke：中風
MI：心肌梗塞，Myocardial infarction
PAD：周邊動脈血管疾病，Peripheral artery disease

Plavix® 75mg 處方資訊摘要

每錠含 75mg Clopidogrel (hydrogen sulphate) 衛署藥輸字第 022932 號

【適應症】Clopidogrel適用於侧肢動脈栓塞事件的次級預防於下列病患：降低近期發生中風、心肌梗塞或周邊動脈血管疾病的侧肢動脈硬化病人之侧肢動脈栓塞事件(如：心肌梗塞、中風或其他因血管病變引起的死亡)的發生。與aspirin併用降低非ST段上升之急性冠心症(不穩定性心絞痛和非Q波型心肌梗塞)病人(包括經皮冠狀動脈介入性治療後放置支架的患者)之侧肢動脈栓塞事件。與aspirin併用可用於以內科治療的ST段上升之急性心肌梗塞病人。不適合接受Vitamin K antagonists的心房纖維顫動患者，併有至少一個發生血管事件危險因子，且屬於出血危險性低者，可與aspirin併用以預防侧肢動脈栓塞及血栓栓塞事件。包括中風。【劑量和用法】成人和老年人：Clopidogrel的建議劑量為每天75mg，一天一次，可和食物同時服用或分開服用。【禁忌】對藥品主成份或其他非活性成份過敏者，嚴重肝功能不良的患者，正在出血的患者如消化性潰瘍或顱內出血的患者，懷孕及授乳婦(請參考"懷孕和授乳"欄)。【警語及注意事項】由於有血液學方面的不良反應和出血的危險，在治療期間應檢驗血球計數，且當出現有出血的臨床症狀時應立即進行適當的檢查(請參考"不良反應"欄)，和其他抗血小板製劑一樣，clopidogrel應小心使用於可能有出血危險的病人，例如：創傷、手術、其他病理狀況或接受aspirin、肝素、glycoprotein IIb/IIIa抑制劑、非固醇類抗炎止痛劑(NSAID)包括Cox-2抑制劑，或選擇性血清素再吸收抑制劑(SSRIs)，病人應小心注意任何可能的出血徵兆，包括隱匿性的出血，特別是在治療開始的第一週及手術或侵入性心臟檢查後，由於可能會增加出血的危險，clopidogrel不建議與口服抗凝血劑併用(請參考"交互作用"欄)。【交互作用】與出血風險有關之藥物：由於潛在加乘效應可能增加出血的危險，與出血風險有關之藥物併用時應小心，口服抗凝血劑：由於可能增加出血的危險，與warfarin併用時應小心，請參考"警語及注意事項"欄。【副作用】已有超過44,000位參加臨床試驗的病人使用clopidogrel來評估其安全性，包括治療超過一年以上的12,000位病人。總體而言，在CAPRIE試驗中clopidogrel 75mg/day與aspirin 325mg/day所出現與臨床相關的不良反應相當且不受年齡，性別和種族的影響。在CAPRIE、CURE、CLARITY、COMMIT及ACTIVE-A試驗中所出現的與臨床相關之不良反應如下：除臨床試驗經驗之外，亦包含自發性不良反應通報。出血是最常被報告的上市後不良反應，大部分的回報病例均發生在用藥的第一個月內。【過量】服用過量的clopidogrel會導致出血時間延長及其他出血的併發症。若發生出血應採取適當之治療。目前並未發現clopidogrel的解毒劑。若需要立即校正過長的出血時間，輸血小板可能可以校正clopidogrel的作用。【藥理特性】藥理治療分類：非Heparin之血小板凝集抑制劑。
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