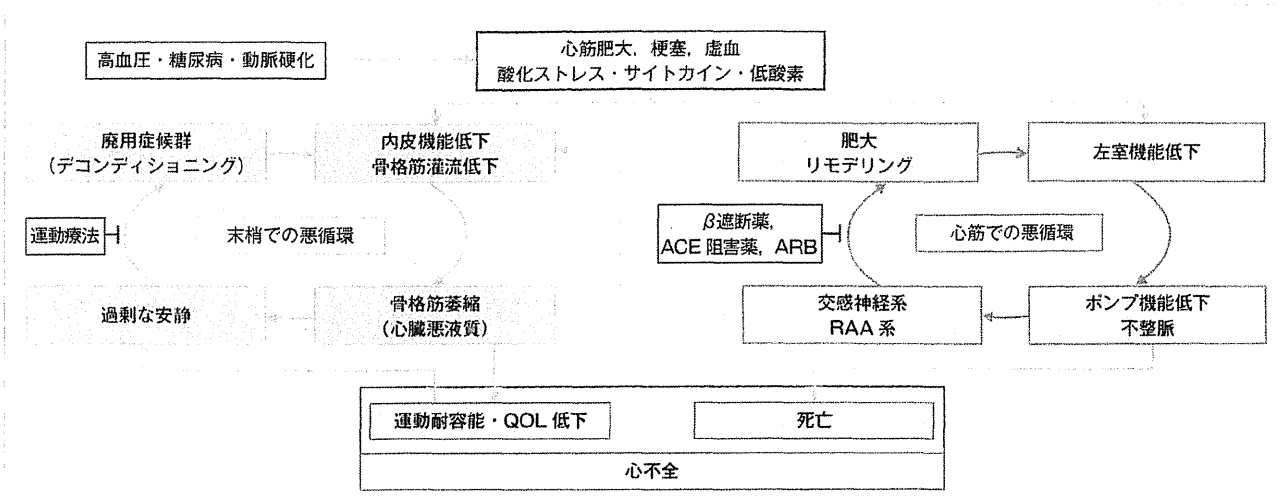

図1 慢性心不全の病態：運動耐容能低下の機序
慢性心不全では，心筋の肥大，梗塞，虚血などが左室機能低下および左室リモデリングを介して心ポンプ機能低下と不整脈を生じ，最終的に運動耐容能低下と死亡をもたらす．しかし運動耐容能低下は，左室機能低下の直接的な結果ではなく，末梢血管内皮機能低下・骨格筋灌流低下・過剰な安静による身体デコンディショニング・骨格筋萎縮など，末梢での悪循環の結果として生じる．
RAA系：レニン・アンジオテンシン・アルドステロン系

表1 慢性心不全に対する運動療法の効果（文献[8]より引用改変）

全身機能に対する効果	a）運動耐容能：改善
	b）末梢効果
	1）骨格筋：筋量増加，筋力増加，好気的代謝改善，抗酸化酵素発現増加
	2）呼吸筋：機能改善
	3）血管内皮：内皮依存性血管拡張反応改善，一酸化窒素合成酵素（eNOS）発現増加
	c）神経体液因子
	1）自律神経機能：交感神経活性抑制，副交感神経活性増大，心拍変動改善，換気応答改善
	2）炎症性サイトカイン：TNF-α・IL-6 低下，CRP 低下
心臓に対する効果	a）左室機能：安静時左室駆出率不変または軽度改善，運動時心拍出量増加反応改善，左室拡張早期機能改善
	b）冠循環：冠動脈内皮機能改善，運動時心筋灌流改善，冠側副血行路増加
	c）左室リモデリング：悪化させない（むしろ抑制），BNP 低下
心理的要因に対する効果	a）不安抑うつ：軽減
	b）QOL：健康関連 QOL 改善
長期予後に対する効果	a）心不全再入院：減少
	b）心イベント：無イベント生存率（死亡または入院）改善

るためと考えられている（図1）．

慢性心不全における運動療法の有効性

これまでの研究により，慢性心不全に対する運動療法には多様な効果があることが明らかにされてきた[7, 8]（表1）．慢性心不全に対する運動療法の最も顕著な効果は運動耐容能の改善であり，これにより患者の労作時自覚症状が軽減する．これまでの報告によると，ベースラインのLVEF平均20～30%，peak VO_2 10～20 mL/分/kgの慢性心不全患者に対して，中等度の運動強度（peak VO_2 の40～70%程度）で2～6ヵ月間の運動療法を施行し，peak VO_2 で15～30%（平均約20%）の増加が得られる．また，拡張不全患者（LVEF＞45%）においても，運動療法により収縮不全患者（LVEF＜35%）と同様の運動耐容能の改善が得られる[10]．

運動療法による運動耐容能増加効果は，心機能を介するものではなく，骨格筋や末梢血管などの末梢機序を介するものである[7, 8]．すなわち，心不全に対する運動療法により，骨格筋の筋肉量・ミトコンドリア容積の増加，骨格筋代謝および機能の改善，呼吸筋機能の改善がみられる．また，末梢血管の内皮依存性拡張反応の改善が認められ，この血管拡張反応の改善度と運動耐容能の改善度が相関する．

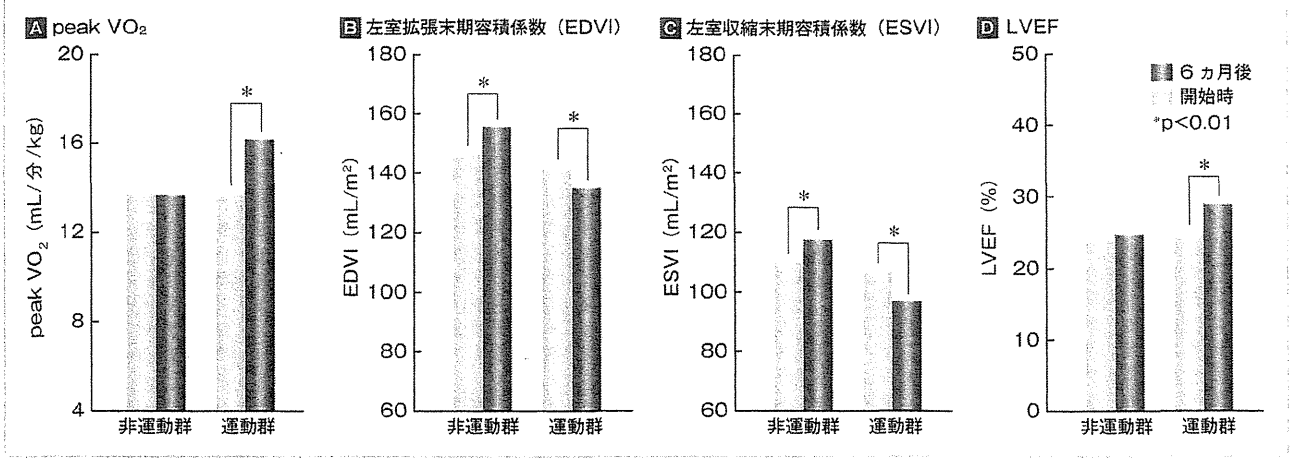

図2 心不全の運動療法の抗リモデリング効果（ELVD-CHF試験）（文献[12]より引用改変）

慢性心不全患者90名（LVEF 25±4%，β遮断薬服用20%）を非運動群（n=45）と運動群（n=45）に無作為割り付けし，6ヵ月後に運動耐容能，心エコー検査を実施した．運動群では最高酸素摂取量（peak VO_2），LVEFが改善し，左室容積（EDVI，ESVI）の縮小がみられたが，非運動群ではむしろ左室拡大がみられた．

心臓に対する効果のうち，LVEFについては運動療法により改善するという報告と不変という報告が混在し，メタ解析ではわずかに改善する（+3%）とされる．一方，拡張機能については運動療法により改善するとの報告が多い[11]．また従来，低心機能患者が運動療法を実施すると左室リモデリングが悪化するのではないかとの懸念があったが，Exercise in Left Ventricular Dysfunction and Chronic Heart Failure（ELVD-CHF）研究[12]では，LVEF＜40%の慢性心不全症例において，むしろ運動療法により左室拡大が抑制され，適切な運動療法は抗リモデリング効果を有することが示されている（図2）．また，左室負荷を反映する血漿B型ナトリウム利尿ペプチド（brain natriuretic peptide；BNP）も運動療法により低下する（図3）[13]．

心不全患者では，交感神経系の活性が亢進し副交感神経系の活性が低下しているが，運動療法によりこれらが正常化に向かう．すなわち，交感神経活性が抑制され血中のノルアドレナリンは低下し（図3），その一方で副交感神経活性が活性化される．また，呼吸中枢のCO_2感受性が改善し，心不全患者でみられる運動時の換気亢進が軽減する．さらに，運動療法により心不全患者の血中サイトカインや炎症マーカーが低下することや，骨格筋の抗酸化酵素遺伝子の発現が増加することが報告されている．慢性心不全の病態悪化に関連するこれら複数の要因の改善は，運動療法が心不全の病態に対して好ましい効果を与えることを示唆している．

運動療法は心不全患者のQOLおよび予後に対しても有効である．運動療法により心不全患者の不安，抑うつが軽減され，健康関連QOLが改善する．長期予後に関しては，2004年のExercise training meta-analysis of trials in patients with chronic heart failure（ExTraMATCH）研究[14]において9つの無作為割り付け試験のメタ解析が行われ，運動療法施行群のほうが対照群に比べ，生存率，イベントフリー生存率（死亡＋入院）が有意に良好であることが示された．また，2009年に発表された大規模臨床試験Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training（HF-ACTION）[15]では，β遮断薬を含む最適薬物治療を実施されている慢性心不全患者に運動療法を上乗せすることにより，心不全悪化を含む心イベントや整形外科的傷害による有害事象が増加することなく，運動耐容能とQOLが改善し，心イベント（心血管死亡＋心不全入院）が13%減少（背景因子補正後は15%減少）することが明らかになった（図4）．

これらのエビデンスを踏まえて，ACC/AHAの『慢性心不全マネジメントガイドライン2009年改訂版』[1]，ヨーロッパ心臓学会（European Society of Cardiology；ESC）の『急性・慢性心不全ガイドライ

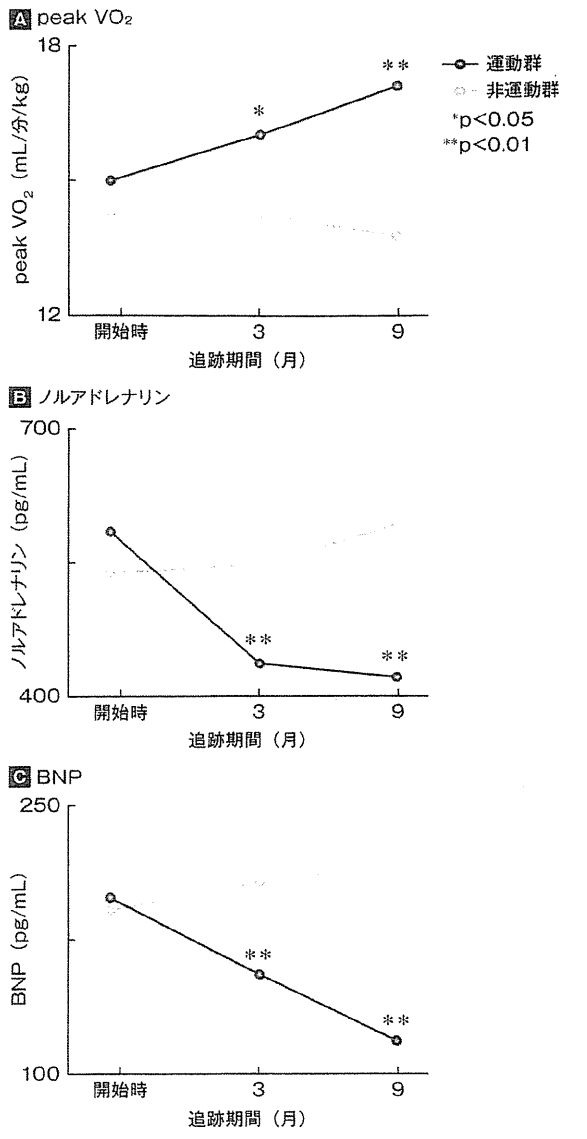

図3 慢性心不全の運動療法が神経体液因子に及ぼす効果（文献[13]より引用改変）

慢性心不全患者（LVEF平均35%）を運動療法群（n＝44）と非運動群（n＝41）とに無作為割り付けし，9ヵ月間追跡したところ，運動療法群においてのみ運動耐容能（peak VO_2）増加（A），ノルアドレナリン低下（B），BNP低下（C）が認められた．

ン2008年版』[16]，日本循環器学会の『慢性心不全治療ガイドライン（2010年改訂版）』[2]，同じく『心血管疾患におけるリハビリテーションに関するガイドライン（2007年改訂版）』[17]では，慢性心不全に対する運動療法を強く推奨している．

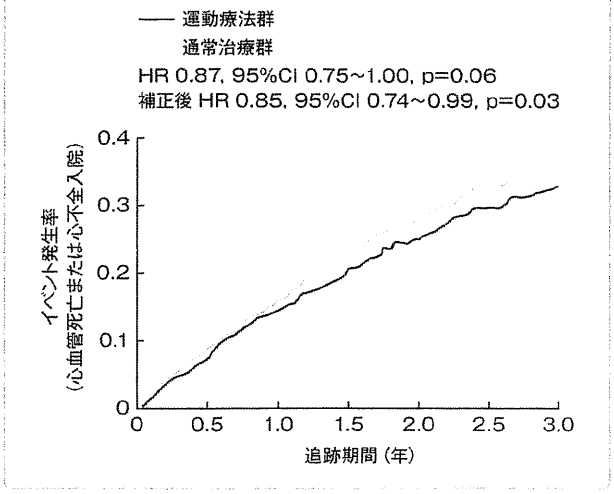

図4 HF-ACTION試験：慢性心不全に対する運動療法の長期予後改善効果（文献[15]より引用改変）

安定慢性心不全患者（LVEF中央値25%）2331人を対象としたHF-ACTION試験において，運動療法群は通常治療群に比べ，イベント発生率（心血管死亡または心不全入院発生率）が13%低かった（p＝0.06）．主要背景因子の補正後，リスク減少率は15%となり統計学的に有意であった（p＝0.03）．

慢性心不全に対するβ遮断薬と運動療法の併用

β遮断薬は心不全患者の運動耐容能を低下させるか

慢性心不全治療におけるβ遮断薬の長期生命予後改善効果については誰もが異存がないところであるが，心不全患者の運動耐容能に及ぼすβ遮断薬の影響に関して以前から2つの懸念があった．第1は，β遮断薬は運動中の心拍数上昇を抑制するため心不全患者の運動耐容能を低下させるのではないかという点であり，第2は，β遮断薬は運動療法による運動耐容能増加を抑制するのではないかという点である[18]．

第1の懸念のβ遮断薬の心不全患者の運動耐容能への悪影響の可能性については，β遮断薬の種類と用量に依存すると考えられている．すなわち，非選択性β遮断薬で直接的な末梢血管拡張作用も有するbucindolol（日本未発売）はpeak VO_2をむしろ低下させるが，α・β遮断薬であるカルベジロールはpeak VO_2を増加も減少もさせない（図5）．さらにbucindololは，心拍数を著し

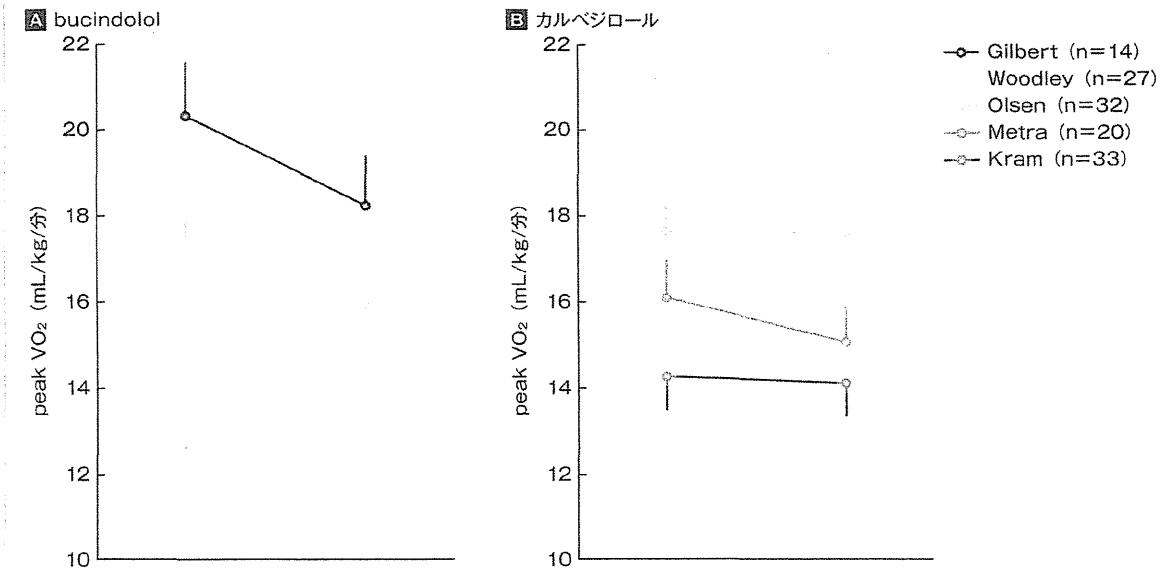

図5 運動耐容能に対するβ遮断薬の効果（文献[19]より引用改変）
A：非選択性β遮断薬であるbucindololは直接的な末梢血管拡張作用を有するが，peak VO_2をやや低下させる．
B：α・β遮断薬であるカルベジロールもまた末梢血管拡張作用を有するが，peakVO_2を増加させる効果はない．

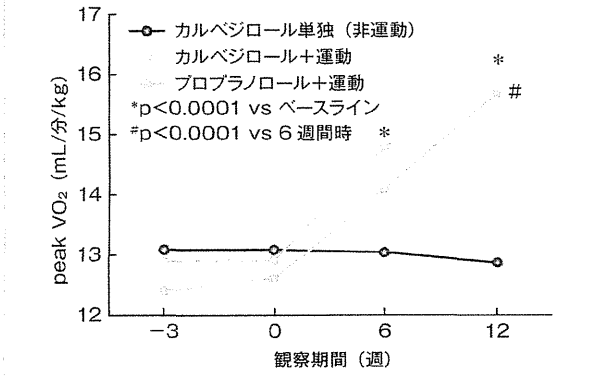

図6 心不全の運動療法とβ遮断薬（文献[20]より引用改変）
β遮断薬服用中の慢性心不全患者23名（平均LVEF 23%）を，プロプラノール＋運動群（n＝7），カルベジロール＋運動群（n＝8），カルベジロール＋非運動群（n＝8）に割り付けた．12週間後の運動耐容能（peak VO_2）は運動療法施行群でのみ改善し，β遮断薬単独では改善しなかった．また，カルベジロールとプロプラノールの間ではpeak VO_2の増加の程度に差がなかった．

く抑制する高用量ではpeak VO_2を低下させるが，低用量ではむしろpeak VO_2をわずかに増加させる[19]．

β遮断薬は心不全の運動療法効果を抑制するか

第2の懸念のβ遮断薬の運動療法における運動耐容能増加抑制の可能性については，現在では，心不全の運動療法における運動耐容能改善効果はβ遮断薬の投与によっても抑制されず（図6）[20]，また，β_1受容体選択薬と非選択薬（カルベジロール）との間でトレーニング効果への影響に差がないとされている[21]．

国立循環器病研究センターにおいて，拡張型心筋症による慢性心不全症例に対してβ遮断薬単独治療を実施した群（β遮断薬単独群）とβ遮断薬導入と運動療法導入をほぼ同時に行った群（β遮断薬・運動併用群）の3ヵ月後のpeak VO_2を比較したグラフを図7に示す[18]．β遮断薬単独群ではpeak VO_2に有意な改善は認めなかったが，β遮断薬・運動併用群では有意な改善を認めた．また，図には示されていないが，左室拡張末期径の縮小の程度や血中BNPの下降の程度は両群で同等であった．したがって，β遮断薬治療と運動療法はそれぞれの有益な効果を相殺することなく併用できるといえる．

β遮断薬治療と運動療法の併用時の運動処方

一般的に，心臓リハビリテーションにおける運動処方の決定方法には，①心拍数予備能（Karvonenの式；k＝0.4～0.6）を用いる方法，②peak VO_2の40～60%あるいは嫌気性代謝閾値（anaerobic threshold；AT）を用いる方法，③自覚的運動強度（Borg指数13「やや

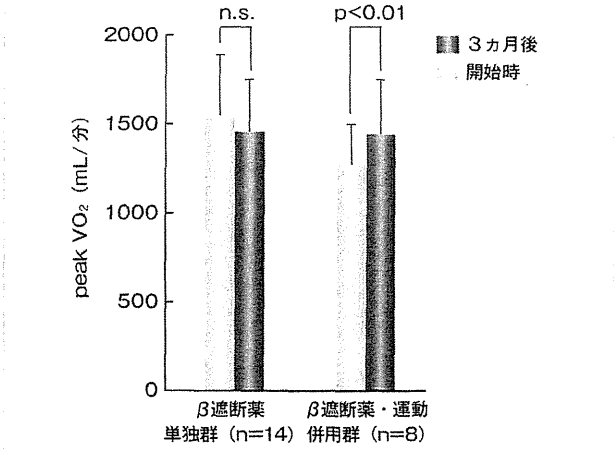

図7 慢性心不全患者に対するβ遮断薬・運動療法併用療法が運動耐容能に及ぼす効果（文献[10]より引用改変）

きつい」レベル）を用いる方法，がある[17]．β遮断薬は最大負荷時の到達心拍数を減少させるため，これらのうち心拍数を用いる運動処方の際には以下に述べる注意が必要である．

まず第1に，Karvonenの式を用いる場合，最高心拍数として（220－年齢）などの予測最大心拍数推定法を用いるのではなく，実測された到達最高心拍数を用いるべきである．なぜなら，70歳であれば計算上の予測最大心拍数は150回／分となるが，β遮断薬投与中の心不全患者で実際に最大負荷で150回／分まで到達することはまれなためである．

第2に，実測された到達最高心拍数を用いる場合であっても，安静時と最大負荷時心拍数の差が小さい場合は，わずかの心拍数の違いで負荷量が大きく変化することになり，心拍数による運動強度決定の精度が低下するため注意が必要である．とくに，慢性心不全患者では，もともと運動に対する心拍数反応が低下しているうえ，β遮断薬の投与によって安静時心拍数と最大負荷時心拍数の差が小さくなっているため，心拍数による運動強度決定の精度が低下している．たとえば，安静時心拍数が60回／分で最大負荷100 W時の到達心拍数が90回／分の場合，わずか3回／分の違いで負荷量が10 W異なることになる．このような場合には，呼気ガス分析を併用した症候限界性心肺運動負荷試験（cardiopulmonary exercise testing；CPX）で求めたATまたはpeak VO_2の40～60%（通常は60%で可）の強度を目安にして監視下で注意深く運動療法を導入する必要がある．

β遮断薬治療と運動療法併用時の注意点

慢性心不全に対する運動療法導入初期に，体重の増加やうっ血の増強を伴う一過性の心不全の増悪が出現することがある．とくに，β遮断薬と運動療法を同時に導入する際には注意が必要である．ただし，多くの場合，水分制限や利尿薬の一時的増量，運動量の一時間減量で対処可能である．

また，β遮断薬と運動療法を同時に導入する際には，β遮断薬の段階的増量に伴い同一運動負荷量での心拍数が低下するため，頻回の運動処方の見直しが必要となる．国立循環器病研究センターでは，急性心筋梗塞後患者などでは心臓リハビリテーション開始1週間後と3ヵ月後に実施するCPXを，慢性心不全患者では1週間後・1ヵ月後・3ヵ月後の計3回実施し，開始1ヵ月時点で運動処方の見直しを追加実施し，それ以外にも必要に応じて医師が運動処方の見直しを行うことにしている．

慢性心不全治療におけるその他の薬物と運動療法の併用

降圧薬，血管拡張薬（利尿薬）と運動療法の併用時の注意点

慢性心不全患者では，β遮断薬以外にもACE阻害薬・ARB・利尿薬が併用投与されていることが多い．これらの患者では，運動に伴う末梢血管拡張・発汗により血圧が下降し，低血圧症状（めまい・ふらつき・転倒など）を生じる可能性があるため注意が必要である．また，利尿薬投与中の患者では，夏期には大量の発汗により脱水にならないよう適度に水分を補給することが必要であるが，逆に運動後に口渇により水分や炭酸飲料の摂取量が過剰にならないよう注意が必要である．したがって，

この際の心不全管理は，「1日1000 mL」といった定量の水分摂取量による管理方式ではなく，「最適体重±1 kg」といった体重管理方式とするほうが望ましい．

血糖降下薬，抗凝固薬，抗血小板薬と運動療法の併用時の注意点

近年，多疾患保有心不全患者の増加に伴い，血糖降下薬，抗凝固薬，抗血小板薬などを投与中の心臓リハビリテーション参加症例が増加している．経口血糖降下薬やインスリンで治療中の糖尿病患者では，運動療法の導入により糖尿病コントロールが改善し，血糖値が徐々に下降してくるため，空腹時に運動する場合に低血糖症状の出現に注意することが必要である．とくに，屋外での運動療法時にはブドウ糖を携帯することを勧める．

抗凝固薬・抗血小板薬投与中の患者では，運動中の転倒や打撲が巨大血腫発生につながることがあるため，転倒・打撲イベントを避けるよう注意が必要である．また，心臓リハビリテーションの経過中，運動中の息切れやめまいの新規出現の原因が無症候性の消化管出血による貧血の進行であったというケースもあり，全身管理を念頭に置くべきである．

慢性心不全治療における治療アドヒアランスと心臓リハビリテーション

服薬アドヒアランスと疾病管理プログラム

近年心不全患者が高齢化し[22]，高齢心不全患者は，死亡率が高いだけでなく，退院後の再入院率が6ヵ月後で約50%，1年後では約60～70%ときわめて高いことが報告されており[23,24]，患者本人のQOLのみならず社会問題としても重大である．しかも，再入院の原因は，「左室収縮機能の進行性低下」ではなく，「管理不十分や治療アドヒアランス不良によるうっ血（体液貯留）の増悪」と「感染・腎不全・貧血・糖尿病・慢性閉塞性肺疾患などの非心臓性併存疾患（noncardiac comorbidities）」が主要因であることから[22,25,26]，むしろ併存疾患を含めた全身的な「疾病管理」の重要性が指摘されている[27]．

これに関してFitzgeraldら[28]は，入院歴のある心不全患者のうち，退院後の標準治療薬（ACE阻害薬・ARB・β遮断薬・抗アルドステロン薬）の服用率が80%未満の服薬アドヒアランス不良群は，服用率80%以上のアドヒアランス良好群に比べて予後（全死亡率・心血管疾患入院率）が不良であり，背景因子を補正後も服薬アドヒアランスは独立した予後規定因子であったと報告している．すなわち，心不全患者の長期予後改善のためには，患者の服薬アドヒアランス（治療アドヒアランス）をいかに維持・向上させるかが重要な課題である．

この課題に対する解決策として，慢性心不全の「疾病管理プログラム（disease management program）」が注目されている．疾病管理プログラムとは，医師・看護師・薬剤師・栄養士・理学療法士・訪問看護師などからなる多職種チームが，退院前教育，食事・服薬指導，カウンセリング，退院後の電話や訪問を含む介入［多職種介入（multidisciplinary intervention）］を統合的・計画的に実施するプログラムであり，これにより慢性心不全患者の再入院率が低下し，QOLが改善し，医療費を節減できたとの報告が増加しつつある[29-31]．

心不全疾病管理プログラムとしての心臓リハビリテーション

Davidson[32]らは，入院した中等症の心不全患者を対象として，外来心臓リハビリテーション介入として，①週1回の監視下運動療法，②心不全専門看護師による心不全評価および多職種による教育指導，③在宅運動療法指導，④電話相談を3ヵ月間実施した結果，外来心臓リハビリテーション介入群は通常治療群に比べ，3ヵ月時点でのQOLと6分間歩行距離が有意に良好であり，12ヵ月後時点では6分間歩行距離の延長に加え，心不全重症度が低く，再入院率が有意に低かったと報告している（図8）．すなわち，心不全に対する外来心臓リハ

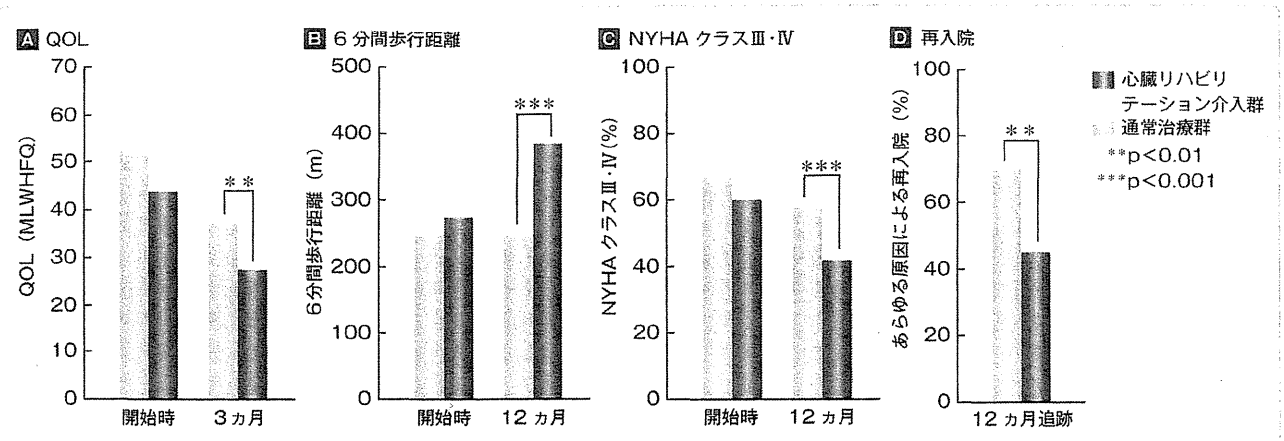

図8 心不全疾病管理プログラムとしての心臓リハビリプログラム（文献[32]より引用改変）

入院した心不全患者105名（平均62歳，NYHAクラスIII 64%）を，心臓リハビリテーション介入群53名と通常治療群52名に無作為割り付けし，心臓リハビリテーション介入群に対して，週1回の監視下運動，心不全専門看護師による教育指導と心不全チェック，在宅運動療法指導，電話相談を3ヵ月間実施し，12ヵ月後までの予後を追跡した．その結果，介入群においてQOLの改善（A），6分間歩行距離の改善（B），NYHAクラスIII・IV度の重症心不全比率の低下（C），およびあらゆる原因による再入院率の低下（D）が認められた．

ビリテーションプログラムは運動耐容能を改善するのみならず，再入院予防効果を有する疾病管理プログラムとして有用と考えられる．

国立循環器病研究センターでは，慢性心不全患者に対する外来心臓リハビリテーションを積極的に実施している．そこでは，運動処方に基づく運動療法を実施するとともに，主に循環器専門看護師が，①慢性心不全の治療アドヒアランス遵守・自己管理への動機づけとその具体的方法を指導するとともに，②心不全の早期兆候をチェックし増悪や再入院を未然に防止する対策を講じている．具体的には，毎回の運動療法実施前に問診・体重測定を実施し，心不全増悪兆候がある場合には担当医に連絡し，利尿薬の一時的増量・運動負荷量の一時的軽減などの処置を検討する．この処置により心不全増悪による入院を免れた症例も複数経験している．

外来心臓リハビリテーションが疾病管理プログラムとして機能するメリット

外来心臓リハビリテーションが実際に疾病管理プログラムとして機能するメリットを**表2**に示す．心臓リハビリテーションプログラムは心不全看護師主導の通常の心不全管理プログラムに比べて，①入院中から開始し，退院後まで切れ目なく継続できる，②心不全の管理だけでなく，心筋虚血監視・不整脈監視・運動指導・冠危険因子是正までの多面的介入が可能である，③多職種チームとしてすでに活動中であり新規のチーム構築が不要である，④循環器内科医の協力を得ることが容易である，⑤運動療法による心不全病態改善効果（血管内皮機能改善，自律神経機能改善，抗動脈硬化作用，炎症性サイトカイン抑制）が期待できる，⑥日本では慢性心不全の心臓リハビリテーションはすでに保険適応承認済みで，採算面での安定性が期待できる，といった多くのメリットを有しており，すでに心不全の疾病管理プログラムとしての条件が整っていると考えられる．

日本における現状と今後の課題

日本における慢性心不全の心臓リハビリテーションと薬物療法の兼ね合いに関して，2つの重要な課題がある．第1は，外来心臓リハビリテーション実施施設の少なさである．日本では，平成18年4月以降，慢性心不全が「心大血管リハビリテーション」の対象疾患として承認されており，対象となる慢性心不全の条件として，①LVEF ≦ 40%，②血中BNP ≧ 80 pg/mL，③peak VO_2 ≦ 80%のいずれかを満たすこととされている．また，『慢性心不全治療ガイドライン』において運動療法が推奨されており，保険診療として慢性心不全に対する心臓リハビリテーションを実施する環境は整っている．しかし，

表2 外来心臓リハビリテーションが心不全疾病管理プログラムとして機能するメリット

1) 入院中（退院前）から開始し退院後（外来）まで切れ目のない疾病管理が可能
2) 心不全の管理に加えて，心筋虚血監視・不整脈監視・運動指導・冠危険因子是正まで可能・・・心不全看護師主導の心不全管理プログラムに比べ，より多面的な介入
3) 多職種による心疾患対応チームとしてすでに活動中・・・新規のチーム構築が不要
4) 循環器内科医が関与するプログラムである・・・運営上あるいは緊急時に循環器内科医の協力を得ることが容易
5) 運動療法による心不全病態改善効果（血管内皮機能改善，自律神経機能改善，抗動脈硬化作用，炎症性サイトカイン抑制）が期待できる・・・単なる生活指導プログラムではなく心不全病態への介入プログラムである
6) 日本では慢性心不全の心臓リハビリテーションはすでに保険適応承認済み・・・採算面で安定している

外来心臓リハビリテーション実施施設がいまだきわめて少ない点が大きな問題であり，今後，外来心臓リハビリテーション実施施設の大幅な増加が必要である[33]．

第2の課題は，慢性心不全に対する心臓リハビリテーションの社会的認知度の低さである．これまでの慢性心不全治療において，心臓リハビリテーションは「薬物療法」と対比されて「非薬物療法」として分類され，あたかも両者が対立的あるいは二者択一的関係にあるかのように理解される傾向があった．しかし，上述したとおり，慢性心不全の心臓リハビリテーションは運動療法のみではなく，薬物治療へのアドヒアランス向上や生活指導を含んで心不全の治療・管理全般を最適化する包括的プログラムと理解すべきであり，薬物療法と協調的に活用すべきものである．この点に関して，医療者が患者に対して心臓リハビリテーション参加を積極的に推奨することがきわめて重要であり，今後，患者・家族のみならず医療者への啓発や医学教育カリキュラムへの心臓リハビリテーションの組み込みが必要である[33]．

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Profile

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1976年 京都大学医学部卒業，1980年 国立循環器病センター研究所，1986年 バーモント大学内科心臓部門，1988年 国立循環器病センター研究所 冠循環研究室長，2003年 京都大学医学部 循環器内科臨床教授，2006年 国立循環器病センター 心臓血管内科 部長，2011年 国立循環器病研究センター 循環器病リハビリテーション部 部長（心臓血管内科併任），現在に至る．

ひとくちメモ

急性冠症候群患者における心臓リハビリテーション

後藤葉一

1. 心臓リハビリテーションとは：心臓リハビリテーション（心リハ）とは，心血管疾患患者の身体的・心理的・社会的状態を改善し，基礎にある動脈硬化の進行を抑制し，再発・再入院・死亡を減少させ，快適で活動的な生活を実現することを目指して，医学的評価・運動療法・冠危険因子是正・患者教育およびカウンセリングを行う包括的プログラムを指す．虚血性心疾患に対する外来通院心リハにより，運動耐容能・冠危険因子・QOL・長期予後（総死亡率）の改善が得られることが確立されている[1]．

日・米・欧の診療ガイドラインでは，最近発症の急性冠症候群（ACS）のみならず，冠血行再建（冠動脈バイパス術・冠動脈インターベンション）施行後，安定狭心症，慢性心不全患者に対して外来心リハプログラムへの参加を強く推奨している．現在，わが国では診療報酬制度上，心リハは「心大血管疾患リハビリテーション」と呼称され，継続期間は開始日から150日間とされ（延長可能），施設基準として(I)と(II)がある．

2. 心臓リハビリテーションの時期的区分：ACSに対する心リハは時期的区分として，発症後4～7日までの入院中にCCUや病棟で実施される「急性期心リハ」，それ以後3～6か月間にわたり外来で実施される「回復期心リハ」，3～6か月以降生涯にわたり在宅で自己管理により実施される「維持期心リハ」とに分けられる（図1）．

3. 回復期心臓リハビリテーション：回復期心リハでは，①運動負荷試験による予後リスク評価，②運動処方に基づく積極的な運動療法，③生活習慣改善を含む二次予防教育，④復職・心理カウンセリングなどを体系的に実施する．通常，入院中に回復期心リハプログラムへのエントリーを済ませ，退院後に外来通院心リハを継続する．

4. 運動処方：運動処方とは，対象患者に対して運動療法を安全かつ有効に実施するために指示される運動トレーニングの具体的内容のことであり，①運動の種類，②運動強度，③運動持続時間，④運動の頻度，の4つの要素についての指示を含む．運動処方の決定方法については，ガイドライン[2]を参照されたい．

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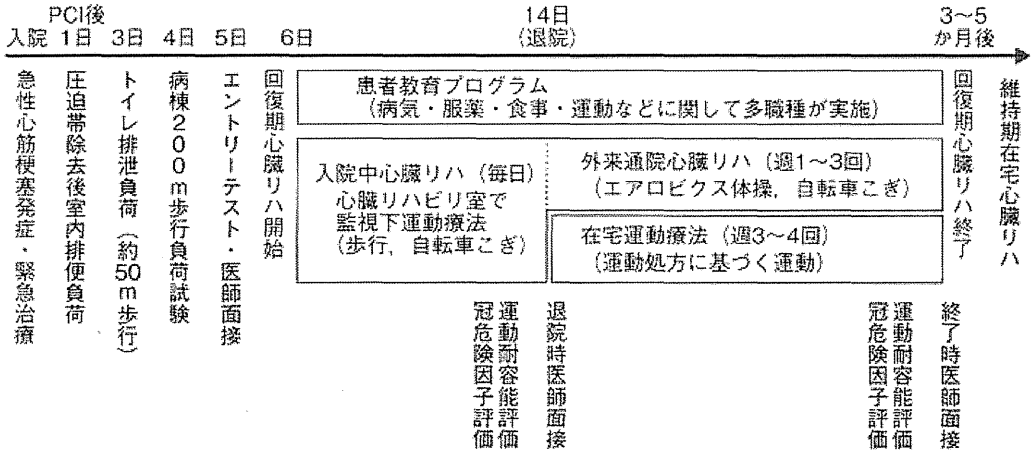

図1　急性心筋梗塞心臓リハビリテーションプログラム（国立循環器病研究センター）

Cardiac rehabilitation for patients with acute coronary syndrome. Yoichi Goto : Department of Cardiovascular Rehabilitation/Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center. 国立循環器病研究センター心臓血管内科・循環器病リハビリテーション部部長

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ORIGINAL ARTICLE
Vascular Medicine

Effect of Intensive Lipid-Lowering Therapy With Rosuvastatin on Progression of Carotid Intima-Media Thickness in Japanese Patients

– Justification for Atherosclerosis Regression Treatment (JART) Study –

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for the Justification for Atherosclerosis Regression Treatment (JART) Investigators

Background: A recent trial in Western countries has shown that rosuvastatin slows progression of carotid intima-media thickness (IMT) in patients with modest carotid IMT thickening and elevated levels of low-density lipoprotein cholesterol (LDL-C). We conducted a prospective, randomized, open-label, blinded-endpoint trial to determine whether rosuvastatin is more effective than pravastatin in slowing progression of carotid IMT in Japanese patients.

Methods and Results: Adult patients with hypercholesterolemia who had a maximum IMT ≥1.1 mm were randomly assigned to receive rosuvastatin or pravastatin. The primary endpoint was the percent change in the mean-IMT, which was measured by a single observer who was blinded to the treatment assignments. The trial was stopped on April 2011 according to the recommendation by the data and safety monitoring committee. A total of 348 patients (173 rosuvastatin; 175 pravastatin) were enrolled and 314 (159 rosuvastatin; 155 pravastatin) were included in the primary analysis. Mean (SD) percentage changes in the mean-IMT at 12 months were 1.91% (10.9) in the rosuvastatin group and 5.8% (12.0) in the pravastatin group, with a difference of −3.89% (11.5) between the groups (P=0.004). At 12 months, 85 patients (59.4%) in the rosuvastatin group achieved a LDL-C/high-density lipoprotein cholesterol ratio ≤1.5 compared with 24 patients (16.4%) in the pravastatin group (P<0.0001).

Conclusions: Rosuvastatin significantly slowed progression of carotid IMT at 12 months compared with pravastatin. (*Circ J* 2012; **76:** 221–229)

Key Words: Carotid intima-media thickness; Dyslipidemia; Randomized controlled trial; Rosuvastatin; Statins

Despite advances in treatment, atherosclerotic vascular disease, such as coronary artery disease (CAD) or ischemic stroke, is a major cause of mortality in Japan. Dyslipidemia is a major risk factor for atherosclerosis, and the results of large-scale clinical trials have shown that lipid-lowering therapy with 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) effectively reduce the risk of cardiovascular events across a wide range of cholesterol levels.[1–5] Under these circumstances, recent guidelines recommend treatment goals for serum cholesterol levels according to the risk

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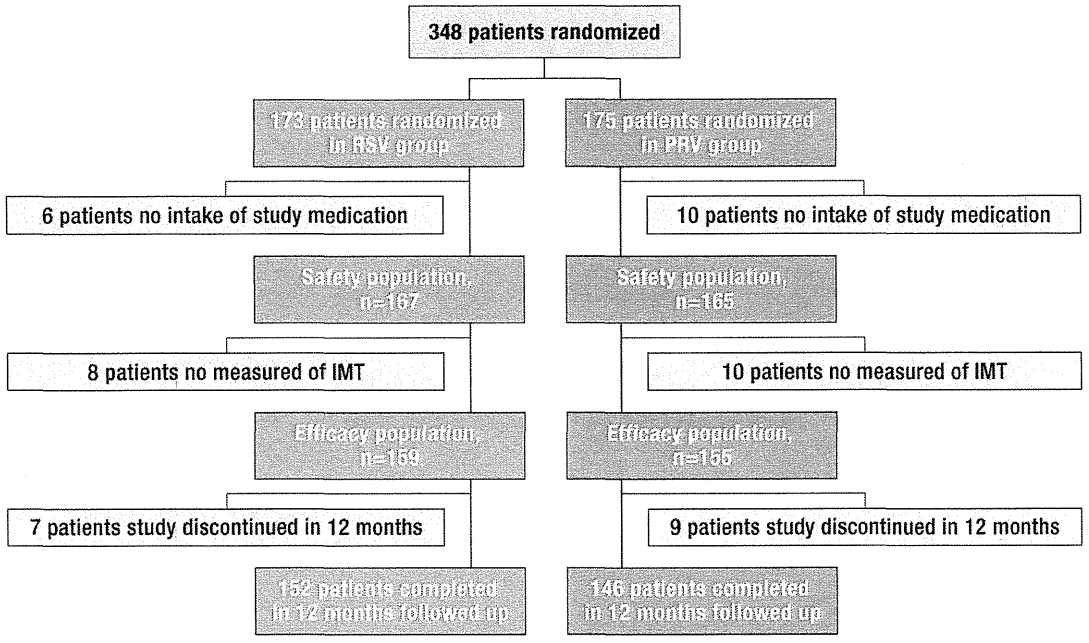

Figure 1. Flow chart of the patients enrolled into the trial. RSV, rosuvastatin; PRV, pravastatin; IMT, intima-media thickness.

category in which an individual patient is classified.[6–9]

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In addition, recent clinical trials and meta-analyses have shown that intensive lipid-lowering therapy with statins slows the progression or induces regression of atherosclerosis.[10–13] These results indicate that progression of coronary plaques can be suppressed by achieving very low levels of low-density lipoprotein cholesterol (LDL-C)[10,11] and that regression of atheroma volume can occur when substantial reduction of LDL-C is accompanied by an increase in high-density lipoprotein cholesterol (HDL-C).[12,13] Although current guidelines recommend aggressive achievement of LDL-C goals in certain high-risk patients, these recent results suggest that aggressive treatment may also be beneficial in relatively low-risk patients.

Carotid artery intima-media thickness (IMT) is a reasonable marker for cardiovascular risk assessment because a decrease in carotid IMT correlates with a decrease in the risk of cardiovascular events.[14,15] In a randomized controlled trial conducted in Western countries, rosuvastatin, one of the strongest statins to date, provided significant reductions in the rate of progression of maximum carotid IMT in middle-aged individuals with modest carotid IMT thickening and elevated LDL-C.[16] However, it remains uncertain whether these results are generalizable to Japanese patients. Recently, an open-label study showed that rosuvastatin resulted in significant regression of coronary plaque volume in Japanese patients,[17] but this finding has not been confirmed in a randomized controlled trial. On the basis of these findings, we conducted a randomized controlled trial to determine whether intensive therapy with rosuvastatin is more effective than conventional therapy with pravastatin in slowing atherosclerotic progression in Japanese patients by measuring carotid IMT. This trial was stopped according to the recommendation by the data and safety monitoring committee. Here, we report the final results.

Methods

Study Design and Ethical Considerations

This multicenter, prospective, randomized, open-label, blinded-endpoint (PROBE) trial was conducted between June 2008 and April 2011 in Japan. The trial was conducted in accordance with the Declaration of Helsinki and the ethical principles for clinical studies in Japan. Its protocol was reviewed and approved by the institutional review board of each participating center. All patients provided written informed consent.

Eligibility Criteria

The rationale and design of the trial have been reported previously.[18] In brief, eligible patients were those with elevated LDL-C (serum level ≥140 mg/dl) aged 20 years or older who had a maximum IMT ≥1.1 mm measured at the carotid artery. Serum LDL-C levels were measured by using direct homogeneous assay. Otherwise, serum LDL-C levels were calculated using Friedewald's formula:[19]

LDL-C=total cholesterol (TC)–HDL-C–(triglyceride [TG]/5)

Patients were excluded if they required lipid-lowering agents other than trial treatments and prespecified ones (ie, anion-exchange resin, probucol, or ethyl icosapentate); had received statin therapy within 1 month of starting the trial; were suspected of having severe carotid artery stenosis (≥80%) or severe calcification; had familial hypercholesterolemia or secondary hypercholesterolemia; had fasting serum TG level ≥400 mg/dl; had a history of hypersensitivity to statins; had uncontrolled hypertension; had type 1 diabetes mellitus (DM) or uncontrolled type 2 DM; experienced myocardial infarction or stroke within past 3 months; had severe congestive heart failure (New York Heart Association class III–IV); had active hepatic disease, renal disorder (serum creatinine level ≥2 mg/dl

Table 1. Baseline Characteristics

	Rosuvastatin (n=159)	Pravastatin (n=155)	P value
Sex, Male	79 (49.7%)	76 (49.0%)	0.908
Age (mean±SD) (years)	63.9±8.9	63.3±9.1	0.521
Elderly (≥65)	83 (52.2%)	73 (47.1%)	0.366
Blood pressure (mean±SD) (mmHg)			
Systolic	132.4±17.0	131.0±18.0	0.483
Diastolic	76.7±11.1	74.9±13.5	0.213
JAS2007 category			0.432
I	2 (1.3%)	1 (0.6%)	
II	52 (32.7%)	59 (38.1%)	
III	79 (49.7%)	72 (46.5%)	
Secondary prevention	26 (16.4%)	23 (14.8%)	
CHD risk factors			
Family history of premature CHD	29 (18.2%)	26 (16.8%)	0.733
Smoking	30 (18.9%)	31 (20.0%)	0.800
eGFR* (mean±SD) ($ml \cdot min^{-1} \cdot 1.73 m^{-2}$)	73.3±15.4	72.8±17.3	0.797
Medical history			
Hypertension	102 (64.2%)	103 (66.5%)	0.669
Diabetes mellitus	70 (44.0%)	68 (43.9%)	0.978
Low HDL-C	11 (6.9%)	15 (9.7%)	0.375
Cerebral infarction	8 (5.0%)	8 (5.2%)	0.958
Cerebral hemorrhage	0 (0%)	0 (0%)	
Arteriosclerosis obliterans	4 (2.5%)	2 (1.3%)	0.428
Coronary disease	26 (16.4%)	23 (14.8%)	0.712
Other medical treatment			
Antihypertensive drug	88 (55.3%)	87 (56.1%)	0.910
Antidiabetic drug	37 (23.3%)	39 (25.2%)	0.792
Aspirin	25 (15.7%)	24 (15.5%)	0.953
LDL-C (mean±SD) (mg/dl)	166.9±23.3	166.1±20.8	0.732
Max-IMT (mean±SD) (mm)	1.66±0.59	1.61±0.52	0.443
HbA_{1c} (mean±SD) (%)**	6.23±0.83	6.27±0.85	0.712

*eGFR=$194 \times Cr^{-1.094} \times age^{-0.287}$ (for men) and $194 \times Cr^{-1.094} \times age^{-0.287} \times 0.739$ (for women). Rosuvastatin group, n=156; pravastatin group, n=154 because of missing measurements.
**We used the National Glycohemoglobin Standardization Program value. Rosuvastatin group, n=152; pravastatin group, n=150 because of missing measurements.
JAS, Japan Atherosclerosis Society; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; IMT, intima-media thickness; HbA_{1c}, hemoglobin A_{1c}.

or creatinine clearance <$30 ml \cdot min^{-1} \cdot 1.73 m^{-2}$), or elevated creatine kinase level (>500 IU/L); were being treated with cyclosporine; were confirmed or suspected of having a malignant tumor; had hypothyroidism, hereditary muscular disease, a familial history of these diseases, or a history of drug-induced muscular disorders; or had a history of drug abuse or alcoholism. Pregnant women, breast-feeding women, or women who were potentially pregnant or wished to become pregnant during the trial were also excluded.

Trial Treatments

Patients were randomly assigned to receive rosuvastatin 5 mg (intensive therapy) or pravastatin 10 mg (conventional therapy) in a 1:1 ratio (step 1). Both trial treatments were planned to be administered once daily orally for 24 months. Treatment allocation was computer-generated by a central randomization facility using a dynamic allocation method with balancing factors of maximum IMT, serum LDL-C level, presence/absence of DM (including impaired glucose tolerance), and center. If eligibility of the patient was confirmed, the investigator contacted the data center through the interactive web response system and was notified of the allocated treatment. Allocation was concealed to the investigators until they contacted the data center.

In the rosuvastatin group, the LDL-C goal was defined as <80 mg/dl for primary prevention and <70 mg/dl for secondary prevention. If the patient did not achieve the LDL-C goal, the daily dose of rosuvastatin was increased to 10 mg (step 2), and prespecified lipid-lowering agents were added thereafter (step 3). In the pravastatin group, the LDL-C goal was defined according to the Japan Atherosclerosis Society (JAS) guideline.[9] In this guideline, the LDL-C goal was defined according to the risk category. In primary prevention, the goal was <160 mg/dl for the low-risk group, <140 mg/dl for the intermediate-risk group, and <120 mg/dl for the high-risk group. For secondary prevention, the goal was <100 mg/dl. If the patient did not achieve these LDL-C goals, the daily dose of pravastatin was increased to 20 mg (step 2), and prespecified lipid-lowering agents were added thereafter (step 3). In both treatment groups, concomitant use of anion-exchange resin, probucol, and ethyl icosapentate was allowed during the trial.

Table 2. Changes in the Primary and Secondary Endpoints

	Rosuvastatin			Pravastatin			Change (mm)		Change (%)	
		Change (mm)	Change (%)		Change (mm)	Change (%)	Difference	P value	Difference	P value
Primary										
Mean-IMT (mm)										
Baseline	0.919±0.223 (157)			0.868±0.194 (153)						
12 months	0.923±0.186 (146)	0.012±0.093 (145)	1.91±10.9 (145)	0.904±0.191 (146)	0.042±0.094 (144)	5.80±12.0 (144)	−0.030±0.094	0.008	−3.89±11.5	0.004
24 months*	0.906±0.169 (67)	−0.003±0.103 (67)	0.44±11.2 (67)	0.916±0.215 (75)	0.045±0.131 (73)	6.43±14.2 (73)	−0.048±0.119	0.019	−5.99±12.9	0.007
Secondary										
Max-IMT (mm)										
Baseline	1.55±0.60 (159)			1.53±0.51 (155)						
12 months	1.51±0.57 (147)	−0.01±0.31 (147)	1.18±20.7 (147)	1.52±0.54 (149)	0.01±0.24 (149)	1.10±17.7 (149)	−0.02±0.27	0.446	0.08±19.3	0.972
24 months*	1.50±0.55 (72)	0.02±0.35 (72)	2.91±24.5 (72)	1.50±0.55 (76)	0.03±0.32 (76)	2.49±22.5 (76)	−0.02±0.34	0.771	0.42±23.5	0.913
IMT-Cmax (mm)										
Baseline	1.34±0.51 (154)			1.29±0.46 (153)						
12 months	1.28±0.42 (143)	−0.02±0.29 (142)	0.74±16.8 (142)	1.30±0.49 (147)	0.02±0.22 (147)	2.54±18.4 (147)	−0.03±0.26	0.304	−1.80±17.6	0.388
24 months*	1.24±0.36 (71)	−0.06±0.40 (70)	−0.65±21.1 (70)	1.30±0.56 (77)	0.08±0.33 (77)	5.90±26.7 (77)	−0.14±0.37	0.028	−6.55±24.2	0.103
IMT-Bmax (mm)										
Baseline	1.62±0.68 (151)			1.61±0.58 (149)						
12 months	1.72±0.68 (137)	0.12±0.42 (135)	10.9±32.3 (135)	1.75±0.63 (145)	0.14±0.42 (144)	12.0±35.8 (144)	−0.02±0.42	0.640	−1.02±34.2	0.804
24 months*	1.81±0.67 (70)	0.25±0.45 (69)	20.7±39.4 (69)	1.67±0.62 (75)	0.13±0.57 (75)	16.0±51.9 (75)	0.12±0.51	0.180	4.74±46.3	0.540
IMT-Imax (mm)										
Baseline	1.26±0.65 (146)			1.18±0.58 (144)						
12 months	1.29±0.72 (134)	0.05±0.48 (133)	8.34±51.5 (133)	1.23±0.57 (141)	0.06±0.31 (139)	10.1±35.7 (139)	−0.01±0.40	0.856	−1.79±44.1	0.738
24 months*	1.41±0.70 (68)	0.20±0.66 (65)	24.0±70.9 (65)	1.21±0.57 (71)	0.11±0.40 (69)	15.2±43.3 (69)	0.08±0.54	0.369	8.83±58.3	0.383

*Data of patients who had completed 24 months follow-up at study discontinuation. Data are mean±SD, ( ) = n. IMT, intima-media thickness.

Outcome Measures

Medical histories were obtained from all patients before enrollment. Laboratory data including serum lipid levels were obtained at baseline. Follow-up visits were scheduled at 1, 2, 4, 6, 12, 18, and 24 months. At each visit, serum levels of lipids (TC, LDL-C, HDL-C, and TG) were measured. Treatment compliance was also investigated at each follow-up visit. Laboratory tests were performed at 1, 4, 6, 12, and 24 months. Laboratory data were analyzed at the central laboratory. Systolic and diastolic blood pressures (SBP/DBP) were measured at 0 (baseline), 12, and 24 months.

Patients were scheduled to undergo ultrasonographic examinations at 0 (within 3 months before enrollment), 12, and 24 months, and B-mode images were obtained according to the guidelines for ultrasonic assessment of carotid artery disease.[20] For the measurement of carotid IMT, 2 longitudinal images were obtained in the 3-cm segment proximal to the tip of the flow divider of the right and left common carotid arteries. The outcome was measured at the far wall of the common carotid artery in which the eligibility criterion of maximum IMT ≥1.1 mm was confirmed. A single observer who was blinded to the treatment assignments measured the mean-IMT in the core laboratory using Intimascope® (Media Cross Co Ltd, Tokyo, Japan).[21] It averaged 60 points of IMT values in the segment 2 cm proximal to the dilation of the carotid bulb. In addition, investigators at each institution measured the max-IMT (maximum IMT at the far wall of the common carotid artery), IMT-Cmax (maximum common carotid artery IMT), IMT-Bmax (maximum carotid bulb IMT), and IMT-Imax (maximum internal carotid artery IMT). The primary endpoint defined in the protocol was the percent change in the mean-IMT from baseline to the end of 24 months.[18] The secondary endpoints included the max-IMT, IMT-Cmax, IMT-Bmax, IMT-Imax, serum lipid levels, and LDL-C/HDL-C ratio. For the safety analysis, we classified adverse events under 3 categories in the protocol. We defined an adverse event as "mild" if the patient had signs or symptoms, but could continue the study with no other treatment, "moderate" if the patient had signs or symptoms, but could continue the study with any treatment and "severe" if the patient could not continue the study.

Statistical Analysis

A sample size of 200 patients in each group was determined to detect a 0.35% difference (SD 1%) in the percent change in the mean-IMT between the rosuvastatin group (assumed to have a percent change of 0.35%) and the pravastatin group (assumed to have a percent change of 0%) with a power of 0.90 and a 2-sided type-I error level of 0.05. These assumptions were obtained from the results of a previous trial.[16]

In the efficacy analysis, the full analysis set (FAS) was defined as the primary analysis set. The FAS included all randomized patients who met major eligibility criteria and received at least one dose of trial treatment and had at least one assessment for carotid IMT according to the guideline.[22] The safety analysis included all patients who received at least one dose of trial treatment and had at least one safety assessment. Between-group comparisons at baseline were performed using the chi-square test. In the primary analysis, the percent change in the mean-IMT was compared between the treatment groups using a t-test. In the secondary analyses, the changes in continuous variables were compared using a t-test and the percentages of categorical variables were compared using Fisher's exact test. All data were analyzed by using SAS® System Release 9.2 (SAS Institute, Cary, NC, USA). All reported P values are 2-sided.

Results

Trial Profile and Patient Population

The trial was stopped on April 2011, according to the recommendation of the safety monitoring committee. The finding of superiority of rosuvastatin led to the decision to terminate the trial. Therefore, we report the analysis of data at 12 months as the final results. **Figure 1** is a flow diagram of the trial. A total of 348 patients (173 rosuvastatin group; 175 pravastatin group) were enrolled into the study. Of these, 332 (167 rosuvastatin group; 165 pravastatin group) were included in the safety analysis and 314 (159 rosuvastatin group; 155 pravastatin group) were included in the FAS.

The demographic and baseline characteristics were well balanced between the treatment groups (**Table 1**). Approximately half of the patients were men. In both treatment groups, nearly half of the patients were classified into category III (primary prevention high-risk group) according to the JAS guideline.[9] In addition, more than 60% of patients had hypertension and nearly half patients had DM (including impaired glucose tolerance). At 12 months, mean (SD) daily dose was 7.7 (2.8) mg for rosuvastatin and 14.5 (5.0) mg for pravastatin.

Carotid IMT

Compared with pravastatin, rosuvastatin significantly slowed progression of the mean-IMT (**Table 2**). Mean (SD) percent change in the mean-IMT at 12 months was 1.91% (10.9%) in the rosuvastatin group and 5.80% (12.0%) in the pravastatin group, with a difference of −3.89% (11.5%) between the treatment groups (P=0.004). Similar results were obtained after adjusting for the mean-IMT at baseline (P=0.021). The mean-IMT was decreased in 65 patients (44.8%) in the rosuvastatin group and in 40 (27.8%) in the pravastatin group at 12 months (P=0.003). Median percent change in the mean-IMT at 12 months was 0.00% in the rosuvastatin group and 3.45% in the pravastatin group at 12 months (**Figure 2**). The mean percent change in IMT-Cmax was also smaller in the rosuvastatin group, but the difference was not statistically significant (**Table 2**). Percent changes in the max-IMT, IMT-Bmax, and IMT-Imax were similar between the treatment groups.

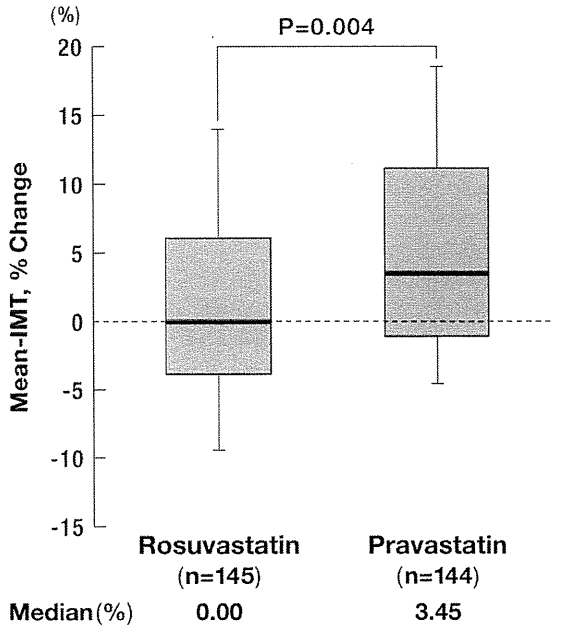

Figure 2. Percent changes in the intima-media thickness (IMT) at 12 months after starting the trial treatment. The box plots give the median levels (middle horizontal line in each box), the interquartile ranges (delineated by the bottom and top of each box: rosuvastatin group, −3.73–6.07%; pravastatin group, −4.61–11.1%), and outliners falling below the 10th percentile (rosuvastatin group, −9.41%; pravastatin group, −4.62%) or above the 90th percentile (rosuvastatin group, 14.00%; pravastatin group, 18.52%) at 12 months, respectively.

As secondary endpoints, we analyzed the correlations between LDL-C/HDL-C and the mean-IMT, and the max-IMT, but neither of them was statistically.

Serum Lipid Levels and Other Parameters

Compared with pravastatin, rosuvastatin significantly lowered mean serum levels of LDL-C, TG, the LDL-C/HDL-C ratio, and nonHDL cholesterol (**Table 3**). The significant reduction in lipid parameters in both groups maximized at 2 months and continued during the study period. Rosuvastatin lowered the LDL-C level by 47.9%; mean (SD) serum level decreased from 163.8 (30.9) mg/dl at baseline to 83.7 (23.9) mg/dl at 12 months.

Both treatments improved lipid management. At 12 months, 145 patients (91.2%) in the rosuvastatin group and 95 (61.3%) in the pravastatin group achieved the LDL-C goal recommended by the JAS guideline. In addition, rosuvastatin significantly improved the LDL-C/HDL-C ratio. At 12 months, 85 patients (59.4%) in the rosuvastatin group and 24 (16.4%) in the pravastatin group achieved LDL-C/HDL-C ≤1.5 (P<0.0001), while 124 (86.7%) and 64 (43.8%) achieved LDL-C/HDL-C ≤2.0, respectively (P<0.0001).

SBP and DBP (SD) were, respectively, 132.4/76.6 (17.0/11.1) mmHg at baseline, 128.9/73.0 (12.7/8.8) mmHg at 12 months and 130.1/75.3 (14.3/10.3) mmHg at 24 months in the rosuvastatin group. Compared with baseline, SBP at 12 and 24 months and DBP at 12 months were significantly lowered (P=0.003, P=0.0002, P=0.016; respectively) in the rosuvastatin group. In the pravastatin group, SBP/DBP (SD) were 131.0/74.9 (18.0/13.5) mmHg at baseline, 128.0/73.1 (13.5/10.3) mmHg

Table 3. Changes in Lipid Parameters

	Rosuvastatin		Pravastatin		Difference	P value
		Change (%)		Change (%)		
LDL-C (mg/dl)						
Baseline	163.8±30.9 (156)		165.1±29.1 (153)			
2 months	86.2±21.8 (150)	−47.0±12.9 (149)	124.7±26.7 (149)	−23.3±14.2 (148)	−23.7±13.6	<0.0001
12 months	83.7±23.9 (143)	−47.9±16.9 (142)	117.4±22.7 (146)	−27.7±13.1 (144)	−20.2±15.1	<0.0001
24 months*	85.8±21.7 (70)	−47.8±15.5 (69)	120.0±20.6 (67)	−26.6±12.4 (67)	−21.2±14.1	<0.0001
HDL-C (mg/dl)						
Baseline	54.2±12.1 (157)		54.8±13.2 (154)			
2 months	57.2±12.6 (151)	6.3±13.6 (151)	57.1±13.4 (149)	5.7±15.5 (149)	0.6±14.6	0.723
12 months	58.5±13.7 (144)	8.7±16.9 (144)	57.8±15.2 (147)	6.9±18.5 (146)	1.9±17.7	0.367
24 months*	56.6±15.9 (70)	7.2±20.7 (70)	59.2±13.7 (68)	5.9±16.9 (68)	1.4±18.9	0.672
TG (mg/dl)						
Baseline	149.6±80.3 (157)		136.1±69.8 (154)			
2 months	124.3±75.2 (151)	−11.2±39.3 (151)	126.7±59.5 (149)	2.5±42.3 (149)	−13.7±40.8	0.004
12 months	118.1±59.0 (144)	−13.6±38.7 (144)	131.7±67.2 (147)	4.5±42.4 (146)	−18.1±40.6	0.0002
24 months*	124.8±66.4 (70)	−13.0±41.6 (70)	123.5±67.8 (68)	7.8±53.7 (68)	−20.8±47.9	0.012
LDL-C/HDL-C ratio						
Baseline	3.1±0.8 (156)		3.2±1.1 (153)			
2 months	1.6±0.6 (150)	−49.5±13.3 (149)	2.3±0.8 (149)	−26.0±18.4 (148)	−23.5±16.0	<0.0001
12 months	1.5±0.6 (143)	−51.1±17.3 (142)	2.2±0.7 (146)	−30.8±16.0 (144)	−20.3±16.6	<0.0001
24 months*	1.6±0.5 (70)	−50.1±14.5 (69)	2.1±0.7 (67)	−29.2±14.7 (67)	−20.8±14.6	<0.0001
NonHDL-C (mg/dl)						
Baseline	193.0±32.2 (157)		191.9±32.1 (154)			
2 months	110.4±25.6 (151)	−42.6±12.2 (151)	150.1±29.0 (149)	−20.8±13.3 (149)	−21.9±12.8	<0.0001
12 months	106.8±25.9 (144)	−44.1±14.2 (144)	143.7±26.1 (147)	−24.0±12.6 (146)	−20.2±13.4	<0.0001
24 months*	110.7±22.2 (70)	−42.8±14.5 (70)	144.0±20.8 (68)	−23.4±12.2 (68)	−19.4±13.4	<0.0001

*Data of patients who had completed 24 months follow-up at study discontinuation.
Data are mean±SD, ( )=n.
LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglycerides.

at 12 months and 128.5/73.0 (13.5/7.7) mmHg at 24 months. There was no significant change during the study period in the pravastatin group. Between the treatment groups, both SBP and DBP showed no significant difference at 12 and 24 months.

Cardiovascular and Cerebrovascular Events as a Secondary Endpoint for the Efficacy Evaluation

At 12 months of treatment, a cardiovascular event occurred in one of the 155 patients in the pravastatin group and a cerebrovascular event occurred in one of the 159 patients in the rosuvastatin group. Event rates were similar between the treatment groups.

Safety

During the follow-up, 1 patient in the pravastatin group died (**Table 4**). The most common adverse event was myalgia (3.59% in the rosuvastatin group, 0% in the pravastatin group). Further, 5 patients (2.99%) in the rosuvastatin group and 1 (0.60%) in the pravastatin group reported arthralgia. Back pain occurred in 2 (1.20%) and 1 patients (0.60%) in the rosuvastatin and pravastatin groups, respectively. The most common laboratory changes were those of liver enzymes. In the rosuvastatin group, 4 patients (2.40%) had elevated alanine aminotransferase and 3 (1.80%) had increased aspartate aminotransferase levels. Regarding HbA_{1c}, there was a change from baseline of +0.12% in the rosuvastatin group and −0.01% in the pravastatin group.

Although "mild" adverse events that needed no treatment were imbalanced between the rosuvastatin (58 events, 34.7%) and pravastatin groups (24 events, 14.5%), there was no clinical meaningful difference in adverse events that needed any treatment ("moderate" plus "severe") between the groups (37 events, 22.2% and 39 events, 23.6%, respectively).

Discussion

Our results have shown that intensive lipid-lowering therapy with rosuvastatin slowed progression of the mean-IMT more effectively than conventional therapy with pravastatin in Japanese patients within a relatively short treatment period. At 12 months, the percent change in the mean-IMT was significantly lower in the rosuvastatin group. The mean-IMT was obtained by averaging 60 points of IMT at the far wall of the common carotid artery using Intimascope®. IMT at the far wall of the common carotid artery is a reliable marker for atherosclerosis,[20] and the computer-automated IMT measurements with higher axial resolution are considered to be more reliable than the manual 3-point method.[21] These factors support the reliability and precision of our results. The data of the max-IMT, IMT-Cmax, IMT-Bmax and IMT-Imax were less objective and reproducible than the data of the mean-IMT, because they were measured in each institution. This may be a reason why significant differences in the percent change between treatment groups were not observed.

This treatment effect on atherosclerotic progression was consistent with reports from recent studies. A prospective cross-sectional study of patients with asymptomatic CAD showed regression of the carotid IMT following 16 weeks of

Table 4. Adverse Events in the Safety Population

	Rosuvastatin (n=167)	Pravastatin (n=165)
Any event	95 (56.9%)	63 (38.2%)
Serious adverse event	18 (10.8%)	18 (10.9%)
Death	0 (0%)	1 (0.60%)
Cardiac		
Myocardial infarction	1 (0.60%)	2 (1.21%)
Coronary stenosis	1 (0.60%)	0 (0%)
Supraventricular tachycardia	1 (0.60%)	0 (0%)
Coronary angioplasty	0 (0%)	3 (1.82%)
Nerve		
Subarachnoid hemorrhage	1 (0.60%)	0 (0%)
Transient ischemic attack	1 (0.60%)	0 (0%)
Lacunar infarct	1 (0.60%)	0 (0%)
Thalamic hemorrhage	0 (0%)	1 (0.60%)
Musculoskeletal		
Myalgia	6 (3.59%)	0 (0%)
Arthralgia	5 (2.99%)	1 (0.60%)
Back pain	2 (1.20%)	1 (0.60%)
Heaviness	2 (1.20%)	0 (0%)
Pain in extremity	1 (0.60%)	0 (0%)
Musculoskeletal stiffness	1 (0.60%)	0 (0%)
Muscular weakness	0 (0%)	1 (0.60%)
Rhabdomyolysis	0 (0%)	1 (0.60%)
Muscle spasms	0 (0%)	1 (0.60%)
Tendinitis	0 (0%)	1 (0.60%)
Dysmyotonia	0 (0%)	1 (0.60%)
Hepatobility		
Liver function abnormality	1 (0.60%)	0 (0%)
Kidney		
Hematuria	1 (0.60%)	0 (0%)
Kidney failure	1 (0.60%)	0 (0%)
Laboratory tests		
Alanine aminotransferase increased	4 (2.40%)	0 (0%)
Aspartate aminotransferase increased	3 (1.80%)	0 (0%)
Creatine phosphokinase increased	4 (2.40%)	2 (1.21%)
Creatine increased	0 (0%)	1 (0.60%)

treatment with rosuvastatin 10 mg/day.[23] In the Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin (METEOR) trial, a 40-mg dose of rosuvastatin significantly slowed progression of the maximum IMT over the 12 carotid artery sites, including the common carotid, carotid bulb, and internal carotid, in middle-aged individuals.[16] In the Coronary Atherosclerosis Study Measuring Effects of Rosuvastatin Using Intravascular Ultrasound in Japanese subjects (COSMOS), a mean daily dose of 16.9 mg rosuvastatin induced regression of coronary plaque volume in patients with stable CAD.[17] We consider this consistency, irrespective of ethnicity, indicates the beneficial effects of intensive therapy on atherosclerosis. Furthermore, in our trial the change in the mean-IMT in the rosuvastatin group, +0.012 mm, was similar to the annual increase of 0.01–0.015 mm in the common carotid artery IMT associated with aging in healthy Japanese.[20] This result suggests that rosuvastatin may halt atherosclerosis progression caused by factors other than aging. Although we could not fully assess the treatment effects at 24 months because of the trial's termination, rosuvastatin may further slow progression of atherosclerosis in the longer term, considering the results of the METEOR trial over 2 years.[16]

This beneficial effect on atherosclerosis seems to be mainly derived from the reduction in LDL-C levels. Japanese studies have reported that rosuvastatin has a strong LDL-C lowering effect and clinical benefit.[24,25] In our trial, rosuvastatin lowered the mean LDL-C level to 83.7 mg/dl at 12 months (mean reduction, 47.9%), with a mean daily dose of 7.7 mg. In the METEOR trial and COSMOS, rosuvastatin also lowered the serum LDL-C level to approximately 80 mg/dl and this lipid-lowering effect led to slowing of progression or induction of regression of atherosclerosis.[16,17] Another Japanese study has also shown that the incidence of cardiovascular events increased when LDL-C levels were >80 mg/dl.[26] Although the current JAS guideline recommends lowering the LDL-C level to 100–160 mg/dl according to the risk category of the patient,[9] the findings indicate that intensive therapy to lower LDL-C to 80 mg/dl is beneficial in Japanese patients as well as Westerners. Though HbA_{1c} increased 0.12% at 12 months from baseline in the rosuvastatin group (P=0.003) in this study, considering the total balance between benefit and safety, our results suggest that intensive lipid-lowering therapy with rosuvastatin is effective.

With regard to atherosclerosis regression, the serum HDL-

C level plays an important role. In a meta-analysis that combined raw data from 4 randomized trials, reduction of LDL-C to <87.5 mg/dl provided coronary atherosclerotic regression when accompanied by an approximately 7.5% increase in HDL-C.[13] In that meta-analysis, the relationship between the change in percent atheroma volume and the LDL-C/HDL-C ratio was calculated, and the result was that the LDL-C/HDL-C ratio should be managed to <1.5 to decrease atheroma volume. In our trial, more than half of the patients achieved LDL-C/HDL-C ≤1.5 with the use of rosuvastatin. Although further study with a longer term is needed, our results indicate the favorable effect of rosuvastatin on the LDL-C/HDL-C ratio.

Carotid IMT is associated with future risk of atherosclerotic vascular events.[15] The Atherosclerosis Risk in Communities (ARIC) study has shown that for every 0.19-mm increment in carotid IMT, risk of death or myocardial infarction increased by 36% in middle-aged patients.[27] In another study, patients with a mean-IMT >1.15 mm had a 94% likelihood of CAD.[28] This predictive value of the carotid IMT has not yet been confirmed in Japanese patients, who have cardiovascular events less frequently than those in Western countries. However, even low-risk patients may benefit from intensive therapy. For example, the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial included healthy persons without hyperlipidemia but with elevated levels of high-sensitivity C-reactive protein, and revealed that rosuvastatin significantly reduced the incidence of major cardiovascular events.[29] That result suggests the possibility that favorable treatment effects may lead to a reduction in atherosclerotic events even in low-risk patients.

Study Limitations

Some limitations should be mentioned. First, we adopted the PROBE design, which might have induced bias in the assessment of the outcomes. Although the mean-IMT, the primary endpoint, was measured by a single observer who was blinded to the treatment assignments, the secondary endpoints were measured by investigators who were aware of the allocated treatments. Thus, open-label treatments might affect the investigators' measurements. Second, we could not fully acquire data at 24 months because of early termination of the trial. Third, early termination also led to a reduction in statistical power to detect treatment effects on the secondary endpoints. Treatment effects of longer term treatment, including secondary endpoints, should be assessed in a future clinical trial.

Conclusions

Intensive lipid-lowering therapy with rosuvastatin slows progression of the mean-IMT within 12 months. To our knowledge, this is the first randomized controlled trial in Japan to assess the effects of lipid-lowering therapy on carotid IMT, and we have found that Japanese patients benefit from intensive therapy as well as those in Western countries. In addition, intensive therapy may reduce the risk of atherosclerotic vascular events. Further study is warranted to confirm the effects of rosuvastatin in the longer term. Currently, we are conducting an extension study and the results will be reported in the near future.

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Appendix

The following people participated in this trial.
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Intensive Lipid-Lowering Therapy for Slowing Progression as Well as Inducing Regression of Atherosclerosis in Japanese Patients

Subanalysis of the JART Study

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SUMMARY

This paper describes a subanalysis of the JART Study comparing rosuvastatin and pravastatin treatment. A total of 314 subjects were analyzed in this subanalysis, 282 of whom were eligible for evaluation of the relationship between LDL-C and carotid mean-IMT change. In the subanalysis, we evaluated the extent to which intensive lipid-lowering therapy slowed the mean-IMT progression by a correlation analysis between LDL-C and mean-IMT change after 12 months of statin treatment. Nearly half were male (49.4%) and elderly (49.7%). The majority (84.4%) were treated for primary prevention. Patients with hypertension and diabetes mellitus accounted for 65.3% and 44.0%, respectively. At the 12-month measurement point, mean-IMT change was correlated with LDL-C (R = 0.187; P = 0.0016), LDL-C/HDL-C ratio (R = 0.152; P = 0.0105), and non-HDL-C (R = 0.132; P = 0.0259). Mean-IMT after 12 months was divided into 4 subgroups by LDL-C at 12 months; < 80, ≥ 80 to < 100, ≥ 100 to < 120, and ≥ 120 mg/dL. A trend analysis using the Jonckheere–Terpstra test showed statistical significance (P = 0.0002). Even for prevention in Japanese patients who have lower risk of atherosclerotic disease than Western patients, lowering the LDL-C level to below the therapeutic target prevented mean-IMT progression after 12 months more strongly. These findings suggest that more intensive control of LDL-C to levels lower than those in current JAS guidelines should be required to achieve slowing of progression as well as induction of regression of atherosclerosis. (Int Heart J 2013; 54: 33-39)

Key words: Carotid intima-media thickness, LDL-cholesterol, Dyslipidemia, JART Study, Regression analysis, Prognostic factor, Factor analysis

In the preceding Justification for Atherosclerosis Regression Treatment (JART) Study,[1] the effect of intensive lipid-lowering therapy using statin medications on the change in the carotid intima-media thickness (IMT) was evaluated in Japanese patients with hyper-low-density lipoprotein-cholesterol (LDL-C) who had a maximum IMT of ≥ 1.1 mm measured by carotid artery ultrasound. As a result, statin treatment for dyslipidemia indicated a benefit with respect to the reduction or prevention of the progression of atherosclerosis even in Japanese patients. This paper describes a subanalysis of the JART Study and proposes a quantitative therapeutic target for positive LDL-C control to reduce or prevent the progression of atherosclerosis and prevent the subsequent development of cardiovascular events.

It is well understood that the progression of atherosclerosis is associated with increased risks such as occurrence of stroke,[2] coronary heart disease (CHD),[3,4] and peripheral arterial disease (PAD).[5] It was also reported that the progression of atherosclerosis affects the long-term prognosis.[6] The progression of atherosclerosis is caused by multiple factors, and LDL-C is well known to be one of the key factors. The results of recent clinical trials and meta-analyses have indicated that the progression of atherosclerotic plaques can be suppressed by achieving very low levels of LDL-C.[7-9]

In Japan, the Japan Atherosclerosis Society guideline (JASGL)2007[10] criteria are generally used as the target levels

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for LDL-C control for both primary prevention (LDL-C of < 160 mg/dL for low risk, < 140 mg/dL for middle risk, and < 120 mg/dL for high risk) and secondary prevention (LDL-C of < 100 mg/dL). In the United States, the National Cholesterol Education Program Expert Panel on Detection, Education, and Treatment of High Blood Cholesterol in Adults (NCEP ATP) III[11] suggests a therapeutic target for LDL-C of < 100 mg/dL for high-risk patients, while the revised NCEP ATP III indicates a therapeutic target for LDL-C of < 70 mg/dL for ultra-high-risk patients.[12] However, these criteria were epidemiologically based on directory comparisons between LDL-C levels and clinical events such as stroke, CHD, or PAD.

Atherosclerosis is considered to show systemic progression, and therefore the carotid IMT can be an index for estimating the degree of systemic atherosclerosis. However, there are few available reports evaluating the relationship between the therapeutic target for LDL-C and the progression of atherosclerosis. In particular, there have been few studies in Japanese patients with hypercholesterolemia whose risk of atherosclerotic disease may be lower than that of western patients. Therefore, in this subanalysis, the quantitative relationship between LDL-C and carotid mean-IMT change was evaluated in Japanese patients with hyper-LDL-C who had an IMT of ≥ 1.1 mm measured by carotid artery ultrasound and had been treated with statins for ≥ 1 year.

Methods

Purpose of the subanalysis: As this report describes the results of a subanalysis of the JART Study, representing a multicenter, randomized, open-label, blinded endpoint (PROBE) trial comparing rosuvastatin and pravastatin groups, the details of the trial design and medication regimen have been released.[1] The purpose of this subanalysis was to determine the relationship between LDL-C and carotid mean-IMT change, and therefore the rosuvastatin and pravastatin treatment groups in the JART Study were merged into a single group of statin treatment. The LDL-C level was calculated using Friedewald's formula[13] as follows: LDL-C = total cholesterol (TC) – high-density lipoprotein-cholesterol (HDL-C) – (triglyceride (TG)/5).

Measurement of carotid IMT: Patients were scheduled to undergo ultrasonographic examinations at 0 (within 3 months before enrolment), 12, and 24 months, and B-mode images were obtained according to the guidelines for ultrasonic assessment of carotid artery disease.[14] However, the JART Study was terminated prematurely according to a recommendation by the data and safety monitoring committee. Therefore, the main comparison focused on 0 (baseline) and 12 months, because data at 24 months were only available in half of the subjects.

For measurement of the carotid IMT, two longitudinal images were obtained in the 3-cm segment proximal to the tip of the flow divider of the right and left common carotid arteries. The outcome was measured at the far wall of the common carotid artery, in which the eligibility criterion of a maximum IMT of ≥ 1.1 mm was confirmed. A single observer who was blinded to the treatment assignments measured the mean IMT in the core laboratory using an Intimascope® (Media Cross Co. Ltd., Tokyo).[15] The device averaged 60 points of IMT values in the segment 2 cm proximal to the dilation of the carotid bulb.

Subjects analyzed: The subjects who were eligible for evaluation of the relationship between LDL-C and carotid mean-IMT change were selected from the JART Study population of 348 patients who had a maximum IMT of ≥ 1.1 mm measured by carotid artery ultrasound and had been treated with statins for ≥ 1 year. Since the JART Study was terminated prematurely, measurement data up to 12 months instead of 24 months were analyzed.

The baseline characteristics of the analyzed subjects, including demographic data, JASGL2007 category, medical history, and others were calculated and summarized as the mean ± SD for continuous data and the frequency (percentage) for discrete data. Key parameters including lipids, HbA1c, and carotid mean-IMT at baseline and 12 months were summarized as the mean ± SD.

Correlation analyses for mean-IMT: First, simple correlation analyses were performed for mean-IMT change at 12 months and each variable, namely TC, LDL-C, HDL-C, TG, LDL-C/HDL-C ratio, non-HDL-C, HbA1c, systolic blood pressure (SBP), and diastolic blood pressure (DBP) at baseline and 12 months as well as the percentage changes after 12 months. The relationships were summarized as the coefficient of correlation (R) and standardized coefficient of correlation (standardized R), and statistical analyses of the R values against the null hypothesis of $R = 0$ were performed using a significance level of $\alpha = 0.05$. Finally, the carotid mean-IMT change after 12 months was classified into 4 subgroups by the LDL-C at 12 months, as < 80, ≥ 80 to < 100, ≥ 100 to < 120, and ≥ 120 mg/dL, in consideration of the JASGL2007 and NCEP ATP III categories. Although < 70 mg/dL is the lowest criterion recommended in the NCEP ATP III categories, < 80 mg/dL, which was in the vicinity of the boundary point in the first quarter, was selected as an alternative to balance the number of subjects in the subgroups because very few subjects met the < 70 mg/dL criterion. The data for the carotid mean-IMT after 12 months were also divided into 4 subgroups (quartiles) by the corresponding LDL-C absolute change from baseline as < –85, ≥ –85 to < –60, ≥ –60 to < –45, and ≥ –45 mg/dL.

The fundamental statistics for the mean-IMT change in each subgroup were calculated and a graph was prepared using a box-and-whisker plot. In addition, to evaluate the trend in the mean-IMT by categories, the Jonckheere–Terpstra test was performed using a significance level of $\alpha = 0.05$.

Safety analyses for subgroups: The safety analysis included all patients who received at least one dose of trial treatment and had at least one safety assessment. To determine any differences in the safety profiles among the subgroups, the frequencies of adverse drug reactions (ADRs) were summarized by the classification of the LDL-C level. The ADRs were classified by preferred term (PT) and system organ class (SOC) of Medical Dictionary for Regulatory Activities (MedDRA). The comparisons among the subgroups were conducted visually, but not statistically.

Results

A total of 314 subjects were analyzed in this subanalysis, 282 of whom were eligible for evaluation of the relationship between LDL-C and carotid mean-IMT change. The safety population included 289 subjects who were evaluated for the