CLINICAL RESEARCH

50%超速効型混合型インスリン1日2回投与法は食後血糖管理，血糖日内変動の安定化に有用である

～30%製剤，25%製剤からの変更による検討～

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■ はじめに

食後高血糖は大血管障害の独立した危険因子であり[1,2]，HbA1c，食前血糖に加えて食後血糖も管理することの重要性が明らかになってきた．HbA1c，食前血糖，食後血糖のすべてを改善するためには，食後血糖の上昇を抑え，血糖の日内変動を安定化することが必要である．

その目的のためには，インスリンのbasal-bolus療法は食前，食後の血糖を改善させてHbA1cを低下させる有用な治療法である[3]．しかし一方で，内因性インスリン分泌が比較的保たれている場合では，昼の注射が困難，高齢などの理由より注射回数が少ない簡便なインスリン療法が求められるケースも少なくない．

インスリンリスプロ混合製剤－50（以下，Mix 50）は，現在わが国で使用可能な混合型インスリンアナログ製剤のなかでは最も超速効型成分の割合が高く，ほかのインスリン製剤に比べて強力な食後高血糖抑制効果が期待される．

今回，われわれは入院中に30%製剤あるいは25%製剤の1日2回注射からMix 50の1日2回注射に変更し，血糖日内変動，食後血糖増加量の変化を検討したので報告する．

表　患者背景

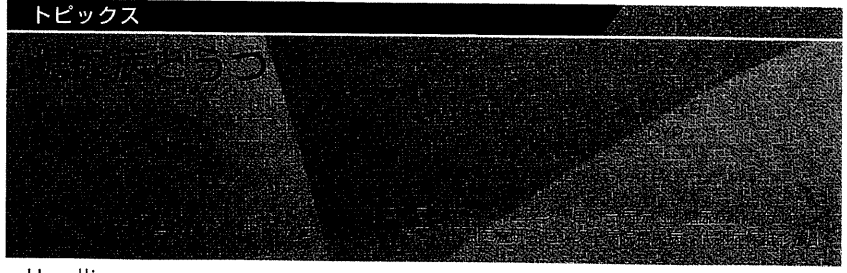
性別（男性/女性）	7/6
年齢（歳）	64.0 ± 12.4
糖尿病罹病期間（年）	14.3 ± 6.3
BMI（kg/m^2）	23.1 ± 3.1
HbA1c（%）	9.4 ± 1.2

■ 対象と方法

対象は天理よろづ相談所病院内分泌内科通院中で，30%製剤あるいは25%製剤の1日2回注射を行っても血糖コントロール不良（HbA1c≧7.4%）である2型糖尿病患者13例である．患者背景を表に示す．入院中これらの患者から同意を得た後，Mix 50の1日2回注射法に変更した．変更前のインスリンは，4名がインスリンアスパルト30%混合製剤（30 Mix），8名が速効型ヒトインスリン30%混合製剤，1名がインスリンリス

本論文でのHbA1cは，特に断りのないかぎり本文・図表ともに従来のHbA1c（JDS値）に0.4%を加えたHbA1c（国際標準値）で表記した（糖尿病，53：450～467，2010）

トピックス



Headline

1. 糖尿病患者のうつ病有病率は一般人口より約2倍高く，うつ病が先行した場合は糖尿病発症リスクが60%，糖尿病が先行した場合はうつ病発症リスクが15%それぞれ上昇する．
2. うつ病患者で糖尿病発症リスクが上昇する原因として，うつ病に特徴的な生理学的要因と療養行動上の要因に加えて抗うつ薬が影響している可能性がある．
3. 糖尿病患者がうつ病を併発しやすい原因には，糖尿病と診断されたり治療を受けていることの心理的・社会的負担が重要な影響を及ぼしている可能性が示唆されている．
4. うつ病併存糖尿病群はうつ病を併存しない糖尿病群と比較して，全死亡，心血管疾患死ともに有意に上昇する．
5. 選択的セロトニン再取込み阻害薬（SSRI）にはCYP450アイソザイム阻害作用を有しているものが多く，CYPの代謝基質である経口血糖降下薬や脂質代謝改善薬を投与する場合には副作用発現頻度上昇に注意が必要である．

精神疾患，なかでもうつ病が様々な身体疾患と併存しやすく，患者の健康寿命を障害する要因になっている可能性が高いという研究結果が，精神科や内科，外科その他のいわゆる身体科領域の別なく注目を集めつつある．その背景として近年のうつ病患者数の増加と，社会や医療経済に対する影響の増大があげられる．

WHOは2004年に障害調整生存年数（disability adjusted life years；DALYs）に基づく疾病負担を報告している[1]が，これによると高所得国においては既に2004年の時点で単極性うつ病が疾病負担の主要原因の第1位であり，さらに2030年には全世界で1位になると予測している．日本においても2000年に報告された「健康日本21」によると，簡易DALYsを用いた疾病負担で「うつ」が2位（9.8%）であり，疾病の分類方法が異なるため単純には比較できないもののWHOの報告に矛盾しない結果であった．わが国における気分障害の患者数は厚生労働省の報告[2]によると，1996年に43.3万人であった総患者数が12年後の2008年には104.1万人と，約2.4倍に増加しており，なかでもうつ病患者数は20.7万人から70.4万人と近年著しく増加していることが報告されている．また平成18（2005）年度厚生労働科学研究では国際疾病分類第10版（international classification of diseases 10th revision；ICD-10）による日本人のうつ病の生涯有病率は6.6%，12か月有病率は2.1%であったと報告しており，これは言い換えると過去1年間に約50人に1人がうつ病に罹患し，約15人に1人が一生に1回はうつ病に罹患することを示している．

このようにうつ病は有病率の高い疾患であるが，糖尿病もまた有病率が高いことからう

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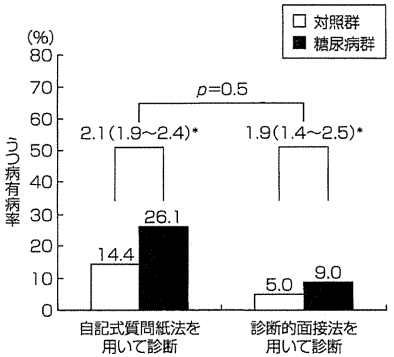

図1　糖尿病患者におけるうつ病有病率：横断研究のメタ解析
＊オッズ比（95%CI）
（文献3）より改変）

つ病併存症例を診療する機会は少なくないが，糖尿病患者のうつ病併存率は一般人口のうつ病有病率と比較して高いことが報告されており，両疾患の併存率の高さは各疾患の有病率の高さのみによるものではないと考えられている．

うつ病併存糖尿病症例は，良好な血糖コントロールの維持が困難なことに加えて肥満，高血圧症や脂質異常症といった他の慢性疾患を合併しやすいとされている．その結果，糖尿病合併症が進展しやすく健康寿命が短縮すること，糖尿病関連医療費が増大することなど様々に患者負担が増大する可能性が高いという臨床上の問題を有している．さらに新しい抗精神病薬，抗うつ薬が使用されるのに伴い，第二世代抗精神病薬に代表される精神科領域の薬剤と肥満・代謝異常との関連や，生活習慣病治療薬との相互作用など，糖尿病診療医が認識しておくべきポイントは増えてきている．

本稿では糖尿病とうつ病の併存に関する疫学的知見を紹介したのち，両疾患が併存しやすい背景について概説し，うつ病併存糖尿病患者を診察するうえでの臨床的な注意点について検討していきたい．

はじめに横断研究の結果を紹介する．42の文献を抽出して行われたメタ解析の結果によると，糖尿病患者におけるうつ病の点有病率は，診断的面接法を用いて診断した場合，9～11%（自記式質問紙法では26～31%）と，糖尿病のない集団と比較して約2倍高くなることが報告されている（**図1**）[3]．この結果は1型・2型糖尿病の別や性別にかかわらず有意である．特に糖尿病合併症を有する患者群は合併症のない群と比較し，どの合併症を合併している場合でも有意にうつ病の有病率が高くなり（$z=2.59$，$p=0.004$），とりわけ神経障害と性機能障害は相関係数が高いこと，合併症の数や重篤度が増すほどうつ病の有病率が増加すること（$z=1.67$，$p=0.05$）が報告されている（**図2**）[4]．

前向き縦断研究のメタ解析では，うつ病併存糖尿病患者における，糖尿病とうつ病発症の時系列が検討されている．うつ病が先行した場合の糖尿病発症リスクを検討した13の前向き縦断研究（経過中の糖尿病発症：計6,916例）と，糖尿病が先行した場合のうつ病発症リスクを検討した7の前向き縦断研究（経過中のうつ病発症：計6,414例）についてそれぞれメタ解析を行ったところ，前者の糖尿病発症のリスク比は1.60（95%CI:1.37～1.88），後者のうつ病発症のリスク比は1.15（95%CI:1.02～1.30）で，いずれも有意に上昇していた（**図3**）[5]．この結果から，特にうつ病患者に対する糖尿病のスクリーニングの重要性は明らかであるが，反対に糖尿病患者でうつ病の発症リスクが15%上昇するという結果も，糖尿病患者総数の多さを考えると決して看過できない数字であると考えられる．

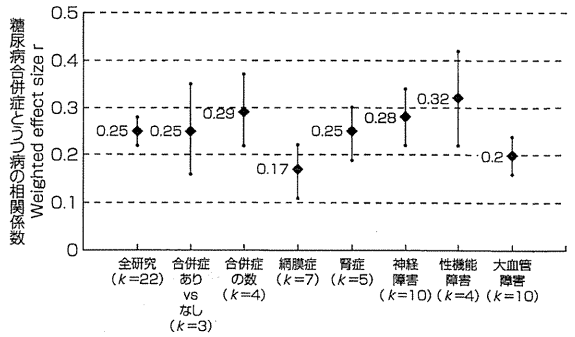

図2　糖尿病合併症とうつ病
図中の数字は相関係数，線は95%信頼区間，k は研究数
（文献4）より改変）

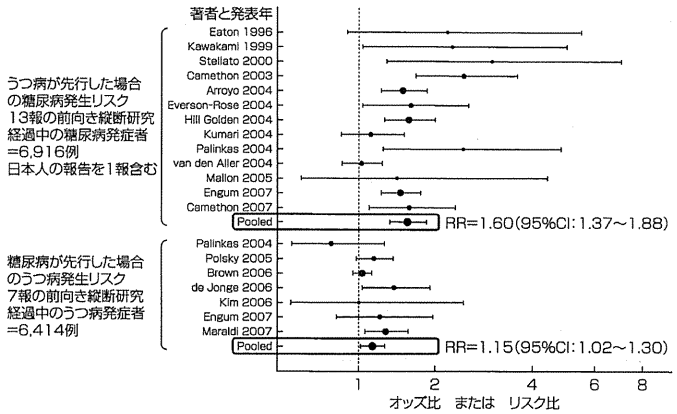

図3　糖尿病患者におけるうつ病有病率：縦断研究のメタ解析
（文献5）より改変）

うつ病患者で糖尿病発症リスクが上昇する機序として，うつ病に特徴的な生理学的要因と療養行動上の要因に加えて抗うつ薬の影響が想定されている．生理学的要因としては①視床下部-下垂体-副腎皮質（hypothalamus-pituitary-adrenal;HPA）系の亢進，②自律神経系の変化（交感神経系の活動が亢進し副交感神経系の活動が低下），③炎症性サイトカイン（interleukin〈IL〉-2，IL-6，tumor necrosis factor〈TNF〉-α など）の増加，④睡眠障害によるインスリン感受性の低下，摂食調節ホルモンの異常（レプチンは減少，グレリンは増加）による過食，⑤セロトニン合成の律速酵素であるトリプトファン水酸化酵素2の遺伝子多型があげられ，療養行動上の要因には⑥食行動の変化（高カロリー食の摂取や過食，食事

時間の不規則さ）と⑦精神運動制止症状（気力・活力の減退，疲労感の増大，活動性の減少）に伴う体重の増加があげられる．上述したうつ病患者の特徴はいずれもインスリン抵抗性を増大させたりインスリン分泌反応を低下させる方向に作用し，うつ病の病態そのものが糖尿病発症のリスク因子になっていると考えられる．

抗うつ薬が糖尿病発症の独立したリスク因子であるかどうかについてはいまだ結論が得られていない．2010年に報告された前向きコホート内症例対象研究[6]において，「重篤なうつ病に罹患しており，かつ抗うつ薬を使用している」症例は「重篤なうつ病に罹患しており，かつ抗うつ薬を使用していない」症例と比較し，糖尿病発症のオッズ比が有意に上昇した（2.61，95%CI:1.25～5.49）と報告されているが，対象症例の精神科診断名や薬剤使用歴などの背景因子が明示されておらず交絡因子が除外されていない．同じく2010年に報告されたDiabetes Prevention Program（DPP）/DPP Outcomes Study（DPPOS）の結果[7]においてもリクルート時の空腹時血糖値，調査期間中の体重変化量などの背景因子をマッチングした場合に，継続的な抗うつ薬の使用は糖尿病発症リスクの上昇と相関していると報告しているが，うつ病の病態そのものが糖尿病発症のリスク因子であることを考えると，抗うつ薬が代謝に及ぼす影響を純粋に評価しているとは言えず，この問題が一定の決着をみるにはさらなる研究成果を待たなくてはならない．

ただし体重増加をきたしやすい抗うつ薬があるのは確かで，ヒスタミン1（H1）受容体遮断作用とセロトニン2C（5-HT2c）受容体遮断作用がともに強い薬剤がそれに相当し，視床下部における食欲亢進作用が一部寄与していると想定されている．具体的には三環系抗うつ薬のアミトリプチリン（トリプタノール®），イミプラミン（トフラニール®），クロミプラミン（アナフラニール®），四環系抗うつ薬のミアンセリン（テトラミド®），マプロチリン（ルジオミール®），その他の抗うつ薬であるトラゾドン（レスリン®，デジレル®），ノルアドレナリン作動性・特異的セロトニン作動性抗うつ薬（noradrenergic and specific serotonergic antidepressant;NaSSA）のミルタザピン（リフレックス®，レメロン®）などの服用に伴う体重増加が知られている．また臨床的には，三環系や四環系抗うつ薬の副作用である抗コリン作用によって口渇をきたすと，炭酸飲料水などの多飲を招きやすいことにも留意が必要である．

仮に糖尿病治療中に大うつ病性障害の合併が疑われ，抗うつ薬の投与を検討する必要が生じた場合には代謝への影響が少ないとされる選択的セロトニン再取込み阻害薬（selective serotonin reuptake inhibitor;SSRI）やセロトニン・ノルエピネフリン再取込み阻害薬（serotonin norepinephrine reuptake inhibitor;SNRI）を第一選択薬とするのが安全であろう．SSRIやSNRIは投与初期に嘔気や食欲不振が出現する頻度が高いため，スルホニル尿素（sulfonylurea;SU）薬やグリニドなど低血糖を起こす可能性がある経口血糖降下薬を服用中の患者に投与する際には，食事摂取量が低下した場合の対応について十分に説明しておく必要がある．また精神科薬剤のなかには肝代謝酵素である各種シトクロムP450（cytochrome P450;CYP）の阻害作用を有するものがあり，薬剤の血中濃度を上昇させ副作用の発生頻度を高める可能性があるため併用薬の選択には注意が必要だが，詳細については後述する．

次に糖尿病患者でうつ病発症リスクが上昇する背景について検討していきたい．上述したうつ病に特徴的な生理学的要因のうち，①HPA系の亢進，③炎症性サイトカインの増加，④睡眠障害，は一部の糖尿病やメタボリックシンドロームの患者でも認められることが報告されている．つまり糖尿病とうつ病は共通する生理学的背景を有するがために，双方向性に両疾患の発症リスクが高まる可能性がある．加えて，糖尿病と診断されたり治療を受けたりしていることの心理的・社会的負担がうつ病発症に重要な影響を及ぼしている可能性を示唆する疫学知見が得られつつある．おもにpopulation-based studyからなる13研究をもとに行われたメタ解析によると，「正常耐糖能の群」と比較して「耐糖能異常のある群」と「診断されていない糖尿病群」ではうつ病発症のオッズ比に有意差を認めなかったが，「すでに糖尿病と診断されている群」のみは「耐糖能異常の群」や「診断されていない糖尿病群」と比較して有意にうつ病発症リスクが上昇していた（**図4**）[8]．この「すでに糖尿病と診断されている群」には糖尿病合併症を併発している症例も含まれている可能性があるが，少なくとも耐糖能異常患者で生じている生理学的変化のみではうつ病発症リスクは上昇しないというのである．糖尿病合併症の発症・進展は，患者にとって身体機能の一部を失うという強い喪失体験であるとともに，「治療に失敗した」という後悔と罪悪感を惹起させる体験であり，うつ病発症リスクの上昇と強い相関があることは先述したとおりであるが，それ以外にも糖尿病と診断を受けること，ライフスタイルの変更を余儀なくされること，薬物治療が開始されること（特にインスリン導入）や家族や周囲の人の協力が得られていないと感じることなどもまた，心理的苦痛の原因となる可能性があることを糖尿病診療医は見落としてはならない．日本糖尿病学会では，糖尿病診療上特に精神医学的配慮をすべき状況をあげて診療医への注意を喚起している（**表1**）[9]．

糖尿病診療における抑うつ症状のスクリーニング方法としてJoslin Diabetes Center and

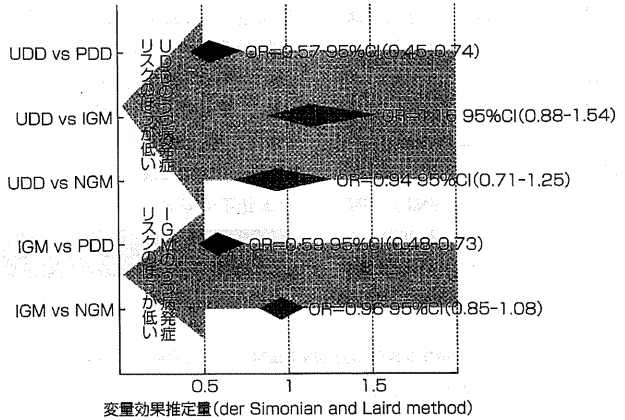

図4　耐糖能異常の有無と糖尿病診断の前後におけるうつ病発症リスク：EDID Research Consortium（文献8）より改変）

NGM:normal glucose tolerance（正常耐糖能），IGM:impaired glucose tolerance（耐糖能異常），UDD:undiagnosed diabetes（未診断の糖尿病），PDD:previously diagnosed diabetes（診断済の糖尿病）．

表1　糖尿病治療上，特に精神医学的配慮が必要な状況

1．糖尿病と診断されたとき
2．治療法が強化されたとき（特にインスリン治療開始時）
3．血糖コントロールが極めて不良，または不安定なとき
4．重症合併症を発症したとき
5．精神科疾患の合併

（文献9）より改変）

Joslin Diabetes clinic Guideline for Adults with Diabetes（2010）ではThe 9-items Patients Health Questionnaire（PHQ-9）やPHQ-2を，糖尿病「燃え尽き症候群」が疑われたり治療へのアドヒアランスが低下したりしているときにはProblem Areas in Diabetes Survey（PAID）の使用を推奨している．自記式うつ病評定尺度としてはPHQ以外にもBeck Depression Inventory（BDI），Self depression Scale（SDS），Center of Epidemiological Studies Depression Scale（CES-D）があり，日本語版の信頼性・妥当性が評価されている．いずれも約2～5分の所要時間で対象患者自身による記載が可能なうえに，感度・特異度ともに十分評価されている．なおPHQ-9は「こころとからだの質問票」[10]のサイトで公開されているので参考にされたい．

うつ病併存糖尿病患者の治療

うつ病併存糖尿病患者の臨床上の問題点は，上述した抑うつ状態に特徴的な生理学的要因と療養行動上の要因に加えて，糖尿病の療養に必要なセルフケア行動や服薬・予約日時の順守といった治療行動へのアドヒアランスが低下するために良好な血糖コントロールを維持することが困難な場合が多いこと，肥満，高血圧や脂質異常症といった他の慢性疾患の合併率が上昇することが促進要因となって，古典的糖尿病合併症や心血管疾患が進展しやすくなることにある．リクルート時の糖尿病の有無，うつ病併存の有無によって4群に分け平均8年間追跡調査した（8万3,624人/年）アメリカの研究によると[11]，年齢・性別などの背景因子の影響を調整した分析の結果，「糖尿病で，かつ抑うつ症状が認められる群」は「糖尿病で抑うつ症状が認められない群」と比較して全死亡，心血管疾患死ともに有意に上昇していた（**図5**）．

これに対し，うつ病併存糖尿病患者において，精神症状の改善と身体医学的予後の改善の両方にアプローチした治療法の効果が検討され，2009年までに11のRCTが報告されている[12]．治療法は大別して①抗うつ薬治療（4RCT，$n=289$），②心理学的治療（3RCT，$n=140$），③薬物療法と心理学的治療の併用療法（4RCT，$n=954$）の3カテゴリーに分類されている．うち，抑うつ症状とHbA1cの両方に改善傾向を認めたのは，①SSRIのフルボキサミンを8週間投与した研究と，②糖尿病教育に加えて認知行動療法（cognitive behavior therapy;CBT）もしくは社会的支援を主体とする集団カウンセリングを行った研究の3報であり，特にCBTの効果については今後非常に期待されているところである．残念ながら現在の日本では，うつ病併存糖尿病患者に対し血糖コントロールの改善をも含めて治療目標値に設定し，手厚い心理学的支援を行う医療供給環境はいまだ整ってはいない．うつ病に対する治療法とは独立して，抑うつ症状の改善が血糖コントロールの改善と相関するというデータもあることから，まずは抑うつ症状の重篤度に応じた適切かつ十分なうつ病の治療を行うことが重要であると考えられる．

既に精神科で治療が開始されているうつ病併存糖尿病患者に経口血糖降下薬や脂質代謝改善薬を開始する場合には，抗うつ薬の持つCYP阻害作用が原因で薬剤の血中濃度が上昇し，副作用の発生頻度を高める可能性があることに注意が必要である（**表2**）[13]．特に

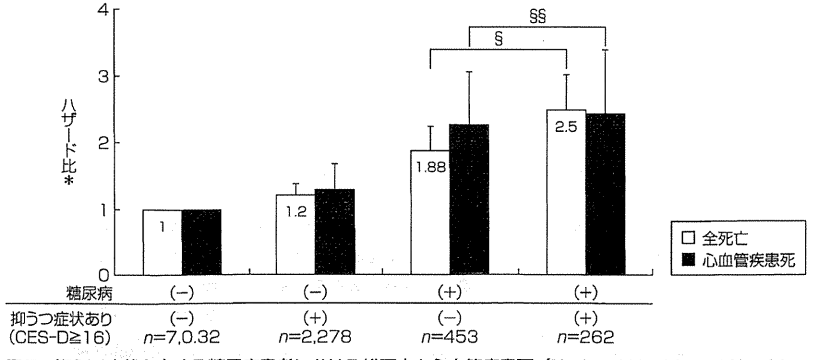

図5　抑うつ症状を有する糖尿病患者における総死亡と心血管疾患死（National Health and Nutrition Examination Survey）（文献11）より改変）

＊：①1982年における年齢，②性，③人種，④経済状態，⑤教育，⑥婚姻の有無，⑦喫煙歴，⑧身体活動度，⑨BMI，⑩アスピリン使用の有無，⑪ベースラインでの合併疾患を各群間でマッチさせたMultivariate Model.
§，§§：（糖尿病あり/抑うつ症状なし）群vs（糖尿病あり/抑うつ症状あり）群間で有意差あり

表2　CYP450の代謝基質と抗うつ薬の阻害作用（文献13）より改変）

CYP450　アイソザイム	1A2	2C9	2D6	3A4
基質	アクトス®	アクトス® アマリール® スターシス® ファスティック®	アクトス® ネシーナ®	アクトス® ネシーナ®
基質		ローコール® リバロ® クレストール®	クレストール®	リポバス® リピトール® クレストール®
基質	インデラル®	ニューロタン® ディオバン®	いくつかのβ遮断薬	カルシウム拮抗薬 ニューロタン®
阻害			競合阻害	
阻害	酵素阻害（1A2＞3A4＞2D6）			
阻害	酵素阻害		酵素阻害（2D6＞3A4＞1A2）	
阻害		酵素阻害（特に2D6に対してが弱い阻害作用）		
阻害			競合阻害	

SSRIは複数のCYP450アイソザイム阻害作用を有しているものが多いため，CYPの代謝基質であるピオグリタゾン（アクトス®），グリメピリド（アマリール®），ナテグリニド（スターシス®，ファスティック®），アログリプチン（ネシーナ®）の血中濃度を上昇させる可能性があり，併用時には低血糖への注意が必要である．脂質代謝改善薬のなかではプラバスタチン（メバロチン®）がCYP3A4の代謝を受けないという報告があるが，それ以外のCYP3A4で代謝されるスタチンを使用する場合には横紋筋融解症の発症リスクの上昇や，抗精神病薬と併用した場合のQTc延長を注意深くモニタリングする必要がある．循環器系薬剤では降圧薬以外にも抗不整脈薬や抗凝固薬など，様々な薬剤との相互作用とそ

れによる重篤な副作用が報告されているので，ぜひ成書を参照していただきたい．

ところで見落としてはならないのは気分障害，特に双極性障害の症例に対し気分安定効果を期待して抗精神病薬が併用されている症例の耐糖能異常である．わが国では第二世代抗精神病薬はそのほとんどが糖尿病患者への投与は禁忌，もしくは慎重投与となっているため耐糖能異常が明らかな患者では中止される場合が多いが，仮に高血圧症や脂質異常症でフォロー中の気分障害の症例に抗精神病薬の処方が開始された場合には，耐糖能異常出現の有無をチェックすることも糖尿病診療医の役割であると考える．

おわりに

糖尿病診療における「うつ」の問題に取り組むための最大の障壁は，「糖尿病診療」と「うつ診療」間にある「分断」だと考えている．一つめは糖尿病診療チームにおける「うつ診療」の知識と経験への分断，そして二つめは精神科医療チームとの連携の分断である．糖尿病診療チームが糖尿病治療にベストを尽くすのみでは，うつ病併存糖尿病患者のQOLや健康寿命の確保は達成できないという現状を踏まえると，われわれ内科医が精神科医療の知識に親和性を高めることも必要である．一方，同様の問題意識は精神科医療チームも抱いているはずで，両科間の対話と連携が進むことがうつ病併存糖尿病の診療を前進させると期待している．

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Q23 せん妄

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point

- せん妄は，軽度の意識障害下に生じる精神的な混乱あるいは錯乱，引き続く行動異常と心得る．
- まずは発症原因を精査してその改善を図り，看護ケアによる対応を第一とする．
- 必要に応じて薬物療法を併用するが，過鎮静，パーキンソン症候群を防ぐ配慮も怠らないようにする．
- 終末期のせん妄も十分コントロール可能であり，積極的な対応が必要である．

Q どのような症状があるのでしょうか？

A せん妄の中心症状としては，時間・場所・人物に関する見当識障害，睡眠・覚醒リズムの障害（夜間不眠と日中傾眠），短時間内の急激な症状変化（傾眠から興奮へ，ないしその逆もあり），短期記憶の障害（数分前のことを覚えていない）が挙げられます．

その他の症状としては，活動性の亢進，不穏・興奮，幻覚（特に幻視，幻聴），錯覚（とくに錯視），まとまりのない会話，周囲に対する注意力の減少，などです．

メモ

●せん妄の評価尺度

せん妄をより簡便に診断するための観察者評価尺度として，『Delirium Rating Scale（DRS）日本語版』[1]があります．また，治療効果の判定には，せん妄の重症度の推移を数時間ごとに連続評価できる『Memorial Delirium Assessment Scale（MDAS）日本語版』[2]が作成されています．

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Q どのような原因で起こるのでしょうか？

A せん妄の詳細な発症メカニズムはいまだ解明されていませんが，せん妄が患者の素因と環境因（外因）との兼ね合い，すなわち以下の３大因子の様々な組合せによって発症することについては，従来から専門家の間でも臨床的合意が得られています[1]．

１．直接因子

脳あるいは中枢神経系に直接ダメージを与える疾患がこれにあたり，薬物中毒性脳症，肝障害・腎障害・酸塩基不均衡などによる代謝性脳症，原発性・転移性脳腫瘍などがあります．

せん妄の起因薬剤としては，抗がん剤，ステロイド，モルヒネを含む鎮痛薬，インターフェロン，免疫抑制剤などの頻度が高く，その他抗生物質，抗ウイルス薬や，抗潰瘍薬のH_2ブロッカーなどでもせん妄が生じることがあります．

また，常習大量飲酒家の患者が入院数日後にアルコール離脱症候群に陥り，激しいせん妄を呈することがありますから，入院時における飲酒歴の聴取は必須といえます．

２．誘発因子

一般に大手術のあとほど，麻酔時間が長くなるほど，術後にせん妄をきたしやすいことが知られています．入院という環境変化，ひいては個室隔離による感覚遮断からくる睡眠・覚醒リズムの障害，治療上の身体拘束や強制臥床などもせん妄を誘発する可能性があります．

また筆者らの経験では，家族サポートが乏しいために心理的に不安定な患者では，せん妄がより起こりやすくなる印象があるので，これも要注意です．

３．準備因子

一般に高齢になるほど，また脳血管障害の既往や認知症ないし認知機能低下があるほどせん妄が生じやすく，多くは反復性の夜間せん妄の形をとります．

Q まずはどう対処したらよいでしょうか？

A せん妄の準備因子は改善できないので，可能な限り直接因子と誘発因子の改善を図ることが治療の第一歩になります．

まず，せん妄の原因になっていると思われる薬剤の変更・減薬などをできるだけ考慮すべきでしょう（ただ現実には少なからず限界があります）．

発熱，脱水，電解質不均衡，酸塩基不均衡によるせん妄も案外多いので，医療の基本に立ち戻って，全身管理に注力しなくてはなりません．終末期には全身状態の改善にもいきおい消極的になりやすいものですが，なるべくダメージの少ない保存的対応を心がけるべきでしょう．

また，一定の効果が見込める看護ケアを忘れてはなりません．たとえば時計やカレンダーの設置といったベッドサイドの環境調整，日中の覚醒を図るためのリハビリテーションのほか，点滴ラインや導尿カテーテルによる違和感，疼痛・呼吸困難などの身体的ストレスを細かくチェックし，その改善を図るようにしましょう．依頼可能であれば家族の面会回数を増やしたり，付き添い時間を長くするなどの工夫でも一定の効果が期待できます．

Q 薬物療法はどのようにすればよいでしょうか？

A 最近せん妄に関する薬物療法のガイドライン作成も試みられてはいますが[3]，まだ決定版はありません．

今のところ，睡眠薬や鎮静作用のある抗うつ薬ないし抗精神病薬といった向精神薬によって睡眠-覚醒リズムの回復を目指すことが薬物療法の基本です．

ちなみに，せん妄に対するこうした向精神薬の投与については，我が国ではチアプリド（グラマリール®）以外，いずれも保険適応外使用であることを忘れてはなりません．

なお万一，不測の事態から司法の場で治療の是非を検証されることになった場合には，薬物の選択の是非よりもむしろ，投与量が適正であったか，投与後の観察が十分であったか，といった点が特に問われるので，常に怠りない注意が必要です．

１．内服可能な場合（表１）

ａ．軽　症

抗うつ薬のトラゾドン（レスリン®）25～50 mg あるいはミアンセリン（テトラミド®）10～20 mg から夕食後ないし就寝前に一括あるいは分割投与します．薬物代謝の遅延が予想される重症患者や高齢者に対しては，血中半減期の短いグラマリール®25～75 mg も初期投与しやすいのですが，副作用としてパーキンソン症候群が現れることがあるので，多少注意が必要です．

ｂ．中等症以上

鎮静効果のより強い抗精神病薬を選択します．

表１　せん妄の薬物療法―内服可能な場合―

軽　症
レスリン® 25～50 mg（分２，夕食後・就寝前）から，150 mg/day まで漸増
テトラミド® 10～20 mg（分１，就寝前）から，60 mg/day まで漸増
グラマリール® 25～75 mg（分２，夕食後・就寝前）から，150 mg/day まで漸増
中等症～重症
セロクエル® 25～50 mg/day（分２，夕食後・就寝前）から，１～２日おきに 100 mg ずつ 600 mg/day まで漸増 頓服として，１回 25～50 mg を４時間おきに追加
ジプレキサ® 2.5～5 mg/day（分１，就寝前）から，20 mg/day まで漸増 頓服として追加も可能だが，高用量にしても効果は上がりにくい
ルーラン® 4～8 mg/day（分２，夕食後・就寝前）から，24 mg/day まで漸増 頓服として，１回 4～8 mg を４時間おきに追加
リスパダール® 0.5～1 mg/day（分２，夕食後・就寝前）から，4 mg/day まで漸増 頓服として，１回 0.25～0.5 mg を４時間おきに追加

す．従来はハロペリドール（セレネース®）0.75～2 mg やクロルプロマジン（コントミン®）12.5～50 mg，レボメプロマジン（ヒルナミン®）10～50 mg から夕食後ないし就寝前に一括あるいは分割投与し，次第に漸増する方法が一般的でしたが，最近は副作用のパーキンソン症候群がより少ない第二世代抗精神病薬が頻用される傾向にあります．

たとえば，リスペリドン（リスパダール®）0.5～1 mg，ペロスピロン（ルーラン®）4～8 mg，クエチアピン（セロクエル®）25～50 mg，オランザピン（ジプレキサ®）2.5～5 mg と少量をまずは単剤で初期投与し，効果に応じて増減する方法が推奨されます．

いずれもせん妄の改善効果はほぼ同等と考えられていますが，副作用プロフィールならびに剤型選択によって使い分けるのがよいでしょう．

第二世代抗精神病薬も主作用と副作用のバランスを考慮すると，いずれもセレネース®やコントミン®などに比して一長一短といわざるを得ませんし，今のところ第二世代抗精神病薬には注射製剤がないこともデメリットです．

いずれの場合にもベンゾジアゼピン系の睡眠薬を併用してよいのですが，鎮静作用よりもむしろ逆説的にせん妄を助長することがあるので，その場合には中止しなくてはなりません．

なお，不穏興奮が持続する重症のせん妄の場合には，経口摂取可能であっても意思疎通が困難で内服も拒否されることが多く，その対応については後述します．

2．内服困難な場合

経口摂取ができないような身体状態にある場合には，血圧は若干低下するものの呼吸抑制がほとんどないセレネース®1 アンプル（5 mg）を生理食塩水 100 mL で希釈して緩徐に点滴静注する方法が最も安全です．心拍呼吸モニタリング下であれば，せん妄の重症度に応じて 1 日 4 アンプル（20 mg）程度まで増量可能です．

セレネース®投与が 1 週間以上にわたる場合には副作用としてのパーキンソン症候群による嚥下障害から誤嚥性肺炎につながりやすいので，抗コリン薬のビペリデン（アキネトン®）1～2 アンプル（5～10 mg）を併用してパーキンソン症状を予防するようにしたほうがよいでしょう．

セレネース®を増量しても入眠が得られない場合には，それに追加してミダゾラム（ドルミカム®）5～10 mg あるいはフルニトラゼパム（サイレース®）1～2 mg を生理食塩水 100 mL で希釈して入眠が得られるまで緩徐に点滴静注します．ただしこれらの薬剤には呼吸抑制作用があるため，心拍呼吸モニタリング下での投与が原則です．

メ モ

●薬剤の副作用と剤型

セロクエル®，ジプレキサ®は鎮静作用が比較的強く，夕方から夜間にかけて投与するのに適していますが，高脂血症や体重増加，さらには高血糖を生じやすく，糖尿病患者には投与禁忌ですので注意が必要です．

ルーラン®，リスパダール®は鎮静作用が比較的弱いため，日中のせん妄に対して投与しやすいという利点がありますが，高用量になると，いずれも（特にリスパダール®で）パーキンソン症候群が出現しやすくなります．またリスパダール®は高プロラクチン血症を生じやすく，特に若年女性で無月経，乳汁分泌などを生じることがあります．

なお特殊な剤型として，ジプレキサ®ザイディス®錠は口腔内で瞬時に溶解するため，嚥下障害のある患者にも投与しやすいという特徴があります．またリスパダール®内用液も錠剤を好まない患者には受け入れられやすいはずです．

Q 重症例に対する薬物療法のコツはあるでしょうか？

A ときに，重症せん妄では拒絶症が高じて，注射や内服を頑として拒否してしまうような不穏・興奮を呈するケースがみられます．こうした激しい不穏・興奮状態に対しては，一時的に多人数のスタッフで四肢抑制して，ドルミカム®10 mg あるいはサイレース®2 mg を緩徐に静注して入眠に導き，その後生理食塩水 100 mL で希釈したセレネース®5～10 mg を輸液ポンプで持続点滴ないしシリンジポンプで持続静注する方法が最も効果的です．入眠したあとでそのまま経過をみるだけでは，多くの場合に不穏・興奮が時をおかず再燃するからです．

しかしながら，前述したセレネース®4 アンプル（20 mg）程度では到底太刀打ちできないような重症せん妄になると，夜間覚醒あるいは不穏になる度にセレネース®点滴を重ねることになり，結局は一晩中不穏が続いて明け方からようやく入眠し，翌日の昼間はすっかり寝込んでしまって，夕方からまた不穏・興奮が再燃する，という悪循環に陥ることが少なくありません．

このような場合には，せん妄が生じてから慌ててセレネース®を投与するのではなく，たとえせん妄が生じていなくても夕方から明け方までの一定時間に，セレネース®とドルミカム®，あるいはセレネース®とサイレース®の組合せの相当量を，輸液ポンプで持続点滴ないしシリンジポンプで持続静注するようにまずは設定します．

これをベースとして，それでも夜間に覚醒したら通常のせん妄と同様に，セレネース®とドルミカム®，あるいはセレネース®とサイレース®の組合せの点滴ないし静注で入眠を図るのです．

そして，翌日の夜は前夜入眠に要した総量を持続点滴ないし持続静注のベース量として，さらに覚醒したら同様にセレネース®とドルミカム®，あるいはセレネース®とサイレース®の組合せの点滴ないし静注で入眠を図ります．つまり，点滴ないし静注の投与指示は日替わりで柔軟に変更して，最終的には夕方からの持続点滴ないし持続静注のみでせん妄の発現を抑制するというわけです．

これは，がん疼痛のコントロールに用いるオピオイドの使用方法，すなわち突発痛に対するレスキュー投与量を持効製剤によるベース投与量に反映させながら増量し，最終的にレスキューを使わなくても済むようにしていく方法とまったく同じであることにお気づきでしょうか．この投与法を用いることで，終末期も含めてせん妄はほぼ全例コントロール可能であると考えるべきです．

ちなみに，この投与法によって夜間安定した睡眠が得られるようになると，長くて 4 週間もすると過鎮静が生じてくるので，投与量

を漸減できるようになり，結果的には睡眠-覚醒リズムが回復してきます．ただ，4週間以上を優に経過しても睡眠-覚醒リズムが回復しない場合には，認知機能が回復しきらず認知障害が残存することがあるので，家族にはあらかじめその可能性を伝えておくほうがよいでしょう．

Q 終末期のせん妄は治らないのでしょうか？

A せん妄の発症頻度は，一般人口では1～2%にすぎませんが，入院時に14～24%，総合病院入院中には56%にまで上昇し，高齢の術後患者では15～53%，集中治療中には70～87%，さらに終末期患者では実に88%にまでせん妄が発現するといわれています[4,5]．

こうしたことから，「高齢者が終末期にせん妄を発症すると生命予後が悪い」といったことばかりが喧伝され，これを「亡くなる直前だからせん妄が発症しても仕方がない」などと拡大解釈して，せん妄に対する治療に消極的になる向きも決して少なくありません．

しかし，終末期のせん妄は家族の苦悩をさらに増大させることになりますし，せん妄の発症要因には容易に是正できるものも多いので，可能な限り原因検索を行い，必要に応じて薬物による適切な鎮静を施すべきです．

本稿で述べたような対応がなされたなら，せん妄はあくまでコントロール可能な症状群であると考えてよいでしょう．

また，特に終末期においては，せん妄によって患者の意思決定能力が損なわれる前に，最終手段としての薬物による鎮静（セデーション）の可否について，患者本人や家族とよく話合い，いわゆるadvance directive（事前指示）を得ておくのが望ましい対応です[6]．

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ORIGINAL ARTICLE
Arrhythmia/Electrophysiology

Report From J-PULSE Multicenter Registry of Patients With Shock-Resistant Out-of-Hospital Cardiac Arrest Treated With Nifekalant Hydrochloride

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on behalf of the J-PULSE Investigators

Background: Nifekalant hydrochloride (NIF) is an intravenous class-III antiarrhythmic agent that purely blocks the K^+-channel without inhibiting β-adrenergic receptors. The present study was designed to investigate the feasibility of NIF as a life-saving therapy for out-of-hospital ventricular fibrillation (VF).

Methods and Results: The Japanese Population-based Utstein-style study with basic and advanced Life Support Education study was a multi-center registry study with 4 participating institutes located at the northern urban area of Osaka, Japan. Eligible patients were those treated with NIF because of out-of-hospital VF refractory to 3 or more precordial shocks and intravenous epinephrine. Between February 2006 and February 2007, 17 patients were enrolled for the study. The time from a call for emergency medical service to the first shock was 12 (6–26) min. The time from the first shock to the NIF administration was 25.5 (9–264) min and the usage dose of NIF was 25 (15–210) mg. When excluding 3 patients in whom percutaneous extracorporeal membrane oxygenation was applied before NIF administration, the rate of return of spontaneous circulation was 86% and the rate of admission alive to the hospital was 79%. One patient developed torsade de pointes.

Conclusions: Intravenous administration of NIF seems to be feasible as a potential therapy for advanced cardiac life-support in patients with out-of-hospital VF, and therefore further study is warranted. (*Circ J* 2010; **74:** 2308–2313)

Key Words: Advanced life support; Anti-arrhythmic drugs/therapy; Cardiac arrest; Defibrillation; Ventricular fibrillation

Sudden cardiac death is a major clinical problem, causing 300,000 to 400,000 deaths annually and 63% of all cardiac deaths in USA.[1] Rapid defibrillation for ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT) is the most crucial intervention to improve survival after cardiac arrest. Amiodarone is being used for the acute treatment of out-of-hospital cardiac arrest because it was shown to be effective for shock-resistant VF in the ARREST and ALIVE trials.[2,3]

Editorial p 2285

Nifekalant hydrochloride (NIF) is a class-III antiarrhythmic agent having a pirimidinedione structure with the selective inhibition of the rapid component of the delayed rectifier K^+ current (IKr).[4,5] The major adverse effect of NIF is proarrhythmic torsade de pointes (TdP).[6] As class-III antiarrhythmic agents, NIF and amiodarone are similar but they do have some differences. NIF is characterized as a pure K^+ channel blocker with a minimal negative inotropic effect.[7,8] Although amiodarone has various pharmacological actions, negative inotropic and chronotropic effects via a β-receptor, Na^+- and Ca^{2+}-channel blocking action seems to be disadvantageous, particularly when amiodarone is administered rapidly to a depressed heart.[9] In the ARREST trial, blood pressure was lower and pressor treatment was required more in amioda-

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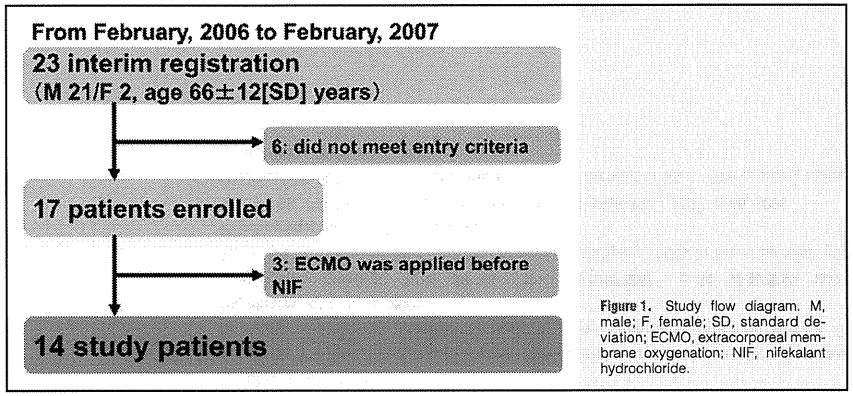

Figure 1. Study flow diagram. M, male; F, female; SD, standard deviation; ECMO, extracorporeal membrane oxygenation; NIF, nifekalant hydrochloride.

rone recipients.[2] Moreover, NIF decreases the defibrillation threshold,[10] whereas amiodarone does not.[11]

On the basis of these unique features of NIF, the present study was designed to investigate the feasibility of NIF as a life-saving therapy to defibrillation for victims of out-of-hospital cardiac arrest.

Methods

Study Design

The J-PULSE (Japanese Population-based Utstein-style study with basic and advanced Life Support Education) study was a multi-center registry study with 4 participating institutes located at the northern urban area of Osaka, Japan; National Cerebral and Cardiovascular Center, Senri Critical Care Medical Center, Mishima Emergency and Critical Care Center, and Osaka University Hospital Trauma and Acute Critical Care Center.

Eligible patients were those treated with NIF because they were adults with electrocardiographically documented out-of-hospital VF, not due to trauma, drowning and acute airway obstruction, or other cardiac rhythms that converted to VF, and because the VF was resistant to 3 counter-shocks, at least 1 dose of intravenous epinephrine, and fourth defibrillator shock. Therapy using NIF did not include the general advice of the Cardiopulmonary Resuscitation and Emergency Cardiovascular Care to administer amiodarone,[12] but instead was used as a replacement for this guideline. NIF was intravenously administered at the dose of 0.15–0.30 mg/kg body weight and then further direct counter-shock was delivered. If VF persisted after further shocks, NIF was additionally used at the dose of 0.15–0.30 mg/kg body weight, and attempts at resuscitation. Percutaneous extracorporeal membrane oxygenation (ECMO)[13] was applied for hemodynamic failure when patients were in refractory cardiac arrest, defined as an absence of return to spontaneous circulation after continuous cardiopulmonary resuscitation (CPR) or in refractory shock, defined as shock not responding to optimal conventional treatment.

This study was approved by the Institutional Review Board, including its provisions for waiver of informed consent. If the patients died, the informed consent was obtained from the family.

Data Recording

Pre-hospital data of the patients' course were prospectively obtained from the ambulance call report in the Utstein-style,[14] including sex, age, initial cardiac rhythm, time course of resuscitation, type of bystander-initiated CPR, return of spontaneous circulation (ROSC) and hospital admission. The times of emergency medical services (EMSs) call receipt and arrival of ambulance car at the scene of cardiac arrest were recorded automatically at EMS center. Data were also obtained from hospital charts, including the prevalence of adverse events of TdP.

Data Analysis

The endpoint in the present study was survival to admission to the hospital. Thus, patients who died in the emergency room were not considered to have been admitted. The endpoint also included ROSC after administration of NIF, which was defined as the documented presence of a measurable pulse and blood pressure. The relationship of clinical and therapeutic variables to survival and ROSC were determined with Fisher's exact test. A value of $P<0.05$ was considered to be statistically significant.

Results

Between February 2006 and February 2007, 23 patients (M 21/F 2, age 66±12 years) were interim registered. From 4 participating institutes (overall annual number of out-of-hospital cardiac arrest, 478; victims of cardiac origin, 173), 15, 5, 2 and 1 patients were enrolled, respectively. Among them, 2 patients did not give informed consent and 4 patients did not meet the entry criteria. Finally, 17 patients (M/F 15/2; median age (range) 68 (46–89) years) were studied in the present study (Figure 1). Initial electrocardiogram (ECG) rhythm was VF in 13 patients (76%) and asystole in the remaining 4 patients. A total of 12 patients (71%) were witnessed by a bystander, and 7 patients (41%) received bystander CPR by a witness. A doctor car was used in 11 patients (65%), and ECMO was used in 13 patients (76%).

Table 1. Pt Characteristics and Time Course* of Resuscitation Procedures

Pt	NIF following ECMO	Dr. Car	Age (years)	Sex	Initial ECG rhythm	EMS call from collapse (min)	Arrival of EMS at the scene of collapse (min)	First DC by EMS (min)	Arrival of Dr. Car (min)	No. of DC before hosp. arrival	Use of Epi	Arrival at hosp. (min)	First DC at hosp. (min)	No. of DC after hosp. arrival	NIF (min)	ECMO (min)	ROSC (min)	Death (min)
1	–	–	63	M	VF	−7	4	6	–	9	+	28	30	2	31	–	33	Survived
2	–	–	68	M	VF	−3	9	12	–	6	+	48	50	3	70	75	57	Survived
3	–	–	76	M	VF	−1	5	5	–	8	+	37	40	5	63	–	42	Survived
4	–	+	65	M	VF	NW	4	7	13	4	+	31	34	3	22	52	50	Survived
5	–	+	46	M	Asyst	0	4	26	13	7	+	57	63	2	61	–	–	83
6	–	+	89	M	Asyst	NW	7	14	21	11	+	66	83	2	49	–	73	113
7	–	+	54	F	VF	NW	6	9	17	2	+	26	41	6	42	67	53	Survived
8	–	+	64	M	VF	0	6	9	29	5	+	51	64	3	35	61	93	Survived
9	–	+	81	M	VF	0	3	6	23	5	–	43	227	4	32	244	NR	Survived
10	–	+	56	M	VF	NW	2	19	8	1	+	22	28	2	28	40	40	Survived
11	–	+	74	M	VF	−1	4	8	13	4	+	35	56	4	25	54	–	381
12	–	+	72	M	VF	0	3	14	13	5	+	37	53	2	32	52	52	Survived
13	–	+	71	M	VF	NW	4	6	8	5	+	26	34	3	28	51	88	Survived
14	–	+	60	M	VF	NW	6	10	11	4	+	43	56	2	35	54	56	Survived
15	+	–	78	F	VF	−2	7	19	–	4	+	38	103	5	283	71	–	2,144
16	+	–	64	M	Asyst	−5	4	–	–	0	+	24	47	3	55	53	129	Survived
17	+	–	76	M	Asyst	NW	7	26	–	1	+	26	38	10	49	41	41	Survived

Pt, patient; NIF, nifekalant hydrochloride; ECMO, extracorporeal membrane oxygenation; Dr., doctor; EMS, emergency medical service; DC, direct counter-shocks; hosp, hospital; Epi, epinephrine; ROSC, return of spontaneous circulation; VF, ventricular fibrillation; asyst, asystole; NW, not witnessed; NR, not recorded.
*Time (min) shows the interval from the EMS call.

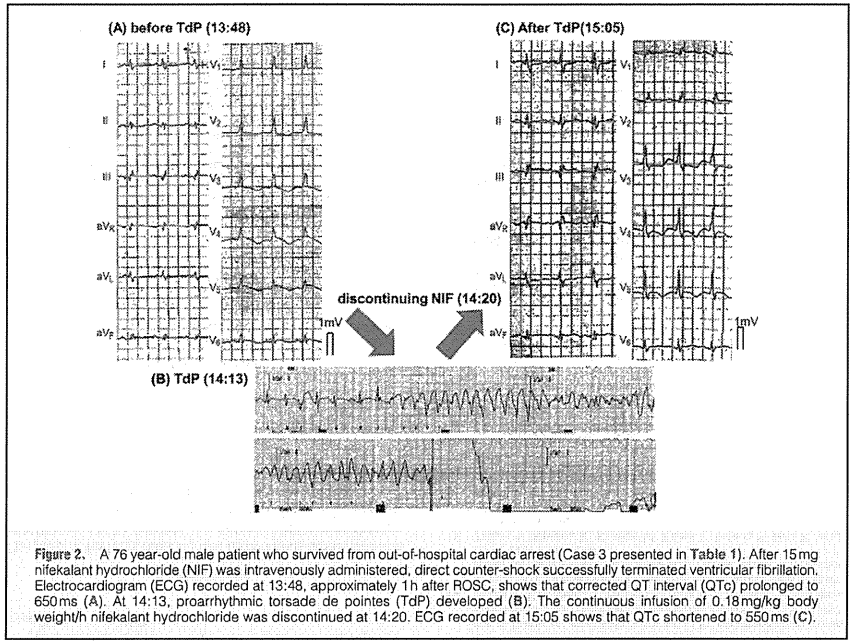

Figure 2. A 76 year-old male patient who survived from out-of-hospital cardiac arrest (Case 3 presented in Table 1). After 15 mg nifekalant hydrochloride (NIF) was intravenously administered, direct counter-shock successfully terminated ventricular fibrillation. Electrocardiogram (ECG) recorded at 13:48, approximately 1 h after ROSC, shows that corrected QT interval (QTc) prolonged to 650 ms (A). At 14:13, proarrhythmic torsade de pointes (TdP) developed (B). The continuous infusion of 0.18 mg/kg body weight/h nifekalant hydrochloride was discontinued at 14:20. ECG recorded at 15:05 shows that QTc shortened to 550 ms (C).

Table 2. Relationship of Clinical and Therapeutic Variables to Survival* and ROSC

Patients	All (n=17)	Exclude ECMO before NIF (n=14)	
	Survival, n (%)	Survival, n (%)	ROSC, n (%)
Age			
65 years≤	7/10 (70.0)	6/8 (75.0)	7/8 (87.5)
<64 years	6/7 (85.7)	5/6 (83.3)	5/6 (83.3)
Gender			
Female	1/2 (50.0)	1/1 (100)	1/1 (100)
Male	12/15 (80.0)	10/13 (76.9)	11/13 (84.6)
Initial cardiac rhythm			
VF	11/13 (84.6)	11/12 (91.7)	11/12 (91.7)
Not VF	2/4 (50.0)	0/2 (0)	1/2 (50.0)
By-stander CPR			
Yes	4/7 (57.1)	3/5 (60.0)	4/5 (80.0)
No	9/10 (90.0)	8/9 (88.9)	8/9 (88.9)
NIF dose			
25–210 mg	7/8 (87.5)	6/7 (85.7)	6/7 (85.7)
10–25 mg	6/9 (66.7)	5/7 (71.4)	6/7 (85.7)
Epinephrine			
Use	12/16 (75.0)	10/13 (76.9)	11/13 (84.6)
No use	1/1 (100)	1/1 (100)	1/1 (100)
ECMO			
Use	11/13 (84.6)	9/10 (90.0)	9/10 (90.0)
No use	2/4 (50.0)	2/4 (50.0)	3/4 (75.0)

CPR, cardiopulmonary resuscitation. Other abbreviations see in Table 1.
*Survival to admission to the hospital.

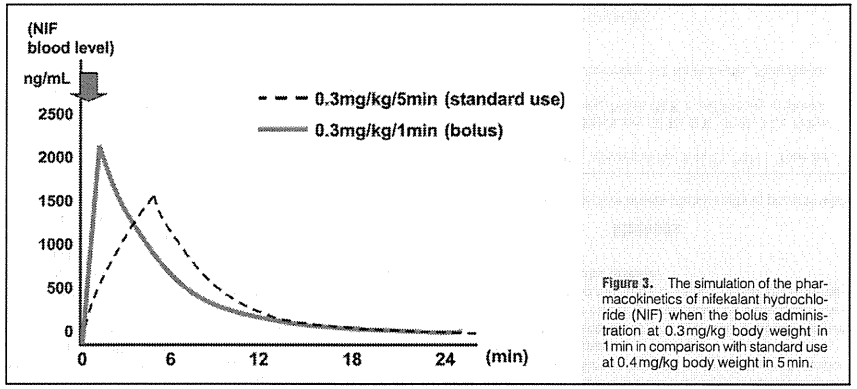

Figure 3. The simulation of the pharmacokinetics of nifekalant hydrochloride (NIF) when the bolus administration at 0.3 mg/kg body weight in 1 min in comparison with standard use at 0.4 mg/kg body weight in 5 min.

The characteristics and the time interval from the EMS call in individual patients were summarized in Table 1. The median time from a call for EMS to the first shock was 12 (6–26) min. In particular, in patients who were witnessed by a bystander, the median time from the collapse to the EMS call was 1 min. The median time from the first shock to the NIF administration was 25.5 (9–264) min and the median usage dose of NIF was 25 (15–210) mg.

When excluding 3 patients in whom ECMO was applied before NIF administration (Figure 1), the rate of ROSC was 86% (n=12 out of 14 patients) and the rate of admission alive to the hospital was 79% (n=11 out of 14 patients). The time from NIF administration to ROSC was within 10 min in 3 patients, 10 to 30 min in 6 patients and over 30 min in 3 patients, respectively (median: 20 min). One ROSC patient died in the emergency room and were not admitted to the hospital. One patient developed TdP (7%), which was transiently induced and disappeared after discontinuing the administration of NIF (Figure 2).

We then determined the relationship of clinical and therapeutic variables to ROSC and admission alive (Table 2). The rate of admission alive to the hospital was 91.7% in patients in whom initial ECG rhythm was VF, whereas it was 0% in those in whom initial ECG rhythm was asystole (P=0.033). The ROSC rate was 91.7% in patients in whom initial ECG rhythm was VF, whereas it was 50% in those in whom initial ECG rhythm was asystole (P=0.275). Between patients with and without ECMO, the rate of admission alive to the hospital (with ECMO, 90% vs without ECMO, 50%) and the ROSC rate (with ECMO, 90% vs without ECMO, 75%) did not differ in the present study.

Discussion

The major finding of the present multicenter registry study is that the ROSC rate and the rate of admission alive to the hospital in out-of-hospital VF patients treated with NIF was high, 86% and 79%, respectively.

NIF for Out-of-Hospital Cardiac Arrest

According to the Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care,[12] intravenous amiodarone should be considered for VF or pulseless VT patients after 3 unsuccessful direct counter-shocks. However, amiodarone was not commercially available until June, 2007 in Japan. Therefore, as alternative for amiodarone, the present study was designed to investigate the feasibility of NIF as a life-saving therapy to defibrillation for victims of out-of-hospital cardiac arrest.

NIF has several advantageous characteristics particularly for emergency care. First, NIF is easily soluble and applicable to secure golden time for resuscitation. Second, its half life is relatively short (T1/2,β, 1.53±0.23 h),[5] achieving rapid action and clearance. Third, NIF has only a small cardiac depressant effect and might improve the defibrillation threshold. Fourth, an extracardiac adverse event is not usual.

We previously reported that the intravenous administration of NIF was useful in the emergency treatment of inhibiting drug-refractory VT/VF in high-risk patients, including those with extensive anterior acute myocardial infarction and those who had been already treated with oral amiodarone, oral sotalol, and/or implantable cardioverter defbrillator.[6] However, there have been few single center studies regarding the effect of NIF on patients with shock-resistant, out-of-hospital VF. The rate of admission alive to the hospital was 67% (37 survivors of 55 patients treated with NIF),[15] which was comparable with the present results, where the data were collected from 4 established emergency departments. However, over 20 min spent until NIF was administered following the first shock. When considering the characteristics unique of NIF that decreases the defibrillation threshold,[16] the earlier NIF can be used in the course of cardiac arrest, the greater is the likelihood of at least acute survival.

While proarrhythmic properties of amiodarone are relatively minor as demonstrated in the previous studies,[16] proarrhythmic TdP is the major adverse effect of NIF.[6,17] However, as reported in the previous single center study, the occurrence of TdP was 5% (1 of 21 patients treated with NIF),[18] as low as the present result. The previous study demonstrated that the sensitivity of IKr channels could be modified by its genetic polymorphism or surroundings such as catecholamine, potassium, and pH.[19]

In the present study, the median usage dose of NIF was 25 mg. If a patient's body weight is 60–70 kg, the standard ini-

tial dose should be ~20 mg, 0.3 mg/kg body weight. Figure 3 shows the simulation of the pharmacokinetics of NIF when the bolus administration at 0.3 mg/kg body weight was performed in a minute in healthy subjects (unpublished data). In this compartment model, the blood concentration of NIF appears to be comparable with that following the standard administration at 0.3 mg/kg body weight/5 min. Although the blood concentration could peak within 10 min in this simulation, it often took 10 to 30 min to recover spontaneous circulation in the present collapsed patients with limited cardiac output by closed chest massage.[20]

Study Limitations

Several limitations of the present study should be mentioned. First, the small number of patients precludes any firm conclusion in this setting designed as a pilot study. Further larger clinical studies with a blinded, randomized design are required. However, resuscitation for out-of-hospital cardiac arrest patients is always critical and is a race against time. It is therefore difficult to explain the study design and its process (eg, blindness and randomization) to potential trial participants. Second, the prognosis after the admission, especially the survival to hospital discharge, was not presented. Third, since intended as a pilot study of various critically ill patients, the present data did not include type of disease, cardiac function (after ROSC or coronary intervention, or under percutaneous ECMO support), serum K^+ and pH concentrations. Fourth, in the recent intensive strategy of the emergency medicine,[21–24] it seems to be hard to distinguish the pharmacological effect of NIF from the mechanical effect of percutaneous ECMO (with the adjunctive therapeutic hypothermia) on CPR.

Conclusions

The present findings indicate that intravenous administration of NIF seems to be feasible as a potential life-saving therapy for advanced cardiac life-support in patients with out-of-hospital VF and therefore further study is warranted.

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Conflict of Interest

None.

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ORIGINAL ARTICLE
Preventive Medicine

Depression and Outcomes in Hospitalized Japanese Patients With Cardiovascular Disease

– Prospective Single-Center Observational Study –

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Background: Several studies have suggested that depression poses a risk in cardiovascular patients. The aim of the present study was to evaluate the prevalence of depression and its effect on cardiovascular events and mortality in Japanese inpatients with cardiovascular disease.

Methods and Results: A total of 505 patients hospitalized with cardiovascular disease (28% female; mean age, 61±14 years; 31% ischemic heart disease; 47% New York Heart Association [NYHA] class II–IV; 25% implantation of pacing devices) were enrolled in the present prospective observational study. The Zung Self-Rating Depression Scale (SDS) was used to screen for depression. The primary outcome was the time to death or cardiovascular event, and the secondary outcome was death. In total, 109 patients (22%) were diagnosed with depression (Zung SDS index score ≥60). NYHA class III/IV, defibrillator implantation, and being unmarried were independently associated with depression. During an average follow-up period of 38±15 months, 92 patients (18%) reached the primary outcome. There was a higher incidence of the primary outcome in patients with depression than in those who were not depressed (P<0.01). Depressed patients had a significantly higher rate of mortality than non-depressed patients (P<0.01). Depression was an independent predictor of the primary outcome (hazard ratio, 2.25; 95% confidence interval: 1.30–3.92, P<0.01).

Conclusions: Depression was not uncommon in Japanese inpatients with cardiovascular disease and was associated with cardiovascular outcomes. (*Circ J* 2011; **75:** 2465–2473)

Key Words: Cardiovascular disease; Depression; Inpatient; Mortality; Outcome

Several studies have suggested that depression is a possible risk factor for adverse outcomes in patients with coronary artery disease or heart failure.[1–7] While cardiac events may cause and prolong depression in patients with cardiac disease,[8–10] the prevalence of depression is reported to be approximately 20% in outpatients with coronary artery disease and 30–40% in outpatients with heart failure.[6,11–14] In patients hospitalized for acute myocardial infarction, 16–45% are depressed,[6,8,11] and the presence of depressive symptoms is a significant risk factor for subsequent cardiac events in elderly myocardial infarction patients.[15] In hospitalized heart failure patients, depression is also common and is independently associated with poor outcomes.[2,3,16,17] Understanding these issues could help cardiologists identify inpatients with depression and deliver the most appropriate care.

Cultural and ethnic differences influence depressive symptoms and the interpretation of depression as an illness.[18–20] In Japan, there have been few reports about the prevalence of depression and its effect on patients with cardiovascular disease.[14,15,21] To date, there have been no reports concerning the prevalence of depression in hospitalized patients with cardiovascular disease in Japan.

The aim of the present study was to evaluate the prevalence of depression and the effect of depression on subsequent cardiovascular events and mortality in Japanese patients hospitalized with cardiovascular disease.

Methods

We conducted a prospective observational study in patients who

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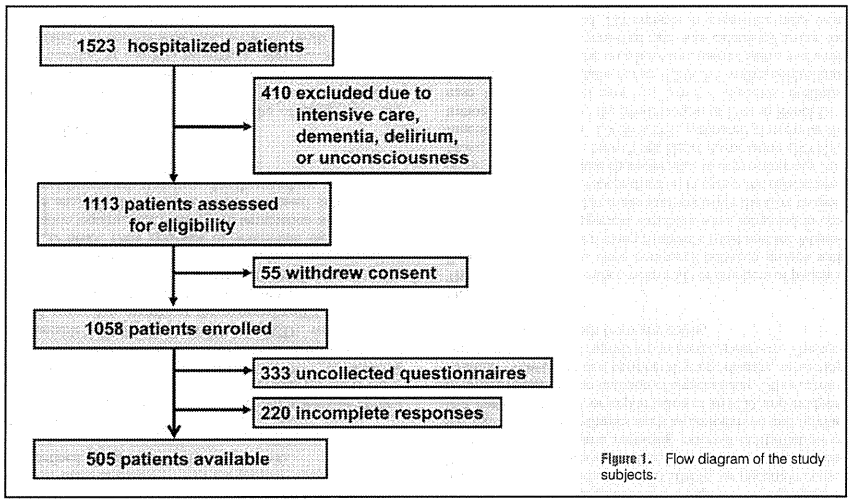

Figure 1. Flow diagram of the study subjects.

were admitted to the cardiology department of Tokyo Women's Medical University Hospital between June 2006 and April 2008. Patients with dementia, delirium, or other conditions that make it difficult to complete a self-reported written questionnaire (eg, unconsciousness, in intensive care, end-stage of another life-threatening disease) were excluded. The protocol was approved by the institutional review board of Tokyo Women's Medical University. All patients gave written informed consent.

Cardiovascular Disease

In the present study, structural heat disease consisted of the following disorders: left ventricular (LV) systolic dysfunction and/or marked LV dilatation (unless secondary to severe valve regurgitation), LV diastolic dysfunction associated with congestive heart failure, coronary heart disease, right heart disease with at least moderate right ventricular dilation, moderate or severe tricuspid regurgitation, pulmonary hypertension, LV hypertrophy, left-sided valvular disease, and congenital heart disease. Coronary artery disease was defined as positive stress test findings, coronary angiography demonstrating at least 75% of stenosis or coronary spastic angina as documented on an acetylcholine provocation test, a history of prior myocardial infarction, or a history of revascularization procedures. Valvular and congenital heart diseases were diagnosed on angiographic, hemodynamic or echocardiographic findings or a history of valvular or congenital cardiac surgery. Aortic and mitral regurgitation were defined as valvular disease with at least moderate regurgitation on color-flow Doppler echocardiography. Non-ischemic cardiomyopathies were defined as ventricular myocardial abnormalities in the absence of coronary artery disease, or valvular, pericardial or congenital heart disease. Pulmonary artery hypertension was defined as an increase in mean pulmonary arterial pressure of ≥25 mmHg with a pulmonary wedge pressure of ≤15 mmHg at rest, as estimated on right heart catheterization. Aortic disease, peripheral artery disease and other vascular diseases were diagnosed on angiographic or echocardiographic findings, or a history of vascular surgery or intervention. Arrhythmias and conduction disorders without structural heart disease included atrial, supraventricular and ventricular arrhythmias, sick sinus syndrome and atrioventricular block in the absence of structural heart disease. Hypertension was defined as a systolic blood pressure ≥140 mmHg, a diastolic blood pressure ≥90 mmHg, or a history of treatment for hypertension. LV ejection fraction (LVEF) was calculated using left ventriculography, echocardiography or radionuclide angiography.

Assessment of Depression

Most patients received psychological questionnaires within a few days after hospital admission. For patients who initially required intensive treatment, these questionnaires were given after their transfer to the general cardiology wards. The Zung Self-Rating Depression Scale (SDS) has been used to screen for depression and to measure the severity of depression in numerous settings.[22–26] The Zung SDS is a self-reporting, 20-question instrument that assesses the psychological and somatic symptoms of depression. It has good internal consistency and validity, encompassing most DSM-IV criteria for major depression.[26–32] The Zung SDS has been found to be the primary discriminating variable for distinguishing depressed from non-depressed people.[33] It has shown a positive likelihood ratio for major depression of 3.3 (95% confidence interval [CI]: 1.3–8.1), and negative likelihood ratio of 0.35 (95%CI: 0.2–0.8).[34] The Zung SDS has also been used in clinical studies to assess depression in cardiovascular disease.[15,31–37] Ten questions are positively worded, and 10 are negatively worded. Each question is scored on the following 4-point scale: 1, a little of the time; 2, some of the time; 3, good part of the time; and 4, most of the time. To obtain a total score, the positive items are reversed, and then the items are summed. This raw score is converted to a 100-point scale (SDS index). Zung SDS index scores range from 25 to 100 and are interpreted as follows: within the nor-

Table 1. Patient Characteristics

	Total (n=505)	Depression (n=109)	No depression (n=396)	P value
Age (years)	61±14	61±13	59±15	0.45
Female	143 (28)	36 (33)	107 (27)	0.26
Cardiovascular disease				0.24
Coronary artery disease	159 (31)	24 (22)	135 (34)	
Non-ischemic cardiomyopathy	114 (23)	30 (28)	84 (21)	
Valvular heart disease	65 (13)	15 (14)	50 (13)	
Arrhythmia without structural heart disease	143 (28)	32 (29)	111 (28)	
Pulmonary artery hypertension	3 (1)	1 (1)	2 (1)	
Congenital heart disease	6 (1)	2 (1)	4 (1)	
Others	15 (3)	5 (5)	10 (3)	
Plasma BNP on admission (pg/ml)	251 (4–4,335)	378 (5–4,335)	215 (4–3,400)	<0.01
NYHA functional class on admission (I/II/III/IV)	269/191/30/15	41/45/16/7	228/146/14/8	<0.01
NYHA functional class at discharge (I/II/III/IV)	275/206/23/1	41/46/21/1	234/160/2/0	<0.01
LVEF (%)	48±15	49±15	46±16	0.11
eGFR (ml·min^{-1}·1.73 m^{-2})	61±14	61±14	61±14	0.73
Current smoker	70 (14)	14 (12)	56 (14)	0.72
History of atrial fibrillation	85 (17)	16 (15)	69 (17)	0.49
Medical comorbidities				
Hypertension	166 (32)	29 (27)	137 (35)	0.11
Diabetes	86 (17)	16 (15)	70 (18)	0.46
Dyslipidemia	141 (28)	23 (21)	118 (30)	0.06
Hemodialysis	32 (6)	10 (9)	22 (6)	0.18
Cerebrovascular disease	8 (1.5)	2 (2)	6 (2)	0.81
Major depression	8 (1.5)	5 (5)	3 (1)	0.01
Implanted pacing devices before admission				
Pacemaker/CRT-P	54 (11)	13 (12)	41 (10)	0.64
ICD/CRT-D	73 (14)	26 (24)	47 (12)	0.02
Implanted pacing devices at discharge				
Pacemaker/CRT-P	64 (13)	13 (12)	51 (13)	0.79
ICD/CRT-D	95 (19)	29 (27)	66 (17)	0.01
Medications at the time of questionnaire				
β-blockers	248 (49)	52 (48)	196 (49)	0.74
ACE inhibitors/ARBs	278 (55)	60 (55)	218 (55)	0.99
Spironolactone/eplerenone	120 (24)	37 (34)	83 (21)	0.68
Calcium channel blockers	284 (56)	54 (50)	230 (58)	0.11
Aspirin	172 (34)	29 (27)	143 (36)	0.06
Warfarin/heparin	142 (28)	34 (32)	108 (27)	0.64
Amiodarone/nifekalant	60 (12)	22 (20)	40 (10)	<0.01
Intravenous inotropics	3 (1)	2 (2)	1 (0.3)	<0.01
Intravenous vasodilator	5 (1)	4 (4)	1 (0.3)	<0.01
Antidepressants	8 (2)	5 (5)	3 (1)	0.01
Medications at discharge				
β-blockers	259 (51)	57 (52)	202 (51)	0.81
ACE inhibitors/ARBs	308 (61)	72 (66)	236 (59)	0.21
Spironolactone/eplerenone	136 (27)	40 (37)	96 (24)	0.01
Calcium channel blockers	289 (57)	55 (50)	234 (59)	0.10
Aspirin	186 (37)	33 (30)	153 (39)	0.10
Warfarin	160 (32)	44 (40)	116 (29)	0.03
Amiodarone	68 (13)	25 (23)	43 (11)	0.05
Antidepressants	8 (2)	5 (5)	3 (1)	0.01
Education				0.33
High school	314 (62)	74 (68)	240 (61)	
College	124 (25)	24 (22)	100 (25)	
Others	67 (13)	11 (10)	56 (14)	
Marital status				<0.01
Unmarried	35 (7)	13 (12)	22 (6)	
Married	448 (89)	83 (76)	365 (92)	
Widowed	22 (4)	13 (12)	9 (2)	
Work status				0.02
Employed	205 (41)	32 (29)	173 (44)	
Housewife	89 (18)	26 (24)	63 (16)	
Unemployed/retired	211 (42)	51 (47)	160 (40)	

Data given as n (%) or mean±SD or median (range).
BNP, B-type natriuretic peptide; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; CRT, cardiac resynchronization therapy; CRT-P, CRT with a pacemaker; ICD, implantable cardioverter defibrillator; CRT-D, CRT with a defibrillator; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker.

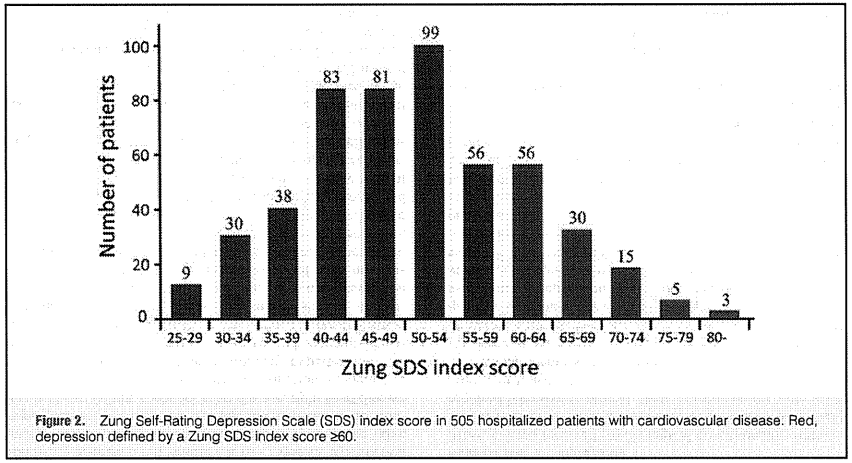

Figure 2. Zung Self-Rating Depression Scale (SDS) index score in 505 hospitalized patients with cardiovascular disease. Red, depression defined by a Zung SDS index score ≥60.

mal range, <50; mildly depressed, 50–59; moderately depressed, 60–69; and severely depressed, ≥70. Because the psychological and physical symptoms of depression may overlap with those of cardiovascular disease, there is a possibility that cardiovascular symptoms may be attributed to depression. Previous studies with cardiovascular disease have often used a cut-off index score of 50 (raw score 40) as a definition of depression.[15,34–37] Higher depression scores (eg, SDS score index ≥60) are associated with increased morbidity and mortality in patients with coronary artery disease.[37,38] A cut-off index score of 60 has been shown to detect clinical depression while avoiding an abundance of false-positive results in patients with cardiovascular or other disease.[10,39–41] In the present study, depression was defined as a Zung SDS index score ≥60.

Follow-up

After discharge, patients were seen as outpatients or at their general practitioner's clinic at 1–3-month intervals up to October 2010. Patients receiving pacing device therapy, including pacemakers, cardiac resynchronization therapy (CRT) and implantable cardioverter defibrillators (ICD), were also followed every 3–6 months at the pacemaker/ICD clinic. The occurrence of ventricular tachyarrhythmias requiring ICD therapy, including shock and anti-tachycardia pacing, was obtained by reviewing event details and electrograms stored on the ICD disks. Only episodes of ventricular tachycardia or fibrillation requiring ICD therapy for termination were included in the analysis. Information about deceased subjects was obtained from medical records, family members, their general practitioners and the admitting hospital.

Clinical Outcomes

The primary outcome was a composite of death from any cause or cardiovascular events from the time of enrollment to the first event. Cardiovascular death was defined as death due to myocardial or cerebral infarction, other vascular causes, heart failure or documented sudden cardiac death. Cardiovascular events included non-fatal myocardial infarction, hospitalization for heart failure, unstable angina, revascularization, stroke, refractory arrhythmia, and ventricular tachyarrhythmia requiring ICD therapy. Unstable angina was defined according to the Braunwald criteria.[42] Revascularization included angioplasty, stenting and coronary artery bypass grafting. Heart failure was defined on the basis of symptoms and signs such as dyspnea, rales and ankle edema and the need for treatment with diuretics, vasodilators, positive inotropic drugs or an intra-aortic balloon pump. Stroke was defined as a new focal neurological deficit of vascular origin lasting >24 h. Stroke was further classified by etiology, including intracranial hemorrhage, ischemia (diagnosed on computed tomography or magnetic resonance imaging if available) or uncertain cause. Refractory arrhythmia was defined as supraventricular or ventricular tachyarrhythmia requiring external defibrillation or pacing, i.v. anti-arrhythmics such as amiodarone and nifekalant, catheter ablation, or implantation of an ICD, and bradyarrhythmia requiring implantation of a pacemaker. Other cardiovascular events included peripheral artery disease, dissecting aortic aneurysm, and rupture of an aortic aneurysm. The second outcome was death from any cause.

Statistical Analysis

The data are given as either mean±SD or numbers of patients. Baseline clinical data were compared between groups with and without depression using Student's t-test and the Mann–Whitney U-test. Categorical variables were subjected to chi-squares analysis. Multivariate analysis using the Cox proportional hazards model was performed to assess the relationship of the following baseline characteristics to depression: age ≥65 years, female gender, New York Heart Association (NYHA) functional class III/IV, LVEF≤35%, estimated glomerular filtration rate (eGFR) by the Modification of Diet in Renal Disease formula $<60\,\mathrm{ml\cdot min^{-1}\cdot 1.73\,m^{-2}}$,[43] diabetes mellitus, hemodialysis, implantation of an ICD/CRT with a defibrillator (CRT-D), β-blocker use on admission, marital status and work status. Cumulative event-free rate was calculated using the Kaplan–Meier method. Differences in event-free rates were compared using the log-rank test. Multivariate analysis using the Cox proportional hazards model was performed to assess the relationships between depression and the primary outcome, independent of the following confounders at discharge: age ≥65 years, female gender, NYHA functional class III/IV, LVEF≤35%, eGFR $<60\,\mathrm{ml\cdot min^{-1}\cdot 1.73\,m^{-2}}$, diabetes mellitus, hypertension and implantation of an ICD/CRT-D. P<0.05 was considered significant. SPSS version 11.01 (SPSS, Chicago, IL, USA) was used for analysis.

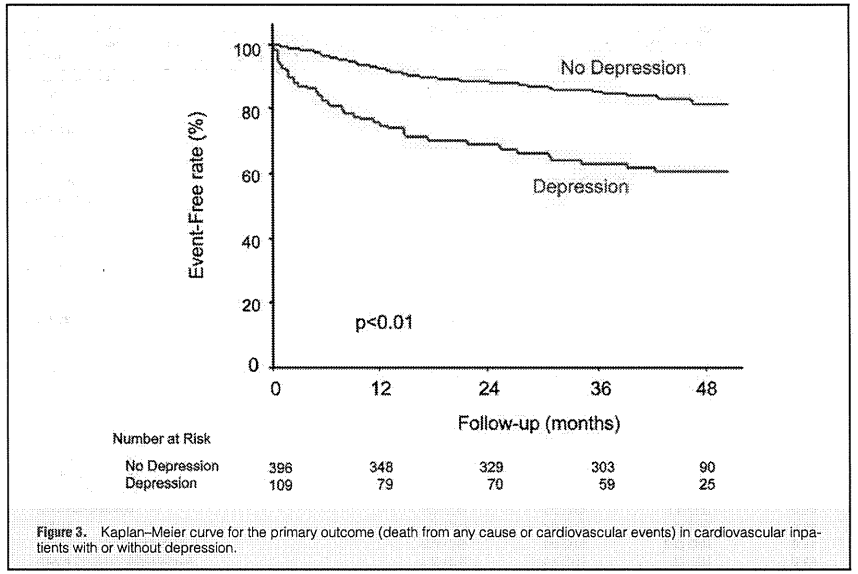

Figure 3. Kaplan–Meier curve for the primary outcome (death from any cause or cardiovascular events) in cardiovascular inpatients with or without depression.

Results

Patients

Of the 1,523 consecutively hospitalized patients, 1,058 patients were enrolled in the present study. Seven hundred and twenty-five questionnaires were collected (collection rate of 68%). Of these, 505 questionnaires had valid responses (response rate of 48%), and these patients were available to participate in the study (Figure 1). The patient characteristics are shown in Table 1. The mean age on admission was 61±14 years, and 28% of the patients were female. A total of 159 patients (31%) had coronary artery disease, 236 (47%) were rated as being in NYHA functional class II–IV on admission, and 127 (25%) had implanted pacing devices on admission. Eight patients (2%) had been treated for major depressive disorder prior to admission. All 505 patients were discharged from hospital, and 230 (46%) were in NYHA functional class II–IV at discharge. At discharge, 159 (31%) had implanted pacing devices. Regarding concomitant medications at discharge, 259 patients (51%) were taking β-blockers, and 68 patients (13%) were taking amiodarone. Eight patients (2%) who were diagnosed with major depression by a psychiatrist were taking antidepressants. No patients were receiving non-pharmacological therapy such as cognitive behavior therapy.

Depression Prevalence

The Zung SDS index scores of all studied patients at baseline are shown in Figure 2. In total, 109 patients (22%) had depression. A comparison of patients' clinical characteristics according to the presence or absence of depression is shown in Table 1. There was no significant difference in age, gender, underlying cardiovascular disease, coexisting conditions or implanted devices between groups. The plasma B-type natriuretic peptide (BNP) level on admission and NYHA functional class on admission and at discharge were higher in patients with depression than in those who were not depressed. There was a higher rate of ICD/CRT-D implantation on admission in patients with depression. There were higher rates of amiodarone/nifekalant use, i.v. inotropic use, i.v. vasodilator use and antidepressant use at the time of the questionnaire in patients with depression. There was no significant difference, however, in the rate of β-blocker use between patients with (48%) and without depression (49%). There were higher rates of spironolactone/eplerenone use, warfarin use and antidepressant use at discharge in patients with depression. Compared with patients without depression, fewer depressed patients were married or employed. Multivariate analysis showed that ICD implantation (hazard ratio [HR], 1.92; 95%CI: 1.00–3.80, P=0.04), NYHA functional class III/IV (HR, 3.03; 95%CI: 1.38–6.67, P<0.01), and unmarried status (HR, 4.32; 95%CI: 2.31–8.09, P<0.01) were significantly associated with depression.

Depression and Clinical Outcomes

During an average follow-up period of 38±15 months, 92

Table 2. Cause of Death and Rate of Cardiovascular Events

	Depression (n=109)	No depression (n=396)	P value
Death from any cause	21	20	<0.01
Cardiovascular death	18	17	<0.01
Sudden death	1	8	0.42
Heart failure	17	5	<0.01
Myocardial infarction	0	2	0.45
Cerebral infarction	0	1	0.59
Peripheral artery disease	0	1	0.59
Non-cardiovascular death	3	3	0.08
Infection-related death	1	1	0.32
Surgery-related death	1	0	0.06
Hepatocellular carcinoma	0	1	0.59
Hepatic failure	1	0	0.06
Pulmonary hemorrhage	0	1	0.59
Hospitalization for heart failure	22	30	<0.01
Hospitalization for unstable angina	2	3	0.31
Hospitalization for revascularization	5	5	0.02
Hospitalization for stroke	0	1	0.59
Hospitalization for refractory arrhythmia	1	3	0.86
Ventricular tachyarrhythmia requiring ICD therapy	3	9	0.77
Hospitalization for other cardiovascular events	1	2	0.61

Abbreviation see in Table 1.

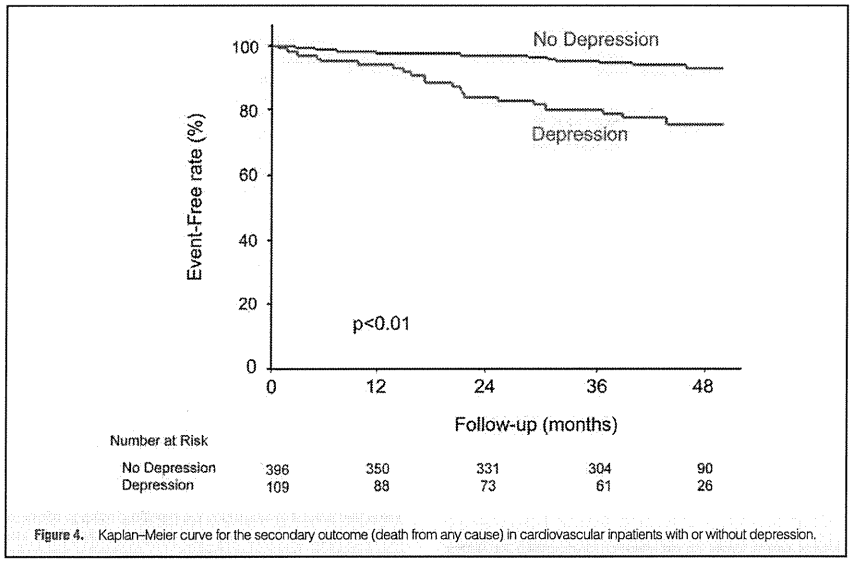

Figure 4. Kaplan–Meier curve for the secondary outcome (death from any cause) in cardiovascular inpatients with or without depression.

patients (18%) reached the primary outcome. Kaplan–Meier curves for the primary outcome are shown in Figure 3. There was a significantly higher incidence of the primary outcome in patients with depression than in those without depression. Causes of death and each cardiovascular event are listed in Table 2. Kaplan–Meier curves for death from any cause are shown in Figure 4. There was a significantly higher mortality in patients with depression than in those who were not depressed.

Multivariate analysis showed that patients with depression had an increased risk of the primary outcome: death from any cause and cardiovascular events (HR, 1.98; 95%CI: 1.32–2.98, P<0.001; Table 3). This risk was independent of whether patients met the criteria of NYHA functional class III/IV, LVEF≤35% and eGFR <60 ml·min^{-1}·1.73 m^{-2}.

Discussion

The present study has shown that the prevalence of depression was 22% in hospitalized patients with cardiovascular disease. ICD/CRT-D implantation, NYHA functional class III/IV at baseline, unmarried status, and unemployment were associated with depression. Furthermore, higher mortality and death from any cause and cardiovascular events were more prevalent in patients with depression than in those who were not depressed. Finally, depression was shown to be an independent factor for worsening clinical outcome.

Depression is often comorbid with chronic physical disease. The World Health Organization World Health Survey reported that an average of 9.3–23.0% of subjects with one or more physical diseases, such as angina, arthritis, asthma and diabetes, also suffer from depression.[44] A large study based on National Health Interview Survey data of 30,801 US adults reported that the 12-month prevalence of major depression was 9.3% in subjects with coronary artery disease, 9.3% in subjects with diabetes, 8.0% in subjects with hypertension and 7.9% in subjects with congestive heart failure, compared with 4.8% in those with no chronic medical disorder.[45] Recently, the American Heart Association recommended routine depression screening in patients with coronary artery disease using the 2- and 9-item tests from the Patient Health Questionnaires (PHQ-2 and PHQ-9).[46] Sowden et al reported that approximately 9% of 3,504 screened inpatients in cardiac care units had positive PHQ-2 scores (≥3). Of these patients, 74.1% had a PHQ-9 score ≥10, but the details of the patients' clinical backgrounds are unknown.[47] Previous studies have used several methods to measure depression, including the Beck Depression Inventory, SDS, the Hospital Anxiety and Depression Scale, and the Centre for Epidemiologic Studies Depression Scale (CES-D).[5,8] The Sowden et al PHQ-2 cut-off score was higher than that in general use (≥2)[48] to avoid false-negative results. The prevalence of patients with a PHQ-2 ≥2 was at least 15% in the Sowden et al study.[47] In the present study, 22% of all cardiovascular disease inpatients met the criteria for depression (Zung SDS index score ≥60).

The prevalence of depression in the present inpatients was comparable to the prevalence reported previously in Western countries, but the methods for measuring depression varied. In the present patients, ICD/CRT-D implantation and NYHA functional class III/IV as baseline were associated with depression. Previous studies have indicated that ICD implantation improves quality of life (QOL) in most ICD patients,[49,50] but an underlying disease or comorbidity, poor social support, or ICD-specific problems, such as frequent shocks and poor understanding of ICD therapy, increase depressive symptoms and reduce the QOL for ICD patients.[10,50–52] This is an important problem in clinical practice because the number of ICD implantations being carried out to prevent sudden cardiac death is increasing. A meta-analysis showed that depression is common among patients with heart failure, and substantially higher rates of clinically significant depression are present among patients with more severe heart failure.[53] In the present study, concomitant use of amiodarone/nifekalant, i.v. inotropics and i.v. vasodilators at the time of the questionnaire was higher in patients with depression. These findings might be due to a higher proportion of moderate to severe heart failure patients among patients with depression. More than half of the heart failure patients in Japan have non-ischemic etiologies, unlike in Western countries, where the majority of heart failure patient have ischemic etiologies.[54–56] From the present results, regardless of the etiology, severe heart failure, higher plasma BNP and higher NYHA functional class were associated with depression and are risk factors for cardiovascular events and mortality. The prevalence of heart failure increases with age, and depression will be expected to rise in coming years because of the growing elderly population.

Table 3. Multivariate Analysis for the Primary Outcome

	HR (95%CI)	P value
NYHA class III/IV	2.07 (1.14–3.72)	0.01
Implantation of ICD/CRT-D	4.04 (2.15–7.06)	<0.01
eGFR <60 ml·min^{-1}·1.73 m^{-2}	3.26 (1.84–5.76)	<0.01
LVEF≤35%	2.06 (1.03–4.13)	0.04
Depression	2.25 (1.30–3.92)	<0.01
Female gender	1.02 (0.55–1.87)	0.94
Age≥65 years	0.83 (0.48–1.44)	0.83
Diabetes	1.47 (0.74–2.94)	0.26
Hypertension	0.97 (0.53–1.74)	0.91

HR, heart rate; CI, confidence interval. Other abbreviations see in Table 1.

Single or widow status was associated with depression. Regarding socioeconomic status, the employment rate was lower in patients with depression, although work status was not a statistically independent factor for depression. Education also was not related to depression. Using national survey data, Inaba et al reported that the depression score according to CES-D is higher in women, single people, and people with lower incomes in both Japan and the USA, but there is no association between education and depression in Japan; however, depression is inversely related to education in the USA.[57] The present findings that higher prevalences of single people and people with low employment status, but not level of education, were seen in patients with depression might be due to certain common features of Japanese patients with depression.

There are several mechanisms to consider concerning the relationships between depression and poor outcomes in patients with cardiovascular disease.[6] First, behavioral problems decrease patient compliance. Depressive symptoms have been associated with poor adherence to medications, diet, fluid restriction, and exercise as well as poor social support.[2,6,58,59] In the present subjects, poor social status, such as being unmarried or unemployed, was associated with depression. Poor social support also has been reported to be independently associated with worse cardiovascular outcome.[60] Second, biological mechanisms are involved in poor cardiovascular outcomes. Several events have been associated with these poor outcomes, including changes in cardiac autonomic tone, activation of the sympathetic nervous system, enhanced activity of the hypothalamic–pituitary–adrenal axis, and elevated inflammatory and pro-inflammatory processes.[1,2,6,61] Although depression is associated with poorer outcome in patients with cardiovascular disease, its pathophysiologic mechanisms are not completely understood. In the present study, death due to heart failure and hospitalization for heart failure were major adverse cardiovascular events, and the rates of these events were significantly different between patients with and without depression. There was significantly higher use of spironolactone/eplerenone and warfarin at discharge in patients with depression than in those who were not depressed. This difference might be related to a

higher rate of coexisting heart failure in patients with depression. Recently Zuluaga et al suggested that the association between depression and higher long-term mortality in patients hospitalized for heart failure is explained largely by the presence of comorbidities, physical inactivity, and disability.[62] Moreover, several reports concluded that therapy for depression improved depressive symptoms but not cardiovascular outcomes in patients.[6,63,64] In the present study, antidepressant use was higher in patients with depression, but the small rate of usage of these drugs did not contribute to patient outcomes. Depression may be merely a surrogate marker of poor prognosis but it may be an important marker, especially in patients with heart failure. The management of depression and cardiovascular disease, including proactive follow-up by nurses or care managers,[65] intervention with cognitive behavioral therapy, or social support,[66] is important for improving compliance and therapeutic outcomes in patients with cardiovascular disease and depression.

Study Limitations

There were some limitations in the present study. First, this was a single-center cohort study. The clinical characteristics of the present patients might not reflect those of general cardiovascular patients in Japan because the present institution is a university hospital. The prevalence of coronary heart disease was only 31%, and half of the patients were in NYHA functional class II–IV. In addition, there was a treatment bias. Therefore, the present results have limited generalizability in overall cardiac care. Second, the present patients were not consecutively enrolled, and many patients who received emergent or intensive care were not enrolled because it was not possible for them to complete the questionnaire. Moreover, there was an approximately 50% response rate for the Zung SDS questionnaire in the enrolled patients. This self-report 20-item written questionnaire was used as a convenient screening method but was limited by the document return rate from all subjects and the validity of the responses. From these limited data, we could not determine the contribution of depression to clinical condition in several patients with cardiovascular disease. Third, the questionnaire was not completed before discharge. The primary aim of the present study was to evaluate the prevalence and distribution of depression in hospitalized patients. Moreover, the length of hospital stay ranged from a few days to several months because cardiovascular diseases are heterogeneous. For long-term prognosis, an assessment immediately before discharge might be more appropriate. Previous research has demonstrated, however, that depression at the time of hospitalization, not only before discharge, is associated with poor prognosis in patients with cardiovascular disease.[66–69] Although this problem exists, the present results demonstrate the importance of assessment at an early stage of management of cardiovascular patients. Four, because the number of subjects in the present study was relatively small, subgroup analysis was not feasible. To clarify these issues, large multicenter clinical investigations that include several regions in Japan are needed.

Conclusion

The present results suggest that depression is not uncommon in Japanese cardiovascular inpatients, especially in those with heart failure or who are on ICD therapy. Depression is associated with subsequent cardiovascular outcomes or mortality and may be an important marker of poor prognosis.

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Disclosures

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