発作性心房細動を有する脳梗塞・一過性脳虚血発作患者の急性期病院退院時の抗凝固薬選択：SAMURAI-NVAF 研究

Choice of warfarin and NOACs for secondary prevention of stroke in NVAF: the SAMURAI-NVAF study

豊田一則、有廣昇司、SAMURAI 研究班

【目的】近年の脳梗塞患者の急性期病院退院時の抗凝固薬選択状況を、多施設共同前向き SAMURAI-NVAF 研究にて解明する。【方法】2011/9 月～2013/6 月に登録された NVAF を有する脳梗塞/TIA 患者のうち、院内死亡例を除く 668 例を対象とした。退院時か入院 30 日後のより早い時点(中央値 23 日)で選択された抗凝固薬を調べた。【成績】420 例(63%)がワルファリン(W)、143 例(21%)がダビガトラン(DTI)、72 例(11%)がリバーロキサバン(XaI)を服用し、33 例は抗凝固薬を服用せず。発症前 W 服用者 204 例のうち 160 例(78%)が W を服用、27 例が DTI に、17 例が XaI に変更した。7 か月毎に 3 期に区切ると、W 服用者が漸減(70%, 69%, 48%)、DTI は不変(23%, 21%, 19%)、XaI が漸増(0.5%, 7%, 26%)した。W 服用者は DTI、XaI 服用者に比べて $CHADS_2$ 中央値(4, 4, 3)や CHA_2DS_2-VASc(6, 5, 5, ともに $p<0.001$)が高く、CHA_2DS_2-VASc の要因のうち心不全(27%, 12%, 13%, $p<0.001$)、脳梗塞/TIA 既往(29%, 15%, 15%, $p=0.001$)、血管病(18%, 11%, 7%, $p=0.019$)、女性(47%, 34%, 40%, $p=0.020$)がより多かった。年齢(79±10, 73±9, 74±10 歳)、体重(54±12, 62±11, 59±12 kg)、クレアチニンクリアランス(52±26, 72±23, 67±25 ml/min, ここまで $p<0.001$)、抗血小板併用割合(12%, 10%, 1%, $p=0.020$)にも群間差を認めた。W 服用者は罹患潅流域の 33%を超える梗塞(29%, 8%, 13%)、入院時 NIHSS 中央値(10, 3, 6)、7 日後同値(5, 1, 1)、退院時 mRS(3.5, 1, 2, 全て $p<0.001$)が高かった。【結論】NOAC 承認後 2 年間で、NVAF を有する脳梗塞/TIA 患者の過半数が、急性期病院退院時にワルファリンを服用していたが、NOAC 服用者が漸増してきた。NOAC は軽症で虚血予測尺度の低い患者に用いられやすい傾向が見られた。

キーワード：　心原性脳塞栓症、心房細動、抗凝固療法

ワルファリン療法中に脳梗塞/TIA を発症した NVAF 患者の臨床的特徴：SAMURAI-NVAF 研究

Characteristics of NVAF patients who had ischemic stroke during warfarinization: SAMURAI-NVAF Study

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【目的】非弁膜症性心房細動(NVAF)を有し，有効な強度でのワルファリン療法中に脳梗塞または一過性脳虚血発作(TIA)を発症した患者の臨床的特徴と関連因子を明らかにする．【方法】SAMURAI-NVAF 研究に登録された，発症 7 日以内に入院または外来での診療を開始された NVAF を有する急性期脳梗塞または TIA 患者を対象とした．発症前に新規抗凝固薬を内服中であった患者は除外した．発症前にワルファリンを内服中であり，来院時 PT-INR 2.0 以上または 70 歳以上かつ PT-INR 1.6 以上であったワルファリン不応群(以下，不応群)，有効な強度未満であったワルファリン強度不十分群(以下，不十分群)，ワルファリン非内服群(以下，非内服群)の 3 群に対象を分類し，臨床的特徴を比較検討した．【結果】対象は 697 例(女性 44.9%，年齢中央値 79 歳)，不応群は 54 例(全体の 7.7%，女性 33.3%，年齢 79 歳)，不十分群は 167 例(各々24.0%，47.9%，79 歳)，非内服群は 476 例(各々68.3%，45.2%，79 歳)であった．来院時 NIHSS スコアは不応群，不十分群，非内服群の順に低かった(中央値 3 vs. 8 vs. 9 ; p<0.001)．対象を不応群とその他の群に分類し，年齢，性別，$CHADS_2$ スコアの各コンポーネント，脂質異常症，喫煙歴，BNP，CRP，HbA1c，左房径によるロジスティック回帰分析を行うと，脳卒中または TIA 既往(OR 3.27，95%CI 1.76-6.10，p<0.001)と左房径拡大(1mm 毎の OR 1.04，95%CI 1.00-1.08，p=0.043)が不応群の独立した関連因子であった．【結論】NVAF を有し，有効な強度でのワルファリン療法中に脳梗塞または TIA を発症した患者は，ワルファリン強度不十分または非内服患者と比較して軽症であった．また，脳卒中または TIA 既往を有することが多く，左房径が拡大していた．

非弁膜症性心房細動を伴うTIA・軽症脳梗塞例への抗凝固療法：the SAMURAI-NVAF study

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【背景】非弁膜症性心房細動（NVAF）を有するTIA・軽症脳梗塞例の急性期における抗凝固療法の現状およびその安全性について検討した。

【方法】対象は、2011年9月から2013年10月までの多施設前向き観察研究 （SAMURAI-NVAF研究） 登録例のうち、入院時NIHSS スコア≦3 の TIA・軽症脳梗塞例。急性期の抗凝固療法と、発症後30日以内の虚血性および出血性イベント発症について検討した。

【結果】退院時までのデータが固定された778例中、233例（平均年齢74.3±9.9歳、男性159例）を解析対象とした。入院期間の中央値は16日（IQR 12-23日）で、全例で入院中に抗凝固療法が開始された。未分画ヘパリンは170例（74%）に対し投与され、発症から投与までの間隔は中央値で0日（IQR 0-1日）であった。一方、経口抗凝固薬はワルファリン124例（55%）、ダビガトラン79例（35%）、リバーロキサバン36例（16%）が投与された。発症から投与までの間隔はそれぞれ中央値で2日（IQR 1-4日）、3日（IQR 2-5日）、3日（IQR 2-6日）であり、ヘパリンとの併用または切り替えを行った症例はワルファリン97例（80%）、NOAC 73例（71%）であった。ヘパリン投与期間はワルファリン投与群の8日 （IQR 6-12日）に対し、NOAC投与群で4日（IQR 3-5日）と有意に短かった（$p<0.0001$）。30日以内の虚血性イベント発症を7例（3.0%；ヘパリン4例、ダビガトラン1例、ヘパリン＋ワルファリン2例）に認め、出血性イベント発症は1例のみ（0.4%；ワルファリン投与例での消化管出血）であった。経口抗凝固薬単独で加療を開始した群におけるイベント発症はなかった。

【結論】NVAFを有するTIA・軽症脳梗塞例の急性期における抗凝固療法を、発症早期から安全に導入できた。

非弁膜症性心房細動を伴う急性期脳梗塞例に対する早期抗凝固療法: the SAMURAI-NVAF study

Early anticoagulant therapy for the initial treatment of acute stroke/TIA: an interim report of the SAMURAI-NVAF study

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【背景】非弁膜症性心房細動を伴う急性期脳梗塞患者に対する抗凝固療法早期開始の有効性は不明である。
【方法】対象は、2011 年 9 月から 2013 年 10 月までの多施設前向き観察研究 (SAMURAI-NVAF 研究) 登録例のうち、発症 48 時間以内に抗凝固療法が開始された TIA・脳梗塞患者で、rt-PA 静注/血管内治療施行例は除外した。発症早期の抗凝固療法の現状と、発症後 30 日以内の虚血性・出血性イベント（7 日後の NIHSS が 4 点以上増悪した症候性出血性梗塞を含む）について検討した。
【結果】退院日あるいは入院後 30 日までのデータが確定された 778 例のうち、370 例 （61.4% ; 平均年齢 77.2±9.9 歳、男性 225 例）を解析対象とした。48 時間以内の治療内容は、未分画ヘパリン単独 211 例（57.0%)、ワルファリン単独 37 例（10.0%)、ヘパリン・ワルファリン併用 95 例（25.7%)、新規経口抗凝固薬（NOAC）単独 14 例（3.8%)、ヘパリン・NOAC 併用 13 例（3.5%）であった。虚血性イベントは 13 例（3.5% ; 虚血性梗塞再発 12 例、他臓器への塞栓 1 例)、出血性イベントは 9 例（2.4% ; 症候性出血性梗塞 5 例、頭蓋内出血 1 例、頭蓋外出血 3 例）に認めた。頭頸部主幹動脈閉塞を有する例では有さない例と比べ、虚血性イベントに差はなかったが（4.0% 対 3.1%, p=0.63)、出血性イベントは有意に多かった（4.6% 対 0.5%, p=0.01)。年齢・性別・BMI・発症前 HAS-BLED score・梗塞サイズ・入院時 NIHSS で調整した多変量解析では、主幹動脈閉塞は出血性イベントのリスクを増大させた（OR 10.36; 95% CI 1.46-213.57)。
【結論】本研究で早期抗凝固療法を開始した例では、虚血性・出血性イベントの発症率は過去の報告と比べ少なかった。主幹動脈閉塞の存在が出血性イベントに関連することが示唆された。

*NVAF*を有する脳梗塞・*TIA*患者への抗凝固薬の再発予防効果：*SAMURAI-NVAF*研究 中間解析

Preventive effects of oral anticoagulants for Stroke/TIA patients with NVAF

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【目的】非弁膜症性心房細動（NVAF）を有する急性期脳梗塞・TIA患者を対象とした抗凝固療法の選択と治療成績に関する多施設前向き観察研究（SAMURAI-NVAF研究）における退院後のイベントについて中間解析を行う.

【方法】参加18施設から2011年9月～2013年11月に登録された891例のうち，退院時に抗凝固療法をうけ登録3ヶ月時点の追跡調査が終了している624例（76.8±9.8歳，女性41%）を対象とした．抗凝固薬の選択状況と，退院後の追跡期間中に生じた虚血イベント（脳梗塞/TIA再発，急性冠症候群など），出血イベント（国際血栓止血学会基準での大出血）についてその発症率を含めて検討した.

【結果】624例のうち，退院時にワルファリンが407例（W群）に，新規経口抗凝固薬が217例（NOAC群：ダビガトラン135例，リバーロキサバン82例）に選択された．NOAC群はW群と比較して，CHADS2 （中央値［IQR］；3［3-4］vs 4［3-5］，p<0.001），HAS-BLED（3［2-4］vs 3［3-4］，p=0.032），退院時mRS（1［0-2］vs 3［1-5］，p<0.001）がいずれも低かった．観察期間（中央値95日）における虚血イベントは17例（W群14例，NOAC群3例，p=0.1339）で，その発生率はW群6.31%/年，NOAC群2.81%/年であり(log-rank χ2 2.01, p=0.156），出血イベントは18例（W群15例，NOAC群3例）で，W群6.56%/年，NOAC群2.74%/年であった(log-rank χ2 2.39, p=0.122）．脳イベントについては再発脳梗塞が10例（W群8例，NOAC群2例），出血性脳卒中が3例（すべてW群）であった.

【結語】NOACはワルファリンと比較してリスクスコアの低い軽症例に選択され，観察期間中の虚血・出血イベントも少なかった．本研究は2016年3月まで追跡調査を行う予定である.

公募演題（一般演題（日本語セッション））

No.1001250

腎機能別にみたNVAFを有する脳梗塞/TIA患者の特徴と抗凝固薬の選択 SAMURAI-NVAF研究

Stroke/TIA patients with NVAF according to renal function: SAMURAI-NVAF study

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【目的】非弁膜症性心房細動(NVAF)を有する脳梗塞/TIAの患者における腎機能別の特徴と抗凝固薬の選択を明らかにする．【方法】2011年9月から2013年10月の期間に，NVAFを有する発症7日以内の急性期脳梗塞/TIA多施設共同研究(SAMURAI-NVAF研究)に登録された813例のうちクレアチニンクリアランス(CCr)値の得られた787例を対象とした．患者をCCrの値により軽度(CCr≥50mL/min, n=466)，中等度(30≤CCr<50, n=205)，高度(CCr<30, n=116)腎障害に分類し検討した．【結果】CCr低下に伴い，高齢(軽度 73±9歳，中等度 83±7歳，高度 85±9歳，p<0.0001，以下同順序)で女性が増加した(34%，59%，62%，p<0.0001)．$CHADS_2$スコアは高くなり(中央値[IQR] 2[1-3]，2[2-3.5]，3[2-4])，そのうちうっ血性心不全(18%，25%，29%)，高血圧(68%，68%，84%)，75歳以上(44%，92%，87%)が高頻度であった(全てp<0.05)．HAS-BLEDスコアも同様に高値で(2[2-3]，2[2-3]，3[2-3]，p<0.001)，うち高血圧，65歳以上(81%，99%，97%)の割合が高く(全てp<0.05)，アルコール摂取(27%，12%，7%，p<0.001)の頻度が低下した．入院時(7[2-16]，11[4-20]，11[4-21])と7日目(2[0-12]，5[1-16]，5[2-19])のNIHSSは高値であった(ともにp<0.0001)．MR T2*WIでの微小出血を有する割合(30%，38%，42%，p<0.01)が増加した．CCrが低下するほど，退院時抗凝固薬にワルファリン(WF)を選択する割合が多かった(51%，68%，83%，p<0.001)．一方でダビガトラン(29%，11%，1%)とリバーロキサバン(16%，11%，4%)は低下するほど使用頻度が低下した(いずれもp<0.01)．退院時mRSは2[1-4]，4[1-5]，4[2-5]と高値になった(p<0.0001)．【結論】腎機能障害が高度になるほど高齢者，女性が多く，$CHADS_2$スコア，HAS-BLEDスコアが高かった．また退院時転帰は不良であった．抗凝固薬として，腎機能障害が高度なほどWFが選択されており，Ccr≥50でも半数以上でWFが選択されていた．

発表形式：一般演題（口演）

演題応募区分：A4:　抗凝固＆治療

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演題名：非弁膜症性心房細動を有する脳梗塞患者への多施設共同 SAMURAI-NVAF 研究：デザインと中間成績

抄録本文：

【目的】SAMURAI-NVAF 研究（ClinicalTrials.gov NCT01581502, UMIN 000006930）は、新規抗凝固薬（NOAC）の登場に伴う非弁膜症性心房細動（NVAF）を有する急性期脳梗塞患者への抗凝固薬の選択内容の変化とその治療効果を、解明することを目的とした、厚生労働科学研究費の助成を受けた国内多施設共同研究である。その研究デザインと、現在までの中間解析結果を報告する。

【方法】国内18施設による多施設共同前向き観察研究。対象は発症7日以内に入院または外来診療を開始したNVAFを有する急性期脳梗塞・一過性脳虚血発作（TIA）患者。患者基本情報、急性期。慢性期の抗凝固療法の選択内容と、2年後までの虚血・出血イベント発症を調べる。登録期間を2011年9月～2014年3月とし、1000例の登録を目標とする。

【成績】2013/8 月までに 805 例が登録された。このうち院内死亡例を除く 735 例において、退院時か入院 30 日後のより早い時点(中央値 23 日)で選択された抗凝固薬の内訳は、455 例(62%)がワルファリン(W)、152 例(21%)がダビガトラン、95 例(13%)がリバーロキサバン、33 例が抗凝固薬なし。W 服用者は DTI、NOAC2 剤の服用者に比べて $CHADS_2$ や CHA_2DS_2-VASc が高く(ともに $p<0.001$)、年齢、体重、クレアチニンクリアランス(ここまで $p<0.001$)、抗血小板併用割合($p=0.008$)にも群間差を認めた。W 服用者は入院時や 7 日後の NIHSS（重症度尺度）や退院時 mRS（自立度尺度）が高かった(全て $p<0.001$)。

【結論】NOAC 承認後 2 年間で、NVAF を有する脳梗塞/TIA 患者のうち軽症で虚血予測尺度の低い患者に、NOAC 服用者が漸増してきた。NOAC が用いられやすい傾向を認めた。わが国における NVAF を有する脳梗塞患者に対する抗凝固療法の実態を解明し、適切な治療法を解明できるよう、今後研究を進める。

キーワード：脳血管障害，抗凝固薬

（/制限文字数 735文字）

日本人脳血管障害患者においてリバーロキサバンが抗凝固能に及ぼす影響の検討

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【背景・目的】リバーロキサバンは J-ROCKET AF 試験の結果に基づき，本邦では独自の用量が設定されている．日本人脳血管障害患者におけるリバーロキサバンの抗凝固能に及ぼす影響とその関連要因を明らかにする．

【方法】対象は 2012 年 7 月から 2013 年 8 月に入院した非弁膜症性心房細動を有する脳血管障害患者連続 107 例．リバーロキサバン開始 3 日後以降の定常状態で，早朝内服前(0H)・食後 4h 後(4H)・食後 9h 後(9H)に PT(Recombiplastin/HemosIL®)，aPTT(Actin/Sysmex®)を測定し，anti-Xa chromogenic assay (STA®-Liquid Anti-Xa/Stago®)を用いて算出した血漿中濃度(Riv)との相関を検討した．また，Riv(4H)の関連要因について重回帰分析を行った．

【結果】104 例は女性 34 例，年齢 75±9 歳，中等度腎機能障害 37 例[CrCl <50 ml/min (Cockcroft-Gault 式)]，10mg/日内服は 49 例であった．

PT 中央値は 0H で 12.8 秒，4H で 19.3 秒，9H で 16.2 秒，aPTT 中央値は 31 秒，42 秒，37 秒，Riv 中央値は 13.5ng/ml，169ng/ml，63ng/ml であった．PT 及び aPTT は共に Riv と正の相関を示した(ρ=0.818，0.624)．年齢，性別，腎機能，リバーロキサバン投与量，抗血小板薬併用の有無，粉砕投与の有無による重回帰分析では，粉砕投与の有無が Riv(4H)に唯一独立した関連要因であった(P<.0001)．粉砕投与群では非粉砕投与群と比較し，4H の PT(中央値 16.0 秒 vs 19.7 秒，P=0.002)，aPTT(中央値 36.5 秒 vs 42 秒，P=0.040)ともに有意に短く，Riv(4H)も有意に低値であった(中央値 61.5ng/ml vs184ng/ml，P<.0001)．

【結語】aPTT・PT は Riv と正の相関を示し，特に PT で優れていた．Riv(4H)は ROCKET AF 試験や J-ROCKET AF 試験の結果と同等あるいはやや低値であった．粉砕投与時は抗凝固能の減弱を考慮する必要がある．　(731 文字/制限文字数 735 文字)

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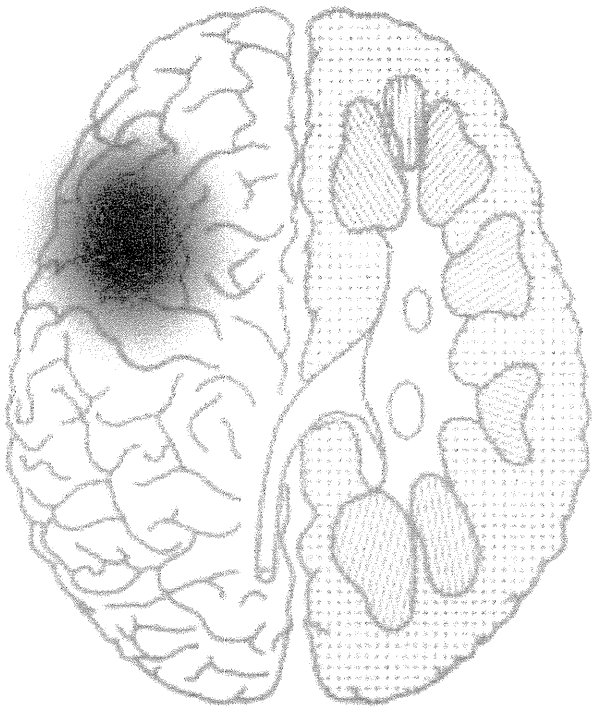

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Cerebrorenal Interaction and Stroke

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Abstract

Beyond the original meaning of chronic kidney disease (CKD) as high-risk state for future dialysis, CKD is now known as an established risk factor for cardiovascular diseases. Stroke is a major player of cardiovascular disease and has deep two-way relationships with CKD. CKD is an evident risk factor for stroke. Meta-analyses of cohort studies and trials indicate that proteinuria/albuminuria increases the risk of stroke by 71–92%, and reduced glomerular filtration rate increases the risk by 43%. In addition, CKD has a strong relationship with subclinical brain damage including white matter changes, microbleeds, cognitive impairment, and carotid atherosclerosis. CKD is prevalent in acute stroke patients; patients with estimated glomerular filtration rate <60 ml/min/1.73 m^2 or proteinuria amounted to 46% of total ischemic stroke patients and 39% of total intracerebral hemorrhage patients in our institute. Acute and chronic management of stroke are influenced by CKD. Therapeutic effects of several antithrombotic and thrombolytic agents, including recently-developed novel oral anticoagulants, are affected by renal function. Moreover, reduced glomerular filtration rate is independently associated with increased 1- and 10-year mortalities in the end. Stroke also has deep relationships with end-stage kidney disease. Stroke occurs much more commonly in dialysis patients than general population or CKD patients without need for dialysis. The triggers of ischemic and hemorrhagic stroke in patients with end-stage kidney disease include special characteristics unique to dialysis, such as drastic hemodynamic change, dialysate and anticoagulants, and vascular calcification. As cohorts of dialysis patients become older, more hypertensive, and more diabetic than before, stroke become more prevalent and more serious events in dialysis clinics. Now, clinicians should have much interest in the association between CKD and cerebrovascular diseases, so-called the cerebro-renal interaction.

More than ten years have passed since the National Kidney Foundation in the United States first advocated the concept of chronic kidney disease (CKD) [1], and it is now seen as a major public health problem. According to the 2002 ver-

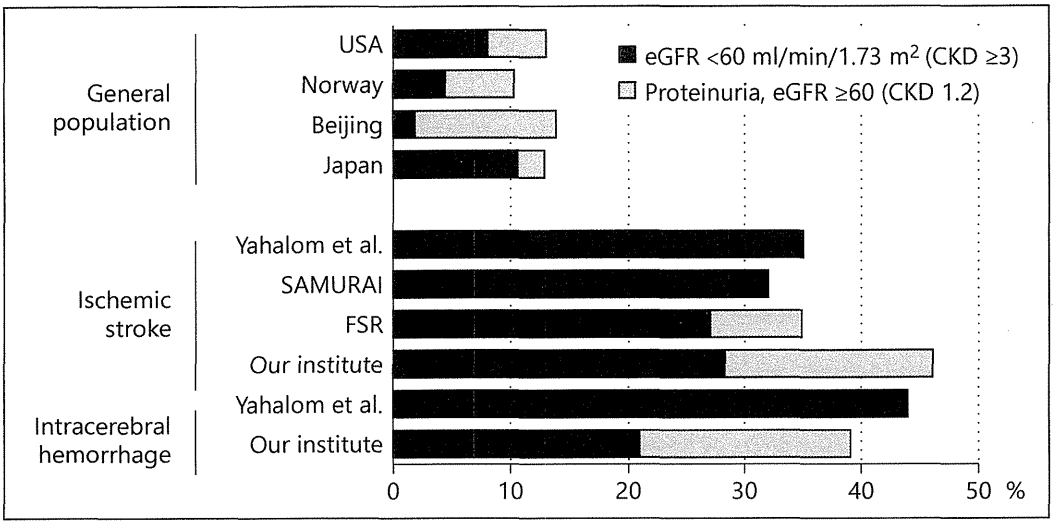

Fig. 1. The prevalence of eGFR <60 ml/min/1.73 m^2 or proteinuria in both the general population and stroke patients. Cited from refs. 2–5 and 12–14. Note that both eGFR and proteinuria in stroke patients were measured during the acute stage of stroke, and thereby might have been affected by stroke damage.

sion of the guideline, the prevalence estimates of CKD in the United States (1999–2004) were as follows [1]: 1.8% (95% CI 1.4–2.3%) for stage 1 (estimated glomerular filtration rate (eGFR) >90 ml/min/1.73 m^2 and albuminuria); 3.2% (95% CI 2.6–3.9%) for stage 2 (GFR 60–89 ml/min/1.73 m^2 and albuminuria); 7.7% (95% CI 7.0–8.4%) for stage 3 (GFR 30–59 ml/min/1.73 m^2), and 0.35% (0.25–0.45%) for stage 4 (GFR 15–29 ml/min/1.73 m^2) [2]. Estimates were 2.7 ± 0.3, 3.2 ± 0.4, 4.2 ± 0.1, and 0.2 ± 0.01%, respectively, in Norway (1995–1997) [3]; 7.4% (95% CI 6.9–7.8%), 4.7% (4.4–5.1%), 1.8% (1.5–2.0%), and none, respectively, in Beijing [4], and 0.6, 1.7, 10.4, and 0.2% (including CKD stage 5 without dialysis), respectively, in Japan (2005) [5] (fig. 1). Thus, more than one tenth of the general population worldwide is estimated to have CKD, and its prevalence increases dramatically with age.

Beyond the original meaning of CKD as a high-risk state for future dialysis, CKD is now known to be an established risk factor for cardiovascular diseases. This message was clarified by the Kaiser Permanente Renal Registry involving more than one million adults [6]. An independent, graded association was observed between a reduced eGFR and the risk of death and cardiovascular events including stroke. Since then, many studies have proven the positive association of CKD with risk and outcomes of cardiovascular disease. The reason for the positive association is partly the high prevalence of traditional cardiovascular risk factors in CKD patients. In addition, nontraditional risk factors, including endothelial dysfunction, maladaptive arterial remodeling,

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homocysteinemia, coagulation disorders, impaired endothelial release of tissue plasminogen activator (t-PA), extravascular coagulation, anemia, and higher levels of inflammatory cytokines and oxidative stress, seem to increase the risk of cardiovascular disease. In 2008, a consensus conference on cardiorenal syndromes was held to identify and classify dysfunction of the heart and kidneys whereby acute or chronic dysfunction in one organ induces acute or chronic dysfunction in the other organ [7]. Now, cardiologists cannot overlook CKD.

Stroke is a major player in cardiovascular disease and it has strong two-way relationships with CKD. Nevertheless, clinicians are often more indifferent to the association between CKD and cerebrovascular diseases, the so-called cerebrorenal interaction, than the cardiorenal interaction [8]. For example, cerebrovascular disease was rarely discussed in the lengthy *Contributions to Nephrology* series. This may be due to the fact that both renal and cerebral pathophysiologies are quite difficult for nonexperts to grasp and fully understand. Therefore, we have prepared this volume entitled 'Brain, stroke, and kidney'.

Now, let us think about the cerebrorenal interaction, particularly with respect to stroke. First, the glomerular afferent arterioles of the juxtamedullary nephrons and the cerebral perforating arteries share an anatomical feature. These small, short vessels directly arise from large high-pressure arteries, and are thus exposed to high pressure. They have to maintain a strong vascular tone in order to provide a large pressure gradient over a short distance [9]. Severe hypertensive vascular damage occurs first in such strain vessels. Since albuminuria reflects glomerular damage distal to the juxtamedullary afferent arterioles, albuminuria may also be an early sign of damage to the cerebral perforating arteries.

Second, CKD is an evident risk factor for stroke. Meta-analyses of both cohort studies and trials indicate that proteinuria/albuminuria increases the risk of stroke by 71–92% [10], and reduced eGFR (<60 ml/min/1.73 m^2) increases the risk by 43% [11]. In addition, CKD has a strong relationship with subclinical brain damage, including white matter changes, microbleeds, cognitive impairment, and carotid atherosclerosis. Of these, cognitive impairment and dementia are becoming as serious a burden as stroke worldwide.

Third, CKD is prevalent in acute stroke patients. Patients with eGFR <60 ml/min/1.73 m^2 based on the creatinine level during acute stroke accounted for 35% of total ischemic stroke patients and 44% of total intracerebral hemorrhage (ICH) patients in an Israeli hospital [12], and 32% of total patients receiving intravenous recombinant t-PA from the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) rt-PA Registry in Japan

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[13]. Patients with eGFR <60 ml/min/1.73 m^2 or proteinuria accounted for 46% of total ischemic stroke patients and 39% of total ICH patients in our institute and 34.9% of total ischemic stroke patients in the Fukuoka Stroke Registry [14] (fig. 1).

Fourth, acute and chronic stroke management strategies are influenced by CKD. A good example of this is the recently developed novel oral anticoagulants. Atrial fibrillation is a major risk factor for initial and recurrent stroke. To judge the indications and dosage of dabigatran and factor Xa inhibitors for stroke patients having atrial fibrillation, many neurologists are now familiar with the Cockcroft-Gault equations. Therapeutic effects of other antithrombotic and thrombolytic agents also seem to be affected by renal function. For example, in our multicenter SAMURAI rt-PA Registry [13], reduced eGFR was associated with early symptomatic ICH, mortality, and a modified Rankin scale score ≥4 at 3 months after intravenous thrombolysis in ischemic stroke patients.

Fifth, reduced eGFR is independently associated with increased 1- and 10-year mortalities [12, 15]. Two groups reported that proteinuria, but not a reduced eGFR, was associated with a poor functional outcome after ischemic stroke [14, 16]. Thus, the kidneys cannot be ignored by stroke neurologists.

Stroke also has strong relationships with end-stage kidney disease (ESKD). Stroke and other cardiovascular diseases occur much more commonly in dialysis patients than in the general population or in CKD patients who do not require dialysis [17, 18]. The triggers for ischemic and hemorrhagic strokes in ESKD patients include traditional cardiovascular risk factors, CKD-related nontraditional risk factors, and special characteristics unique to dialysis, such as drastic hemodynamic change, dialysate, anticoagulants, and vascular calcification. As cohorts of dialysis patients become older, more hypertensive, and more diabetic than before, strokes become more prevalent and more serious events in dialysis clinics. Strokes in ESKD patients pose problems, such as the contraindication to some pharmacotherapy (like dabigatran) and the difficulty of continuing dialysis under good conditions when severe neurological deficits remain. Though thrombolysis is not contraindicated for ESKD patients, even thrombolysis experts often have had limited experience with this therapy for ESKD patients [19].

In this volume, clinical and epidemiological specialists on 'Brain, stroke and kidney' present superb reviews for clinicians. I hope that you, the reader, enjoy this collection and that it promotes both further understanding and multidisciplinary collaboration between nephrologists and neurologists.

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Antithrombotic Therapy for Pregnant Women

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Special Theme Topic:
Stroke During Pregnancy or Delivery

Antithrombotic Therapy for Pregnant Women

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Abstract

Coagulability increases during pregnancy, and thromboembolism can easily occur. Venous thromboembolism is a cause of death in pregnant women, but arterial thrombosis such as ischemic stroke in pregnancy is also not uncommon. In pharmacotherapy for thromboembolism in pregnant women, fetal toxicity and teratogenicity must be carefully considered. As anticoagulants in pregnant women, unfractionated heparin and low-molecular-weight heparin are recommended, but warfarin is not recommended since it has a low molecular weight and crosses the placenta. Various types of new oral anticoagulant drugs have been available in Japan since 2011. However, the Japanese package inserts for these anticoagulants advise quite cautious administration in pregnant women. The guidelines on pregnant women include less information about antiplatelet drugs than anticoagulant drugs. Aspirin may cause teratogenicity and fetal toxicity, and perinatal mortality is increased. However, when low doses of aspirin are administered as antiplatelet therapy, the US Food and Drug Administration has assigned pregnancy category C, and treatment is relatively safe. Neurosurgeons and neurologists commonly encounter pregnant women with thromboembolism, such as ischemic stroke. Up-to-date information and correct selection of drugs are necessary in consultation with specialists in perinatal care.

Key words: acute stroke, anticoagulation, antiplatelet therapy, thromboembolism, venous thrombosis

Introduction

Coagulability increases during pregnancy, and thromboembolism can easily occur, primarily of the venous system. Venous thromboembolism is a cause of death in pregnant women, but arterial thrombosis such as ischemic stroke in pregnancy is also not uncommon. In pharmacotherapy for thromboembolism in pregnant women, fetal toxicity and teratogenicity must be carefully considered. However, since pregnant women are usually excluded from pharmaceutical clinical trials for ethical reasons, information on toxicity and teratogenicity in pregnancy is limited. This study presents an overview of the current status and problems with antithrombotic therapy in pregnant women, based on the "Guidelines for indication and management of pregnancy and delivery in women with heart disease (JCS 2010)"[3] by the Japanese Circulation Society (JCS) Joint Working Group (fiscal year 2009); and the "Guidelines for management of anticoagulant and antiplatelet therapy in cardiovascular disease (JCS 2009)"[4] by the same group (fiscal year 2008).

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Pregnancy and Thromboembolism

Plasma fibrinogen, von Willebrand factor, and factors V, VII, VIII, IX, X, and XII are increased and activated in late pregnancy, thus increasing the risk of thromboembolism. Therefore, thromboembolism is clearly a danger in pregnant women at high risk for embolism, such as those with valvular heart disease, but thromboembolism such as cerebral sinus venous thrombosis may also occur in pregnant women without such risk factors. In addition, the effects of estrogen and elastase during pregnancy may cause evident structural changes in blood vessel walls, leading to increased fragility. For example,

patients with Marfan's syndrome tend to develop aortic dissection. The structure of cerebral and cervical blood vessel walls may also be affected. Moreover, compression of the inferior vena cava due to uterine enlargement may lead to deep vein thrombosis (DVT). Therefore, pregnancy is a risk factor for thromboembolism, particularly venous thrombosis.

Nevertheless, the safety of antithrombotic drugs as treatment, as mentioned above, has not been well established. Fetal toxicity and teratogenicity are major concerns of drug administration in pregnancy, and are affected by placental transfer of drugs and the stage of pregnancy (Table 1).

Anticoagulant Drugs in Pregnant Women

The JCS Joint Working Group provides the following recommendations for anticoagulant therapy in pregnancy.

Class I: In pregnant women with a prior history of DVT but no other risk factors, follow-up observation until delivery and warfarin administration for 4–6 weeks postpartum is recommended.

Class IIb:

1. In pregnant women with a prior history of DVT and other risk factors (e.g., congenital or acquired blood dyscrasias), prophylactic administration of low-molecular-weight heparin or moderate dose-adjusted unfractionated heparin starting during pregnancy and warfarin administration for 4–6 weeks postpartum are recommended.
2. In all patients with a prior history of DVT, use of elastic stockings pre- and postpartum is recommended.
3. In patients requiring long-term warfarin therapy who wish to become pregnant, planned pregnancy with a switch from warfarin to dose-adjusted heparin, or promptly switching from warfarin to dose-adjusted heparin when pregnancy is confirmed at an early stage by frequent pregnancy testing is recommended.

Therefore, unfractionated heparin or low-molecular-weight heparin is recommended in pregnant women; whereas warfarin is not recommended. Table 2 summarizes the effects of anticoagulant drugs in patients during pregnancy and breastfeeding.[3] Table 3 shows the US Food and Drug Administration (FDA) pregnancy categories for these drugs.[1]

Unfractionated heparin and low-molecular-weight heparin do not cross the placenta because of their high molecular weight and do not cause harm to the fetus. However, in Japan, the use of low-molecular-weight heparin for thromboembolism prophylaxis in patients with a history of valvular heart disease or DVT is not covered by health insur-

Table 1 Pregnancy stage, teratogenicity, and fetal toxicity

Pregnancy stage	Teratogenicity and fetal toxicity
Fertilization to day 27	no effect stage: malformations do not occur (no fertilization, no implantation, or miscarriage)
Days 28 to 50	absolutely sensitive stage: important fetal organ formation, highest risk of teratogenicity
Days 51 to 112	relatively sensitive stage: genitalia and palate formation not yet complete, teratogenicity such as cleft palate
Day 113 to delivery	potentially sensitive stage: risk of teratogenicity is rare, attention must be paid to fetal toxicity

Table 2 Effects of anticoagulant drugs in patients during pregnancy and breastfeeding

Drug	Classification	FDA category	Characteristics/adverse reactions	Teratogenicity	Breastfeeding during use	Package insert	
						Pregnancy	Breastfeeding
Warfarin	coumarin derivative	D	teratogenicity, fetal hemorrhagic complications	yes	allowed	contra-indication	contra-indication
Heparin	unfractionated heparin	C	bone demineralization with long-term administration (fractures in mothers), higher incidence of thrombosis than with warfarin, risk of heparin-induced thrombocytopenia	no	allowed	contra-indication	
Enoxaparin	low-molecular-weight heparin	B	reports of heparin-induced thrombocytopenia, not indicated for thrombus prophylaxis in cardiovascular disease	no	allowed	relative contra-indication	relative contra-indication
Dalteparin	low-molecular-weight heparin	B	reports of heparin-induced thrombocytopenia, not indicated for thrombus prophylaxis in cardiovascular disease	no	allowed	contra-indication	contra-indication

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