Table 3 US Food and Drug Administration (FDA) pregnancy categories

The FDA-assigned pregnancy categories as used in the Drug Formulary are as follows:

Category A
Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).

Category B
Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.

Category C
Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Category D
There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Category X
Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

Reproduced with permission from *Drugs in Pregnancy and Lactation, 8th ed.*, ©2008 Lippincott Williams & Wilkins.[1]

ance. Consequently, unfractionated heparin is generally administered. Noteworthy adverse reactions with heparin include hemorrhage, which is a common complication with all antithrombotic drugs, and heparin-induced thrombocytopenia. Another important adverse reaction in pregnant women is possible fractures due to bone demineralization caused by long-term administration of heparin. In addition, because of increased heparin-binding proteins, increased circulating plasma volume, increased clotting factors, and problems with renal clearance, the need for heparin during pregnancy is greater than in non-pregnancy. Since January 2012, home heparin self-injection in pregnant women after mechanical heart valve replacement or those with a history of DVT has been covered by health insurance.

Warfarin, the leading oral anticoagulant drug, has a low molecular weight and does cross the placenta. Therefore, warfarin administration during the absolutely and relatively sensitive stages (days 28 to 112) can cause abnormalities in fetal osteogenesis and chondrogenesis, as well as central nervous system malformations such as microencephaly. These teratogenic effects are considered dose-dependent. In addition, because enzyme systems and vitamin K-dependent clotting factors are undeveloped in the fetus, the effects of warfarin are more easily manifest

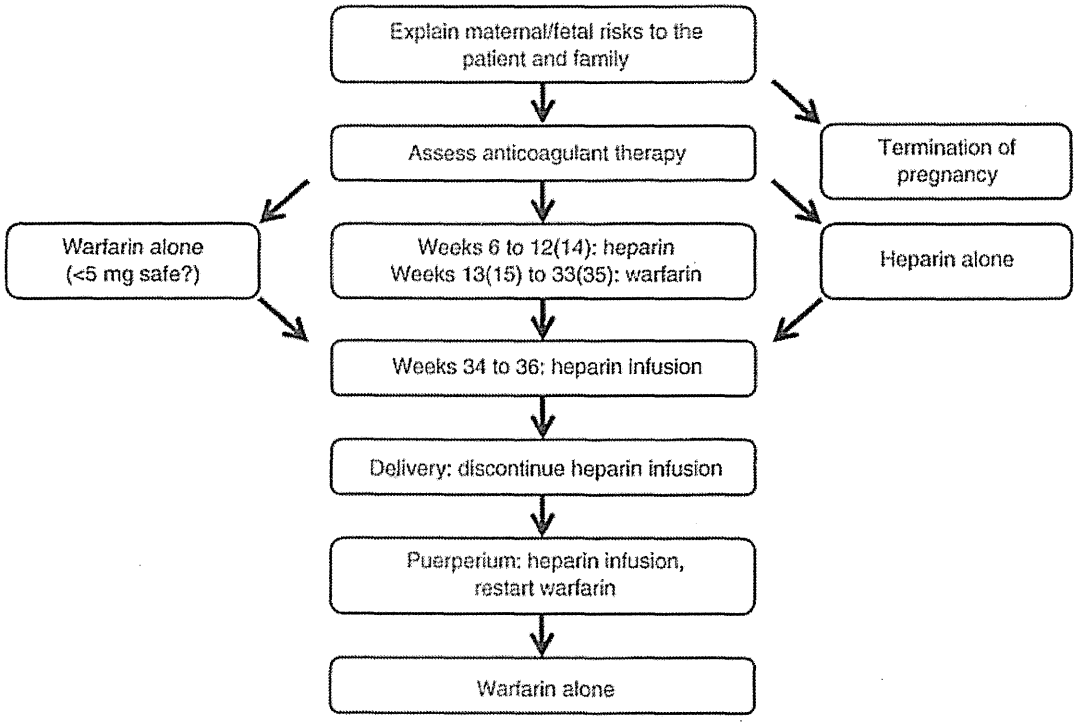

Fig. 1 Anticoagulant therapy in pregnant women with mechanical heart valve replacement. Modified with permission from the *Circulation Journal* (76: 240–260, 2012), ©2012, the Japanese Circulation Society.[3]

in the fetus than in mothers. Therefore, to prevent teratogenicity in the absolutely and relatively sensitive stages, and to prevent complications such as fetal intracranial hemorrhage in the later period of pregnancy due to decreased clotting factors, warfarin administration is not recommended in pregnant women.

Figure 1 shows anticoagulant therapy in pregnant women after mechanical heart valve replacement,[3] consisting of warfarin and heparin administration from week 14 to about week 33 of pregnancy. The rationale based on guidelines is that the prophylactic effects of heparin on thrombus are uncertain.[1,4] Moreover, the rationale for a daily dose of warfarin ≤ 5 mg is based on the dose-dependence of warfarin teratogenicity. However, an oral warfarin dose of 5 mg is considered quite high in Japanese patients, so warfarin should be carefully administered while monitoring the prothrombin time (international normalized ratio). The guidelines from the American Heart Association/American Stroke Association[2] recommend that the following options may be considered for pregnant women with ischemic stroke or transient ischemic attack and high-risk thromboembolic conditions such as hypercoagulable state or mechanical heart valves: adjusted dose unfractionated heparin throughout pregnancy, for example, a subcutaneous dose every 12 hours with monitoring of activated partial thromboplastin time; adjusted-dose low-molecular-weight heparin with monitoring of anti-factor Xa throughout pregnancy; or unfractionated heparin or low-molecular-weight heparin until week 13, followed by warfarin until the middle of the third trimester and reinstatement of unfractionated heparin or low-molecular-weight heparin until delivery (Class IIb, Level of Evidence C). Because home heparin self-injection is now covered by health insurance, the number of patients using heparin is thought to be increasing.

Various types of new oral anticoagulant drugs have been available in Japan since 2011, and these can be clinically used in patients with non-valvular atrial fibrillation and those undergoing lower limb orthopedic surgery. These new agents include the direct thrombin inhibitor dabigatran and the activated factor X inhibitors edoxaban, rivaroxaban, and apixaban. In large-scale clinical trials, these new oral anticoagulants have reduced hemorrhagic complications to the same or greater extent than warfarin, and in particular, the incidence of intracranial hemorrhage compared to warfarin is markedly decreased.[5] In addition, argatroban, an intravenous direct thrombin inhibitor, is now widely used as an alternative to heparin for treatment of the acute phase of cerebral infarction and in heparin-induced thrombocytopenia. However, the Japanese package inserts for these anticoagulants advise quite cautious administration in pregnant women. In other words, dabigatran, edoxaban, and apixaban should only be used when the benefits outweigh the risks, and rivaroxaban should not be given to pregnant women. Argatroban has been assigned pregnancy category B by the FDA, but the Japanese package inserts specify that argatroban should not be administered to pregnant women.

Antiplatelet Drugs in Pregnant Women

Venous thrombosis occurs more often than arterial thrombosis in pregnant women, and the guidelines include less information about antiplatelet drugs than anticoagulant drugs. Table 4 summarizes the effects of antiplatelet drugs in patients during pregnancy and breastfeeding.[3] Aspirin, the leading antiplatelet drug, may cause teratogenicity and fetal toxicity such as premature closure of the ductus arteriosus, and perinatal mortality is increased. But when low doses of aspirin are administered as antiplatelet therapy, the FDA has assigned pregnancy category C, and treatment is relatively safe. However, the drug package insert says "contraindicated (regardless of dose) in pregnant women within 12 weeks of the expected date of delivery (pregnancy week 28 or later)." Therefore, a full explanation and

Table 4 Effects of antiplatelet drugs in patients during pregnancy and breastfeeding

Drug	FDA category	Characteristics/adverse reactions	Teratogenicity	Breastfeeding during use	Package insert	
					Pregnancy	Breastfeeding
Aspirin (low dose)	C	considered relatively safe, do not use in pregnancy week 28 or later regardless of dose	no	potential toxicity	relative contraindication	contraindication
Dipyridamole	B	hypotension, worsening of angina pectoris	no	probably allowed	relative contraindication	contraindication
Ticlopidine	B	hemorrhage, liver dysfunction	no	potential toxicity	relative contraindication	contraindication

Revised with permission from the *Circulation Journal* (76: 240–260, 2012), ©2012, the Japanese Circulation Society.[3]

Table 5 Information in Japanese package inserts regarding use of antiplatelet drugs in pregnant women

Drug	Guideline for use in pregnant women
Aspirin	up to week 28: may be used if risks outweigh the benefits, week 29 and later: do not use
Clopidogrel	may be used if risks outweigh the benefits
Ozagrel	may be used if risks outweigh the benefits
Cilostazol	do not use in pregnant women
Ticlopidine	do not use in pregnant women

informed consent are necessary for administration in the third trimester of pregnancy.

The Japanese package inserts for clopidogrel and ozagrel recommend use only when the benefits outweigh the risks (Table 5). Cilostazol and ticlopidine are contraindicated in pregnant women. On the other hand, aspirin and ozagrel are reported to be effective in preventing placental thrombosis in pregnant women with autoimmune disorders such as antiphospholipid syndrome.

Conclusion

In the present paper, the author, who is not a specialist in perinatal medicine, has discussed using antithrombotic drugs in pregnancy based on guidelines and package insert information. Searching the literature often found disagreement between information in FDA categories, Japanese guidelines, Japanese package inserts, and overseas package inserts, but this was not further pursued. Neurosurgeons and neurologists also 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.

Conflicts of Interest Disclosure

The author declares that he has no conflict of interest.

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1) Briggs GG, Freeman RK, Yaffe SJ: *Drugs in Pregnancy and Lactation, 8th ed.* Philadelphia, PA, Lippincott Williams & Wilkins, 2008
2) Furie KL, Kasner SE, Adams RJ, Albers GW, Bush RL, Fagan SC, Halperin JL, Johnston SC, Katzan I, Kernan WN, Mitchell PH, Ovbiagele B, Palesch YY, Sacco RL, Schwamm LH, Wassertheil-Smoller S, Turan TN, Wentworth D; American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Clinical Cardiology, and Interdisciplinary Council on Quality of Care and Outcomes Research: Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 42: 227–276, 2011
3) JCS Joint Working Group: Guidelines for indication and management of pregnancy and delivery in women with heart disease (JCS 2010): digest version. *Circ J* 76: 240–260, 2012
4) JCS Joint Working Group: [Guidelines for management of anticoagulant and antiplatelet therapy in cardiovascular disease (JCS 2009)] (Japanese). Kyoto, the Japanese Circulation Society. Available at http://www.j-circ.or.jp/guideline/pdf/JCS2009_hori_h.pdf. Accessed April 17, 2013
5) Uchiyama S, Ibayashi S, Matsumoto M, Nagao T, Nagata K, Nakagawara J, Tanahashi N, Tanaka K, Toyoda K, Yasaka M: Dabigatran and factor Xa inhibitors for stroke prevention in patients with nonvalvular atrial fibrillation. *J Stroke Cerebrovasc Dis* 21: 165–173, 2012

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リバーロキサバン内服中に発症した頭蓋内出血に対するプロトロンビン複合体製剤を用いた止血治療の経験

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[背景]リバーロキサバン(Riv)内服中に発症した頭蓋内出血に対する，プロトロンビン複合体製剤(PCC)を用いた緊急止血治療は有望であるが，その是正効果は確立していない．当施設での2症例の経験を報告する．

[症例1]71歳男性．陳旧性脳梗塞・1型糖尿病・高血圧症の既往を有し，Riv 15mg/日・シロスタゾール100mg/日を内服していた．肝腎機能は正常であった．Rivの最終内服から約10.5時間後に左被殻出血を発症し，当院に搬送され，約11.5時間後にPCC 1000単位を投与した．血腫増大や神経徴候の増悪はなかった．aPTT(秒)/PT-INRはPCC投与前・投与1時間後でそれぞれ41/1.26，40/1.08であった．

[症例2]87歳の高齢・低体重の女性．高血圧症・慢性心不全・慢性心房細動の既往を有し，Riv 10mg/日を内服していた．肝機能は正常であったが，CCr(Cockcroft-Gault式)27ml/minと高度腎機能障害を認めた．Rivの最終内服から約0.5時間後に左視床出血と外傷性左急性硬膜下血種を発症し，他院より当院に搬送された．Rivの最終内服より約6時間後にPCC1000単位を投与したが，脳室内血腫及び急性硬膜下血腫の増大がみられた．aPTT(秒)/PT-INRはPCC投与前・投与1時間後でそれぞれ47/1.67，49/1.42であった．2症例ともPCC投与に伴う塞栓症などの有害事象はなかった．

[結語]リバーロキサバン内服下の頭蓋内出血に対する迅速治療として，プロトロンビン複合体製剤の有用性は，さらなる検討が必要である．(595字)

リバーロキサバン内服中に発症した頭蓋内出血に対するプロトロンビン複合体製剤を用いた止血治療

岡田卓也[1] 豊田一則[1] 岡本章[2] 宮田敏行[3] 飯原弘二[4] 長束一行[5] 峰松一夫[1]
国立循環器病研究センター　脳血管内科[1] 臨床検査部[2]
分子病態部[3] 脳神経外科[4] 脳神経内科[5]

National Cerebral and Cardiovascular Center

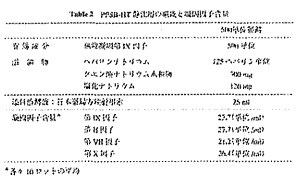
背景・目的

- リバーロキサバン(Riv)内服中に発症した重症出血性合併症に対する，プロトロンビン複合体製剤(PCC:prothrombin complex concentrate)を用いた止血治療は有望であるが，その治療効果は確立していない.
- 当施設では倫理委員会の承認の下に，PCC投与を行っている.
- Riv内服下で頭蓋内出血を発症した2症例の経験を報告する.

PCC(PPSB®-HT「ニチヤク」)

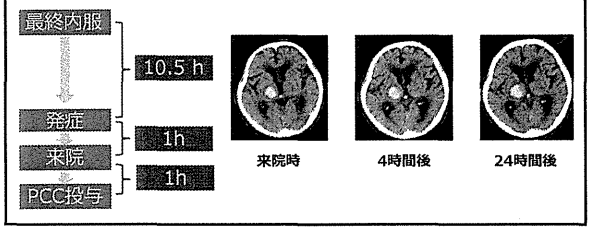
- 高力価の血液凝固第Ⅸ因子を含有し，第Ⅱ，Ⅶ及びX因子も含有するプロトロンビン複合体濃縮製剤.
- 効能：血液凝固第Ⅸ因子欠乏患者の出血傾向を抑制.
- 作用：**血液凝固第Ⅸ因子は活性化により第Ⅷ因子，Ｃａ²⁺及びリン脂質と複合体を形成．第Ⅹ因子を活性化し止血に関与する.**

31613円(500単位)



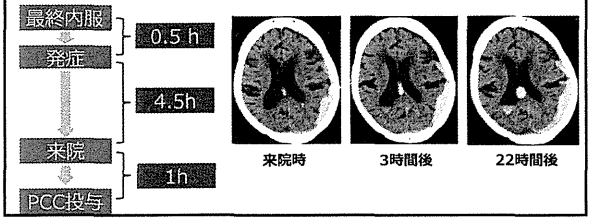
症例1 71歳男性

[臨床経過]
発作性心房細動・陳旧性脳梗塞・1型糖尿病・高血圧症の既往を有し，Riv(15mg/日)・シロスタゾール(100mg/日)を常用.
最終内服から約10.5時間後に**右視床出血**を発症.
最終内服から約12.5時間後にPCC(PPSB®-HT)1000単位を投与.
血腫の増大や臨床症状の**増悪なく経過**.



症例2 87歳女性

[臨床経過]
慢性心房細動・高血圧症の既往あり，Riv10mg/日を常用.
最終内服から約0.5時間後に**左視床出血**を発症し転倒.
外傷性左急性硬膜下血腫を同時に発症.
最終内服から約6時間後にPCC1000単位を投与.
保存的に加療し**左視床出血は増大しなかったが，急性硬膜下血腫及び脳室内血腫は増大**.



症例のまとめ

	症例 1	症例 2
Rivaroxaban投与量	15mg	10mg
減量基準項目		
腎機能障害(CCr<50ml/min)		✓
慎重投与項目		
高齢者(75歳以上)		✓
低体重(50kg以下)		✓
出血既往		
HAS-BLEDスコア	4	2
併用抗血小板薬	✓	
脳微小出血 (T2*WI)	2箇所	未施行
血小板数 (/μl)	12.0万	12.1万
最終内服-発症時刻 (h)	10.5	0.5
最終内服-PCC投与時刻 (h)	12.5	6.0

PCC投与の効果

	症例 1		症例 2	
	投与前	後	投与前	後
最終内服からの経過時間(hr)	11.5	13.5	6.0	7.0
aPTT(秒)	41	40	47	49
PT(秒)	15.6	13.4	19.5	16.7
PT-INR	1.26	1.08	1.67	1.24
Riv血中濃度	81	115	213	242
血腫増大	なし		あり	
血栓塞栓症の合併	なし		なし	

2例の止血効果の違いについて

患者背景要因
- ✓ **症例2で高齢・低体重・腎障害**

薬効の差
- ✓ **最終内服時間**
  (11.5 vs **6.0時間前**)
- ✓ **Riv推定血中濃度**
  (81 vs **213 ng/ml**)

初回血腫量
- ✓ **症例2で血腫量大，多発**

出血機序
- ✓ **症例2で外傷性**
- ➢ 傷害血管の違い？？
  (血管数，血管径)

Maxeiner H, Neurosurgery 2002.

PCCによる止血療法のエビデンス

	投与量	対象	Riv投与量/目標血中濃度	是正効果		
				凝固マーカー		止血効果
Perzborn	25IU/kg 50IU/kg	ラット	2mg/kg	PT ○		出血時間 △ (50IU/kgのみ)
Godier	40IU/kg	ウサギ	3,5,10mg/kg	PT ○	aPTT ○	出血量 ×
Dinkelaar	0-4IU/ml	*in vitro* (健常人)	200-800ng/ml	PT ×		
Marlu	corresponding to 12.5/25/50IU/kg	*in vitro* (健常人)	20mg, OD	Thrombin generation test △ (50IU/kgのみ)		
Körber	25IU/kg 50IU/kg	健常人	80ng/ml 200ng/ml	PT ○	aPTT ○	
Eerenberg	50IU/kg	健常人	20mg, BID	PT ○		

Perzborn E et al, Thromb Haemost 2013.
Dinkelaar J et al, Journal of Thrombosis and Haemostasis 2013.
Körber MK et al, Clin Appl Thromb Hemost 2013.
Godier A et al, Anesthesiology 2012.
Marlu R et al, Thromb Haemost 2012.
Eerenberg et al, Circulation 2011.

拮抗・中和療法の展望

➢ **PCCのRivaroxabanへの拮抗作用を検証した非盲検、単一施設、並行群比較第Ⅰ相臨床試験**

方法：Riv 20mg を１日２回，4日間投与した健常成人34人を対象にPCC(3-factor, 4-factor)50IU/kgの単回急速静注群と生食100ml単回急速静注群の３群に無作為に割り付けた．

結果：30分以内にPCC両群ともPTの短縮を認めた．(3-factor >4-factor)

Levi et al , ISTH 2013(abstract)

➢ **Andexanet alfa(Xa因子の組み換え蛋白, PRT064445)**

リバーロキサバンやアピキサバンなどの直接型Xa阻害薬や間接型Xa阻害薬に中和効果を示した．
現在第Ⅱ相試験を終えた段階．

Lu G, Nat. Med. 2013.

結語

- ✓ リバーロキサバン内服下の出血性合併症に対する迅速治療として，プロトロンビン複合体製剤1000単位の投与はPT延長に対する是正効果はみられたが，止血効果は不明．
- ✓ 製剤の有効性及び最適な用量の探索が必要．

臨床研究

新規経口抗凝固薬服用中の出血合併症への対応策

豊田一則

はじめに

新規経口抗凝固薬（novel oral anticoagulant：NOAC）が国内で臨床使用され始めて（2011年3月ダビガトラン上市），2年半が過ぎた。実体験から非弁膜症性心房細動（non-valvular atrial fibrillation：NVAF）患者への虚血イベント抑止に関する有効性をワルファリンとNOACで比べて論じるには，まだ少し時期が早く思えるが，NOACの安全性，言い換えれば出血イベントの少なさを実感している。しかしながら，抗凝固薬である限りは，合併症としての出血を根絶することはできない。したがって，NOAC服用者に対してもワルファリン患者と同様に出血を予防する手段を講じ，出血時の緊急止血法を確立させる必要がある。

NOAC使用の入門書として筆者らは分担して『心原性脳塞栓症と経口抗凝固薬』を執筆，上梓し，そのなかで国立病院機構九州医療センターの矢坂正弘医博がNOACによる出血事故とその対応策について詳しく解説された[1]。ここではより新たな知見を含めて，この課題への再検討を試みる。

Key word
anticoagulation
antidote
dabigatran
intracranial hemorrhage
prothrombin complex concentrates

Management of bleeding complications in patients taking novel oral anticoagulants

Kazunori Toyoda :
Department of Cerebrovascular Medicine,
National Cerebral and Cardiovascular Center
国立循環器病研究センター 脳血管内科

Ⅰ．NOAC服用中の出血合併症の実態

NVAF患者におけるNOACとワルファリンないしアスピリンのイベント抑制効果は，いずれも大規模臨床試験で検討され，NOACがワルファリンと同等以上の，またアスピリンを超える脳卒中・全身塞栓症抑止効果を示した[2~5]。もう一つの重要な所見は，NOACはワルファリンと同等以上，アスピリンと同程度に大出血（国際血栓止血学会基準）を抑止した点であろう。図1にRELY[2]，ROCKET AF[3]，ARISTOTLE[4]，AVERROES[5]における各薬剤群の大出血年間発症率を示す。前三者がワルファリンとの比較試験で，AVERROESは何らかの理由でワルファリンを選べない患者を対象としたアピキサバンとアスピリンの比較試験である。試験間で患者背景に多少の相違があり，とくにROCKET AFはより高リスクの患者を集めているので，NOAC間の絶対的発症率の比較は行えない。この結果から，NOACは出血合併症の観点からワルファリンよりも概して安全で，アスピリンと同程度の安全性を保つと言えそうである。この傾向は大出血のなかでも頭蓋内出血で明らかで，NOACによって頭蓋内出血の危険がざっと半減している。このことから，NVAF患者の塞栓症予防を講じる際にNOACを選ぶこと自体が，抗凝固療法患者への出血合併症軽減策

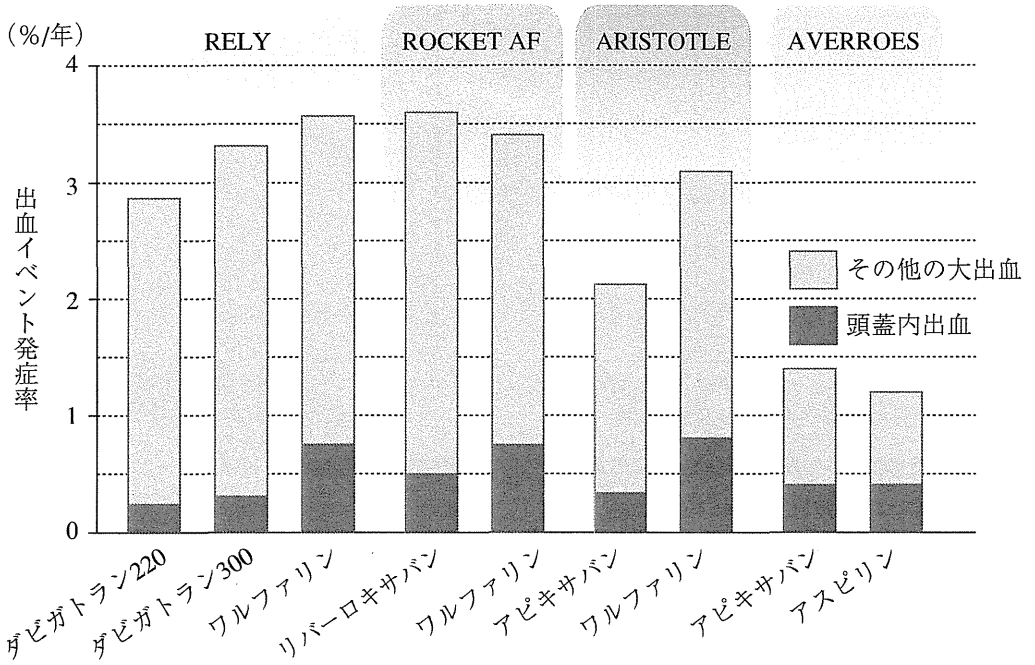


図1．大規模臨床試験におけるNOACとワルファリンないしアスピリンの大出血発症率
（文献2～5より引用改変）

となっている。

図1の各薬剤群での頭蓋内出血発症率をよく見ると（試験間の絶対的発症率の比較を控えよと書いたばかりであるが），アスピリンを含めて抗血栓薬服用者での頭蓋内出血発症率は本来高々0.5％/年ぐらいであり，ワルファリンのみ発症率が突出している。したがって，NOACを頭蓋内出血の起こりがたい薬と考えるよりも，ワルファリンを頭蓋内出血の起こりやすい薬と考えるほうが，より適切かもしれない。凝固カスケードは活性化凝固第Ⅶ因子が組織因子と結合することに始まり，とくに脳実質には組織因子が多く存在すること，第Ⅶ因子は血管損傷を見つける見張り役であることなどが，知られている。ワルファリンは第Ⅶ因子を阻害するため，脳実質出血をくい止める凝固系の初期消火作業を邪魔してしまうが，NOACは第Ⅶ因子を阻害しないため初期消火を妨げず，結果として脳出血が起こりがたくなるのであろう。

では，実臨床でNOAC患者の出血合併症は，どの程度報告されているであろう。ダビガトランの国内市販後半年間の調査（推定使用例数約70,000例）では，重篤出血138例（死亡14例）が，またリバーロキサバンの国内市販後約1年間の調査（同約35,000例）では，重篤出血178例192件（死亡10例）が報告された。このうち出血発現日が明らかな症例について，投与から出血事故発現までの日数を図示する（図2）。ダビガトラン，リバーロキサバンの両剤とも，出血発現の勾配が初期数日間でとくに険しく，事故の過半数が投与開始後28日（↑）以内に起こっている。このことから，NOAC患者の出血合併症を防ぐために，とくに開始後早期の注意が必要であることがわかる。では，どのような点に配慮すれば，出血を防げるであろうか。

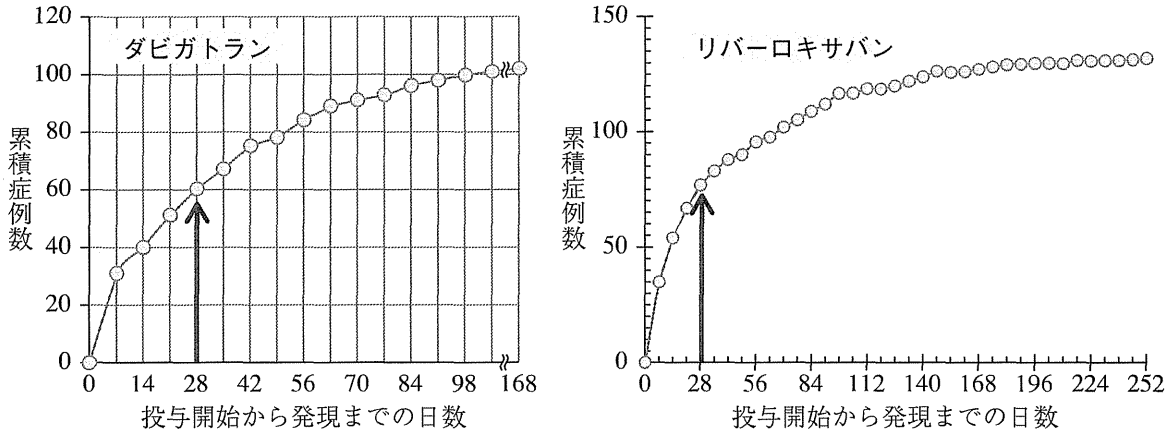
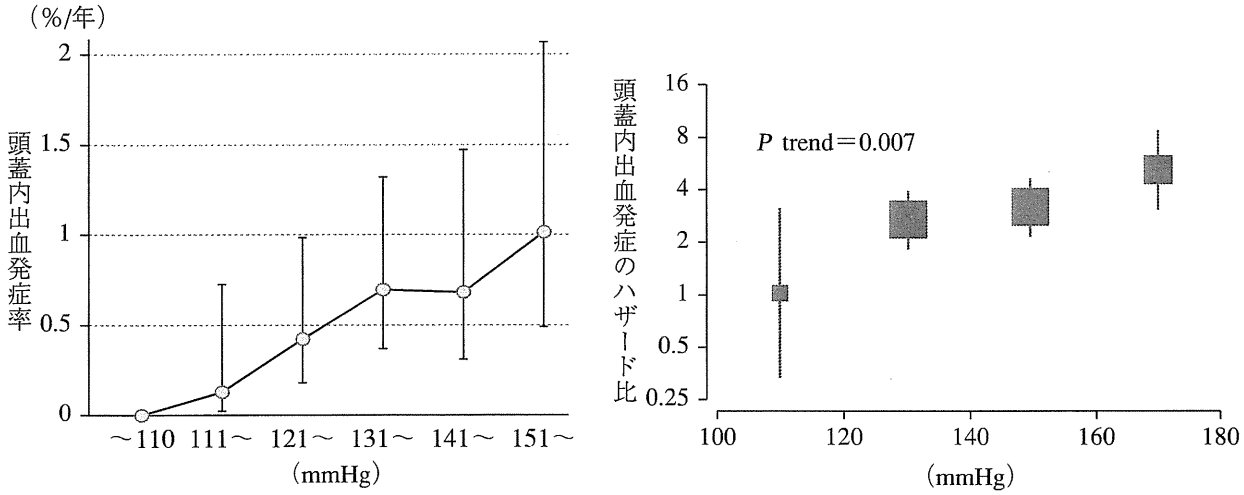


図2. 国内市販後調査における重篤出血の発現時期（各製造元企業の報告による）

Ⅱ. 出血合併症の予防策

NOAC服用者の出血合併症を防ぐ一番の策は，出血を起こしやすい患者にNOACを用いないことであり，易出血者とは高齢者，抗血小板薬併用者，低体重者（用量固定で服用する場合），腎機能障害者（腎排泄の比率が高い薬剤を服用する場合）などを指す。また，頭蓋内出血に関しては東アジア人種，脳血管障害既往，転倒傾向，微小脳出血多発などが，消化管出血に関しては消化管潰瘍既往などが出血の誘因となる。しかしながら，これらの要因の多くは，ワルファリン服用下出血合併症の誘因でもある。したがって，NVAFに関して何らかの抗凝固薬が必要な患者には，各種NOACないしワルファリンのうち最適と考えられるものを，注意深く用いざるを得ない。NOACはいずれも二用量が設けられているので，添付文書に従った正しい用量の設定が重要である。

前章では，NOAC投与開始後早期に，出血への配慮がとくに必要と述べた。では，この時期に，何を目安にして出血に配慮するべきか。NOACはワルファリンのような頻回のモニタリングと用量調整が要らないことを売り文句にしているが，見方を換えれば市販の凝固学的マーカーでは薬効を評価しがたい。しかしながら，細かな薬効評価はともかく，薬効が強すぎることの警告として，市販のマーカーを利用できる。たとえばダビガトランはトロンビンを直接阻害するので，トロンビンによる内因系凝固経路のポジティブフィードバック機構が抑えられ，その結果，活性化部分トロンボプラスチン時間（activated partial thromboplastin time：aPTT）が延長する。RELY試験においても，aPTTのトラフ値が80秒を超えると大出血のリスクが高まると報告された[2]。当施設ではダビガトラン血中濃度（ヘモクロットによるトロンビン阻害活性測定）とaPTTを比べた結果などから，ピーク値，トラフ値に限らずaPTTが60秒を超えると要注意，70秒を超えると減量ないし中止を考えている。しかしながらaPTTは試薬間差が小さくないので，この目安値を他施設に汎化できず，参考例の一つと考えていただきたい。一方で，リバーロキサバン，アピキサバン，エドキサバンは活性化凝固第X因子（Xa）を阻害するので，プロトロンビン時間（prothrombin time：PT）の律速段階である組織因子・活性化第Ⅶ因子複合体形成のポ



BAT：観察最終回（出血発症直近）の外来収縮期血圧　　PROGRESS：観察期間中に到達した収縮期血圧

図3．BAT研究，PROGRESSサブ解析での収縮期血圧と頭蓋内出血発症の相関関係（文献6，7より引用改変）

ジティブフィードバック機構が抑えられ，その結果PTが延長する。しかしながらPTも試薬間差が大きく，易出血性の閾値をどこに設けるかを含めてまだ検討すべき余地が多い。将来的に抗Xa活性の応用が期待される。これらの凝固マーカーと，腎機能（クレアチニン，クレアチニンクリアランス），貧血の程度（ヘモグロビンなど）を投与開始前と開始2週間後（慎重を期すなら1週間後）に測定し，大きな異常を認めなければ，それ以降はたとえば半年ごとのモニタリングで良いと思う。

介入による改変が可能な出血誘因に，血圧高値が挙げられる。2013年9月現在，改訂作業の大詰めを迎えている日本高血圧学会の『高血圧治療ガイドライン2014』では，「抗血栓薬服用中の高血圧患者の血圧管理」の項を新たに設け，「高血圧は抗血栓薬（抗血小板薬，抗凝固薬）服用中の頭蓋内出血の危険因子であるため，抗血栓薬を服用している患者においては厳格な血圧管理を行う」ことをグレードBで推奨することで，合意を得ている。この根拠となる臨床情報として，国内多施設共同観察研究であるBAT研究と，国際臨床試験PROGRESSのサブ解析が引用されている[6,7]。BAT研究では抗血小板薬ないしワルファリン服用4,009例において，観察期間中に頭蓋内出血を発症した群で発症前に外来血圧が漸増していること，頭蓋内出血発症を予測する至適な閾値が130/81mmHgであることが示された（図3左）[6]。また，PROGRESS登録者のうち抗血栓薬服用者を選んで行ったサブ解析では，降圧薬実薬群が偽薬群に比べて頭蓋内出血発症を46％減らし，観察期間中に到達した収縮期血圧と頭蓋内出血発症との間にBATと同様のthe lower，the betterの関係が見られた（図3右）[7]。また，2013年に発表されたSPS3試験では，抗血小板薬単剤ないし二剤を用いたラクナ梗塞患者に対して，収縮期血圧130mmHg未満に積極的に降圧した患者群が，130～149mmHgを目指した群よりも脳出血発症率を有意に低く抑えた（ハザード比0.37，95％CI 0.15～0.95）[8]。以上より，NOAC服用患者においても，可能であれば収縮期血圧を130mmHg未満に下げたほうが，頭蓋内出血を確実に予防できるであろう。その一方で，BAT研究，PROGRESSサ

表1．重篤出血発症時に考えられる緊急中和治療（欧州心臓律動学会からの提言）

製　剤	投与量の目安	備　考	わが国での市販製剤 （中和治療薬としては未承認）
プロトロンビン複合体	25U/kg	※1～2回の追加投与可能 ※臨床でのエビデンスなし	PPSB®-HT静注用「ニチヤク」
活性化プロトロンビン複合体	50IK/kg 最大で200IE/kg/日	※プロトロンビン複合体を上回る効果は示されていない	ファイバ注射用 オートプレックス
活性化第Ⅶ因子製剤	90μg/kg	※動物実験でのエビデンスのみ ※高価	ノボセブン®HI静注用
△　新鮮凍結血漿		※血漿増量剤として用いる． 止血目的には用いない	

（文献11より引用改変）

ブ解析のいずれも，血圧管理と頭蓋内出血以外の大出血発症との間に相関関係を認めなかった。たとえば消化管潰瘍既者に対しては，血圧管理とともに抗潰瘍薬の投与も検討すべきであろう。

Ⅲ．大出血時の緊急対処法

前述した矢坂医博の総説では，NOAC服用者が大出血を起こした際に必ず行うべき処置として，①休薬，②止血処置，③適切な輸液によってバイタルを安定させ，尿量を確保すること，④頭蓋内出血の場合は，十分な降圧を図ることの4点を挙げている[1]。さらに踏み込めば，内服後早期の胃洗浄や活性炭投与，腎排泄の比率が高いダビガトランでは緊急透析なども，選択肢に挙げられる。NOACはいずれも半減期が半日程度と短いため，体表からの出血であればこれらの処置をとりつつ圧迫止血することで，大事に至らずに済むことが多い。問題は頭蓋内，体腔内の大出血発症時である。とくに脳出血は発症直後の血腫拡大が転帰を悪化させるので，緊急止血処置を要する。

従来薬ワルファリン服用下での脳出血には，各種ガイドラインなどでビタミンKやプロトロンビン複合体（第Ⅸ因子複合体），新鮮凍結血漿，活性化第Ⅶ因子製剤の使用が推奨される。このうちビタミンKは，ビタミンK非依存性抗凝固薬であるNOACの中和薬とはならない。血液製剤を用いたNOACの中和について，動物実験や健常者でのデータが報告されているものの，実臨床での知見に乏しく確立した治療法とは言えない。これまでに北米関連諸学会の血栓止血サミット[9]，欧州心臓律動学会[10]，フランス周術期止血ワーキンググループ[11]などから血液製剤を用いたNOACの中和に関する提言がなされている。内容に多少の異同があるが，ここでは欧州心臓律動学会からの提言を例示する（表1）。

筆者らは，現在国内18施設で観察研究（SAMURAI-NVAF研究）を行い，研究の一環としてNOACでの大出血にプロトロンビン複合体（PPSB®-HT）を用いた中和治療例を登録している。その患者説明文書を示す（図4）。投与量として，1,000単位で開始し，必要に応じて合計1,500単位までと目安を定めている。これは欧州での目安用量より低い。この投与方法で，実臨床で脳出血，硬膜下血腫など少数例に止血治療を行い，出血増大，血栓塞栓症の双方とも起こさなかった。

ダビガトラン服用患者さんへ「プロトロンビン複合体」を止血治療として用いることへの同意書

ダビガトラン(プラザキサカプセル)は血液中のトロンビンという凝固因子を抑えて、血液を固まりにくくします。このため、心臓内に血栓(血の塊)を生じ易い心房細動を持つ患者さんの塞栓症予防に応用され、その有効性が実証されています。しかしダビガトラン服用中にひとたび出血すると、止血が困難です。

今回、＿＿＿＿＿＿＿＿様は、ダビガトラン服用中に出血合併症を起こされました。早急に出血を抑えないと、症状の増悪や生命への危険が危惧されます。

ダビガトランは2011年から使われ始めた薬で、出血時の対応法がまだ十分に分かっていませんが、同薬をいったん中止し利尿処置や胃洗浄を行うこと、血液製剤（プロトロンビン複合体、新鮮凍結血漿、遺伝子組み換え凝固第Ⅶ因子）を用いて速やかにダビガトランの効果を減じることなどが、専門の医学会（日本循環器学会）からも提唱されています。

血液製剤には各種の凝固因子が含まれ、投与によって凝固系全般が賦活されます。このうちプロトロンビン複合体（乾燥人血液凝固第Ⅸ因子複合体）については、ダビガトランと同じグループ（抗凝固薬）に属するワルファリンを服用中の患者さんが出血合併症を起こした際に、この製剤を用いて止血治療を行うことがガイドラインでも推奨され、当施設でも多数例への使用経験があります。またトロンビンを作る元になるプロトロンビンが含まれているため、ダビガトラン服用中の出血にも抑制効果が期待できます。

新鮮凍結血漿にもプロトロンビンが含まれ、またワルファリン患者さんへの止血治療にも推奨されています。しかし、新鮮凍結血漿で十分な凝固因子を補うには1リットル程度の点滴が必要なので、急速に投与できません。また遺伝子組み換え凝固第Ⅶ因子にはプロトロンビンが含まれていません。当院ではワルファリン患者さんへの止血治療に、この3剤の中で専らプロトロンビン複合体を用いており、ダビガトランに対する止血手段としても、プロトロンビン複合体がもっとも適切であろうと考えています。

プロトロンビン複合体の副作用として、アナフィラキシー様症状や大量投与による播種性血管内凝固症候群、発熱、顔面紅潮、蕁麻疹、悪寒、腰痛などが報告されており、またダビガトランの効果を抑制し過ぎて逆に血栓塞栓症を起こすかもしれません。このような症状がみられた場合は投与を中止し、適切な処置を行います。

わが国ではこの製剤は血友病Bの治療薬として開発され、ダビガトラン投与中の出血合併症への治療に用いることは健康保険適用ではなく、またダビガトランが発売されたばかりの薬で出血合併症へのプロトロンビン複合体の効果が確立した訳ではないので、患者さんやご家族に投与の理由、予想される効果と副作用について説明した上で、同意が得られた場合に使用します。

本製剤の費用を、患者さん本人や健康保険支払基金へ請求することはありません。

私は＿＿＿＿＿＿＿＿様に対して治療上必要なプロトロンビン複合体（乾燥人血液凝固第Ⅸ因子複合体）に関して上記の説明を行いました。

国立循環器病研究センター　（　　）科

平成　　年　　月　　日　　医師＿＿＿＿＿＿＿＿

私は、現在の疾病の診療に関して、上記の説明を受け、十分に理解した上でプロトロンビン複合体（乾燥人血液凝固第Ⅸ因子複合体）の投与を受けることに同意いたしました。

平成　　年　　月　　日

（患者氏名）＿＿＿＿＿＿＿＿印

代理（家族等氏名）＿＿＿＿＿＿＿＿印

（患者との続柄：　　）

国立循環器病研究センター　Ver 2.0, 2011/8/23 作成

図4．NOAC服用者への緊急止血治療に関する同意書（SAMURAI-NVAF研究）

Ⅳ．近未来の止血治療法

ダビガトランや抗Xa薬の特質を反映した独自の中和剤が，実験医学の領域で開発されている。ダビガトランに対しては，aDabi-FABと呼ばれる抗体が生成され，ダビガトランに対してトロンビンよりも350倍強い結合力をもって，トロンビン阻害に拮抗することが示された[12]。ラットを用いてダビガトラン持続静注後にaDabi-FABを単回投与する

と，1分後の測定でPT，aPTTとも正常化した。一方で，抗Xa薬に対しても，r-Antidoteと名付けられた組み換え蛋白が，おとり（デコイ）として機能する[13]。抗Xa薬はr-Antidoteと結合するが，その後のプロトロンビン活性化能はなく，リバーロキサバンやアピキサバンをラットに持続静注後にr-Antidoteを単回投与すると，5分後にPTが正常化した。これらの即効性を示す中和剤の，実臨床での有効性・安全性が早く証明され，臨床応用が可能になれば，NOACはより使いやすい薬として定着していくであろう。

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急性期脳出血患者への抗凝固療法再開に関する多施設共同観察研究

Reversal, resumption and discontinuation of anticoagulant therapy after warfarin-related intracerebral hemorrhage: a multicenter, prospective, observational study

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【目的】ワルファリン内服中発症の脳出血（WF 関連 ICH）に対する抗凝固療法（AC）補正および再開の実態と患者転帰を調べる。

【方法】10 施設で前向き観察研究を行った。2010 年 4 月から 2011 年 6 月に、WF 関連 ICH 患者を登録し、INR 補正の有無と方法、AC 再開の有無と発症 1 年以内の合併症、1 年後 mRS との関連を調べた。

【結果】53 例（男性 64%、73±9 歳）を登録し、入院時血腫量は中央値 8.4ml（IQR：3.6-19.1）、INR は中央値 2.02（IQR：1.73－2.46）であった。45 例（85%）で、Vit K 単独（24 例）、Vit K と血液製剤（PCC もしくは FFP）併用（19 例）、血液製剤単独（2 例）により INR が補正された。38 例（72%）で 4 日（中央値）後に AC が再開された。1 年後まで追跡できた 50 例では、出血性合併症が 5 例（脳出血 3 例、消化管出血 2 例）に生じ、うち 4 例は AC 再開後であった。血栓・塞栓性合併症は症候性を 6 例（脳梗塞 4 例、肺塞栓症 1 例、末梢動脈塞栓症 1 例）、無症候性を 5 例（下肢静脈血栓症 3 例、心内血栓 2 例）に生じ、うち 8 例は AC 中断中であった。1 年後の転帰不良（mRS5-6）は 15 例（30%）で、多変量解析では、入院時 NIHSS（1 点毎、OR 1.14、95%CI 1.04-1.29、P=0.002）、症候性血栓・塞栓性合併症（OR 9.82、95%CI 1.11-128.6、P=0.039）が転帰不良に独立して関連したが、出血性合併症（OR 2.40、95%CI 0.13-54.6、P=0.549）は関連なかった。

【結論】WF 関連 ICH 発症時に血液製剤による INR 補正は必ずしも多くなかった。全体の 3 割で WF は再開されなかった。発症 1 年間に出血性合併症は 10%に、血栓・塞栓性合併症は 22%に発生した。経過中の症候性血栓・塞栓性合併症は転帰不良に独立して関連した。

（計 800 字　[規定は 800 字以内]）

Systolic Blood Pressure After Intravenous Antihypertensive Treatment and Clinical Outcomes in Hyperacute Intracerebral Hemorrhage

The Stroke Acute Management With Urgent Risk-Factor Assessment and Improvement-Intracerebral Hemorrhage Study

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Background and Purpose—Blood pressure (BP) lowering is often conducted as part of general acute management in patients with acute intracerebral hemorrhage. However, the relationship between BP after antihypertensive therapy and clinical outcomes is not fully known.

Methods—Hyperacute (<3 hours from onset) intracerebral hemorrhage patients with initial systolic BP (SBP) >180 mm Hg were included. All patients received intravenous antihypertensive treatment, based on predefined protocol to lower and maintain SBP between 120 and 160 mm Hg. BPs were measured every 15 minutes during the initial 2 hours and every 60 minutes in the next 22 hours (a total of 30 measurements). The mean achieved SBP was defined as the mean of 30 SBPs, and associations between the mean achieved SBP and neurological deterioration (≥2 points' decrease in Glasgow Coma Score or ≥4 points' increase in National Institutes of Health Stroke Scale score), hematoma expansion (>33% increase), and unfavorable outcome (modified Rankin Scale score 4–6 at 3 months) were assessed with multivariate logistic regression analyses.

Results—Of the 211 patients (81 women, median age 65 [interquartile range, 58–74] years, and median initial National Institutes of Health Stroke Scale score 13 [8–17]) enrolled, 17 (8%) showed neurological deterioration, 36 (17%) showed hematoma expansion, and 87 (41%) had an unfavorable outcome. On multivariate regression analyses, mean achieved SBP was independently associated with neurological deterioration (odds ratio, 4.45; 95% confidence interval, 2.03–9.74 per 10 mm Hg increment), hematoma expansion (1.86; 1.09–3.16), and unfavorable outcome (2.03; 1.24–3.33) after adjusting for known predictive factors.

Conclusions—High achieved SBP after standardized antihypertensive therapy in hyperacute intracerebral hemorrhage was independently associated with poor clinical outcomes. Aggressive antihypertensive treatment may ameliorate clinical outcomes. **(*Stroke*. 2013;44:1846-1851.)**

Key Words: acute intracerebral hemorrhage ■ antihypertensive therapy ■ outcome

Blood pressure (BP) lowering therapy is widely performed as part of general acute management in patients with acute intracerebral hemorrhage (ICH).[1,2] An acute hypertensive response[3] is common in patients with acute ICH, occurring in ≤75%,[4] and elevated BP is associated with hematoma expansion[5,6] and poor outcome.[7–9] Recent trials have demonstrated that rapid BP lowering with antihypertensives is feasible and tolerated,[10,11] and it suppresses hematoma

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expansion.[10] However, the benefit of antihypertensive therapy in acute phase of stroke is still controversial, because the patients with ICH in the recent Scandinavian Candesartan Acute Stroke Trial (SCAST) did not benefit from candesartan,[12] and concerns also exist about excessive depression of BP in the acute phase of ICH, as it may result in renal dysfunction,[13] cerebral ischemia,[14,15] and death.[16] Given these circumstances, the optimal BP target in patients with acute ICH has not been fully elucidated.[1,2]

Moreover, although elevated BP in the acute phase is a proven predictor of worse clinical outcomes in patients with ICH,[7–9,17] the effect of the response to acute BP lowering on the clinical outcomes of patients with ICH has been relatively unclear, because there have been few prospective studies, and antihypertensive regimens (drugs, dosage, and route) and target BPs were not standardized in most such studies.

We hypothesized that a relatively high mean systolic BP (SBP) after BP lowering therapy was associated with worse clinical outcomes than a low mean SBP. The aims of the present study were to clarify the relationship between mean on-treatment SBP and outcomes, and to determine the optimal SBP threshold to avoid worse clinical outcomes in patients with acute ICH.

Methods

Subjects

The Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI)-ICH Study was a prospective, multicenter, observational study to determine the safety and feasibility of early (within 3 hours from symptom onset) SBP reduction to <160 mm Hg with intravenous nicardipine for acute hypertension in patients with spontaneous ICH. The details of the study have been described elsewhere.[18,19] In brief, acute spontaneous supratentorial ICH patients with hypertension (initial SBP >180 mm Hg), who were treated within 3 hours from onset in 10 Japanese stroke centers were enrolled. Other inclusion criteria were: age ≥20 years old; total Glasgow Coma Scale score ≥5; computed tomography <2.5 hours from onset demonstrating a supratentorial intraparenchymal hematoma with manual volume measurement <60 mL; and absence of extensive intraventricular hemorrhage. Patients with unreliable time of symptom onset, ICH because of cerebral neoplasms, arteriovenous malformations, aneurysms, trauma, bleeding diathesis, or coagulopathy, candidates for immediate surgical intervention for ICH, current pregnancy, parturition within the previous 30 days or active lactation, prothrombin time international normalized ratio ≥1.7 because of warfarin intake, and a platelet count <50 000/mm^3 were excluded. Each local ethics committee approved this study. Written informed consent was obtained from all patients or their next of kin.

The patients' clinical background characteristics, including sex, age, cardiovascular risk factors, and comorbidities were collected from medical charts. Routine blood biochemistry examinations were performed on admission. Neurological manifestations were assessed using the National Institutes of Health Stroke Scale (NIHSS) score. Functional outcome was estimated using the modified Rankin Scale.

Hematoma volume was evaluated with noncontrast computed tomography on admission and 24 (±6) hours after the initiation of antihypertensive treatment. The ABC/2 (*length*×*width*×*height*/2) method was used to determine hematoma volume at the bedside by the neurologist or neurosurgeon on admission and at 24 hours.

BP Management and Monitoring

Bolus infusion of 1 mg nicardipine was allowed before the titrating infusion. Titration of intravenous nicardipine was started within 3 hours of symptom onset and continued for 24 hours, based on a standardized protocol[18] to achieve and maintain the target SBP level <160 mm Hg and >120 mm Hg. BP management after the first 24 hours was at the primary neurologist's discretion. Oral antihypertensive agents were started after the first 24 hours.

BP and pulse rate were taken using manual or automated sphygmomanometer under established guidelines. All staffs were familiarized with the sphygmomanometer before the study by using it in general practice. The arm was placed horizontal at the level of the heart as denoted by the midsternal level in a recumbent position. BP and pulse rate were measured every 15 minutes during the initial 2 hours and every 60 minutes in the next 22 hours (30 measurements in the initial 24 hours after the initiation of antihypertensive therapy), as well as at 48 and 72 hours. To test the hypothesis, the mean achieved SBP (aSBP) was defined as the mean of a total of 30 SBPs in the initial 24 hours after the initiation of BP lowering therapy.

Clinical Outcomes

The clinical outcomes included: neurological deterioration corresponding to a decrease of ≥2 points from the baseline Glasgow Coma Scale score or an increase of ≥4 points from the baseline NIHSS score at 72 hours after the initiation of treatment; hematoma expansion >33% from baseline to 24 hours; and unfavorable outcome corresponding to patients with modified Rankin Scale scores of 4 to 6 at 3 months after ICH onset. Patients who underwent surgical intervention for ICH were regarded as having an unfavorable outcome regardless of the modified Rankin Scale score.

Statistical Analysis

Clinical background characteristics including mean aSBP were compared between patients with and without unfavorable outcomes. Univariate analyses were performed using the χ^2 test, Fisher exact test, or the Kruskal–Wallis test, as appropriate. The data are presented as median values (interquartile range) or frequencies [%]). Multivariate logistic regression analyses were performed to elucidate the associations between mean aSBP and outcomes. Sex, age, and prior antithrombotic medication, initial SBP, initial NIHSS score, onset to initial computed tomography examination time, initial hematoma volume, and serum glucose level at baseline, which are known predictors of clinical outcomes based on previous studies, were forced into model 1. In model 1, mean aSBP was entered as a continuous variable or a categorical variable based on quartiles and arbitrarily defined 5 mm Hg interval groups (<130 mm Hg, 130–135 mm Hg, 135–140 mm Hg, 140–145 mm Hg, and ≥145 mm Hg). Alternative model 2 included all variables in Table 1, and a backward stepwise selection procedure was performed using P>0.1 of the likelihood ratio test for exclusion. All statistical analyses were performed using PASW for Windows version 17.0 software (SPSS Inc, Chicago, IL). Results were considered significant at P<0.05.

Results

From July 2009 through June 2011, 211 patients (81 women, median age 65 [interquartile range, 58–74] years, and median initial NIHSS score 13 [8–17]) were included in the SAMURAI-ICH study.[18] Table 1 shows the clinical background characteristics of the included patients. The initial computed tomographic scan was performed at a median of 70 minutes from onset, and baseline hematoma volume was 10.2 (5.6–19.2) mL. The initial SBP was 200 (189–213) mm Hg. The time to reach the target range was 30 (15–45) minutes, and the proportion of time in the target SBP range after having fallen to being within the range was 78.0%. For 7 patients, nicardipine was insufficient, and additional intravenous antihypertensive drugs (diltiazem in 3, nitroglycerin in 3, and isosorbide nitrate in 1) were started 110 (98–120) minutes from starting nicardipine. Seven

Table 1. Baseline Clinical Characteristics

Variables	Total (N=211)	Favorable Outcome (n=124)	Unfavorable Outcome (n=87)	*P* Value
Female, n (%)	81 (38)	50 (40)	31 (36)	0.566
Age, y, median (IQR)	65 (58–74)	62 (55–69)	70 (63–79)	<0.001
History of stroke, n (%)	26 (12)	16 (13)	10 (12)	0.834
Prior antithrombotic medication, n (%)	24 (11)	13 (11)	11 (13)	0.664
Liver cirrhosis, n (%)	10 (5)	7 (6)	3 (3)	0.530
Vascular risk factors, n (%)				
Hypertension	176 (83)	104 (84)	72 (83)	0.853
Diabetes mellitus	29 (14)	17 (14)	12 (14)	1.000
Hyperlipidemia	87 (41)	54 (44)	33 (38)	0.478
Current smoking	67 (32)	44 (36)	23 (26)	0.179
Alcohol intake	120 (57)	73 (59)	47 (54)	0.572
SBP on admission, mm Hg, median (IQR)	200 (189–213)	198 (188–212)	200 (190–216)	0.160
HR on admission, bpm, median (IQR)	80 (70–92)	80 (70–93)	78 (70–90)	0.474
Initial NIHSS score, median (IQR)	13 (8–17)	10 (6–15)	15 (12–20)	<0.001
Onset to CT, minutes, median (IQR)	70 (59–94)	74 (58–97)	65 (60–89)	0.181
Initial hematoma volume, mL, median (IQR)	10.2 (5.6–19.2)	9.0 (4.0–17.9)	14.0 (8.0–25.1)	0.001
Hematoma on left side, n (%)	101 (48)	61 (49)	40 (46)	0.676
Hematoma location, n (%)				0.125
Putamen	121 (57)	76 (61)	45 (52)	
Thalamus	76 (36)	38 (31)	38 (44)	
Lobar	14 (7)	10 (8)	4 (5)	
Biochemistry sign at admission, median (IQR)				
Albumin, g/dL	4.1 (3.9–4.4)	4.2 (4.0–4.5)	4.0 (3.8–4.3)	0.001
Leukocyte count, /μL	6900 (5400–8300)	6800 (5300–8400)	6900 (5600–8300)	0.662
Blood glucose, mg/dL	121 (107–144)	121 (105–145)	124 (107–143)	0.595
Total cholesterol, mg/dL	194 (169–224)	202 (176–226)	186 (156–211)	0.002
Creatinine, mg/dL	0.70 (0.60–0.90)	0.70 (0.60–0.90)	0.70 (0.60–0.90)	0.530
Mean aSBP, mm Hg, median (IQR)	137 (133–142)	137 (131–141)	139 (134–143)	0.012

Favorable outcome: patients with modified Rankin scale 0–3 at 3 mo from onset. Unfavorable outcome: patients with modified Rankin scale 4–6 at 3 mo from onset or who received hematoma evacuation surgery.

aSBP indicates achieved systolic blood pressure; CT, computed tomography; HR, heart rate; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; and SBP indicates systolic blood pressure.

patients received hematoma evacuation surgery after starting antihypertensive treatment and being regarded as having an unfavorable outcome. As shown by the variables in Table 1, patients with an unfavorable outcome were older (70 [63–79] years versus 62 [55–69] years; $P<0.001$) and had a higher initial NIHSS score (15 [12–20] versus 10 [6–15]; $P<0.001$) and hematoma volume (14.0 [8.0–25.1] mL versus 9.0 [4.0–17.9] mL; $P=0.001$) than those with a favorable outcome. Levels of serum albumin (4.0 [3.8–4.3] g/dL versus 4.2 [4.0–4.5] g/dL; $P=0.001$) and total cholesterol (186 [156–211] mg/dL versus 202 [176–226] mg/dL; $P=0.002$) were lower in patients with unfavorable than with favorable outcomes. The mean aSBP was higher in patients with unfavorable (139 [134–143] mm Hg) than with favorable (137 [131–141] mm Hg) outcomes ($P=0.012$).

Neurological deterioration was observed in 17 (8%), hematoma expansion in 36 (17%), and unfavorable outcome in 87 (41%) patients. Results of multivariate logistic regression analyses are presented in Table 2 and Figures 1 and 2. Every 10 mm Hg increment of mean aSBP was associated with a 4.5-fold increase in neurological deterioration, a 1.8-fold increase in hematoma expansion, and a 2.0-fold increase in unfavorable outcome after multivariate adjustment (Table 2). Figures 1 and 2 show the correlations between outcomes and mean aSBP as quartiles (Figure 1) and arbitrarily defined 5 mm Hg interval groups (Figure 2); these correlations were

Table 2. ORs and 95% CIs for Every 10 mm Hg Increment in Mean aSBP for Outcomes

	Crude	Model 1	Model 2
Neurological deterioration	3.93 (1.96–7.90)	4.45 (2.03–9.74)	4.43 (1.98–9.90)
Hematoma expansion	1.80 (1.12–2.91)	1.86 (1.09–3.16)	1.80 (1.08–2.98)
Unfavorable outcome	1.57 (1.07–2.28)	2.03 (1.24–3.33)	2.00 (1.23–3.26)
Unfavorable outcome*	1.43 (0.98–2.18)	1.78 (1.05–3.01)	1.69 (1.00–2.89)

Model 1: adjusted for sex, age, prior antithrombotic medication, initial SBP, initial National Institutes of Health Stroke Scale score, onset to initial computed tomography examination time, initial hematoma volume, and serum glucose level at baseline. Model 2: adjusted for variables in Table 1.

aSBP indicates achieved systolic blood pressure; CI, confidence interval; and OR, odds ratio.

*After removing 7 patients who received surgery.

derived using multivariate logistic regression model 1. The thresholds of the mean aSBP quartiles were 132.8, 137.4, and 142.1 mm Hg. Patients with the lowest mean aSBP quartile had a lower rate of neurological deterioration (odds ratio, 0.06; 95% confidence interval, 0.007–0.54), hematoma expansion (0.27; 0.07–0.98), and unfavorable outcome (0.18; 0.06–0.55) compared with those with the highest quartile (Figure 1). Similarly, neurological deterioration (odds ratio could not be estimated because neurological deterioration did not occur in patients with mean aSBP <135 mm Hg) and unfavorable outcome (odds ratio, 0.13; 95% condidence interval, 0.03–0.51) were less common, and hematoma expansion (0.20; 0.04–1.15) was marginally less common in patients with mean aSBP <135 mm Hg than in those with mean aSBP ≥145 mm Hg (Figure 2). The odds ratios of worse clinical outcomes increased gradually as mean aSBP rose. Leaving out the 7 patients with surgery did not change these findings significantly (Table 2).

Discussion

This prospective study demonstrated that acute SBP after standardized intravenous antihypertensive therapy was independently associated with neurological deterioration, hematoma expansion, and unfavorable outcome in patients with acute ICH. The rates of poor clinical outcomes increased gradually as mean aSBP rose.

The relationships between elevated BP after antihypertensive therapy and poor clinical outcomes were partly in line with previous studies.[6–9,20] Ohwaki et al[6] reported that maximum SBP after nonstandardized antihypertensive treatment was independently associated with hematoma enlargement. We previously reported that mean SBP lowering to <138 mm Hg during the initial 24 hours was associated with more favorable early outcome than SBP of 138 mm Hg or higher after antihypertensive therapy mainly with intravenous nicardipine or nitroglycerin.[9] Leira et al[20] showed that high SBP within 48 hours after nonstandardized antihypertensive therapy with intravenous labetalol or captopril in acute ICH patients with BP >185/105 mm Hg was independently associated with early neurological deterioration. However, few data showed the association between response after standardized BP lowering therapy and clinical/radiological outcomes, such as neurological deterioration, hematoma expansion, and unfavorable outcome. Indeed, a large prospective trial using predefined, standardized antihypertensive strategy found that, although a lower SBP target in acute ICH suppressed

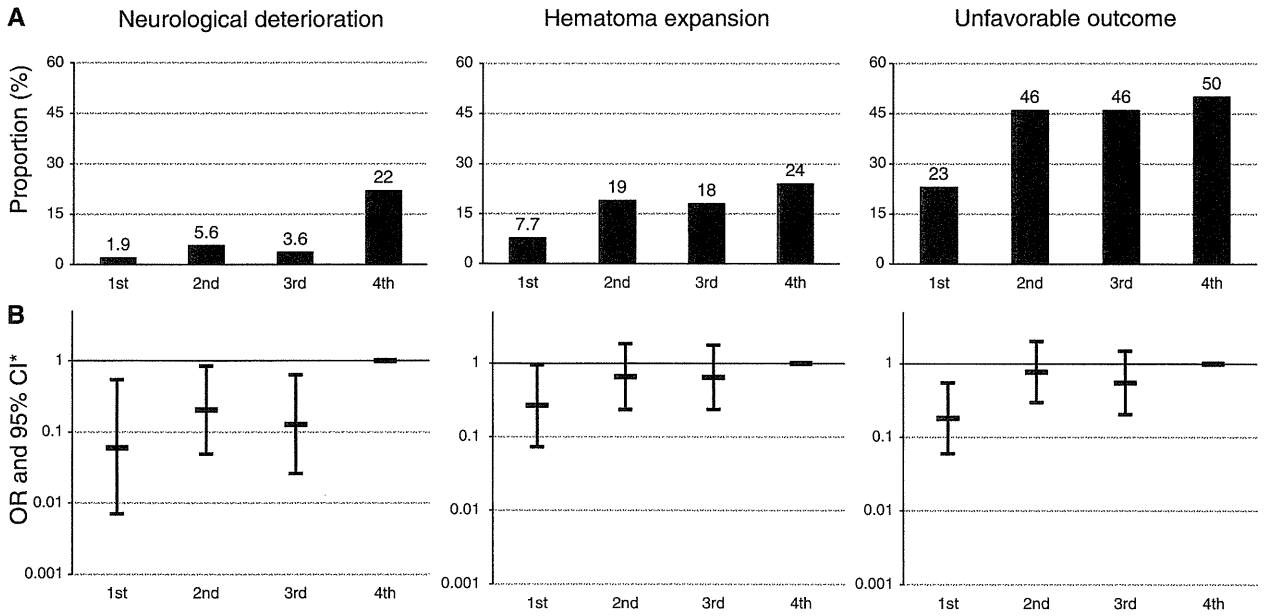

Figure 1. Proportions (**A**) and multivariate-adjusted odds ratios (ORs) with 95% confidence interval (CI; **B**) according to the mean achieved systolic blood pressure (aSBP) quartiles. The thresholds of the mean aSBP quartiles were 132.8, 137.4, and 142.1 mm Hg. *Adjusted for sex, age, prior antithrombotic medication, initial SBP, initial National Institutes of Health Stroke Scale score, onset to initial computed tomography examination time, initial hematoma volume, and serum glucose level at baseline.

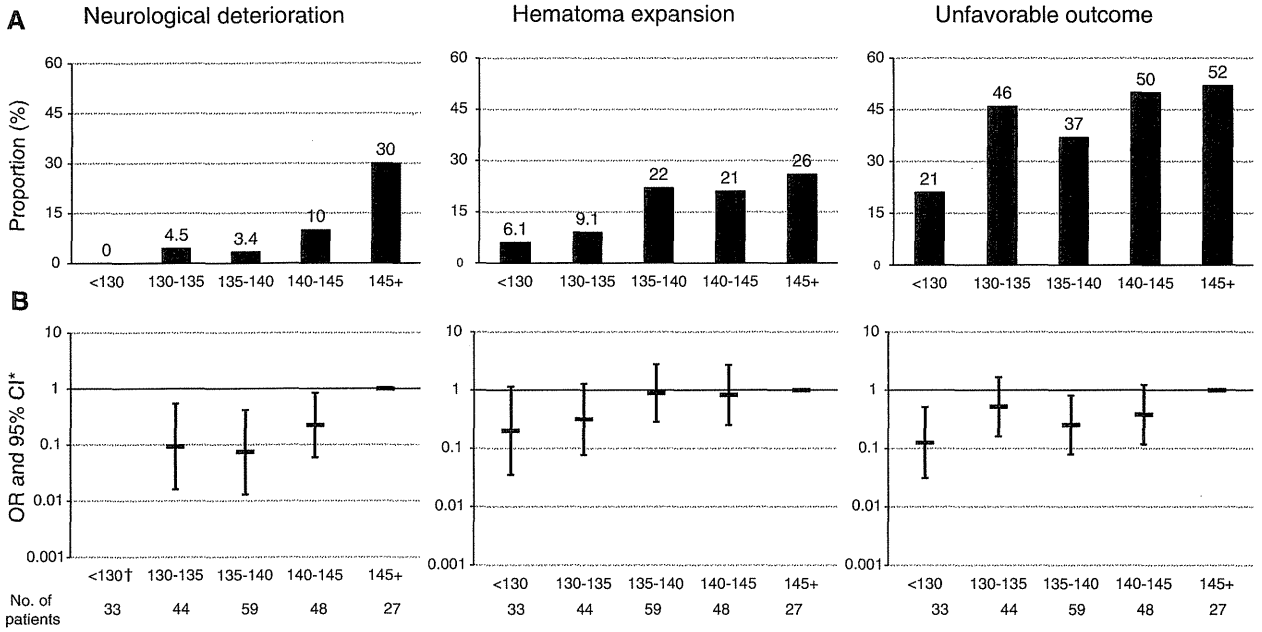

Figure 2. Proportions (**A**) and multivariate-adjusted odds ratios (ORs) with 95% confidence interval (CI; **B**) according to the arbitrarily defined, 5 mm Hg interval mean achieved systolic blood pressure (aSBP) groups. *Adjusted for sex, age, prior antithrombotic medication, initial SBP, initial National Institutes of Health Stroke Scale score, onset to initial computed tomography examination time, initial hematoma volume, and serum glucose level at baseline. †Odds ratio could not be estimated because neurological deterioration did not occur in patients with a mean aSBP <135 mm Hg.

hematoma expansion, the clinical outcome did not differ between the lower and the standard target SBP groups.[10]

The SAMURAI-ICH was a prospective study that included supratentorial ICH patients within 3 hours from onset treated with a standardized antihypertensive regimen regarding the first-choice drug, administration/titration method, and frequency of BP measurement. These homogeneous factors may reduce possible bias. Moreover, frequent BP measurement may contribute to differentiating between patients with and without worse clinical outcomes. Elevated BP in acute ICH promotes further active bleeding, resulting in hematoma expansion.[6] Because hematoma expansion is correlated with early neurological deterioration[20] and poor outcome,[21] high mean aSBP was independently associated with neurological deterioration and unfavorable outcome through hematoma expansion in the present study. Although perihematomal edema was not measured, increased edema[22] is also a potential mechanism for the relatively high proportion of neurological deterioration or unfavorable outcome in patients with high mean aSBP.

The rates of poor clinical outcomes increased gradually as mean aSBP rose with standardized BP lowering. Excessive BP reduction in acute ICH patients is considered to be harmful rather than beneficial.[13–16] The optimal target SBP in patients with acute ICH has been unclear,[1,2] and the present study showed that patients with the lowest quartile, corresponding to mean aSBP <132.8 mm Hg or mean aSBP <130 mm Hg, have the lowest proportions of worse clinical outcomes. On the basis of these results, the optimal threshold for worse clinical outcomes was ≈130 mm Hg, and therefore the optimal target SBP in acute ICH might be ≈130 mm Hg.

There are some limitations in the present study that need to be addressed. First, because the SAMURAI-ICH study was an observational study that did not compare groups with different SBP targets, the optimal target SBP cannot be determined from the results of the present study. It is difficult to differentiate whether high aSBP is a cause or a consequence of worse clinical/radiological outcomes, although neurological deterioration or hematoma expansion was not reported to be followed by subsequent BP elevation.[11] Ongoing large randomized trials[23–25] are expected to resolve these problems. Second, the present target SBP (<160 mm Hg) follows the recent guidelines from the American Heart Association/American Stroke Association[1]; the target level was different from that in the ongoing trials.[23–25] Third, the use of nicardipine in patients with acute ICH may not be always beneficial, because nicardipine has mild antiplatelet properties,[26] although there is no direct evidence of hematoma expansion because of the antiplatelet effect of nicardipine.

In conclusion, high SBP after initiation of standardized antihypertensive treatment was independently associated with neurological deterioration, hematoma expansion, and unfavorable functional outcome in acute ICH. A mean aSBP ≈130 mm Hg was associated with the lowest odds ratios for worse clinical outcomes. Aggressive antihypertensive treatment for such patients may ameliorate clinical outcomes.

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Disclosures

None.

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