＜原　著＞

脳梗塞における血中 von Willebrand 因子活性の変動および抗血小板薬の与える影響についての検討

野村　栄一[1]　郡山　達男[2]　小塚　和子[3]
梶川　博[4]　中村　重信[1]　松本　昌泰[2]

要旨：脳梗塞急性期から亜急性期にかけて血中の von Willebrand 因子（vW 因子）活性を測定し，臨床病型による差異，重症度との関係について検討した．さらに，抗血小板薬の影響についても検討した．対象は発症 48 時間以内に入院した脳梗塞 83 例で，vW 因子活性の測定は入院時および 1 カ月後に行った．vW 因子活性は，対照群と比べ患者群において有意に高値であり，1 カ月後には，入院時よりも有意に上昇した．vW 因子活性の変動は，臨床病型による違いは明らかでなく，重症度と vW 因子活性にも相関を認めなかった．抗血小板薬の有無・種類別の検討では，シロスタゾール投与群で vW 因子活性の上昇が抑えられる可能性が示唆された．脳梗塞の急性期から亜急性期にかけて vW 因子は上昇するが，病型，重症度による差異は明らかではなかった．シロスタゾールは，この上昇を抑制する可能性があり，その意義について検討していく必要がある．

Key words : acute cerebral infarction, von Willebrand factor, anti-platelet drug, stroke severity, cilostazol

（脳卒中 25 : 252—258，2003）

はじめに

von Willebrand 因子（以下，vW 因子）は糖タンパク質の一つであり，血管内皮細胞の Weibel-Palade 体や血小板のα顆粒中に貯蔵され，血中のその値の上昇は，主に血管内皮細胞の傷害や活性化を反映すると考えられている[1][2]．これまで虚血性心疾患[3][4]，虚血性脳血管障害[5]~[12]あるいは閉塞性動脈硬化症[13]等の種々の血管障害の急性期および慢性期，あるいは糖尿病[14]，膠原病[15][16]などの血管内皮の障害される疾患においてその値が上昇することが報告されている．我々もこれまでに各種血管障害[17]，慢性期脳血栓症[18]，頸動脈硬化[19][20]および脳梗塞の急性期および亜急性期における血中 vW 因子活性の上昇[21][22]を報告してきた．

[1]翠清会梶川病院脳神経内科
[2]広島大学大学院病態探究医科学講座脳神経内科学
[3]脳神経センター大田記念病院神経内科
[4]翠清会梶川病院脳神経外科
（2003 年 3 月 26 日受付，2003 年 5 月 13 日受理）

また，血中の vW 因子は，血管内皮細胞の傷害や活性化を反映するばかりでなく，それ自体が，血小板同士の凝集や，血管内皮と血小板の粘着，すなわち病的血栓の形成に大きな役割を果たしており[1][2]，その上昇は虚血性脳血管障害[23][24]や心筋梗塞発症[25]のリスクとなると考えられている．従って，脳梗塞急性期に上昇した血中の vW 因子は，急性期における梗塞巣の拡大や再発に関与している可能性があり，その増加を抑制することは脳梗塞患者の機能予後の改善や再発率の低下につながる可能性がある．今回我々は，脳梗塞急性期患者において血中の vW 因子活性を測定し，新たに臨床病型による差異，重症度との関係，亜急性期における機能的予後との関係について検討した．さらに，retrospective にではあるが，抗血小板薬の与える影響についても検討した．

対象と方法

1998 年 4 月より 2001 年 3 月までの間に当科に発症 48 時間以内に入院し，脳梗塞と診断した以下の条件を

表1　対照群と患者群および臨床病型別の背景因子の比較

	対照群	患者群	p 値	臨床病型別			p 値
				アテローム血栓性脳梗塞	心原性脳塞栓症	ラクナ梗塞	
症例数	66	83		27	21	35	
年齢(平均±標準偏差)	65.8±14.6	68.5±10.2	0.2	69.3±10.2	68.4±13.2	67.8±8.0	0.8
性別(男性/女性)	42/24	54/29	0.9	20/7	8/13	26/9	0.01
1カ月以内の死亡例		6		0	6	0	
高血圧	20	45	0.004	16	12	17	0.7
糖尿病	7	24	0.006	7	4	13	0.3
高脂血症	12	22	0.2	7	4	11	0.6
入院時の JSS(平均±標準偏差)		7.9±7.0		10.8±5.6	13.3±7.7	2.5±2.0*	<0.001
入院1カ月後の FIM の得点(中央値)		108		67	86	119	0.001

JSS, Japan Stroke Scale；FIM, Functional Independence Measure.
対照群と患者群の比較は連続変数については一元配置分散分析，比率については χ^2 独立性の検定を用いた．
各臨床病型間の比較は連続変数については一元配置分散分析および多重比較，順位変数については Kruskal Wallis 検定，比率については χ^2 独立性の検定を行った．
*多重比較により他の群よりそれぞれ有意に低値．

満たす連続83例を対象とした．入院時に頭部CT検査を行い，まず出血性脳卒中を除外した．その後可及的速やかに頭部MRI，MRA，心電図あるいは症例に応じて頸動脈エコーや心エコー検査を行い，発症様式，既往歴，各種検査結果と併せて，NINDSの分類に従い，アテローム血栓性脳梗塞，心原性脳塞栓症，ラクナ梗塞に分類した．今回は一過性脳虚血発作および病型への分類が不能の症例は除外した．また，患者あるいはその家族に対して説明を行い，採血に関して同意を得られなかった症例は除外した．さらに，血栓溶解療法施行例，血中vW因子活性に与える影響が大きいと考えられる炎症性疾患の急性期，肝臓あるいは腎臓疾患，悪性腫瘍の合併例も除外した．

入院時の重症度の評価はJapan Stroke Scale (JSS) により行い，入院1カ月後の機能予後の評価はFunctional Independence Measure (FIM) により行った．血中vW因子活性は入院時および入院1カ月後に測定した．入院時の採血は出来るだけ速やかに，入院1カ月後は早朝空腹時に行った．採血後は直ちに遠心分離し，得られた血漿を−40℃で冷凍保存した．血中vW因子の活性の測定はリストセチンによる固定血小板凝集法により行った．

急性期の治療の選択は，以下の指針に基づき，基本的には主治医の判断により行われた．

1．入院後はオザグレル，アルガトロバンあるいはエダラボン（研究期間の途中より使用可能）の点滴投与あるいはアスピリンの内服（研究期間の途中より効能追加）のいずれかを速やかに使用する．

2．点滴による治療を行った場合は1週間以内に抗血小板薬の内服を開始する．

3．心原性脳塞栓症の場合は入院後2〜4週間以降に抗凝固薬の投与を考慮する．

なお，抗血小板薬の内服については，研究開始時はチクロピジンを使用することを基本としたが，チクロピジンに関する緊急安全情報（1999年6月に血栓性血小板減少性紫斑病，無顆粒球症，重篤な肝障害が警告欄に記載）が配布されて以降は，その内容について説明を行った後，症例に応じて他の抗血小板薬についても説明を行い，同意が得られた場合はアスピリンあるいはシロスタゾールを使用した．

本研究においては抗血小板薬の内服の有無が血中vW因子活性に与える影響についてretrospectiveに検討した．すなわち，入院から1週間以内に内服の抗血小板薬の投薬が開始された50例を抗血小板薬投与群とし，さらにシロスタゾール100mg投与群（20例）と従来からの抗血小板薬（塩酸チクロピジン100mgあるいはアスピリン330mg）投与群（30例）に分類し，非投与群（27例）と比較検討した．なお入院から1カ月以内に死亡した6例については抗血小板薬の有無・種類による検討からは除外した．また，脳卒中，心筋梗塞等の血管イベントの既往のない66例（脳ドック受診者および脳の精査を希望された外来受診者）を

表2　対照群と患者群および臨床病型別のvW因子活性（%）の比較

対照群		患者群	臨床病型別			p値
			アテローム血栓性脳梗塞	心原性脳塞栓症	ラクナ梗塞	
151.4 ± 59.3	入院時	184.9 ± 70.1 *	175.7 ± 68.1	205.6 ± 85.0	179.4 ± 60.8	0.3
	入院1カ月後	197.3 ± 66.4 *	192.6 ± 64.1	214.1 ± 64.1	193.7 ± 70.1	0.6

数値は平均±標準偏差
対照群と患者群の比較はDunnettの検定，臨床病型別の比較は一元配置分散分析および多重比較を用いた．
*対照群に比べ統計学的に有意差あり（Dunnettの検定）．

表3　抗血小板薬の有無・種類別の比較

	チクロピジン	アスピリン	従来の抗血小板薬	シロスタゾール	抗血小板薬（−）	p値
症例数	14	16	30	20	27	
年齢（平均±標準偏差）	70.7 ± 10.4	67.2 ± 12.2	68.8 ± 11.4	69.0 ± 5.9	68.3 ± 10.4	0.97
性別（男性/女性）	8/6	9/7	17/13	17/3	20/7	0.1
高血圧	8	6	14	11	17	0.5
糖尿病	4	2	6	8	9	0.3
高脂血症	3	5	8	5	9	0.8
臨床病型						
アテローム血栓性脳梗塞	6	5	11	8	8	
心原性脳塞栓症	1	6	7	2	6	
ラクナ梗塞	7	5	12	10	13	
入院時のJSS（平均±標準偏差）	8.0 ± 4.9	8.4 ± 8.2	8.2 ± 6.8	5.4 ± 4.7	7.4 ± 7.5	0.3
急性期治療						
オザグレル	0	0	0	2	4	
アルガトロバン	10	6	16	15	9	
エダラボン	0	8	8	0	0	
入院1カ月後のFIM（中央値）	96	89	93	120	103	0.04
vW因子活生（%）						
入院時	183.6 ± 71.2	198.7 ± 82.6	191.6 ± 80.0	162.6 ± 43.7	178.5 ± 62.7	0.3
1カ月後	235.0 ± 57.9	208.3 ± 78.8	220.7 ± 70.0	159.6 ± 47.7 *	199.1 ± 63.5	0.005

JSS，Japan Stroke Scale；FIM，Functional Independence Measure.
チクロピジンとアスピリンの投与群を合計して従来の抗血小板薬群とした．
3群間の比較は連続変数については一元配置分散分析および多重比較，順位変数についてはKruskal Wallis検定，比率についてはカイ二乗独立性の検定を行った．
*多重比較によりシロスタゾール群が他の2群に比べ有意に血中vW因子活性が低値．

対照群とし，患者群と比較検討した．

統計学的解析

2群間の比較は，連続変数については一元配置分散分析，比率についてはχ^2独立性の検定を用いた．3群間の比較は，連続変数については一元配置分散分析および多重比較（Dunnettの検定，Games-Howelの検定），順位変数についてはKruskal Wallis検定，比率についてはχ^2独立性の検定を行った．血中vW因子活性に対する臨床病型あるいは抗血小板薬の影響および経時的変化と臨床病型あるいは抗血小板薬の有無，種類の交互作用については，重複測定分散分析および多重比較（Games-Howellの検定）により検討を行った．また，vW因子活性およびJSS，FIMの相関はSpearmannの順位相関により検定した．解析にはStat View®5.0（SAS Institute Inc.）を使用し，$p<0.05$を有

意とした．

結　果

対象とした患者および対照群の背景因子を表1に示した．患者群は対照群に比べ，年齢，性別，高脂血症の割合に有意差を認めなかったが，高血圧（p＝0.004），糖尿病（p＝0.006）を有する割合が有意に高値であった．次に臨床病型別の臨床背景を比較すると，年齢や高血圧，糖尿病，高脂血症を有する割合は3群で有意差を認めなかったが，性別（p＝0.01）および入院時のJSS（p＜0.001），入院1カ月後のFIMの得点（p＝0.001）は3群で有意に異なっていた．JSSについては，ラクナ梗塞群においてアテローム血栓性脳梗塞群や心原性脳塞栓症群に比べ，有意に得点が低値であった．

次に血中vW因子活性について検討した（表2）．入院時および入院1カ月後の血中vW因子活性の値は対照群に比べ有意に高値であった．患者群において血中vW因子活性は入院時から1カ月後にかけて統計学的に有意に上昇した（p＝0.01）．さらに臨床病型別に検討すると，入院時，入院1カ月後とも3群間で血中vW因子活性に有意差を認めなかった．また重複測定分散分析により，臨床病型によって血中vW因子活性に差を認めず（p＝0.68），臨床病型と血中vW因子活性の経時的変動における交互作用も認めなかった（p＝0.78）．

次に抗血小板薬の内服の有無・種類別の検討（表3）では，年齢，性別あるいは高血圧，糖尿病，高脂血症を有する割合には3群間で有意差を認めなかった．入院から1カ月後のFIMの得点は3群間で有意に異なっていた（p＝0.04）．また，入院時の血中vW因子活性は3群間で有意差を認めなかったが，入院1カ月後の血中vW因子活性は3群間で有意に異なり（p＝0.005），シロスタゾール投与群で他の2群に比べ低値であった．また，重複測定分散分析の結果から，抗血小板薬の有無，種類によって血中vW因子活性に差を認め（p＝0.03），多重比較の結果から，シロスタゾール投与群と他の2群の間で血中vW因子活性の有意差を認めた（図1）．しかし，抗血小板薬の有無，種類と経時的変化には交互作用を認めなかった（p＝0.19）．

入院時の重症度や亜急性期のADLの自立度と血中vW因子活性の関係については，入院時のJSSと入院時の血中vW因子活性の間には相関が見られなかったが（p＝0.88），入院1カ月後のFIMと入院1カ月後の血中vW因子活性の間には有意な負の相関関係を認めた（p＝0.01）（図2）．

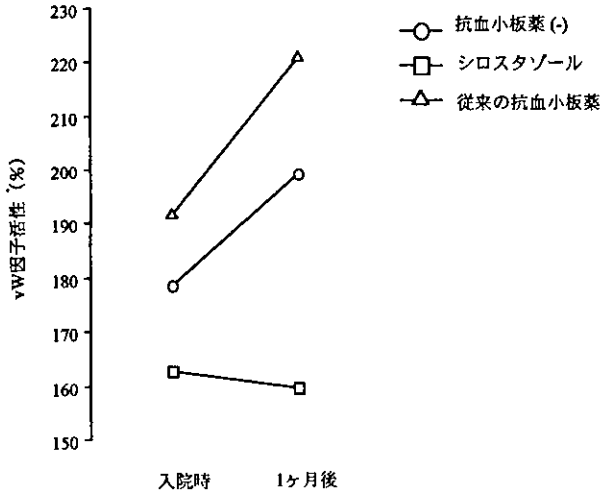


図1　急性期から亜急性期における抗血小板薬の有無・種類別の血中vW因子活性の変動
重複測定分散分析の結果から，抗血小板薬の有無，種類によって血中vW因子活性に与える影響に差を認め（p＝0.03），多重比較（Games-Howellの検定）の結果から，シロスタゾール投与群と他の2群の間でvW因子活性に与える影響に有意差を認めた．

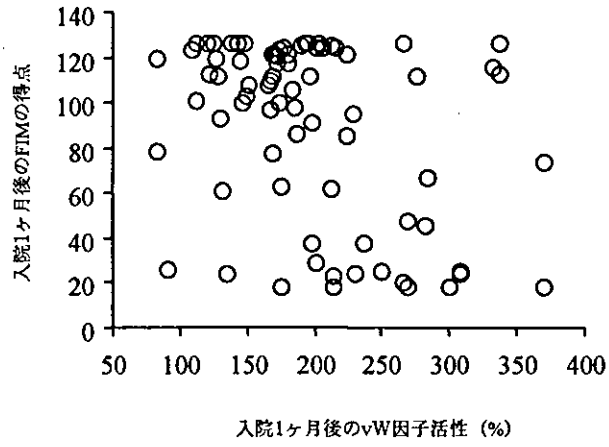


図2　入院1カ月後の血中vW因子活性とFIM（Functional Independence Measure）の得点の関係
FIMの得点は順位変数であるためSpearmannの順位相関により検定し，有意な負の相関関係を認めた（p＝0.01）．

考　察

今回の検討において，血中のvW因子活性は，脳梗塞の急性期から上昇し，入院1カ月後の亜急性期には，

さらに有意に上昇していた．しかし，血中vW因子の変動は，臨床病型別に検討しても病型による差異は明らかでなく，入院時の重症度と血中vW因子活性の間にも相関を認めなかった．一方で，抗血小板薬の内服の有無・種類別に検討すると，シロスタゾール投与群で血中vW因子活性の上昇が抑えられる可能性が示唆された．

血中のvW因子は急性相反応物質として炎症，腫瘍，ストレス等により非特異的に上昇するが[26]，主に血管内皮細胞のWeibel-Palade体に貯蔵されているため，血管内皮の活性化あるいは傷害を反映する指標になるとされる[1][2]．これまで虚血性心疾患[3][4]，虚血性脳血管障害[5]~[12]あるいは閉塞性動脈硬化症[13]等の種々の血管障害の急性期および慢性期においてその値が上昇することが報告されている．

脳梗塞急性期において血中vW因子が上昇することは前述のごとくほぼ確立されているが，重症度との関係，経時的変化[10][12]について検討した物は非常に少ない．我々は最近，脳梗塞急性期から慢性期にかけて，種々の血管内皮因子や接着分子を経時的に測定し，その結果を報告した[21][22][27]．血中vW因子の活性については，以前からの報告と同様に脳梗塞の急性期から上昇していたが，入院から1カ月後の亜急性期にはさらに上昇しており，症例数を増やした本研究においても同様の結果であった．脳梗塞発症後に血中のvW因子が亜急性期においても高値を持続するという報告は以前にもなされており，炎症反応の持続あるいは血管新生の反映の可能性があると考察されているが[10][12]，その機序は未だ明確ではない．以前の検討において，我々は血中の白血球数も同時に測定し，急性期から亜急性期にかけて有意に減少し，その後は6カ月にわたりあまり変動しないことを明らかにし，亜急性期における血中vW因子活性の上昇には炎症の与える影響は小さいのではないかと考察した[21]．本研究においては，血中vW因子活性に影響する他の因子を調べるため，臨床病型による経時的変動の違い，入院時の重症度あるいは亜急性期の機能予後と血中vW因子活性との相関の検討も行った．その結果，臨床病型による差異，重症度との相関は認めなかったが，亜急性期の機能予後と亜急性期の血中vW因子活性の間には逆相関を認めた．したがって，急性期の血中vW因子活性の上昇は，血管内皮の傷害の程度より急性相反応を反映して病型，重症度を問わず上昇している可能性があると考えた．一方，亜急性期にかけてさらに血中vW因子活性が上昇することについては，機能予後と逆相関していることから，血管内皮の持続的傷害あるいは新生を反映する以外に，ADLの悪い状態そのものが血中vW因子活性の上昇に関与している可能性も考慮すべきであると考えた．

血中のvW因子は，血管内皮の活性化および傷害を反映するだけでなく，それ自体が血小板の凝集や血小板の血管内皮への粘着に大きな役割を果たしているとされ[1][2]，その値の上昇は，虚血性脳血管障害[23][24]や心筋梗塞[25]発症の危険因子となる可能性が指摘されている．今回我々は，retrospectiveにではあるが，脳梗塞急性期から亜急性期にかけての抗血小板薬の投与の有無，種類が血中vW因子活性に影響を与えるか否か検討した．その際，アスピリンとチクロピジンの間では，vW因子活性の変動に明らかな差を認めなかったため（表3），今回の検討では両者を従来の抗血小板薬として扱った．その結果，シロスタゾール投与群で血中vW因子活性が抑制される可能性が示唆された．シロスタゾールはホスホジエステラーゼ3およびアデノシン再取込みを阻害し，血小板および血管平滑筋のcAMPの濃度を高めることにより抗血小板，血管拡張作用を発揮する薬剤であるが，脂質降下作用，血管平滑筋増殖抑制作用，血管内皮の保護作用を有する可能性も指摘されている[28]．一方，今回抗血小板薬のアスピリンやチクロピジンを投与した群では血中vW因子活性の抑制効果を認めなかった．抗血小板薬が血中vW因子に与える影響について検討した報告は少ないが，アスピリンは影響を与えなかったとの報告がある[29]．以前我々は，アスピリン，チクロピジン，シロスタゾールの単独あるいは併用療法を慢性期脳血栓症に行い，血小板機能を十分に抑制すれば，血中vW因子活性も抑制されることを報告しているが[18]，薬剤別の検討は行っていない．以上より今回の結果は，抗血小板作用のみならず，それとは別のシロスタゾールの血管内皮保護作用により，血中vW因子活性の上昇が抑制された可能性があると考えた．シロスタゾールは最近，脳梗塞再発予防に有効であることが大規模臨床試験で実証されており[30]．今後は，脳梗塞発症後の比較的急性期から投与し，血中vW因子活性を抑制することが臨床症状の改善あるいは急性期の再発予防に有効であるか否かを検証する必要があると考えた．

謝辞

本研究を行うにあたり，ご協力いただいた翠清会梶川病院の臨床検査技師の平田明子氏に深謝いたします．

文　献

1) Lip GYH, Blann AD : von Willebrand factor : a marker of endothelial dysfunction in vascular disorders? Cardiovasc Res 34 : 255—265, 1997
2) Wagner DD : Cell biology of von Willebrand factor. Annu Rev Cell Biol 6 : 217—246, 1990
3) Haines AP, Howarth D, North WRS, et al : Haemostatic variables and the outcome of myocardial infarction. Thromb Haemost 50 : 800—803, 1983
4) Hamsten A, Blomback M, Wiman B, et al : Haemostatic function in myocardial infarction. Br Heart J 55 : 58—66, 1986
5) Mettinger KL : A study of hemostasis in ischemic cerebrovascular disease.I. Abnormalities in factor VIII and antithrombin. Thromb Res 26 : 183—192, 1982
6) Uchiyama S, Takeuchi M, Osawa M, et al : Platelet function tests in thrombotic cerebrovascular disorders. Stroke 14 : 511—517, 1983
7) Zheng L : Increased factor VIII related antigen in cerebral thrombosis. Thromb Res 32 : 321—324, 1983
8) Wahlberg TB, Blombäck M, Övermark I : Blood coagulation studies in 45 patients with ischemic cerebrovascular disease and 44 patients with venous thromboembolic disease. Acta Med Scand 207 : 385—390, 1980
9) Liu L, Lin Z, Shen Z : Changes of von Willebrand factor and antithrombin III levels in acute stroke : difference between thrombotic and haemorrhagic stroke. Thromb Res 72 : 353—358, 1993
10) Catto AJ, Carter AM, Barrett JH, et al. von Willebrand factor and factor VIII : C in acute cerebrovascular disease. Relationship to stroke subtype and mortality. Thromb Haemost 77 : 1104—1108, 1997
11) Bath PWM, Blann A, Smith N, et al : Von Willebrand factor, P-selectin and fibrinogen levels in patients with acute ischaemic and haemorrhagic stroke, and their relationship with stroke subtype and functional outcome. Platelets 9 : 155—159, 1998
12) Blann A, Kumar P, Krupinski J, et al : Soluble intercellular adhesion molecule-1, E-selectin, vascular cell adhesion molecule-1 and von Willebrand factor in stroke. Blood Coag Fibrinol 10 : 277—284, 1999
13) Woodburn KR, Lowe GDO, Rumley A, et al : Relation of haemostatic, fibrinolytic, and rheological variables to the angiographic extent of peripheral artery occlusive disease. Int Angiol 14 : 219—225, 1995
14) Stehouwer CDA, Nauta JJP, Zeldenrust GC, et al : Urinary albumin excretion, cardiovascular disease and endothelial dysfunction in non-insulin-dependent diabetes mellitus. Lancet 340 : 319—323, 1992
15) Kahaleh MB, Osborn I, Leroy EC : Increased factor VIII/von Willebrand factor antigen and von Willebrand factor activity in scleroderma and in Raynaud's phenomenon. Ann Intern Med 94 : 482—484, 1981
16) Kahaleh MB : The role of vascular endothelium in the pathogenesis of connective tissue disease : endothelial injury, activation, participation and response. Clin Exp Rheumatol 8 : 595—601, 1990
17) 郡山達男，片山禎夫，田中英司ら：各種の血管障害における血栓・止血学的指標—脳血栓症，糖尿病ならびに膠原病性ニューロパチーにおける検討—．臨床神経　33：606—611, 1993
18) 郡山達男，田中英司，片山禎夫ら：慢性期脳血栓症における抗血小板療法の治療効果—血栓・止血学的指標による検討—．臨床神経　34：771—776, 1994
19) 野村栄一，郡山達男，山口慎也ら：頸動脈の動脈硬化性病変の進展に関する予知因子の検討—特に血栓・止血学的指標との関連—．臨床神経　36：741—745, 1996
20) Nomura E, Kohriyama T, Yamaguchi S, et al : Association between carotid atherosclerosis and hemostatic markers in patients with cerebral small artery disease. Blood Coag Fibrinol 9 : 55—62, 1998
21) Nomura E, Kohriyama T, Kozuka K, et al : Sequential changes in von Willebrand factor and soluble thrombomodulin in acute ischemic stroke. J Stroke Cerebrovasc Dis 10 : 257—264, 2001
22) Kozuka K, Kohriyama T, Nomura E, et al : Endothelial markers and adhesion molecules in acute ischemic stroke -sequential change and differences in stroke subtype. Atherosclerosis 161 : 161—168, 2002
23) Qizilbash N, Duffy S, Prentice CRM, et al : von Willebrand factor and risk of ischemic stroke. Neurology 49 : 1552—1556, 1997
24) Folsom AR, Rosamond WD, Shahar E, et al : Prospective study of markers of hemostatic function with risk of ischemic stroke. Circulation 100 : 736—742, 1999
25) Jansson JH, Nilsson TK, Johnson O : von Willebrand factor in plasma : a novel risk factor for re-

current myocardial infarction and death. Br Heart J 66 : 351—355, 1991
26) Pottinger BE, Read RC, Paleolog EM, et al : von Willebrand factor is an acute phase reactant in man. Thromb Res 53 : 387—394, 1989
27) 小塚和子, 郡山達男, 野村栄一ら : 脳梗塞発症から慢性期までの血漿可溶性 P-selectin と E-selectin の経時的変動の検討. 脳卒中 23 : 234—239, 2001
28) Liu Y, Shakur Y, Yoshitake M, et al : Cilostazol (Pletal) : A dural inhibitor of cyclic nucleotide phosphodiesterase type 3 and adenosine uptake. Cardiovascular Drug Reviews 19 : 369—386, 2001
29) Green D, Kucuk O, Haring O, et al : The factor VIII complex in atherosclerosis : effects of aspirin. J Chronic Dis 34 : 21—26, 1981
30) Gotoh F, Tohgi H, Hirai S, et al : Cilostazol Stroke Prevention Study : A placebo-controlled double-blind trial for secondary prevention of cerebral infarction. J Stroke Cerebrovasc Dis 9 : 147—157, 2000

Abstract

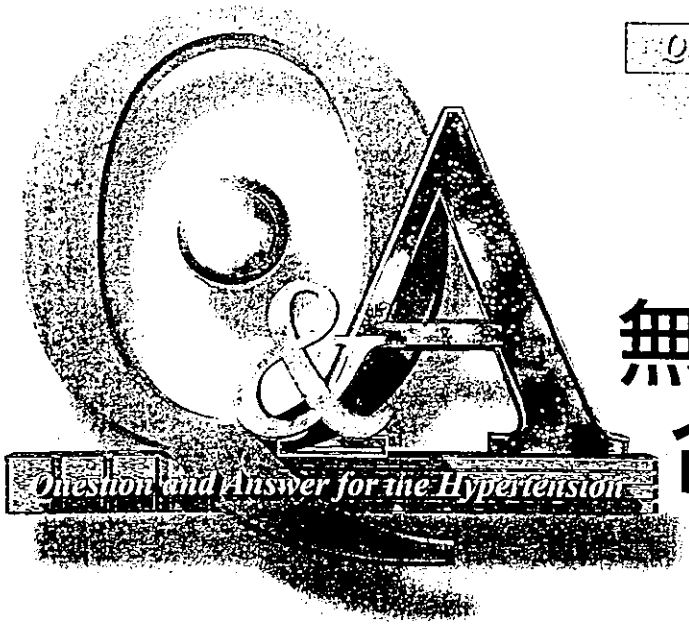
Alterations of plasma von Willebrand factor activity and the influence of anti-platelet drugs in acute cerebral infarction

Eiichi Nomura, M.D., Ph.D[1], Tatsuo Kohriyama, M.D., Ph.D.[2], Kazuko Kozuka, M.D., Ph.D.[3], Hiroshi Kajikawa M.D., Ph.D.[4], Shigenobu Nakamura, M.D., Ph.D.[1] and Masayasu Matsumoto, M.D., Ph.D.[2]

[1]Department of Neurology, Suiseikai Kajikawa Hospital, Hiroshima, Japan
[2]Department of Clinical Neuroscience and Therapeutics, Hiroshima University Graduate School of Biomedical Sciences, Hiroshima, Japan
[3]Department of Neurology, Brain Attack Center, Oota Memorial Hospital, Fukuyama, Japan
[4]Department of Neurosurgery, Suiseikai Kajikawa Hospital, Hiroshima, Japan

We studied the changes of von Willebrand Factor (vWf) activity after acute cerebral infarction (ACI) in order to identify differences in each subtype of ACI and to determine the relationship between the vWf activities and stroke severity. In addition, we investigated the influence of anti-platelet drugs on the vWf activities retrospectively. Eighty-three consecutive patients admitted to our hospital within 48 hours after the onset were enrolled. We diagnosed the patients as ACI by cranial CT and MRI, and classified them into 3 subtypes (atherothrombotic, cardioembolic and lacunar infarction) according to the classification of NINDS. The severity of ACI was evaluated by the Japan Stroke Scale (JSS), and the plasma vWf activities were determined both on admission and one month later. The patients showed significantly higher vWf activities on both admission and after one month as compared to those in the controls. Furthermore, the vWf activities on admission increased significantly over a month. There was no significant difference in sequential changes of vWf activities among the ACI subtypes. The severity of ACI was not associated with the vWf activities on admission. The elevation of the vWf activities could be suppressed in the group of patients treated with cilostazol as compared to the other groups. We conclude that although the vWf activities were increased over one month in the patients with ACI, there was no significant difference among the ACI subtypes, and no relationship with the severity of ACI. The significance of the suppressive effect of cilostazol on the vWf activities in patients with ACI should be investigated in furthers studies.

(Jpn J Stroke 25 : 252—258, 2003)



無症候性脳梗塞を合併した高血圧

松本昌泰
Matsumoto Masayasu
広島大学大学院医歯薬学総合研究科
病態探究医科学講座
脳神経内科学(第三内科)教授

症例提示　65歳　男性

現病歴

16年前ころより会社健診で高血圧を指摘され，近医にて降圧治療を受けていた．さらに，血糖高値や高脂血症を指摘され，2年前からは糖尿病の薬物療法を受け始めた．頭重感を感じることが多くなり，当科を受診した．

身体所見

身長163cm，体重53kg，血圧150/90mmHg，脈拍80/分 整

既往歴・家族歴・嗜好品

母，弟に糖尿病．喫煙は20本/日．飲酒習慣(−)．

検査所見

空腹時血糖値112mg/dL，HbA_{1c} 8.9％，総蛋白6.8g/dL，アルブミン3.5g/dL，T-CHO 236mg/dL，TG214mg/dL，HDLコレステロール 33mg/dL，血清クレアチニン値0.8mg/dL，尿素窒素11mg/dL，尿酸4.6mg/dL，尿蛋白(+)，心電図では陳旧性心筋梗塞所見を認める．

Q1 降圧に先立ち，脳の循環状態を評価するためにすべきことは？

1. 問診で具体的な症状を尋ねる
2. 両側頸動脈の血管雑音の聴取
3. 眼窩部の血管雑音の聴取
4. 認知機能障害の有無の確認
5. 頸動脈の積極的な触診

Q2 本症例の降圧薬で第一選択薬はどれか？

1. Ca拮抗薬
2. ACE阻害薬
3. アンジオテンシンⅡ受容体拮抗薬(ARB)
4. β遮断薬
5. 利尿薬

A1

血圧値だけで判断して，高血圧症例に降圧薬を投与することが多いが，無症候性脳梗塞を合併した高血圧症例では，安易に降圧薬を投与して，急激に血圧を下げることで脳血流も低下してしまい，かえって脳卒中を誘発する恐れがある．そのため降圧療法に入る前に，まず簡便な方法で脳血管障害の有無を確認する必要がある．そして，無症候性脳血管障害が認められた場合には，その臨床病型や発症メカニズムを可及的に究明すべきである．

問診ではBrain Attackキャンペーンで取り上げられている5つの主要な症状(表)に関して，より具体的に患者に尋ね，最近一過性の虚血発作があったかどうかを確認する．また，診察上では両側頸動脈および眼窩部の血管雑音の聴取は必須で，雑音があれば脳血管障害があることになり，脳梗塞を疑って精査を行う．ただし，積極的な頸動脈の触診は，頸動脈に狭窄があった場合に病態を悪化させる可能性があるので，避けなければいけない．さらに，認知機能を評価し，脳血管障害の有無を確認する．

そして，これらによって無症候性脳梗塞の疑いが考えられる場合には，速やかに専門医に紹介すべきである．

表　Brain Attackキャンペーンに用いられている脳卒中警告症状

身体の片側の顔，腕，脚に突然脱力や痺れが出現する
突然目がみえなくなったり，物がぼやけてみえる，とくに片目に起こる
言葉が喋れなくなったり，話をしたり，理解するのが困難となる
突然原因不明の激しい頭痛
訳のわからないめまい感，ふらつき感や突然の転倒，とくに上記症状を伴う場合

A2

本症例では血管雑音が聴取され，精査のために実施した頭部MRI検査では中大脳動脈・前大脳動脈の分水嶺部に梗塞病変を認め，アテローム血栓性脳梗塞の病型に相当する無症候性脳梗塞と診断した．そのため，降圧療法に際しては，脳血流低下による血流不全をきたさないよう細心の注意が必要である．

本症例は当院受診前に，降圧薬としてCa拮抗薬とACE阻害薬が投与されていたが，脈拍が80拍/分であったため，反射性頻脈を懸念してCa拮抗薬は避けるべきと思われる．脳血管障害を伴う症例に対してはT/P比が長く，マイルドな降圧薬が望ましい．また，糖尿病であることから，耐糖能に影響を与えない降圧薬を選択する必要がある．そのため，本症例ではARBやACE阻害薬が第一選択薬として考えられる．さらに，ARBやACE阻害薬は心・腎を含めた標的臓器に対しても安全性も高く，脳にもポジティブであることから，その効果が期待できる．なお，Ca拮抗薬に関しては脳血管障害に対するエビデンスがたくさん得られていることから，頻脈などの症状がみられない場合は，ジヒドロピリジン系の長時間作用型Ca拮抗薬を少量から使うことが有用な場合もある．

本症例における降圧目標値は，140/90mmHgを一次目標として考え，急激な降圧は避ける．そして，半年～1年ほどかけて，130/80mmHg前後まで徐々に下げる．なお，降圧薬を開始した最初の4週間は，副作用や薬効からくる血行力学的な病態の変化に注意し，家庭用血圧計などを参考にして1週間毎に診察することも必要と思われる．そして，病状が安定していれば，PROGRESSで示されているように130/80mmHg程度まで緩徐に下げることは構わないと考えられる．

特別企画

LIFE Discussion 第3回
糖尿病合併高血圧症の治療
—臓器保護を中心に—

○司会
順天堂大学内科学教授
河盛隆造 氏

わが国の糖尿病患者数は依然として増加傾向にあり，死亡原因の上位に数えられる心疾患，脳血管疾患，末期腎不全の基礎疾患として，その重大性はますます高まっている。特に糖尿病では高血糖のみならず，高血圧，高脂血症，インスリン抵抗性，肥満などを併発することが多く，それが血管合併症のリスクを一段と高める結果となっている。本座談会ではこのうち糖尿病合併高血圧症に注目し，脳・心・腎の各専門家を交えて，その治療の在り方を話し合っていただいた。

糖尿病患者はさらに増加 早期からの厳格な血圧コントロールが重要

河盛：昨年実施された厚生労働省の糖尿病実態調査によると，HbA_{1c}が6.1％以上で間違いなく糖尿病であろうと考えられる方は，1997年の前回調査から5年間に50万人増えて740万人になりました。また，HbA_{1c}が5.6～6.0％で，糖尿病の可能性が高いと考えられる方は，200万人増えて880万人になりました。おそらく慢性的に高血糖状態を来していて，糖尿病と診断可能な方は1,200万人以上にのぼると考えられます。

このような糖尿病の増加に伴い，既に空腹時血糖値も高くなって受診される患者さんの5割以上が高血圧を合併しているということを，日常診療の場で経験します。また，糖尿病早期での高血圧が動脈硬化を進展させることが明らかになっています。

最近発表されたJNC7をはじめ，各種の高血圧治療ガイドラインでも，糖尿病合併高血圧症例には一段と厳しい降圧目標値が設定されており，さらに糖尿病が早期・軽症の時期から臓器障害を防ぐため，厳格に血圧管理をしなければいけないとの認識が深まりつつあります。

そこで，本日は糖尿病合併高血圧症の治療について，特に臓器保護の面から，脳・心・腎の各エキスパートにご意見をお伺いしたいと思います。

まず最初に，木村先生，腎保護という点では，JNC7の降圧目標値をどうお考えですか。

木村：JNC7では糖尿病か腎障害があれば，降圧目標は130/80mmHg未満とすることが提言されています。しかし，そもそもJNC6では，糖尿病や腎障害があれば130/85mmHg未満，尿蛋白1g/日以上ならば125/75mmHg未満まで下げることが提言されていました。

したがって，JNC7では腎保護に関する降圧目標が一歩甘くなった印象を受けますが，一般臨床医にわかりやすく提言するため，130/80mmHgという中間的なラインで統一したのでしょう。

ただ，欧州高血圧学会と欧州心臓病学会による新しい高血圧治療ガイドラインでは，糖尿病で尿蛋白が1g/日以上であれば，依然として降圧目標は125/75mmHg未満とされていますので，糖尿病があれば130/80mmHg未満，さらに尿蛋白が1g/日以上であれば125/75mmHg未満を目指すというのが妥当なのではないかと思います。

河盛：松本先生，糖尿病患者における高血圧と脳血管障害との関連についてはどうお考えですか。

松本：昨今，糖尿病が大きく増えてきたこととも関連して，脳卒中の臨床病型に大きな変化が見られます。高血圧が一番のリスクファクターとされるsmall vessel型の脳出血やラクナ梗塞に代わり，動脈硬化を基盤とするlarge vessel型のアテローム血栓性脳梗塞が増加しています。

糖尿病はこのsmall vessel型とlarge vessel型のいずれにも関連が深いのですが，それらの予防という点においては，いずれにしても，血糖コントロールより血圧コントロールがより重要だと言えます。

糖尿病のスタディとして有名なUKPDSでは，厳格な血圧コントロールにより脳卒中リスクが44％減少しました。日本人の脳血管障害が欧米化するなか，これはあらためて注目すべき重要なデータだと思います。

河盛：百村先生，糖尿病患者における心血管障害に対しては，血圧をどのようにコントロールしていくべきなのでしょうか。

百村：疫学的には糖尿病患者で血圧値が120/70mmHgを超えた時点で既に心血管系イベント発症リスクは上昇していますし，UKPDS36でも収縮期血圧が120mmHg未満の場合に最も心血管系イベント発症のリスクが低いと示されました。

一方，糖尿病患者で降圧による心血管イベントの抑制を証明した大規模臨床試験を見てみると，実際に達成された血圧は，拡張期が80mmHg未満という点ではほぼ一致しているものの，収縮期については140mmHg程度という結果が多くなっており，厳格な血圧コントロールの難しさを反映していると思われます。

JNC7では疫学的データと大規模臨床試験の結果を踏まえ，降圧目標として捉えやすいというところで130/80mmHg未満に設定されたものと思われます。

脳保護：ロサルタンに特有な血小板凝集抑制作用

河盛：降圧治療においては，しばしば臓器保護におけるbeyond blood pressure lowering effectが注目されます。脳におけるロサルタンのbeyond blood pressure lowering effectについては，松本先生いかがですか。

松本：LIFE試験の結果を見ると，ロサルタン群はβ遮断薬のアテノロール群に比べ，脳卒中発症リスクを有意に抑制しています(リスク低下率24.9％，$p=0.001$)。実薬同士で比較した大規模臨床試験では初めて，従来クラスの降圧薬に比べてロサルタンのほうが脳卒中抑制効果を示したということで，大変注目されました。その後，脳卒中の臨床病型ごとの結果も報告され，ロサルタンは脳出血や脳塞栓症も抑制していたことがわかりましたが，特にアテローム血栓性脳梗塞を有意に抑制していたことがわかりました(表1)。

アンジオテンシンⅡ受容体拮抗薬(AIIA)はAT_1受容体の作用を抑制しますが，それによってRhoキナーゼを介したNADPHオキシダーゼの活性化を抑制し，スーパーオキサイド(O_2^-)の産生抑制につながると考えられます。ラジカルストレスに弱い脳にとって，これは非常に重要な作用だと言えるでしょう。

また，ロサルタンの代謝のなかで一時的に産生されるEXP-3179は血小板凝集抑制作用やCOX-2抑制作用を有することが報告されており，こうしたロサルタン特有の作用が微小循環レベルを含めてポジティブに脳保護に影響しているのではないかと考えられます。

百村：LIFE試験では心房細動例を対象としたサブ解析の結果も発表されていて，心房細動例ではロサルタン群がアテノロール群に比べ，脳卒中発症リスクを44％も低下させています(表2)。心房細動例における脳卒中は心原性血栓が主因ですので，こうした成績の背景にはロサルタンの血小板凝集抑制作用による血栓形成の抑制が示唆されます。

河盛：「高齢者では急激に血圧を下げすぎると痴呆が起こらないか」という質問をよく受けますが，どのように答えておられますか。

表1. LIFE：脳卒中減少の内訳

エンドポイント	ロサルタン (n=4,605)	アテノロール (n=4,588)	ハザード比	リスク低下率	p値
全脳卒中死	40	62	0.65	35%↓	0.032
全脳卒中	232	309	0.75	25%↓	0.001
アテローム血栓性脳梗塞(脳塞栓を除く)	170	233	0.73	27%↓	0.002
脳塞栓症	36	48	0.76	24%↓	0.22
脳出血	27	34	0.80	20%↓	0.38
その他	1	4	0.25	75%↓	0.22

(Reid I., International AII Symposium 2003)

表2. LIFE：心房細動患者サブグループ解析

エンドポイント	ロサルタン (n=150)	アテノロール (n=174)	リスク低下率	p値
一次エンドポイント(心血管系疾患死，脳卒中，心筋梗塞)	36	64	40%↓	0.018
心血管系疾患死	20	37	42%↓	0.053
脳卒中	18	37	44%↓	0.040
心筋梗塞	11	7	N.D.	NS
総死亡	30	48	33%↓	0.092
心不全による入院	15	23	N.D.	NS

(52nd Annual Scientific Session of the American College of Cardiology)

○出席者（発言順）

名古屋市立大学大学院医学研究科臨床病態内科学教授
木村玄次郎 氏

広島大学大学院病態探究医科学脳神経内科教授
松本昌泰 氏

虎の門病院循環器センター内科部長
百村伸一 氏

松本：確かに動脈硬化が非常に進展していて，脳循環障害が既にあるような場合は注意が必要です。ルベオーシスのような虚血性眼症，あるいは一過性片眼性失明などの形で一過性脳虚血発作(TIA)の存在の有無を問診し，頸動脈や眼窩部での動脈雑音の聴取や頸動脈エコーなどによる診断を行い，問題がないことを確認してから徐々に降圧すべきです。このように慎重に降圧を行うのなら，高齢者の脳保護に関しても血圧はthe lower the betterであり，痴呆や認知機能の低下という面でも同様だと思います。

高齢者では，収縮期高血圧が脳卒中発症に非常に高く関与することが知られていますが，LIFE試験における収縮期高血圧サブ解析では，ロサルタン群がアテノロール群に比べ，脳卒中発症リスクを40％も減少させており，高齢者においてもその効果が期待されるところです。

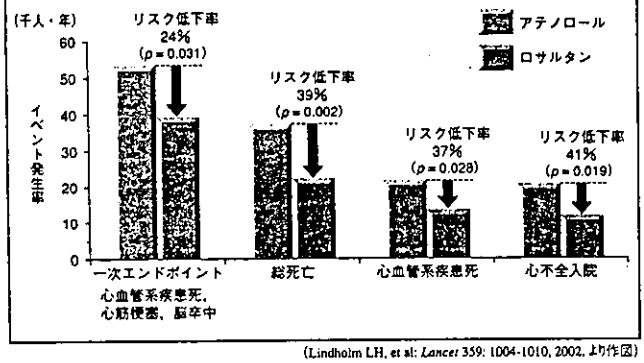
糖尿病合併例で著明に表れるロサルタンの beyond blood pressure lowering effect

河盛：それでは百村先生，心臓におけるbeyond blood pressure lowering effectについてお願いします。

百村：ACE阻害薬とAIIAには心不全の予後を改善する効果が認められています。その根底には，RA系遮断による心筋リモデリングの抑制が考えられています。LIFE試験では心肥大を伴う高血圧患者を対象としていましたが，ロサルタンは心肥大の退縮効果に優れることが示されました。これもリモデリング抑制作用の表れと考えてよいでしょう。

AIIAはそのほかにも，血管内皮機能の改善，血栓形成の抑制，抗炎症作用など，さまざまな作用を有することが示唆されており，降圧以外の心保護作用が心血管イベントの抑制に貢献していると考えられます。特に糖尿病合併高血圧例のような心血管系イベント発症のリスクが高い患者でこうした心保護作用は如実に表れます。LIFE試験では糖尿病患者を対象としたサブ解析で，全患者群で有意差が認められなかった心血管系疾患死において，ロサルタン群はアテノロール群に比べて有意に抑制(図1)したのは評価できます。

図1. LIFE：糖尿病患者サブグループ解析



(Lindholm LH, et al: *Lancet* 359: 1004-1010, 2002. より作図)

ロサルタンは腎症を伴う 2型糖尿病患者の予後改善に有用

河盛：木村先生，腎保護という点についてはどのようなことが言えますか。

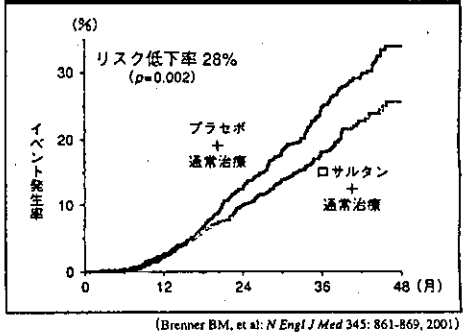
木村：レニン・アンジオテンシン(RA)系抑制薬の腎保護作用は既に確立しており，JNC7でも腎障害がある場合は，RA系抑制薬だけが適応になっています。糖尿病患者でも微量アルブミン尿，顕性腎症，末期腎不全という各段階で，RA系抑制薬が抑制作用を持つことが示されています。特に高血圧合併2型糖尿病の予後改善に関するほとんどのエビデンスがAIIAで得られていることから，米国糖尿病学会(ADA)は高血圧合併2型糖尿病にAIIAを推奨しています。

例えばRENAAL試験では，腎症を伴う2型糖尿病患者にAIIA・ロサルタンを投与することによって，末期腎不全への進展のリスクがプラセボ群に比べて28％抑制されました(図2)。興味深いのは，血清クレアチニン値の倍増後も，ロサルタンを投与し続けることによって，末期腎不全への進展が抑制されたことです。このことから，ロサルタンは腎機能低下例においても腎保護効果を示すことが認められ，ロサルタンを継続投与するという新しい治療スタンスも見えてきました。

河盛：実際，ロサルタンはRENAAL試験の結果を受けて，2型糖尿病性腎症への適応拡大を申請中ですね。

木村：ロサルタンを血圧が変わらない範囲で増量しても蛋白尿はさらに減少するというエビデンスもありますので，腎臓に対するロサルタンのbeyond blood pressure lowering effectは明らかだと思います。

図2. RENAAL：末期腎不全(透析，腎移植)の進行抑制



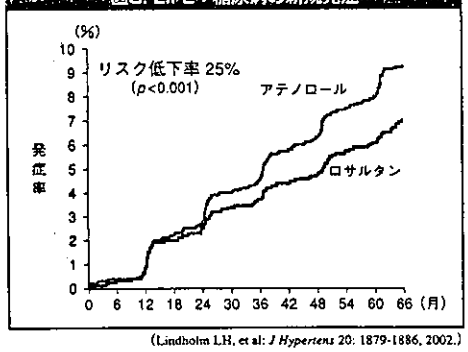
(Brenner BM, et al: *N Engl J Med* 345: 861-869, 2001)

糖尿病の発症抑制も視野に入れた降圧薬選択を

河盛：高血圧や高脂血症の大規模臨床試験では，投与する薬剤によって糖尿病の発症率に差が見られることが知られており，ある種のACE阻害薬やスタチンは糖尿病の発症を抑制することがわかっています。ロサルタンについてもこうした効果が指摘されており，LIFE試験ではアテノロール群に比べ，ロサルタン群は糖尿病新規発症を25％抑制しました(図3)。これからは，既に発症している糖尿病だけでなく，糖尿病発症リスクのある予備軍では，発症予防まで視野に入れた降圧薬選択が必要になってきたと言えます。

糖尿病は高血糖のほかにも高血圧，高脂血症，インスリン抵抗性などが絡み合って「血管の病気」を惹起する疾病であることから，総合的に治療していかなければなりません。本日は糖尿病合併高血圧症の治療をテーマにお話を伺ってまいりましたが，糖尿病を専門とする立場からは，血圧や血清脂質に比べ達成率の低いと言われる優れた血糖コントロールにも，ぜひ積極的に取り組んでいただきたいと念じて，この座談会を終わりたいと思います。本日は，貴重なご意見をありがとうございました。

図3. LIFE：糖尿病の新規発症



(Lindholm LH, et al: *J Hypertens* 20: 1879-1886, 2002.)

Circ J 2003; **67**: 287–294

Sustained Reduction of Serum Cholesterol in Low-Dose 6-Year Simvastatin Treatment With Minimum Side Effects in 51,321 Japanese Hypercholesterolemic Patients

—— Implication of the J-LIT Study, a Large Scale Nationwide Cohort Study ——

Yuji Matsuzawa, MD; Toru Kita, MD*; Hiroshi Mabuchi, MD**; Masunori Matsuzaki, MD†; Noriaki Nakaya, MD††; Shinichi Oikawa, MD‡; Yasushi Saito, MD‡‡; Jun Sasaki, MD§; Kazuaki Shimamoto, MD§§; Hiroshige Itakura, MD¶ (Chairman of Central Committee); the J-LIT Study Group

The Japan Lipid Intervention Trial (J-LIT) study, a nationwide cohort study utilizing the clinical practice of general physicians, was designed to clarify the relationship between the incidence of coronary heart disease and serum lipid concentrations during simvastatin therapy, as well as the safety of the therapy, in a large number of Japanese hypercholesterolemic patients. All the enrolled patients were treated with simvastatin. The current study analyzed the lipid lowering effect and safety of the low-dose simvastatin therapy used in the J-LIT study. Open-labeled simvastatin was given to 51,321 patients at an initial dose of mostly 5 mg/day. After 6 months of the treatment, the average serum total cholesterol (TC) and low density lipoprotein-cholesterol concentrations in all the patients followed up were reduced by 18.3% and 26.0%, respectively, and that of high density lipoprotein-cholesterol increased 2.3% on average. These concentrations were well maintained throughout the 6-year treatment period. A minority of patients (1.4%) unexpectedly had a remarkable reduction in TC concentration by more than 40%. Hyper-responders, even to low-dose statin, were found for the first time in this large-scale and long-term investigation. Overall adverse drug reactions occurred in 3.3% of subjects during the 6-year treatment, the major events being hepatic and musculoskeletal disorders, of which the incidence was less than 1%. Low-dose simvastatin therapy of 5 mg/day effectively controlled the serum TC concentration by reducing it by approximately 20% on average in hypercholesterolemic Japanese patients, a reduction that corresponds to the effect of simvastatin 20 mg/day in Western studies. In addition, the low incidence of drug-related adverse events in this study may be also related to the low dosage of simvastatin. (*Circ J* 2003; **67**: 287–294)

Key Words: Cholesterol-lowering medication; Cohort study; Drug tolerance; Safety; Simvastatin

The Japan Lipid Intervention Trial (J-LIT) study was the first nationwide cohort study conducted to elucidate the relationship between serum lipid concentrations and the incidence of coronary heart disease (CHD), and was designed to reflect ordinary clinical practice for lipid lowering therapy in Japan! In order to maintain patient compliance under these conditions, it was essential for simvastatin to be administered to all patients, and we believed that by analyzing a large amount of clinical data for the correlation between the serum lipid concentrations and prevalence of coronary events under simvastatin treatment, the possible benefit of lipid lowering therapy in prevention of coronary events would be elucidated even without the use of placebo. Our study design was compatible with the ethical standards of the Declaration of Helsinki, which was revised on October 2000 to include the conditions for the use of a placebo control group. Therefore, the present protocol may be a practical method for the confirmation of the effectiveness and safety of other widely used drugs.

There have been a number of epidemiological studies in Western countries that have demonstrated a close relationship between the concentration of serum cholesterol and the incidence of CHD, the most well known being the Framingham study conducted in the USA? In those studies, patients with lower serum cholesterol concentrations had a reduced risk of CHD. In the past, cholesterol-lowering treatments using resins[3] and fibrates[4,5] were reported to reduce the risk of CHD. Recently, statins, including simvastatin, were found to selectively inhibit 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in the cholesterol biosynthetic pathway, and reduce the serum total cholesterol (TC) and low density lipoprotein-cholesterol (LDL-C) concentrations[6] In

(Received August 9, 2002; revised manuscript received December 20, 2002; accepted January 10, 2003)

*Osaka University Graduate School of Medicine, Osaka; *Kyoto University Graduate School of Medicine, Kyoto; **Kanazawa University Graduate School of Medicine, Kanazawa; †Yamaguchi University Graduate School of Medicine, Ube; ††Fussa General Hospital, Tokyo; ‡Nippon Medical School, Tokyo; ‡‡Chiba University Graduate School of Medicine, Chiba; §International University Graduate School of Health and Welfare, Fukuoka; §§Sapporo Medical University School of Medicine, Sapporo, and ¶Ibaraki Christian University, Ibaraki, Japan*

Mailing address: Yuji Matsuzawa, MD, Department of Internal Medicine and Molecular Science, Osaka University Graduate School of Medicine 2-2 B-5, Yamadaoka, Suita, Osaka 565-0871, Japan

Table 1 Demographics and Clinical Characteristics of Japanese Hypercholesterolemic Patients Receiving Long-Term, Low-Dose Simvastatin

Total (N = 52,421)	
Age (years)	*57.9±7.9*
Male, no. (%)	*17,424 (33.2)*
BMI	*24.0±3.2*
Blood pressure (mmHg)	
Systolic	*139±19*
Diastolic	*82±11*
Hospitalization (%)	*0.8*
Hypertension (%)	*45.2*
Diabetes mellitus (%)	*15.4*
Obesity (%)	
BMI ≥25	*32.0*
BMI ≥30	*3.7*
ECG abnormality (%)	*18.4*
Family history of CHD (%)	*5.2*
Current smoker (%)	*16.6*
Male (%)	*41.9*
Ex-smoker (%)	*4.5*
Renal disorder (%)	*2.2*
Hepatic disorder (%)	*8.0*
Coronary heart disease (%)	*9.8*
Cerebrovascular disease (%)	*3.0*
Alcohol consumption (%)	*29.1*
Male (%)	*70.7*
FH (%)	*2.6*
Serum cholesterol level (mg/dl)	
TC	*269±34*
HDL-C	*52.6±15.1*
LDL-C	*182±34*
Triglyceride (mg/dl)	*196±169*
Atherogenic index (TC/HDL-C)	*5.6±1.9*

BMI, body mass index; CHD, coronary heart disease; FH, familial hypercholesterolemia; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
Data are presented as the mean±SD.

the Scandinavian Simvastatin Survival Study (4S), simvastatin significantly reduced the mortality of patients with hypercholesterolemia[7] and other statins have also been reported to reduce the incidence of CHD[8–11]

The dose of statins prescribed in Japan is lower than that in Western countries; for example, the daily dose of simvastatin approved in Japan is 5–10 mg in contrast to 20–40 mg in Western countries[12] The present study examined the safety and drug tolerance, as well as the efficacy of long-term treatment, of relatively low dose simvastatin in Japanese hypercholesterolemic patients.

Methods

Patient Selection

In the J-LIT study, 54,203 Japanese hypercholesterolemic (TC ≥220 mg/dl) patients were screened from November 1992 through June 1993 by 6,511 investigators, almost all of whom were general practitioners, at 5,289 institutions from all 47 prefectures in Japan. Of those patients, 52,421 study subjects (17,424 men aged 35–70 years and 34,997 postmenopausal women) under 70 years of age were recruited and of them, 47,294 were eligible as the primary prevention cohort, and the remaining 5,127 patients with a history of CHD were enrolled as the secondary prevention cohort. Patients who had previously been treated with lipid-lowering agents were screened for eligibility after a washout period of at least 4 weeks, and the washout period was at least 12 weeks for those previously treated with probucol. Exclusion criteria included a recent (≤1 month) history of myocardial infarction (MI) or stroke, a history of severe MI or stroke, uncontrolled diabetes mellitus, serious concurrent hepatic or renal disease, secondary hypercholesterolemia, malignant disease, or other illness with a poor prognosis.

Study Design

The design of the J-LIT study has been reported previously in detail[1] During the screening period at the local recruiting site, body weight and blood pressure were determined, and fasting serum lipid profiles were measured twice consecutively. Every 6 months after enrollment, body weight, blood pressure, and serum lipid concentrations were measured and drug compliance, number of cigarettes smoked (none, 1–10, 11–19 or ≥20 per day), alcohol consumption (none, <25, 25–49 or ≥50 g/day) and amount of exercise (none, occasional, frequent or every day) were recorded. Hepatic and renal functions were assessed and an electrocardiogram was obtained every 12 months. Every patient started treatment with open-labeled simvastatin 5–10 mg/day, and lipid concentrations, adverse events and CHD events were monitored for 6 years. Diet and exercise therapies for hyperlipidemia were recommended by the investigators. Other lipid-lowering agents were added only when the investigator considered that the patient's serum TC concentration had not responded adequately to simvas-

Table 2 Sequential Changes of Treatment Profiles in Cholesterol-Lowering Therapy During 6 Years Follow-up

	Year						
	0	*1*	*2*	*3*	*4*	*5*	*6*
Simvastatin							
5 mg monotherapy	*n = 48,428*	*39,519*	*32,900*	*28,981*	*25,461*	*22,823*	*20,518*
10 mg monotherapy	*1,729*	*2,081*	*2,069*	*2,025*	*1,966*	*1,812*	*1,668*
Other monotherapy	*1*	*168*	*249*	*293*	*295*	*261*	*229*
Simvastatin monotherapy total	*50,158*	*41,768*	*35,218*	*31,299*	*27,722*	*24,896*	*22,415*
Simvastatin + other lipid-lowering agent	*1,163*	*1,688*	*1,968*	*2,133*	*1,993*	*1,813*	*1,845*
Other lipid-lowering agent	*0*	*56*	*235*	*463*	*509*	*525*	*814*
No or Unknown medication	*0*	*6,576*	*10,419*	*11,655*	*12,074*	*12,190*	*11,821*
Total	*51,321*	*50,088*	*47,840*	*45,550*	*42,298*	*39,424*	*36,895*
Simvastatin total	*51,321*	*43,456*	*37,186*	*33,432*	*29,715*	*26,709*	*24,260*
5 mg (%)	*49,495 (96.4)*	*40,946 (94.2)*	*34,561 (92.9)*	*30,694 (91.8)*	*27,065 (91.1)*	*24,246 (90.8)*	*21,994 (90.7)*
10 mg (%)	*1,825 (3.6)*	*2,332 (5.4)*	*2,365 (6.4)*	*2,422 (7.2)*	*2,334 (7.9)*	*2,183 (8.2)*	*2,018 (8.3)*
Other (%)	*1 (0.0)*	*178 (0.4)*	*260 (0.7)*	*316 (0.9)*	*316 (1.1)*	*280 (1.0)*	*248 (1.0)*

tatin monotherapy. No restrictions were placed on treatments for other medical conditions. The LDL-C concentration in patients with serum triglyceride (TG) concentrations under 400 mg/dl was calculated using the Friedewald formula![3] At the beginning of this study, each patient was informed of the study purpose and was given information on drug efficacy and the need for long-term treatment.

Examination of Adverse Events

All adverse events were graded by the collaborating investigators according to the direct relation to simvastatin as definite, possible, unclear or not, as judged from the available information. All simvastatin-related adverse events were pooled and described as adverse drug reactions (ADRs). Cases of patient death were evaluated by the Endpoint Classification Committee, and all adverse events were reviewed by the Adverse Event Subcommittee, which consisted of 3 specialists who were not part of the J-LIT study group. The adverse events, such as hepatic dysfunction (aspartate aminotransferase (AST) ≥80 IU/L, alanine aminotransferase (ALT) ≥80 IU/L, γ-glutamyl transpeptidase (γ-GTP) ≥100 IU/L, or a diagnosis of hepatobiliary disorder), thrombocytopenia (platelets <100,000/mm^3, presence of purpura or pancytopenia), musculoskeletal disorder (rhabdomyolysis, elevated creatine kinase (CK) concentration (≥1,000 IU/L) and elevated creatine kinase concentration (≥600 IU/L) with muscle symptoms), and other serious adverse events, were reviewed in detail. Hepatitis was diagnosed as AST or ALT ≥120 IU/L, or γ-GTP ≥150 IU/L with abnormal AST or ALT (≥80) as judged by an investigator, rhabdomyolysis as CK ≥10,000 IU/L with muscular symptoms, and myopathy as muscle symptoms (malaise, muscular pain or cramp) with CK ≥1,900 IU/L in men or ≥1,500 IU/L in women.

Statistical Analysis

Differences between groups in baseline characteristics were compared using the unpaired t-test or the chi-square test. Results are expressed as mean±SD, and differences were considered statistically significant at $p<0.05$. Continuous variables within and between subgroups were assessed using the paired or unpaired t-test, or trend test. Analysis of covariance was used for this purpose when a significance in between-group incompatibility existed at baseline. Differences in categorical data between groups were compared using the chi-square test. Patients who received at least one dose of simvastatin during the trial was included in the analysis of adverse events. All statistical calculations were performed using SAS software (version 6.12, SAS Institute, Inc, Cary, NC, USA).

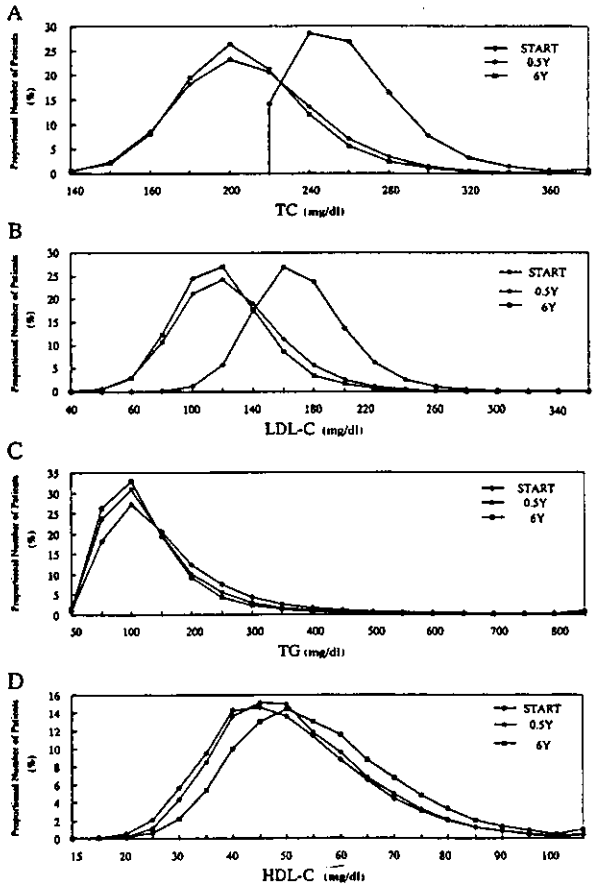


Fig 1. Distribution of proportional number of patients by serum lipid concentration at baseline, after 6 months and 6 years of low-dose simvastatin therapy. (A) Total cholesterol, (B) LDL-C, (C) triglyceride and (D) HDL-C.

Results

Patient Follow-up

The patients' clinical characteristics have been described before[1] and the baseline characteristics of the current 52,421 cohort members are summarized in Table 1. The average age was 57.9 years and 33% were male. After enrollment, 1,100 patients were excluded for the following reasons: violation of initial dosage (68 patients), missing follow-up data (1,025 patients) and unwillingness to participate (7 patients). Sequential changes in the treatment profile of the different cholesterol-lowering therapies during the 6 years of follow-up is summarized in Table 2. Of 51,321 patients, the majority (96.4%) received the most common starting dose of simvastatin 5 mg/day, and only

Table 3 Sequential Changes in Lipid Concentrations During Simvastain Treatment

	Baseline (mg/dl)	*6 months*		*6 years*	
		(mg/dl)	*(%)*	*(mg/dl)*	*(%)*
TC	*269±34*	*220±37**	*(−18.3)*	*217±34**	*(−19.3)*
LDL-C	*182±33*	*135±35**	*(−26.0)*	*129±32**	*(−28.9)*
TG	*196±169*	*167±126**	*(−14.7)*	*155±103**	*(−21.0)*
HDL-C	*52.6±15.1*	*53.8±14.8**	*(2.3)*	*58.1±15.7**	*(10.5)*

Data are presented as the mean±SD.
**p<0.0001 vs Baseline.*

Table 4 Percent Change in TC and Number of Patients With Adverse Drug Reactions in the Hypercholesterolemic Patients Receiving Long-Term, Low-Dose Simvastatin Therapy

	Reduction in TC (%)						
	>40	31–40	21–30	11–20	≤10	Lipid data missing	Total
All ADRs*	24 (3.29)	146 (3.16)	427 (2.70)	458 (2.73)	282 (3.04)	333	1,670
Hepatic*	8 (1.10)	57 (1.23)	148 (0.94)	147 (0.88)	81 (0.87)	59	500
Musculoskeletal*	10 (1.37)	50 (1.08)	126 (0.80)	138 (0.82)	70 (0.75)	45	439
Digestive*	4 (0.55)	8 (0.17)	47 (0.30)	65 (0.39)	66 (0.71)	101	291
Skin*	0 (0.00)	12 (0.26)	40 (0.25)	44 (0.26)	30 (0.32)	59	185
Total no. of patients (%)	729 (1.4)	4,618 (9.0)	15,827 (30.8)	16,780 (32.7)	9,279 (18.1)	4,088 (8.0)	51,321 (100)

*No. of incodence (%), described in Tables 6–8.

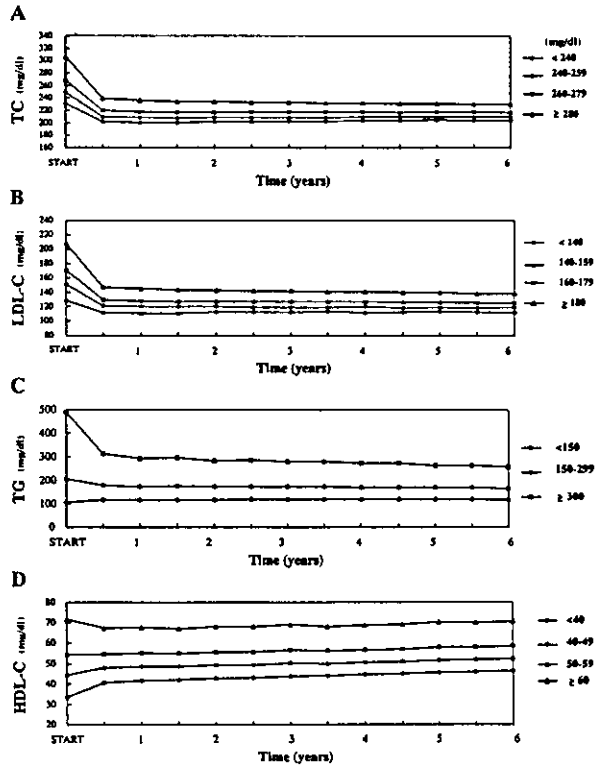


Fig 2. Sequential changes in the serum lipid concentrations as a function of the duration of simvastatin treatment for groups of patients categorized by their baseline lipid concentrations. (A) Total cholesterol, (B) LDL-C, (C) triglyceride, (D) HDL-C.

3.6% (1,825 patients) started at 10 mg/day, with 1 patient starting at 7.5 mg/day. At the 6th year, 36,895 patients remained in the study. The average follow-up period was 5.3±1.4 years (0.5–6.0 years). At the 6th year, 20,518 patients had received simvastatin 5 mg/day alone, 1,668 patients had received simvastatin 10 mg/day alone, 1,845 patients had received other lipid-lowering drugs in addition to simvastatin and 814 patients had received other lipid-lowering drugs. The ratio of patients treated with simvastatin 10 mg/day to those on 5 mg/day slightly increased during the course of treatment, nonetheless, more than 90% of patients remained on 5 mg/day for 6 years. The cumulative treatment term was 174,769 patient-years and the average term of drug treatment was 3.41 years per patient.

Changes in Serum Lipid Concentrations

After 6 months of treatment, the distribution curve of patient number by serum TC and LDL-C concentrations shifted lower in comparison with the baseline in all the patients followed up (Fig 1). The average reduction in serum TC and LDL-C was 18.3% and 26%, respectively, after 6 months, and these concentrations were maintained during the 6-year treatment period (Table 3). After 6 years of treatment, TC and LDL-C concentrations were reduced by 19.3 and 28.9%, respectively, although a minority (1.4%) had an unexpectedly remarkable reduction by more than 40% in serum TC concentration (Table 4). That group had 1.7-fold more men and 4.4-fold higher incidence of complications of renal disease, 2.2-fold of hepatic disease and 1.8-fold of diabetes mellitus when compared with the group of patients with a 10-20% reduction in TC concentration. In the contrast, the serum high density lipoprotein-cholesterol (HDL-C) concentration increased on average by 2.3% after 6 months of treatment, and kept gradually increasing throughout the treatment period up to 10.5% by the 6th year. Although no change in the serum TG distribution pattern was observed, the average value decreased by 14.7% at the 6th month and by 21 % during the 6-year treatment period in comparison with baseline.

The time course of the effect of treatment on lipid concentrations can be seen when the patient groups are stratified by their baseline lipid concentrations (Fig 2). The serum TC and LDL-C concentrations decreased with the treatment in all groups, but the reduction was greater in the patients with a higher baseline TC or LDL-C concentration (Table 5). The mean concentration of serum HDL-C increased after 6 months of the treatment and continued to increase during the treatment period. The serum HDL-C concentration after 6 years of treatment did not change in patients whose baseline HDL-C was 60 mg/dl or more, but in those with a baseline concentration less than 60 mg/dl the increase in serum HDL-C after the treatment was greater as the baseline concentration decreased. The serum TG concentrations decreased markedly in patients with a higher baseline TG concentration, particularly in patients with the highest range of concentrations (TG ≥300 mg/dl) for whom the reduction was 41.4% of the baseline. On the other hand, the TG concentration increased slightly in the group with a low baseline TG concentration.

Clinical Adverse Effects

Overall, treatment with simvastatin was well tolerated. ADRs were reported in 1,670 patients (2,470 events), and the overall frequency of ADRs during the treatment for 6 years was 3.3% of subjects (Table 4). The incidence of ADRs is demonstrated with the patient groups stratified by the reduction in serum TC concentration during the treatment (Fig 3, Table 4). There was no significant difference in the incidence of ADRs in these groups, except in the patients with less than 10 % decrease in TC concentration

Table 5 Baseline Serum Lipid Concentration and Percent Changes at 6 Years With Low-Dose Simvastatin Therapy in Japanese Hypercholesterolemic Patients

Baseline serum lipid concentration (mg/dl)	*n*	*% changes*	*p value for trend test*
TC			
<240	*2,836*	*−12.0±12.8*	
240–259	*6,059*	*−16.5±11.7*	
260–279	*5,771*	*−19.4±11.2*	
≥280	*6,404*	*−24.4±11.7*	
			<0.001
LDL-C			
<140	*1,193*	*−13.5±22.2*	
140–159	*3,134*	*−21.9±17.9*	
160–179	*4,918*	*−26.8±16.1*	
≥180	*9,129*	*−33.3±14.6*	
			<0.001
TG			
<150	*9,960*	*17.3±55.7*	
150–299	*8,352*	*−17.6±40.1*	
≥300	*2,500*	*−41.4±35.9*	
			<0.001
HDL-C			
<40	*3,322*	*40.7±61.8*	
40–49	*5,684*	*18.0±24.6*	
50–59	*5,055*	*8.3±21.4*	
≥60	*5,692*	*−0.4±20.9*	
			<0.001

% changes are presented as the mean±SD.

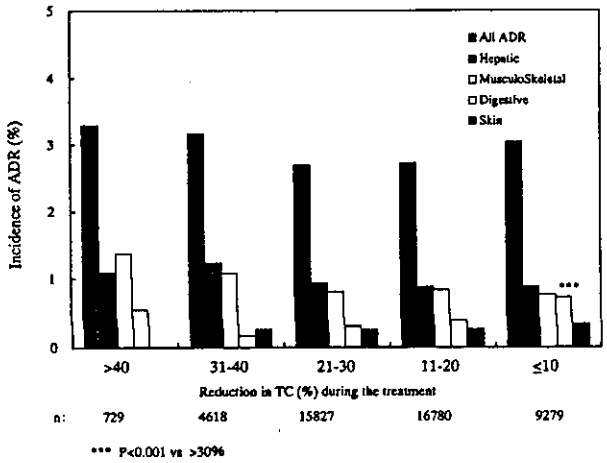


Fig 3. Incidence of adverse drug reactions in long-term, low-dose simvastatin therapy as a function of the change in the total cholesterol concentration during the treatment.

who showed an increase in the incidence of digestive ADRs. The incidence of musculoskeletal ADRs had a tendency to increase slightly in proportion to the reduction of TC concentration, and the added incidence in the group of patients with a greater than 30% decrease in serum TC concentration was significantly higher when compared to the group with a 20–30% decrease.

The ADRs summarized by different organ system are shown in Table 6. The most frequently observed ADRs were hepatic disorders in 500 cases (838 events) with an incidence of 0.97%. Of these, 411 cases (82%) represented abnormal laboratory values without clinical significance (Table 7). Hepatitis occurred in 80 patients with an incidence of 0.16%. There were 3 cases of elevated AST and/or ALT greater than 500 IU/L. The severity of hepatic disorders was mild in 421 cases, and moderate in 79 cases. None

Table 6 Summary of Adverse Drug Reactions (ADRs) in Hypercholesterolemic Japanese Patients on Long-Term, Low-Dose Simvastatin Therapy

ADR	*n (no. of patients)*
Hepatic (described in Table 7)	*838 (500)*
Musculoskeletal (described in Table 8)	*492 (439)*
Digestive	*352 (291)*
Abdominal symptoms	*187*
Diarrhea	*45*
Nausea	*31*
Anorexia	*27*
Miscellaneous	*62*
Generalized	*220 (200)*
Malaise	*49*
Headache	*39*
Dizziness	*38*
Weakness	*29*
Miscellaneous	*65*
Skin	*190 (185)*
Rash	*131*
Pruritus	*47*
Miscellaneous	*12*
Kidney	*108 (96)*
BUN increased	*39*
Hematuria	*20*
Miscellaneous	*49*
Neurological	*101 (93)*
Sleep disorder	*25*
Numbness	*23*
Miscellaneous	*53*
Blood	*71 (62)*
Anemia	*27*
Miscellaneous	*44*
Laboratory test abnormality	*71 (67)*
Uric acid increased	*26*
Miscellaneous	*45*
Miscellaneous	*27 (26)*

of the cases was considered serious by the Adverse Event Subcommittee. The second most common ADRs were musculoskeletal disorders (439 cases, 492 events), which

Table 7 Hepatic Disorders as Adverse Drug Reaction (ADR) in Hypercholesterolemic Japanese Patients on Long-Term, Low-Dose Simvastatin Therapy

ADR	Mild	Moderate	Serious	Total
Hepatitis	9	71	0	80
Fatty Liver	20	7	0	27
Cholelithiasis	1	0	0	1
Liver function test abnormality	408	3	0	411
AST increased	206	2	0	208
ALT increased	232	1	0	233
γ-GTP increased	115	2	0	117
ALP increased	48	0	0	48
LDH increased	83	0	0	83
Bilirubin increased	16	0	0	16
Miscellaneous	25	0	0	25
Total	755	83	0	838
No. of patients	421	79	0	500

AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, γ-glutamyltranspeptidase, ALP, alkaline phosphatase; LDH, lactate dehydrogenase.
Serious = life-threatening condition, Moderate = requiring medical treatment or discontinuation of simvastatin treatment, Mild = others.

Table 8 Musculoskeletal Disorders as Adverse Drug Reaction (ADR) in Hypercholesterolemic Japanese Patients on Long-Term, Low-Dose Simvastatin Therapy

ADR	Total (with elevated CK)
Rhabdomyolysis	0
Myopathy	4 (4)
Myalgia	97 (32)
Muscle cramp	36 (9)
Muscle atrophy	1 (0)
Arthralgia	8 (1)
Myoglobin increased	2 (1)
Elevated CK (IU/L)	
≥1,900 (Men), ≥1,500 (Women)	2
≥1,000	21
≥600 with symptoms	18
Other	303
Total	492
No. of patients	439

CK, creatine phosphokinase.

occurred with incidence of 0.86% (Table 8). Among them, 344 events had an elevated CK concentration; 6 patients showed a 10-fold increase of the normal values and 4 patients were considered to have myopathy because of the occurrence of pathognomonic symptoms. There was no case of rhabdomyolysis as defined by the ADR assessment subcommittee as CK greater than 10,000 IU/L with muscular symptoms. The significant increase of musculoskeletal ADRs that accompanies treatment with fibrate agents was not observed. Among the digestive adverse reactions, abdominal symptoms were reported in 187 cases (0.36%) and for skin reactions, a rash developed in 131 cases (0.26%) (Table 6). Twenty five patients had a sleep disorder (0.05%).

Information for 10 patients who died or were hospitalized because of simvastatin-related adverse events is summarized in Table 9. One death was caused by thrombocytopenia in the 3rd month of the treatment. That patient received 9 drugs concomitant to the simvastatin, and the platelet count had not been determined prior to or at the start of simvastatin therapy. The platelet count was less than 10,000/μL after 3 months of the therapy, and the patient died 5 days after the finding of thrombocytopenia, which the reporting physician did not considered to be related to the simvastatin. However, the relationship of thrombocytopenia to simvastatin could not be denied. Of 9 patients requiring hospitalization from possible serious ADRs, 3 had thrombocytopenia.

The frequency of overall ADRs was 9.6 cases per 1,000 patients-year and that of death and hospitalization was 57 cases per 1,000,000 patients-year.

Discussion

The J-LIT study is the first prospective cohort study to successfully establish a correlation between serum lipid concentrations and the incidence of CHD in Japanese hypercholesterolemic patients. In this study, low-dose simvastatin (mostly 5 mg/day) administered for 6 years effectively reduced serum TC and LDL-C concentrations, and increased the HDL-C concentration, in Japanese subjects with hypercholesterolemia and the treatment was safe and well tolerated. The number of participating subjects was approximately 50,000 and the total study period of 6 years simulated long-term simvastatin treatment for patients with hypercholesterolemia. A study without placebo control was required to obtain information of the safety and efficacy of simvastatin in Japanese patients for following reasons. First, this long-term and large-scale study was only possible through ordinary standard clinical practices in Japan. Under those conditions, administering simvastatin to every subject was critical to ensure the compliance of patients, because the availability of the well established health insurance to every Japanese patient without exception meant that this study provided no additional financial incentive to the participants. Second, statins are already a proven effective treatment for hypercholesterolemia and it was difficult to convince physicians and patients to participate if the lives of the hypercholesterolemic patients in the placebo group would be compromised because of the possible consequences of coronary events. In this regard, the study plan is in agreement with the October 2000 revised Declaration of Helsinki and could be a practical method for assessing the effectiveness and safety of other widely used drugs with life saving effects.

Hypercholesterolemia has been identified as a major risk factor for CHD[1,14] and previous studies have demonstrated that cholesterol-lowering medication can reduce the risk of CHD[2-10] or death[6] Of those medications, simvastatin, which

Table 9 Summary of Death and Hospitalization in Hypercholesterolemic Japanese Patients Receiving Long-Term, Low-Dose Simvastatin Therapy

ADR	*Sex*	*Age (years)*	*Month of treatment*	*Details*
Thrombocytopemia	*M*	*56*	*3*	**Platelet <1.0×10⁴/μL Death 5 days after emergency hospitalization.*
Thrombocytopenia	*F*	*59*	*30*	**Platelet <2.0×10⁴/μL Simvastatin discontinued, recovery after hospitalization.*
Thrombocytopenia	*F*	*51*	*31*	**Platelet <7.5×10⁴/μL, Not recovered with discontinuation of simvastatin, hospitalization.*
Aplastic anemia	*F*	*62*	*52*	*Subcutaneous hemorrhage continued after cessation of simvastatin. Hospitalization. Simvastatin resumed.*
Myalgia	*F*	*56*	*31*	*CK 1,402 IU/L. Hospitalization because of continued thigh muscle pain.*
Renal failure	*M*	*61*	*2*	*CK 865 IU/L. Dialysis.*
Vertigo, nausea	*F*	*51*	*2*	*Hospitalization because of severe vertigo and nausea. CT normal. Symptoms improved in 1 week after sodium bicarbonate infusion.*
Dizziness	*F*	*66*	*40*	*Hospitalization because of difficulty walking with dizziness. Recovered in 1 month.*
Pancreatitis	*M*	*56*	*53*	*Hospitalization because of vomiting and epigastric pain. Diagnosis stage 4 pancreatitis. Pancreatitis improved after treatment with camostat mesilate.*
Fever, vomiting, diarrhea, Creatinine·BUN ↑	*F*	*66*	*49*	*Hospitalization with fever, vomiting, diarrhea and creatinine·BUN increase. Details unknown.*

**No data for baseline platelet count.*

is a powerful drug for normalizing serum lipid concentrations, is one of the most widely prescribed statins in the world.[5] A comparable long-term large-scale study of simvastatin conducted in a Western country was the 4S study in which the effect of 20–40 mg/day of simvastatin in hypercholesterolemic subjects was examined for 5.4 years on average.[7] In Japan, the recommended starting dose is 5 mg/day, which is 1/4 of the dose used in Western countries,[12] and during the initial 6-month simvastatin treatment period, the serum concentrations of TC and LDL-C decreased 18.3% and 26.0% of their baseline values, respectively. The magnitude of the reductions was similar to those observed in higher dose simvastatin studies performed in Western countries, such as the 4S study. However, the reasons why Japanese patients responded differently from those in Western countries are not clear. We speculate that differences in patient susceptibility to simvastatin because of differences in intrinsic metabolism and/or the nature of dietary intake or genetic factors in both populations could account for the dose difference. In particular, the difference may be related to dietary differences, because there seems to be basically no difference in the pharmacokinetics of the drug and the effect of simvastatin on the reduction of LDL-C has been enhanced by lower fat diet.[15,16] Treatment with low-dose statin in combination with a low-fat diet might benefit patients in Western countries. With the recent progress in understanding the genetic factors associated with hyperlipidemia, the genetic characteristics of both populations that contribute to the difference in dosage may be clarified in the near future.

A minority(1.4%) of the present patient population had an exceptional reduction of serum TC (>40%) with the low dose of simvastatin, and this is the first time such a phenomenon has been documented. That group of patients had more male subjects and a higher incidence of complications of renal disease, hepatic disease and diabetes mellitus when compared with the group of patients whose TC concentration was reduced by 10–20%. In the past, cancer was suggested as a possible cause of hypocholesterolemia,[17] but the reduction reported here may have included other causes. Hyper-responders have an increased risk of death,[19] so patients who show a remarkable decrease in TC or LDL-C concentration with low-dose statin therapy should be monitored closely. We will report on these hyper-responders in detail in another paper.

Patients with hypercholesterolemia require long-term treatment to normalize and maintain their cholesterol concentration, but because these patients frequently have concomitant medical conditions, such as hypertension, diabetes mellitus, and cardiac disease, they are usually treated with multiple medications. Hence, in the selection of cholesterol-lowering drug, safety is an important consideration for daily clinical care.

The well-known ADRs of statins are rhabdomyolysis and hepatitis. Serious cases of rhabdomyolysis have been reported in Western countries, especially with concomitant treatment with substrates or inhibitors of cytochrome P450 3A4 enzyme, such as cyclosporin A and itraconazole. Generally, close monitoring of the patient for rhabdomyolysis is recommended strongly when statins are prescribed. Although there were 4 cases of myopathy with CK elevation in this study, the ADR assessment subcommittee judged that there were no cases of rhabdomyolysis (CK ≥10,000 IU/L with muscular symptoms), which may have been because there was early detection of symptoms and abnormal CK values of patients receiving simvastatin and countermeasures were taken by the physicians who were aware of the risk of musculoskeletal ADRs. In the 4S study, there was a case of rhabdomyolysis that was relieved by discontinuation of simvastatin. The incidence of musculoskeletal ADRs increased in proportion with the magnitude of the increased TC lowering effect, which suggests that the pathophysiology of this ADR is related to the biochemical mechanism of the cholesterol-lowering effect of the drug.

Hepatitis occurred only in 0.16% of the patients in the present study, and none of the cases was serious, which may also be a result of the careful patient monitoring by the physicians. Following the safety information on the drug is critical for the prevention of ADRs.

Thrombocytopenia is an uncommon but serious and sometimes fatal ADR that is associated with a variety of

drugs. One patient in this study died from thrombocytopenia. This patient received 10 different drugs, 5 of which were continued until the death occurred, and so the causal relationship between this complication and simvastatin therapy is unclear. Medication should have been discontinued when the thrombocytopenia was detected and withheld until the platelet count normalized. There is a possibility that simvastatin impairs heamatopoiesis. One case of aplastic anemia occurred and the incidence of aplastic anemia is higher in Japanese patients than in Western countries[18] for reasons that are still unclear.

The rate of serious drug-related adverse events was only 57 cases per 1,000,000 patients-year, and the overall frequency of ADRs over the 6 years was 3.3% of subjects.

We have also reported[19,20] that the concentration of serum cholesterol correlated with the incidence of CHD in Japanese hypercholesterolemic patients with or without a history of CHD in the J-LIT study, which strongly suggests that cholesterol-lowering medication prevents CHD in Japanese hypercholesterolemic patients.

In conclusion, cholesterol-lowering therapy using low-dose simvastatin is highly effective in controlling serum lipid concentration and is safe, and well tolerated by Japanese hypercholesterolemic patients. Additionally, a low fat diet may be beneficial to patients, by decreasing the incidence of drug-related adverse events.

Acknowledgment

This study was partially supported by a grant from Banyu Pharmaceutical Co, Ltd, Tokyo, Japan.

References

1. Matsuzawa Y, Itakura H, Kita T, Mabuchi H, Matsuzaki M, Nakaya N, et al. Design and baseline characteristics of a cohort study in Japanese patients with hypercholesterolemia: The Japan Lipid Intervention Trial (J-LIT). *Curr Ther Res* 2000; **61:** 219–243.
2. Castelli WP, Garrison RJ, Wilson PW, Abbott RD, Kalousdian S, Kannel WB. Incidence of coronary heart disease and lipoprotein cholesterol levels: The Framingham Study. *JAMA* 1986; **256:** 2835–2838.
3. Lipid Research Clinics Program. The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. *JAMA* 1984; **251:** 351–364.
4. Frick MH, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo PA, et al. Helsinki Heart Study: Primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia: Safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med* 1987; **317:** 1237–1245.
5. Oliver MF, Heady JA, Morris JN, Cooper J. A co-operative trial in the primary prevention of ischaemic heart disease using clofibrate: Reports from the committee of principal investigators. *Br Heart J* 1978; **40:** 1069–1118.
6. Todd PA, Goa KL. Simvastatin: A review of its pharmacological properties and therapeutic potential in hypercholesterolaemia. *Drugs* 1990; **40:** 583–587.
7. Pedersen TR, Wilhelmsen L, Faergeman O, Strandberg TE, Thorgeirsson G, Troedsson L, et al. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994; **344:** 1383–1389.
8. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia: West of Scotland Coronary Prevention Study Group. *N Engl J Med* 1995; **333:** 1301–1307.
9. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996; **335:** 1001–1009.
10. Downs JR. Primary prevention of acute coronary events with Lovastatin in men and women with average cholesterol levels: Results of AFCAPS/TexCAPS. *JAMA* 1998; **279:** 1615–1622.
11. Tonkin A, Aylward P, Colquhoun D, Glasziou P, Harris P, Hunt D, et al. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998; **339:** 1349–1357.
12. Goto Y, Itakura H, Goto Y, Oikawa S, Hata Y, Nakaya N, et al. Clinical study of MK-733 (simvastatin): Dose range finding study. *Rinsho-Iyaku* 1989; **5:** 2011–2040.
13. Friedwald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972; **18:** 499–502.
14. Stamler J, Wentworth D, Neaton JD. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA* 1986; **256:** 2823–2828.
15. Chisholm A, Mann J, Sutherland W, Williams S, Ball M. Dietary management of patients with familial hypercholesterolaemia treated with simvastatin. *Q J Med* 1992; **85:** 825–831.
16. Clifton PM, Noakes M, Nestel PJ. Gender and diet interactions with simvastatin treatment. *Atherosclerosis* 1994; **110:** 25–33.
17. Ueyama Y, Matsuzawa Y, Yamashita S, Funahashi T, Sakai N, Nakamura T, et al. Hypocholesterolaemic factor from gallbladder cancer cells. *Lancet* 1990; **336:** 707–709.
18. Nomura T. Japanese clinical statistical data of patients with aplastic anemia. *Nippon Rinsho* 1992; **50:** 735–746.
19. Matsuzaki M, Kita T, Mabuchi H, Matsuzawa Y, Nakaya, N, Oikawa S, et al. Large scale cohort study of the relationship between serum cholesterol concentration and coronary events with low-dose simvastatin therapy in Japanese patients with hypercholesterolemia: Primary prevention cohort study of the Japan Lipid Intervention Trial (J-LIT). *Circ J* 2002; **66:** 1087–1095.
20. Mabuchi H, Kita T, Matsuzaki M, Matsuzawa Y, Nakaya N, Oikawa S, et al. Large scale cohort study of the relationship between serum cholesterol concentration and coronary events with low-dose simvastatin therapy in Japanese patients with hypercholesterolemia and coronary heart disease: Secondary prevention cohort study of the Japan Lipid Intervention Trial (J-LIT). *Circ J* 2002; **66:** 1096–1100.