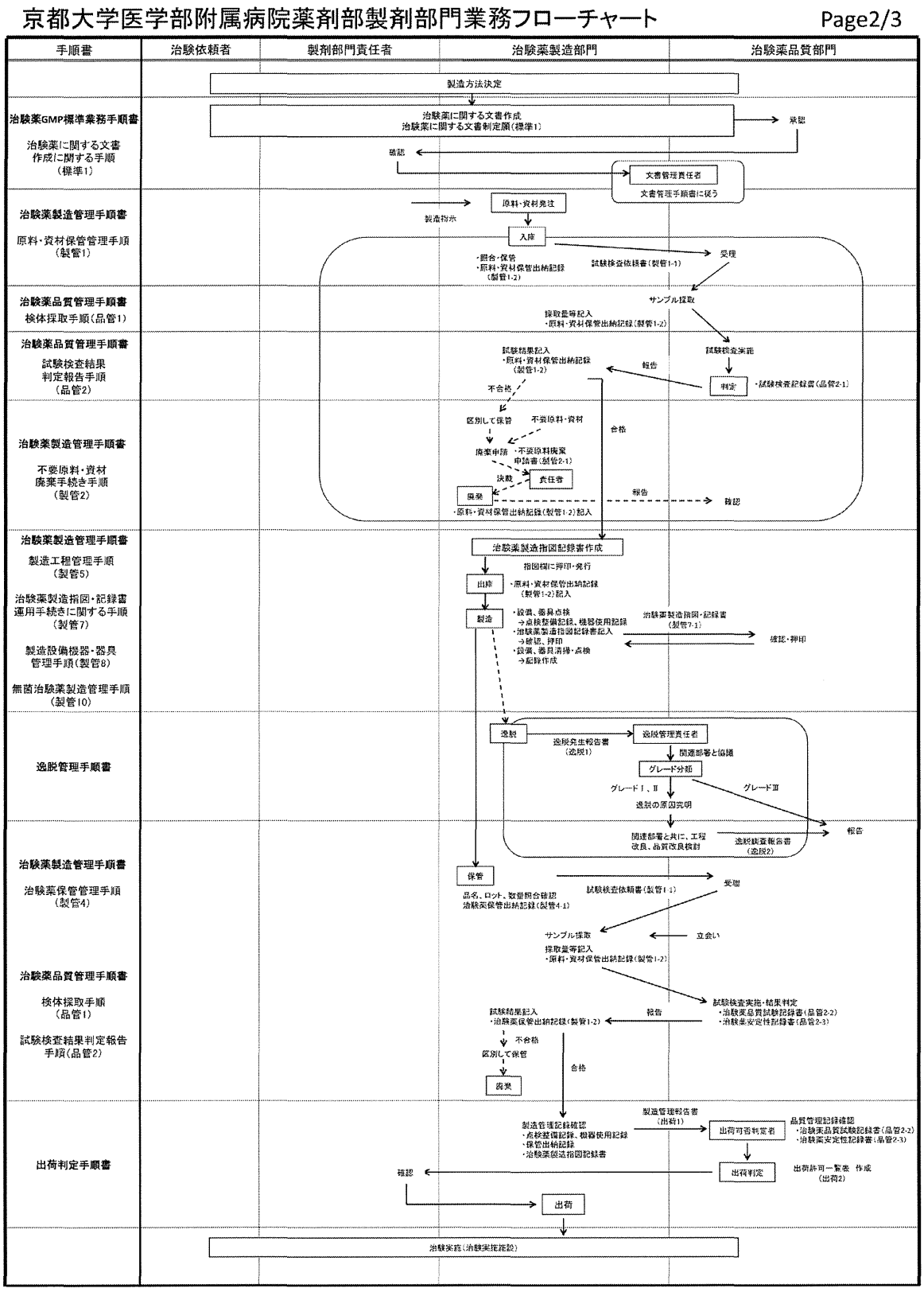

図 2-2　業務フローチャート

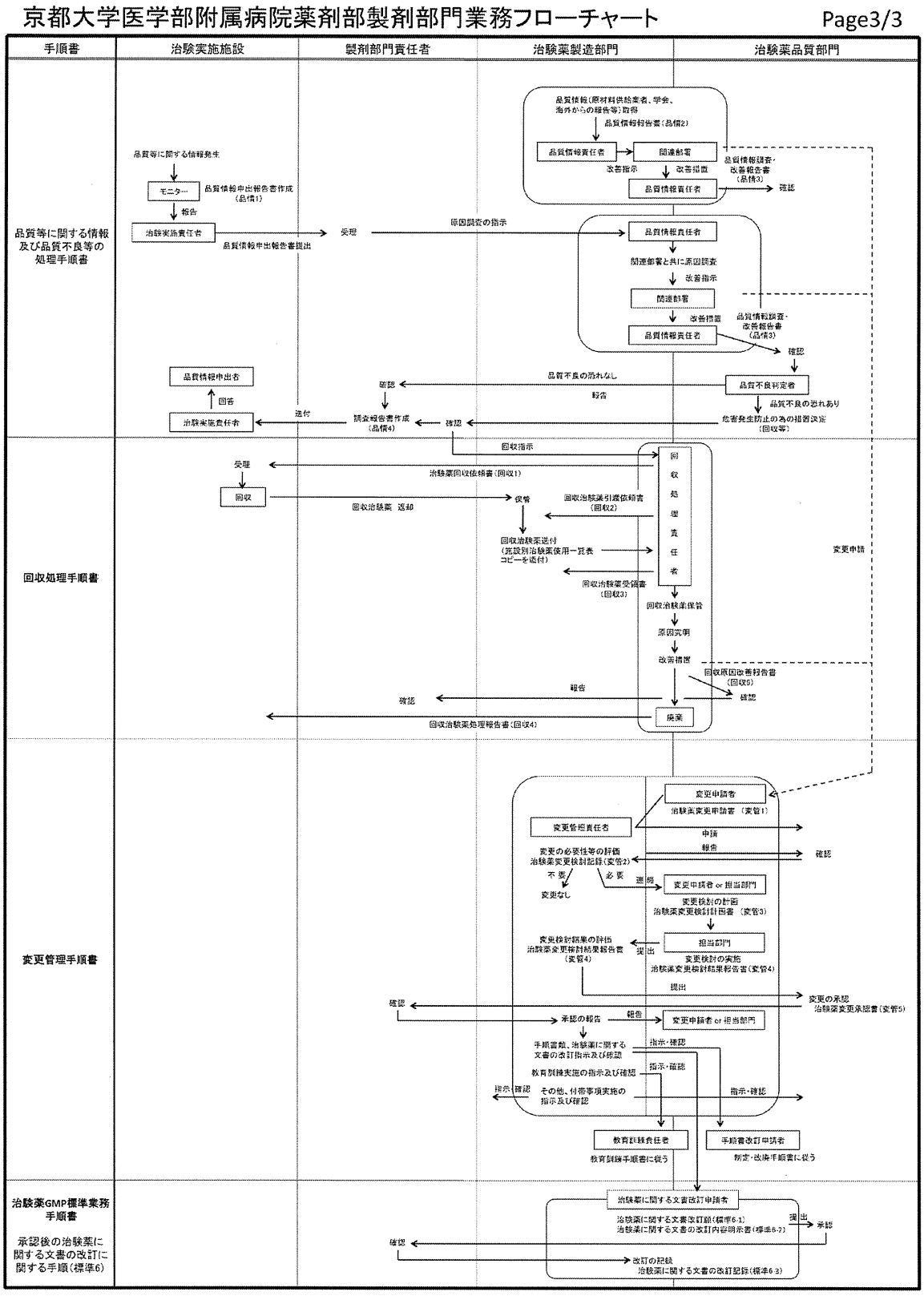

図 2-3 業務フローチャート

表 4　治験薬 GMP と作成手順書の対応評価

治験薬 GMP の項目	対応する手順書
第 1　総則	
1. 目的	＊ 1.〜4. については目的，基本的考え方等の記載のため，対応する手順書はなし
2. 適用範囲	
3. 基本的考え方	
4. 定義	
第 2　治験薬の製造管理及び品質管理	
5. 治験薬製造部門及び治験薬品質部門	治験薬 GMP 標準業務手順書
6. 治験薬の出荷の管理	出荷判定手順書
7. 治験薬に関する文書	治験薬 GMP 標準業務手順書
8. 手順書等	＊治験薬の衛生管理，製造管理，品質管理に関する手順を始め，治験薬の製造管理及び品質管理を適正かつ円滑に実施するために必要な手順書の作成と保管を求めており，これらに対応する 15 冊の手順書を作成した
9. 治験薬の製造管理	治験薬製造管理手順書，衛生管理手順書
10. 治験薬の品質管理	治験薬品質管理手順書
11. 外部試験検査機関等の利用	治験薬品質管理手順書
12. バリデーション及びベリフィケーション	バリデーション及びベリフィケーション手順書
13. 変更の管理	変更管理手順書
14. 逸脱の管理	逸脱管理手順書
15. 品質等に関する情報及び品質不良等の処理	品質等に関する情報及び品質不良処理手順書
16. 回収処理	回収処理手順書
17. 自己点検	自己点検手順書
18. 教育訓練	教育訓練手順書
19. 文書及び記録の管理	文書及び記録管理手順書
20. 委託製造	委託製造手順書
21. 治験薬の製造施設の構造設備	＊対応する手順書なし （記載に基づいて製造設備を整備した）

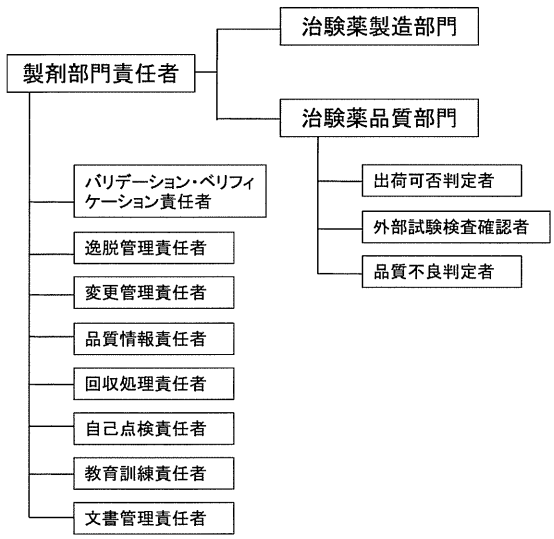

図 3　組織体制図

担当人員について，治験薬 GMP 標準業務手順書に治験薬製造，品質管理に携わる責任者および担当者を任命するための手順を規定し，図 3 に示すような人員配置を行った．なお，本施設においては治験薬の品質管理に係る部門（治験薬品質部門）の担当者が製剤部門責任者を除く責任者を兼務することにより，4 名の人員で人員配置を行った．また，治験薬 GMP への対応について評価を行った．その結果，治験薬 GMP「5.1」および「5.2」で規定される「治験薬の製造管理に係る部門（治験薬製造部門）及び治験薬品質部門を独立しておかなければならない.」を満たしていることが示された（図 3）．また，「20. 委託製造」を除く治験薬 GMP 各項において「あらかじめ指定した者」として任命が求められる担当者について，出荷可否判定者，外部試験検査確認者，バリデーション・ベリフィケーション責任者，逸脱管理責任者，変更管理責任者，品質情報責任者，品質不良判定者，回収処理責任者，自己点検責任者，教育訓練責任者，文書管理責任者として任命する手順が，全て規定されていることが明らかになった（表 5）．委託製造については，本施設においては治験薬の製造工程の全部または一部を治験薬受託製造者に委託しないため，担当者の任命手順は現時点で規定しなかった．これにより，製剤部

表5　治験薬GMPに基づいた人員配置の整合性評価

治験薬GMPの項目	規定	担当者
第1　総則		
1. 目的	なし	−
2. 適用範囲	なし	−
3. 基本的考え方	なし	−
4. 定義	なし	−
第2　治験薬の製造管理及び品質管理		
5. 治験薬製造部門及び治験薬品質部門	治験薬製造部門及び治験薬品質部門を独立しておかなければならない	治験薬製造部門 治験薬品質部門
6. 治験薬の出荷の管理	品質部門のあらかじめ指定した者	出荷可否判定者
7. 治験薬に関する文書	なし	−
8. 手順書等	なし	−
9. 治験薬の製造管理	なし	−
10. 治験薬の品質管理	品質部門のあらかじめ指定した者	出荷可否判定者
11. 外部試験検査機関等の利用	品質部門のあらかじめ指定した者	外部試験検査確認者
12. バリデーション及びベリフィケーション	あらかじめ指定した者	バリデーション・ベリフィケーション責任者
13. 変更の管理	あらかじめ指定した者	変更管理責任者
14. 逸脱の管理	あらかじめ指定した者	逸脱管理責任者
15. 品質等に関する情報及び品質不良等の処理	あらかじめ指定した者 品質部門のあらかじめ指定した者	品質情報責任者 品質不良判定者
16. 回収処理	あらかじめ指定した者	回収処理責任者
17. 自己点検	あらかじめ指定した者	自己点検責任者
18. 教育訓練	あらかじめ指定した者	教育訓練責任者
19. 文書及び記録の管理	あらかじめ指定した者	文書管理責任者
20. 委託製造	あらかじめ指定した者	＊委託製造を行わないため任命は行わない
21. 治験薬の製造施設の構造設備	なし	−

門責任者の下に治験薬ごとに治験薬製造部門と治験薬品質部門を互いに独立して設置し，治験薬の品質を確保するための責任者を任命する体制を構築できていることが示された．

3. 特殊無菌製剤室の衛生管理

ろ過滅菌後，一連の無菌操作法で製造される無菌医薬品については，第十五改正日本薬局方参考情報「29. 無菌医薬品製造区域の微生物評価試験法」に「出発原料の秤量及び溶液調製は，グレードC以上の環境で行う」，「無菌ろ過後，閉塞までのすべての無菌操作はグレードAの環境で取り扱わなければならない」と記載されている[5]．グレードAに管理する必要のあるクリーンベンチおよびグレードCに管理する必要のある無菌室について浮遊微粒子数（粒子径≧0.5 μm）のモニタリングシステムを設置した（**図1-C, 1-D**）．無菌室は温度，湿度，室内空気圧についてもモニタリングを常時行い，その記録は全て保存した．また，特殊無菌製剤室内における衛生管理を適切に行うための清浄度評価手順について，衛生管理手順書に規定した．

衛生管理手順書の規定に従って，ある試験薬の製造法バリデーション，製造準備および試験薬の製造を行った10日間について，作業時，非作業時の浮遊微粒子数，表面付着微生物および浮遊菌を測定した．浮遊微粒子数については，クリーンベンチ内清掃のためにクリーンベンチ内空気の採取孔付近を清拭した時の測定値およびクリーンベンチの電源を切った状態で，無菌室内で作業を行った時の測定値は除外した．表面付着微生物については，1日の作業終了後，殺菌・消毒を行う前および定期的な無菌室の清掃後に測定を行った．また，浮遊菌については，製造作業の終了時および定期的な無菌室の清掃後に測定を行った．浮遊微粒子数は，クリーンベンチ内については作業時71 /m^3，非作業時212 /m^3，無菌室内については作業時244660 /m^3，非作業時212 /m^{3}であった（**表6**）．上記の期間中に表面付着微生物の測定は6回，浮遊菌の測定は2回実施した．表面付

表6　特殊無菌製剤室における浮遊微粒子数の基準値および最大測定値

	浮遊微粒子数（0.5 μm 以上）/m^3			
	クリーンベンチ（グレードA）		無菌室（グレードC）	
	基準値	最大値	基準値	最大値
作業時	≦3530	71	≦3530000	244660
非作業時	≦3530	212	≦353000	212

表7　特殊無菌製剤室における表面付着微生物数および浮遊菌数の最大値

	クリーンベンチ（グレードA）		無菌室（グレードC）	
	規格値	最大値	規格値	最大値
表面付着微生物数（CFU/25cm^2）	＜1	0	≦25	0
浮遊菌数（CFU/m^3）	＜1	0	≦100	0

着微生物については，クリーンベンチ内，無菌室内ともに検出されなかった（表7）．また，浮遊菌についても，クリーンベンチ内，無菌室内ともに検出されなかった．ほかの期間に上記と同様のタイミングで行った表面付着微生物および浮遊菌の測定についても，検出された菌数は全て基準内であった．以上より，作業時，非作業時ともに，浮遊微粒子数，表面付着微生物数および浮遊菌数は，クリーンベンチ内についてはグレードA，無菌室内についてはグレードCの基準をそれぞれ満たすことが明らかになった．

考　察

治験薬は，「医薬品の臨床試験の実施の基準に関する省令」（平成9年厚生省令第28号）に基づき治験薬GMPに従って製造される[1]．他方，臨床試験用の試験薬の製造については明確な規定がなく，様々なグレードの試験薬を用いて臨床試験が実施されてきたと推察される．「革新的医薬品・医療機器創出に関する5か年戦略」に従い，様々な早期探索的臨床試験の制度が確立されてきた．そのなかでは，試験薬の製造に関しても基準が規定されている．マイクロドーズ臨床試験においては，「マイクロドーズ臨床試験の実施に関するガイダンス」のなかで，被験物質の品質管理に対する考え方として治験薬GMPの遵守が求められる旨が記載されている[6]．また，再生・細胞医療においては，「医療機関における自家細胞・組織を用いた再生・細胞医療の実施について」のなかで，加工・品質管理の在りかたについては，「治験薬の製造管理，品質管理等に関する基準（治験薬GMP）」等に規定するところによるものとする旨が記載されている[7]．さらに，平成20年4月より開始された高度医療評価制度においては，実施責任医師の下で試験薬の製造が可能である[8]．製造管理について明確な基準は定められていないものの，第9，17，20回の高度医療評価会議の議事録によると治験薬GMPへの準拠が求められている（http://www.mhlw.go.jp/stf/shingi/2r98520000008zaj.html#shingi67）．今回，京都大学医学部附属病院薬剤部に新たに特殊無菌製剤室を設置し，治験薬GMPに基づいて製造施設の構造設備および製造管理，品質管理の方法を確立した．これにより，質の高い院内製剤を用いて，医師主導の治験，高度医療，マイクロドーズ臨床試験などの臨床試験が実施可能となった．

改正前の治験薬GMPにおいては，治験薬製造施設の基準として「治験薬の製造施設の構造設備基準」が定められていた[4]．本研究における製造設備は治験薬GMP改正の前に設置したため，治験薬の製造施設の構造設備基準に従って設置し，評価を行った．その結果，設置した特殊無菌製剤室は「治験薬の製造施設の構造設備基準」について，一部の項目を満たしておらず，該当しないと判断した項目が4項目あった（表1，表2）．該

当しないと判断した4項目についてそのように判断した根拠は以下の通りである．第1条第三項トについては，製造工程において有毒ガスが発生する品目がないため，第1条第三項リについては，複数の治験薬を同時に製造することはないため該当しないと判断した．また，備えるべき試験検査の設備および器具のうち，第3条第六項イおよびホについては，密封状態検査および発熱性物質試験を行わないため該当しないと判断した．該当しない項目があるものの，本施設における試験薬の製造には当てはまらないため，製造した試験薬の品質は担保できているものと考える．

適合していなかった項目は，以下の4項目であった．第3条第一項ニ(4)については，本施設ではクリーンベンチ内で手作業で試験薬の製造を行っているため，それぞれの作業について作業室を専用にするまたは閉鎖式設備を導入することは困難である．従って，同時期に複数ロットの試験薬製造は行わず，試験薬の調製と充填，閉塞を同時に行わないことで交叉汚染を防止することとした．また，第3条第一項ニ(5)については，治験注射剤の製造器具については専用もしくはディスポーザブル製品を使用しているが，手作業での製造作業を行っているため閉鎖式の製造設備を用いて試験薬の製造を行うことは困難である．同時期に異なる試験薬製造を行わず，製造する試験薬を変更する際には製造設備の清掃を行うことにより交叉汚染を防止することとした．作業所に備えるべき設備のうち，本施設では第3条第二項ホおよびへの設備を有していなかった．本施設ではこれらの装置を設備として整備するのが困難であるため，衛生管理手順書に基づいて管理されたクリーンベンチ内で調製作業および充填作業を行うことにより，試験薬の汚染を防止することとした．これらの項目については，治験薬GMPに適合していないものの，改正治験薬GMPでは開発初期から必ずしも全ての構造設備の要求を満たすことを求めていない．すなわち，開発に伴う段階的な状況やリスクを考慮して，適切だと判断される要件については柔軟に運用することとされている．特に製造施設の構造設備については，治験薬GMP「3.4」において，治験薬の製造スケール等，開発と共に大きく変更されることが必然であり，開発段階に応じた適切な管理が求められるという観点から，「医薬品の製造販売承認の要件及び医薬品の製造業許可の要件として求められる製造所の構造設備を認識したうえで，必要な対応を図ること」と述べられている[1]．従って，本施設においても，「治験薬の製造施設の構造設備基準」を全て満たすものではないが，初期の段階においては個々の試験薬製造に適したバリデーション，ベリフィケーション，試験薬の安定性試験を実施することで，早期探索的臨床試験に応じた適切な管理のもと製造された試験薬の提供が可能であると考えられる．

無菌医薬品製造区域の衛生管理については，第十五改正日本薬局方参考情報「29. 無菌医薬品製造区域の微生物評価試験法」に空気清浄度および環境モニタリングによる環境微生物の管理について記載されている[5]．空気の清浄度については清浄度レベルごとに最大許容粒子数が規定されており，微生物のモニタリングについては，清浄度レベルごとにモニタリングの参考頻度および環境微生物の評価基準が規定されている．本施設での衛生管理において，浮遊微粒子数は無菌医薬品製造のための空気の清浄度，表面付着微生物数および浮遊菌数については環境微生物の評価基準の基準値を満たしていた．他方，グレードAの重要区域のモニタリング頻度は，必ずしも基準を満たしていない．本施設では試験薬の製造を手作業で行っており，クリーンベンチ内に製造途中の中間製品が置かれていることもあるため，製造途中で浮遊菌測定のための機器を搬入し空気の吸引を行うことは試験薬を汚染する原因ともなりうるため困難である．1日の作業終了時に表面付着微生物をモニタリングすることにより衛生管理を行っており，開発段階に応じた適切な衛生管理を行っているものと考える．

治験薬GMPの「3. 基本的考え方」として，治験薬の製造管理および品質管理に係る全ての記録について，後日の確認が取れるように保管すること，開発段階における全ての変更を管理し，文書化し，記録として保存することが挙げられている[1]．今回，治験薬GMPで求められる手順書を作成し，製造

管理，品質管理の各段階において全ての情報に関する文書を作成することにより，確実に記録を残すことができる体制を構築した．このことにより，臨床試験で得られた成果や試験薬の安全性に関する信頼性が担保されると考えられる．さらに，アカデミアで実施した臨床試験の後，治験の実施等，承認を目指した開発のために臨床試験の成果を企業にライセンスアウトする．治験薬GMPに従って製造管理，品質管理，変更等に関する記録が保管されていることで，知財権だけでなく製造に関するノウハウが導出可能となった．従って，アカデミアにおける臨床試験成果が，論文作成の情報となるだけでなく，今後の開発において有用な資料になると考えられる．

トランスレーショナルリサーチの推進のためには，基礎研究者，プロジェクトマネージャー，医師，治験コーディネーター，生物統計家など種々の専門家が協力して行うことが最も大切である．早期探索的臨床試験を実施するにあたり，試験薬の供給は1つの障壁になるため，薬剤師が専門を生かし，チームの一員として院内製剤製造を行うことにより，トランスレーショナルリサーチの推進に寄与することができる．本施設において，治験薬GMPに準拠して製造を行った試験薬を用いた臨床試験が，高度医療評価制度において第3項先進医療として承認され，臨床試験が開始された（http://www.kyoto-u.ac.jp/ja/news_data/h/h1/news6/2010/100901_1.htm）．今回，薬剤部において治験薬GMP基準の臨床試験用院内無菌製剤室を設置したことにより，高品質な試験薬の提供が可能となり，被験者の安全と試験の信頼性を確保した質の高い臨床試験に貢献できたものと考える．

謝　辞

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Benefits of Off-Pump Coronary Artery Bypass Grafting in High-Risk Patients

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Benefits of Off-Pump Coronary Artery Bypass Grafting in High-Risk Patients

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Background—The benefits of off-pump coronary artery bypass graft (OPCAB) compared with conventional on-pump coronary artery bypass graft (CCAB) remain controversial. Thus, it is important to investigate which patient subgroups may benefit the most from OPCAB rather than CCAB.

Methods and Results—Among the patients undergoing first coronary revascularization enrolled in the CREDO-Kyoto Registry (a registry of first-time percutaneous coronary intervention and coronary artery bypass graft patients in Japan), 2468 patients undergoing coronary artery bypass graft were entered into the study (mean age, 67±9 years). Predicted risk of operative mortality (PROM) of each patient was calculated by logistic EuroSCORE. Patients were divided into tertile based on their PROM. Mortality rates and the incidences of cardiovascular events were compared between CCAB and OPCAB within each PROM tertile using propensity score analysis. A total of 1377 patients received CCAB whereas 1091 received OPCAB. Adjusted 30-day mortality was not significantly different between CCAB and OPCAB patients regardless of their PROM range. However, the odds ratio of 30-day stroke in CCAB compared with OPCAB in the high-risk tertile was 8.30 (95% confidence interval, 2.25–30.7; $P<0.01$). Regarding long-term outcomes, hazard ratio of stroke in CCAB compared with OPCAB in the high-risk tertile was 1.80 (95% confidence interval, 1.07–3.02; $P=0.03$). Nevertheless, hazard ratio of overall mortality in the high-risk tertile was 1.44 (95% confidence interval, 0.98–2.11; $P=0.06$), indicating no statistically significant difference between the 2 procedures.

Conclusions—OPCAB as opposed to CCAB is associated with short-term and long-term benefits in stroke prevention in patients at higher risk as estimated by EuroSCORE. No survival benefit of OPCAB was shown regardless of preoperative risk level. **(*Circulation*. 2012;126[suppl 1]:S151–S157.)**

Key Words: coronary artery bypass graft ■ high-risk populations ■ off-pump surgery

As awareness of the potential morbidity of cardiopulmonary bypass and aortic manipulation increased and as surgical tools and techniques were improved, off-pump coronary artery bypass grafting (OPCAB) gained widespread acceptance and entered the mainstream of clinical practice.[1] OPCAB is part of the procedural armamentarium of a growing proportion of surgeons worldwide.

The advantages of OPCAB compared with conventional on-pump coronary artery bypass graft (CCAB) remain a source of controversy, however. Several randomized controlled trials (RCT) have been conducted over the past decade to compare the outcomes of these 2 procedures. Equivalent short-term and long-term angiographic graft patency has been demonstrated, but the benefits of OPCAB with regard to mortality and morbidity remain unclear.[2–5] Several retrospective studies have reported that OPCAB is associated with lower incidences of death and stroke.[6–11] This finding may result, at least partially, from the fact that the benefits of OPCAB are not prominent in RCT that excluded high-risk patients. Thus, it is important to investigate which patient subgroups may benefit the most from OPCAB rather than CCAB. In addition, OPCAB is used more frequently in Japan than it is in the United States or Europe, which may enable a more reliable comparison between CCAB and OPCAB using Japanese data.[12–14]

The Coronary Revascularization Demonstrating Outcome Study in Kyoto (CREDO-Kyoto) is a multicenter registry in Japan enrolling 9877 consecutive patients undergoing first percutaneous coronary intervention or coronary artery bypass graft (CABG).[15] In the present study, we sought to investigate

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the benefits of OPCAB using the data from the CREDO-Kyoto registry. The purpose of the present study was to stratify the patients into subgroups according to the logistic European Systems for Cardiac Operative Risk Evaluation (EuroSCORE)[16,17] and to investigate which patient subgroups can be expected to benefit the most from OPCAB rather than CCAB.

Patients and Methods

Study Population

The CREDO-Kyoto is a multicenter registry in Japan that enrolls consecutive patients undergoing first percutaneous coronary intervention or CABG and that excludes those patients with acute myocardial infarction within 1 week before the index procedure.[15] This study was approved by the Institutional Review Boards or Ethics Committees of all participating institutions. Because the subjects were retrospectively enrolled, written informed consent was not obtained, in accordance with the guidelines for epidemiological studies issued by the Ministry of Health, Labor, and Welfare of Japan. However, 73 patients were excluded because of their refusal to participate in the study when contacted for follow-up.[15]

Between January 2000 and December 2002, 9877 patients were identified as having undergone either percutaneous coronary intervention (6878 patients) or CABG (2999 patients) without history of coronary revascularization. Among the 2999 patients undergoing CABG, 484 patients undergoing concomitant valvular, left ventricular, or major vascular operations were excluded from the current analysis. In addition, 47 patients whose records lacked the data required to calculate the logistic EuroSCORE were also excluded. Therefore, the study group comprised 2468 patients undergoing first isolated CABG.

Data Collection and Definitions

Demographic, angiographic, and procedural data were collected from hospital charts or databases at the various centers by independent clinical research coordinators according to prespecified definitions. Baseline clinical characteristics, such as myocardial infarction, heart failure, diabetes, hypertension, current smoker status, atrial fibrillation, chronic obstructive lung disease, and malignancy were regarded as present when these diagnoses were recorded in the hospital charts. Left ventricular ejection fraction was measured either by contrast left ventriculography or by echocardiography. Chronic kidney disease was regarded as present when creatinine clearance estimated according to the Cockcroft–Gould formula was <60 mL/min. Anemia was defined as a blood hemoglobin level <12 g/dL, as previously described.[15]

End Points

An independent clinical events committee adjudicated events. Death was regarded as cardiovascular in origin unless obvious noncardiovascular causes could be identified. Any death during the index hospitalization was regarded as cardiovascular death. Myocardial infarction was adjudicated according to the definition in the Arterial Revascularization Therapy Study.[18] Within 1 week of the index procedure, only Q-wave myocardial infarction was adjudicated as myocardial infarction. Stroke was defined as any new permanent global or focal neurological deficit that could not be attributed to other neurological or medical processes. In the majority of patients, strokes were diagnosed by neurologists and confirmed by computed tomography or magnetic resonance imaging head scans. Stroke at follow-up was defined as symptomatic stroke.

Primary end point was death from any cause. Secondary end points were cardiovascular death, stroke, myocardial infarction, composite cardiovascular event (cardiovascular death, stroke, or myocardial infarction), and need for any revascularization procedures (CCAB or OPCAB) during the follow-up period.

Table 1. Baseline Characteristics

	CCAB, n=1377		OPCAB, n=1091		*P
Age (y)	66.3±9.5		68.5±9.4		<0.01
75 y or older	259	19%	308	28%	<0.01
Male	1002	73%	784	72%	0.62
Body mass index (%)	23.5±3.2		23.5±3.2		0.61
≥25%	386	28%	327	30%	0.30
N of diseased vessels	2.56±0.74		2.48±0.78		0.01
2-vessel disease	302	22%	266	24%	0.15
3-vessel disease	942	68%	692	63%	<0.01
Left main disease	406	29%	319	29%	0.93
Ejection fraction	58.7±15.0		61.5±13.5		<0.01
<40%	173	13%	84	8%	<0.01
Previous myocardial infarction	485	35%	345	32%	0.07
Heart failure	315	23%	300	27%	<0.01
Atrial fibrillation	79	6%	63	6%	1.00
Proximal LAD disease	797	58%	657	60%	0.25
Total occlusion	659	48%	451	41%	0.01
History of stroke	235	17%	292	27%	<0.01
Peripheral vascular disease	235	17%	253	23%	<0.01
Chronic obstructive pulmonary disease	31	2%	22	2%	0.78
Emergency procedure	73	5%	67	6%	0.38
Diabetes mellitus	636	46%	498	46%	0.81
Diabetes with insulin therapy	184	13%	126	12%	0.18
Hypertension	915	66%	814	75%	<0.01
Hyperlipidemia	705	51%	616	56%	<0.01
Hemodialysis	66	5%	53	5%	1.00
Chronic kidney disease	599	44%	496	45%	0.35
Malignancy	83	6%	79	7%	0.07
Hemoglobin	12.7±2.0		12.6±1.9		0.13
<12 mg/dL	455	33%	364	33%	0.54
Current smoker	355	26%	257	24%	0.14

CCAB indicates conventional on-pump coronary artery bypass graft; LAD, left anterior descending artery; OPCAB, off-pump coronary artery bypass graft.

*P is for comparison among CCAB and OPCAB.

Risk Stratification by Logistic EuroSCORE

EuroSCORE was used to calculate predicted risk of mortality (PROM).[17,16] Based on their PROM, patients were stratified into low-risk (PROM <3%), intermediate-risk (PROM 3% to <6%), and high-risk (PROM ≥6%) tertiles.

Statistical Analyses

All continuous variables were expressed as the mean±standard deviation. Differences in baseline characteristics between the 2 groups were examined by unpaired *t* test and Fisher exact test.

Outcomes after CCAB or OPCAB according to tertiles of PROM were compared by the propensity score-adjusted logistic regression or Cox proportional hazard models.[19] These analyses were performed according to the intent-to-treat principle. The PROM of each patient was calculated based on the logistic EuroSCORE and used to divide patients into tertiles. Propensity scores, ie, the probability that a patient would undergo CCAB or OPCAB, were calculated for each

Table 2. Coronary Artery Bypass Graft Data

	CCAB, n=1377		OPCAB, n=1091		P
N of anastomotic sites	3.3±1.0		3.2±1.3		<0.01
Type of bypass grafts					
Left internal thoracic artery	1260	92%	1024	94%	0.03
Right internal thoracic artery	180	13%	571	52%	<0.01
Right gastroepiploic artery	276	20%	366	34%	<0.01
Radial artery	540	39%	250	23%	<0.01
Saphenous vein	1022	74%	460	42%	<0.01
Total arterial revascularization	355	26%	631	58%	<0.01
N of anastomotic vessels	2.6±0.6		2.4±0.7		<0.01

CCAB indicates conventional on-pump coronary artery bypass graft; OPCAB, off-pump coronary artery bypass graft.

patient according to a logistic regression model that includes the following confounders: age; gender; body mass index; emergency procedure; critical preoperative state (ventricular tachycardia/ventricular fibrillation or aborted sudden death, preoperative cardiac massage, preoperative ventilation before arrival in the anesthetic room, preoperative inotropes or intra-aortic balloon pump, preoperative acute renal failure); previous myocardial infarction, congestive heart failure; stroke; peripheral arterial disease; carotid artery disease; atrial fibrillation; chronic obstructive pulmonary disease; malignancy; hypertension; diabetes; hemodialysis; chronic kidney disease; anemia; current smoker status; left ventricular ejection fraction; total occlusion; proximal left anterior descending disease; triple-vessel disease; left main disease; and use of left internal thoracic artery, right internal thoracic artery, gastroepiploic artery, radial artery, or saphenous vein. The C statistics for the fitted logistic regression model was 0.820, indicating that the model fitting was excellent. These confounding factors were adjusted for by stratifying patients into quartiles according to propensity scores. Differences in odds ratios or hazard ratios across the PROM tertiles were examined by tests for interaction terms.

All reported probability values were 2-sided. All analyses were conducted by a statistician using SAS software version 9.2 (SAS Institute, Cary, NC) and S-Plus version 7.0 (Insightful, Seattle, WA). The authors had full access to the data and take responsibility for their integrity.

Results

Baseline Characteristics and Operative Outcomes

Of the 2468 patients in the CREDO-Kyoto registry, 1377 patients (56%) received CCAB and 1091 (44%) received OPCAB. Baseline characteristics of the patients in the 2 groups are presented in Table 1. The OPCAB group included more high-risk patients, such as those with older age, heart failure, history of stroke, and peripheral arterial disease. The number of diseased vessels per patient was typically higher in the CCAB group. The number of patients with left main disease was similar between the groups.

The average number of anastomotic sites per patient was 3.3±1.0 in the CCAB group and 3.2±1.3 in the OPCAB group (Table 2). Left internal thoracic artery grafts were used similarly in both groups. However, arterial grafts in such vessels as the right internal thoracic artery and the gastroepiploic artery were used more commonly in the OPCAB group. Total arterial revascularization was more common in the OPCAB group.

The 30-Day Outcomes

Unadjusted 30-day mortality was 2.2% in the CCAB group and 0.82% in the OPCAB group. A comparison of 30-day outcomes in the CCAB and OPCAB groups, categorized according to PROM tertile, is presented in Table 3. Propensity-adjusted 30-day mortality was not significantly different between the groups regardless of the PROM range. Proportions of 30-day stroke were similar between the 2 groups in the low-risk and intermediate-risk tertiles, but the odds ratio of 30-day stroke in CCAB compared with OPCAB was 8.30 (95% confidence interval [CI], 2.25–30.7; $P<0.01$). Proportions of 30-day myocardial infarction were similar between the 2 groups in the high-risk tertile. Those composite cardiovascular events were also similar between the 2 groups in the low-risk tertile, but the odds ratio of composite event was 2.72 (95% CI, 1.10–6.72; $P=0.03$) in the intermediate-risk tertile and 2.58 (95% CI, 1.27–5.23; $P=0.01$) in the high-risk tertile.

Long-Term Outcomes

Clinical follow-ups were completed for 98% of the cases at 1 year and for 95% of the cases at 2 years. The median follow-up period was 1314 days. Unadjusted overall mortality rates in the CCAB and OPCAB groups were 4.9% and 4.1% at 1 year, and 14.6% and 14.9% at 5 years, respectively. The Figure shows the Kaplan–Meier curves for all-cause mortality and stroke stratified by PROM. The 3 groups had significantly different rates of all-cause death and stroke ($P<0.01$, respectively).

A comparison of long-term outcomes in the CCAB and OPCAB groups, categorized according to PROM tertile, is presented in Table 4. Propensity-adjusted overall mortality was not significantly different between the CCAB and OPCAB groups regardless of the PROM range, although mortality after CCAB tended to be higher in the high-risk tertile (1.44; 95% CI, 0.98–2.11; $P=0.06$). Adjusted incidence of myocardial infarction was similar between the procedures except in the intermediate-risk tertile. Adjusted incidence of any revascularization was similar between the 2 groups regardless of the PROM range. Adjusted incidence of stoke was similar between the 2 groups in the low-risk and intermediate-risk tertiles, but the hazard ratio of the incidence of stroke in CCAB compared with OPCAB in high-risk tertile was 1.80 (95% CI, 1.07–3.02; $P=0.03$). In addition, the hazard ratios of the incidence of composite cardiovascular events in CCAB compared with OPCAB in the intermediate-risk and high-risk tertiles were 1.68 (95%

Table 3. Propensity Score Analysis of 30-Day Outcomes in 2468 Patients Undergoing Coronary Artery Bypass Graft

	Subgroup by EuroSCORE	N	Events (CCAB vs OPCAB)		Odds Ratio (CCAB vs OPCAB)	95% CI		P
30-day death								
	<3%	793	6	0	...	...	...	...
	3%–6%	860	5	2	4.64	0.68	31.4	0.12
	≥6%	815	19	7	2.35	0.84	6.58	0.10
Composite event*								
	<3%	793	16	5	2.05	0.64	6.55	0.22
	3%–6%	860	21	12	2.72	1.10	6.72	0.03
	≥6%	815	38	14	2.58	1.27	5.23	0.01
Myocardial infarction								
	<3%	793	10	3	1.55	0.33	7.32	0.58
	3%–6%	860	8	5	4.01	1.04	15.5	0.04
	≥6%	815	5	6	0.49	0.13	1.78	0.28
Stroke								
	<3%	793	3	2	1.74	0.26	11.9	0.57
	3%–6%	860	12	6	2.95	0.88	9.92	0.08
	≥6%	815	20	3	8.30	2.25	30.7	<0.01

CCAB indicates conventional on-pump coronary artery bypass graft; CI, confidence interval; OPCAB, off-pump coronary artery bypass graft.

The confounders used to calculate propensity scores are as follows: age; gender; body mass index; emergency procedure; critical preoperative state; previous myocardial infarction; congestive heart failure; stroke; peripheral arterial disease; carotid artery disease; atrial fibrillation; chronic obstructive pulmonary disease; malignancy; hypertension; diabetes; hemodialysis; chronic kidney disease; anemia; current smoker status; left ventricular ejection fraction; total occlusion; proximal left anterior descending artery disease, triple-vessel disease; left main disease; and use of left internal thoracic artery, right internal thoracic artery, gastroepiploic artery, radial artery, or saphenous vein.

*Composite event: cardiovascular death, stroke, or myocardial infarction.

CI, 1.07–2.66; $P=0.03$) and 1.46 (95% CI, 1.03–2.08; $P=0.03$), respectively.

Discussion

Principal Findings

Because the benefits of OPCAB compared with CCAB remain controversial, the present study was designed to identify the patient subgroups that are likely to benefit the most from OPCAB rather than CCAB. Patients were divided into tertiles (low-risk, intermediate-risk, and high-risk) based on their PROM as calculated using the logistic EuroSCORE.

Thirty-day outcomes revealed no significant difference in survival between the CCAB and OPCAB groups regardless of the PROM range. In the high-risk tertile, however, OPCAB was associated with lower incidence of stroke and composite cardiovascular event. Long-term outcomes likewise revealed no significant difference in survival between the CCAB and OPCAB groups regardless of preoperative risk level. In the high-risk tertile, however, stroke rate was significantly higher

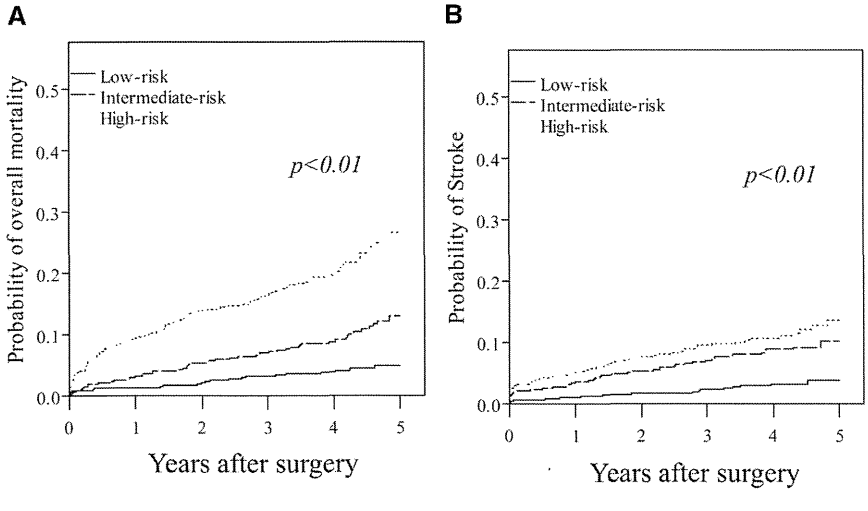

Figure. Kaplan–Meier curves for all-cause death and stroke stratified by predicted risk of operative mortality (PROM). **A**, All-cause death. **B**, Stroke.

Table 4. Propensity Score Analysis of Long-Term Outcomes in 2468 Patients Undergoing Coronary Artery Bypass Graft

	Subgroup by EuroSCORE	N	Events (CCAB vs OPCAB)		Hazard Ratio (CCAB vs OPCAB)	95% CI		P
All-cause mortality								
	<3%	793	17	15	1.08	0.47	2.47	0.86
	3%–6%	860	49	31	1.35	0.77	2.36	0.29
	≥6%	815	85	81	1.44	0.98	2.11	0.06
Composite event*								
	<3%	793	36	18	1.29	0.68	2.47	0.44
	3%–6%	860	81	46	1.68	1.07	2.66	0.03
	≥6%	815	108	78	1.46	1.03	2.08	0.03
Myocardial infarction								
	<3%	793	18	6	1.78	0.60	5.30	0.30
	3%–6%	860	20	8	3.55	1.33	9.50	0.01
	≥6%	815	16	15	0.74	0.32	1.71	0.48
Stroke								
	<3%	793	14	10	1.15	0.46	2.88	0.77
	3%–6%	860	44	24	1.64	0.87	3.09	0.13
	≥6%	815	48	33	1.80	1.07	3.02	0.03
Any revascularization								
	<3%	793	64	33	1.26	0.78	2.02	0.35
	3%–6%	860	51	48	0.75	0.46	1.21	0.23
	≥6%	815	40	48	0.74	0.45	1.22	0.24

CCAB indicates conventional on-pump coronary artery bypass graft; CI, confidence interval; OPCAB, off-pump coronary artery bypass graft.

The confounders used to calculate propensity scores are as follows: age; gender; body mass index; emergency procedure; critical preoperative state; previous myocardial infarction; congestive heart failure; stroke; peripheral arterial disease; carotid artery disease; atrial fibrillation; chronic obstructive pulmonary disease; malignancy; hypertension; diabetes; hemodialysis; chronic kidney disease; anemia; current smoker status; left ventricular ejection fraction; total occlusion; proximal left anterior descending artery disease; triple-vessel disease; left main disease; and use of left internal thoracic artery, right internal thoracic artery, gastroepiploic artery, radial artery, or saphenous vein.

*Composite event: cardiovascular death, stroke, or myocardial infarction.

after CCAB, whereas in both intermediate-risk and high-risk patients the incidence of composite cardiovascular events was higher after CCAB. These results indicate that OPCAB improves both early and late stroke outcomes compared with CCAB in high-risk patients. Still, OPCAB may not be associated with any survival benefit even in high-risk patients.

In the present study, we could not show that OPCAB was associated with survival benefit in high-risk patients, although mortality tended to be higher after CCAB in both 30-day and long-term outcomes ($P=0.10$ and $P=0.06$, respectively). In addition, the incidence of myocardial infarction was similar between the 2 groups in the low-risk and high-risk tertiles but was higher after CCAB in the intermediate-risk tertile. This trend was different from those of other end points. These outcomes might have been influenced by sample size or numbers of events.

CCAB vs OPCAB: RCT and Meta-Analysis

Although a number of RCT comparing CCAB and OPCAB have been performed, until recently, these were not of sufficient size to show statistically significant differences. Several recent studies have been of sufficient size but have failed to demonstrate the superiority of OPCAB compared with CCAB. OPCAB may reduce bleeding or atrial fibrillation, but it is not associated with any significant difference in the incidences of death, myocardial infarction, or stroke.[2–5] A large RCT by Shroyer et al[4] demonstrated that patients undergoing OPCAB had worse composite outcomes and poorer graft patency compared with patients undergoing CCAB. There was no difference in neurocognitive outcomes.

To compensate for the shortcomings of RCT, several meta-analyses also have been performed. Like the RCT, most of these meta-analyses have concluded that mortality, stroke, and myocardial infarction were not reduced in OPCAB.[3,20–22] Moller et al[23] reported that there were no significant differences in mortality, myocardial infarction, stroke, or renewed revascularization in a meta-analysis of 66 RCT. However, Sedrakyan et al[24] reported that OPCAB was associated with benefits in terms of stroke prevention. Another recent large meta-analysis by Afilao et al,[20] which included 59 RCT, compared in-hospital and 30-day outcomes after CCAB and OPCAB, and reported that OPCAB did not reduce mortality or myocardial infarction compared with CCAB. OPCAB was associated with a 30% reduction in stroke, but meta-regression analysis showed that the benefits of OPCAB with

regard to prevention of death, myocardial infarction, and stroke were similar to those of CCAB regardless of patient age, gender, number of grafts, and trial publication date.

CCAB vs OPCAB: Registry

However, several large registry data analyses, including the present study, have provided compelling evidence in favor of OPCAB.[9–11] Puskas et al[9] reported that OPCAB provides significant early mortality and morbidity advantages, especially for women; over the course of 10 years of follow-up, however, OPCAB and CCAB result in similar survival rates, regardless of gender. Hannan et al[10] reported that OPCAB is associated with lower in-hospital mortality and complication rates than CCAB, but long-term outcomes are comparable between the 2 groups, except with regard to the rate of revascularization. An intention-to-treat analysis of 42 477 patients from the Society of Thoracic Surgeons National Adult Cardiac database showed a reduction in risk-adjusted mortality, stroke, and preoperative myocardial infarction in patients undergoing OPCAB.[11]

The reasons for these differences in outcomes between the RCT data and the registry data are unclear. The greater technical difficulty of OPCAB may make it difficult to compare the outcomes of CCAB and OPCAB; in comparison with CCAB, OPCAB is a more technically demanding procedure, especially when it involves branches of the circumflex territory or the peripheral right coronary artery territory. Complete revascularization sometimes may be difficult for inexperienced surgeons. Moreover, the limitations of RCT are attributable, in part, to the limitations involved in patient selection for enrollment. "Truly high-risk" patients are often excluded from such comparisons for ethical reasons. Thus, a comparison of the RCT data with the registry data may play an important role in clarifying the true differences between the 2 procedures and/or the true benefits of OPCAB. Regarding observational studies, the impact of selection bias in determining the operative technique to be used for any given patient in these series may be a confounding variable.

Benefits of OPCAB in High-Risk Patients

As shown in the present study, OPCAB may be associated with better outcomes, particularly in high-risk populations. The observational study by Puskas et al[25] reported that OPCAB as opposed to CCAB is associated with lower operative mortality in higher-risk patients as stratified by The Society of Thoracic Surgeons score (>0.025), and that this benefit increases with increasing predicted risk of mortality. Similarly, Li et al[6] reported that OPCAB is associated with a significantly lower postoperative stroke rate compared with CCAB for older and high-risk patients. The Best Bypass Surgery Trial, a randomized study that compared 30-day outcomes in high-risk patients (EuroSCORE ≥5 and 3-vessel disease) undergoing CCAB or OPCAB,[3] indicated that both procedures can be performed in high-risk patients with a low risk of short-term complications. Because of its small sample size (n=341), however, the study could not reveal any small but clinically relevant differences between the procedures.

Because OPCAB has been performed more frequently in Japan than in European countries or in the United States, Japanese surgeons have accumulated more experience with the OPCAB technique. In 2009, ≈63% of CABG in Japan were conducted without cardiopulmonary bypass, and the 30-day mortality associated with primary elective OPCAB was not >0.6%.[12] The JOCRI study, an RCT conducted in Japan, revealed that OPCAB with multiple arterial grafts was as safe as CCAB, with similar completeness of revascularization and early graft patency.[26] Japanese surgeons' greater familiarity with the OPCAB techniques may enable them to focus more on the advantages of OPCAB in high-risk patients than on the technical difficulty of the procedure. Nevertheless, to clarify the impact of OPCAB compared with CCAB in high-risk patients, further studies must focus on improving research methodology, recruiting high-risk patients, and collecting long-term data.[22]

Study Limitations

There are several important limitations to this study. First, several biases may exist, affecting such matters as indication for revascularization strategy and the level of expertise at CABG for each institution and surgeon involved in the registry. Propensity score analysis may not adequately adjust for these biases. Second, trends in the incidence of myocardial infarction (eg, risk of myocardial infarction in the intermediate-risk tertile) were somewhat different from those in other outcomes. These trends would be adjusted and more strongly supported in a study with a larger sample size. Finally, manipulation and clamping of the aorta is a well-known risk factor for stroke, but we did not have data on whether this was performed in particular patients.

Conclusions

OPCAB as opposed to CCAB is associated with short-term and long-term benefits in terms of stroke prevention in higher-risk patients as estimated based on EuroSCORE. Survival outcomes, however, were not significantly different between CCAB and OPCAB, even in high-risk patients. Further studies are warranted.

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SUPPLEMENTAL MATERIAL

Significant Change using Tukey-Kramer post hoc analysis

Pairwise Timepoint	Chemokines						
	IL-1β	IL-6	KC	MCP-1	MIP-1α	RANTES	TNF-α
0-6	↑				↑		
0-12							
0-18							
0-24							
0-36	↑	↑		↑	↑	↑	
0-48							
6-12	↓				↓		
6-18	↑				↓		
6-24							
6-36		↑		↑			
6-48							
12-18							
12-24							
12-36		↑		↑	↑	↑	
12-48							
18-24							
18-36	↑	↑	↑	↑	↑	↑	
18-48							
24-36		↑		↑	↑	↑	
24-48							
36-48		↓			↓		
6-sham6	↓				↓		
24-sham24							
48-sham48							

Supplementary Table 1: Pairwise comparisons evaluated using Tukey-Kramer post hoc analysis. Arrows indicate a significance level of 5% and the direction of change.

Early angiographic evaluation after off-pump coronary artery bypass grafting

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Objectives: One of the potential drawbacks of off-pump coronary artery bypass is reduced patency compared with conventional coronary artery bypass. This study examined the systematic angiographic evaluation after off-pump coronary artery bypass.

Methods: Of the 1604 consecutive patients who underwent off-pump coronary artery bypass over 6 years, 1422 (89%) who underwent postoperative angiography were analyzed. Generalized estimating equations logistic analyses were used to investigate potential predictors of graft failure (FitzGibbon B or O).

Results: Bilateral internal thoracic arteries were used in 78% of the patients. The mean number of distal anastomoses was 3.7 ± 1.2. The in-hospital mortality rate was 0.4%. Recipient coronary diameter less than 1.5 mm (odds ratio [OR], 1.62; 95% confidence interval [CI], 1.24-2.11) was an independent predictor of graft failure, whereas percent stenosis diameter greater than 75% (OR, 0.71; 95% CI, 0.53-0.93), sequential graft (OR, 0.69; 95% CI, 0.51-0.94), and left main disease (OR, 0.72; 95% CI, 0.53-0.96) were protective factors. In the subanalyses for each conduit, percent stenosis diameter was protective against left internal thoracic artery failure (OR, 0.61), whereas smaller recipient coronary diameter was associated with right gastroepiploic artery and saphenous vein graft failure (OR, 2.37 and 2.36, respectively). Left circumflex artery was associated with gastroepiploic artery graft failure, whereas sequential graft was again protective for the gastroepiploic artery (OR, 4.39 and 0.33, respectively).

Conclusions: Smaller coronary diameter would be a predictor of graft failure, whereas percent stenosis diameter greater than 75%, sequential graft, and left main disease would be protective factors for off-pump bypass grafts. (J Thorac Cardiovasc Surg 2012;■:1-7)

Considerable knowledge has been accumulated since off-pump coronary artery bypass (OPCAB) gained resurgent interest among cardiac surgeons. However, contrary to surgeons' expectations, major outcomes have not been demonstrated to be better with OPCAB than with conventional coronary artery bypass (CCAB).[1,2] Several studies[3] showed that patients undergoing OPCAB experienced reintervention more frequently at follow-up than those undergoing CCAB. Reduced patency in OPCAB may, in part, account for the higher rate of reintervention at follow-up, because OPCAB is a more technically demanding procedure than CCAB.[4] Although some investigators[1] reported equivalent patency rates for OPCAB and CCAB, 2 randomized controlled studies[2,5] have shown that OPCAB was associated with an increased risk of graft failure than CCAB. Shroyer and colleagues[5] demonstrated that the patency rate of the OPCAB arm was lower than that of the on-pump arm on 12-month angiography, and the 1-year composite adverse outcome rate (death from any cause, nonfatal myocardial infarction, and any reintervention procedure) was higher for OPCAB than for CCAB. Several meta-analyses concerning graft patency also showed similar results.[4]

Graft failure is one of the major determinants of clinical prognosis.[6] However, the optimal graft choice for OPCAB has not been determined, and, at present, it is derived from extrapolation of the previous findings in CCAB.[7] High patency rates of arterial conduits at long-term follow-up have been well described in the literature, and attrition seems to be limited to within a few months after the operation.[8] Thus, the early patency of off-pump bypass grafts needs to be evaluated. This study was conducted to examine the findings of the systematic angiographic evaluation done after OPCAB surgery to identify predictors of graft failure.

MATERIALS AND METHODS

Study Design

This was a database study based on Kokura Memorial Hospital patients' medical records. The primary objective of this study was to identify the independent predictors of graft failure on the basis of the postoperative

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Abbreviations and Acronyms

BITA = bilateral internal thoracic artery
CCAB = conventional coronary artery bypass
CI = confidence interval
LAD = left anterior descending
LCx = left circumflex
LITA = left internal thoracic artery
GEA = gastroepiploic artery
GEE = generalized estimating equation
MDCT = multidetector computed tomography
OPCAB = off-pump coronary artery bypass
OR = odds ratio
RCA = right coronary artery
SVG = saphenous vein graft

angiography. In the subanalyses, risk factors for failure of each conduit were explored. This study was approved by the Kokura Memorial Hospital Institutional Review Board, with patient consent waived.

Patients

From January 2000 to December 2005 inclusive, 1604 consecutive patients underwent isolated OPCAB by a single surgeon at Kokura Memorial Hospital. Of these, 1521 patients (95%) underwent systematic angiographic evaluation by means of catheter-based angiography (1422 patients, 89%) or multidetector computed tomography (MDCT; SOMATOM Sensation 16; Siemens AG, Munich, Germany; 99 patients, 6%) before discharge. Because 16-detector row CT has some limitations (eg, lower spatial and temporal resolution), patients who underwent catheter-based angiography comprised the study cohort. Perioperative data were collected prospectively and entered into the institutional database. The definitions of data concerning baseline characteristics conformed to those reported in the European System for Cardiac Operative Risk Evaluation.[9] The definitions of perioperative factors were delineated previously.[10]

Target territories were defined as the left anterior descending (LAD) artery, left circumflex (LCx) artery, or right coronary artery (RCA) on the basis of their anatomy. Percent stenosis diameter was qualitatively assessed by the operating surgeon and dichotomized as greater than 75% or 75% or less in this study.[11] Recipient vessel diameter was determined from an assessment at surgery by means of 1.0-, 1.5-, or 2.0-mm probe insertion.

Surgical Technique

OPCAB was the intended procedure, except for patients with acute myocardial infarction who were in a hemodynamically unstable state even with an intra-aortic balloon pump. There were 77 patients who underwent intended CCAB during the study period. Approximately half of them were in a hemodynamically unstable condition, even with an intra-aortic balloon pump; the remaining patients had previous cardiac surgery and required cardiopulmonary bypass for resternotomy and exposure. All OPCAB procedures were performed under general anesthesia with pulmonary artery pressure monitoring. The heart was approached via median sternotomy. Heparin (100 KIU/kg and an additional dose) was administered to achieve and maintain the activated clotting time at more than 250 seconds. Graft selection was based on the following strategies: (1) Patients with significantly stenosed (≥75%) multivessel disease involving the left coronary arteries received bilateral internal thoracic arteries (BITAs); (2) for the left coronary arteries with less than 75% stenoses, saphenous vein grafts (SVG) or radial arteries were used as additional conduits; (3) for less than 75% and 75% or more stenosed RCAs, SVG and right gastroepiploic arteries (GEAs) were used, respectively. Internal thoracic arteries and GEAs were harvested in a skeletonized fashion using an ultrasonic scalpel (Harmonic Scalpel; Ethicon Endo-Surgery, CVG, Cincinnati, OH) by trained surgeons. Diluted papaverine hydrochloride (1:20) was injected into the arterial conduits from the distal end. The conduits were wrapped in a papaverine-soaked gauze until anastomoses. SVG and radial arteries were dissected using the conventional open harvest technique. SVG was gently dilated by injection of heparin-added blood.

The left internal thoracic artery (LITA) was usually anastomosed to the LAD region, and the right internal thoracic artery (RITA) was anastomosed to the LCx via the transverse sinus. When the RITA was not long enough to reach the LCx system, (1) the proximal portion of the RITA was cut and anastomosed to the side of the LITA graft in a Y-shaped fashion as a composite graft (30% of RITA anastomoses) or (2) the pedicled RITA was directed to the LAD system, whereas the LITA was anastomosed to the LCx system (14% of RITA anastomoses). The choice of BITA configurations was based on the surgeon's preference. Heart positioning was achieved with the help of deep pericardial sutures, suction-type devices (Octopus system, Medtronic, Inc, Minneapolis, Minn; and Acrobat SUV system, Guidant Corporation-Cardiac Surgery, Santa Clara, Calif), and table tilting. Of the sequential grafts, the distal anastomosis was done in end-to-side fashion. Side-to-side anastomoses were made in a diamond shape for SVGs and in a parallel fashion for the arterial grafts. Endarterectomy was performed if a coronary artery had long, calcified plaque. Proximal anastomoses of SVGs and radial arteries were made under a single tangential clamp. When the ascending aorta was not eligible for clamping, proximal anastomotic devices were applied (Symmetry Aortic Connector System, St Jude Medical, Inc, St Paul, Minn; and PAS-Port System, Cardica, Redwood City, Calif).[12] Grafts were intraoperatively evaluated with flowmetry (CardioMeds; Medi-Stim, Oslo, Norway) to detect bypass dysfunction, although the data were not recorded in our database. Intraoperative decisions (eg, re-anastomosis) were made on the basis of the results of the flowmetry. Heparin was reversed with a half-reversal dose of protamine sulfate after completion of all anastomoses. Subcutaneous heparin at a dose of 100 KIU/kg was given twice per day on postoperative days 1 to 4 in every patient to prevent postoperative stroke.[12] Oral aspirin (100 mg) was started on postoperative day 1 and continued thereafter. Other antiplatelets (eg, clopidogrel) were not used.

Angiographic Evaluation

Catheter-based angiography was performed before discharge in the patients, all of whom provided their written informed consent. Postoperative angiography was performed as routine evaluation and is standard of care in Japan. Patients with cerebrovascular disease, renal dysfunction, or respiratory failure were excluded for clinical reasons (83 patients). Most patients underwent angiography within 2 weeks after surgery. The experienced interventional cardiologists who performed angiography reviewed the results. Both native coronary arteries and conduits were selectively visualized, and in at least 2 orthogonal views, the conduit was reviewed and scored on the worst appearance of the proximal anastomosis, body of the conduit, and distal anastomosis according to the FitzGibbon classification.[6] When grafts could not be selectively intubated, an aortogram or a subclavian arteriogram was obtained. Each anastomosis was analyzed separately. A string sign was recorded as FitzGibbon grade B. A patent graft was defined as a graft without 50% or greater stenosis (ie, FitzGibbon A).

Statistical Analysis

Continuous data are expressed as means ±1 standard deviation or medians (interquartile range), and categoric variables are expressed as numbers (proportions). Because the graft patency of multiple anastomoses within a patient cannot be assumed to be independent,[13] generalized estimating equation (GEE) logistic analyses were used to evaluate the influence of the potential predictors (Main Analysis).[14] An event was defined as FitzGibbon grade B or O. The working correlation matrix was set to

exchangeable, and the robust variance estimators were adopted for constructing confidence intervals (CIs) of the odds ratios (ORs). Model variables used in the multivariable analyses were selected a priori on the basis of the previous reports.[15,16] Grafting techniques also were included in the model on the presumption that these were clinically relevant. The following 20 factors were included in the analysis: age (>75 years), sex (female), New York Heart Association classification (≥3), recent myocardial infarction (within 90 days), left ventricular ejection fraction (<50%), chronic renal failure (creatinine >200 μmol/L), hypertension, hypercholesterolemia, diabetes mellitus, left main disease (≥50%), extracardiac arteriopathy, previous cardiac surgery, emergency, operator's experience (first 100 consecutive cases), percent stenosis diameter (>75%), recipient coronary diameter (<1.5 mm), number of anastomoses (continuous), conduits (LITA, RITA, GEA, SVG, and radial artery), territories (LAD, LCx, and RCA), and grafting techniques (sequential, composite, and endarterectomy). In the subanalyses for each conduit, cases with exceptional anastomoses (eg, GEA-LAD anastomosis) were excluded from the GEE models. Subanalysis for the radial artery graft was not performed because there were only 76 radial artery anastomoses (1.4% of all anastomoses). All analyses were performed using SAS version 9.2 (SAS Institute, Inc, Cary, NC). All *P* values quoted are 2-sided.

RESULTS

Patients' Characteristics and Operative Results

The patients' baseline and perioperative characteristics are shown in Tables 1 and 2. Univariate analyses for graft occlusion revealed estimates of naïve ORs by the GEEs. The patients' average age was 68 ± 9 years; 20% of the patients were aged more than 75 years (75% were male, 25% were female). Left main disease 50% or greater was present in 44% of patients. The mean number of distal anastomoses was 3.7 ± 1.2. BITA grafts were used in 78% of patients, and SVGs were used in 41% of patients. Sequential grafting was performed in 76% of patients. Of the 5262 anastomoses, 63% had proximal stenoses greater than 75%. The recipient coronary diameter was less than 1.5 mm in 35% of anastomotic sites. Postoperative morbidity included perioperative myocardial infarction in 33 patients (new Q-wave and creatine kinase-myocardial band >50 IU/L), low output syndrome in 7 patients, new-onset atrial fibrillation in 370 patients, stroke in 8 patients, renal failure necessitating dialysis in 18 patients, and prolonged ventilation (>48 hours) in 42 patients. Operative (within 30 days) and in-hospital mortality were 0.1% and 0.4%, respectively.

TABLE 1. Preoperative characteristics

	Total, N = 1422	Univariate analysis*		
Variable	No. (%)	OR	95% CI	*P* value
Age (y)	68 ± 9			
Age > 75 y	290 (20)	1.39	1.02-1.90	.039
Female sex	379 (25)	1.45	1.08-1.95	.014
NYHA class ≥ 3	265 (19)	0.88	0.62-1.25	.468
Unstable angina	318 (22)	0.81	0.57-1.16	.256
Emergency	109 (8)	0.86	0.50-1.48	.582
Previous MI	614 (43)	0.99	0.75-1.30	.924
Recent MI (<90 d)	140 (10)	1.21	0.76-1.82	.371
LV dysfunction				
Fair (LVEF > 50%)	1093 (77)	Reference		
Moderate (LVEF 30%-50%)	299 (21)	0.75	0.52-1.07	.113
Poor (LVEF < 30%)	30 (2)	0.93	0.38-2.25	.865
Diseased vessels				
1- or 2-vessel disease	450 (32)	Reference		
3-vessel disease	972 (68)	1.20	0.58-2.48	.518
Left main disease	619 (44)	0.69	0.51-0.91	.010
Previous PCI	619 (44)	0.97	0.73-1.28	.815
Previous cardiac surgery	33 (2)	1.64	0.81-3.35	.172
CRF (creatinine > 200 μmol/L)	94 (7)	0.61	0.31-1.19	.145
ESRF on dialysis	70 (5)			
Diabetes mellitus	659 (46)	1.04	0.79-1.38	.771
Taking insulin	163 (11)			
Hypertension	951 (67)	0.93	0.70-1.23	.601
Hypercholesterolemia	793 (56)	1.07	0.81-1.42	.635
COPD	36 (3)	1.16	0.60-2.26	.658
Extracardiac arteriopathy	296 (21)	0.85	0.61-1.19	.350
CVA	240 (17)	1.04	0.71-1.51	.837

OR, Odds ratio; *CI,* confidence interval; *NYHA,* New York Heart Association; *MI,* myocardial infarction; *LV,* left ventricle; *LVEF,* left ventricular ejection fraction; *PCI,* percutaneous coronary intervention; *CRF,* chronic renal failure; *ESRF,* end-stage renal failure; *COPD,* chronic obstructive pulmonary disease; *CVA,* cerebrovascular accident. *Univariate analysis for graft occlusion. Estimates of naïve ORs by the GEEs.

Angiographic Evaluation: Main Analysis

Table 3 shows the distribution and patency rate for each graft (FitzGibbon A). The patency rates of the LITA and RITA grafts were comparable (95.6% and 95.5%, respectively), whereas those of the SVG in the LCx and RCA systems were slightly lower (92.4% and 92.9%, respectively). The patency rate of the GEA grafts when used in the LCx system was markedly low (86.7%); there were only 60 anastomoses with this configuration.

By using the GEE logistic model, 4 variables were found to be independent predictors of overall graft fate (ie, failure or patency; Table 4). Recipient coronary diameter less than 1.5 mm was a risk factor for graft failure (OR, 1.62; 95% CI, 1.24-2.11), whereas percent stenosis diameter greater than 75% (OR, 0.71; 95% CI, 0.53-0.93), sequential graft (OR, 0.69; 95% CI, 0.51-0.94), and left main disease (OR, 0.72; 95% CI, 0.53-0.96) protected against graft failure. Other baseline variables, such as LVEF and diabetes mellitus, or operative factors such as type of conduit and target territory, were not associated with graft failure in the multivariable analysis. Although the patency rate of those patients with coronary endarterectomy was relatively low (82.1%), this technique was not associated with graft failure.

Angiographic Evaluation: Subanalysis for Each Conduit

For LITA grafts, percent stenosis diameter greater than 75% was the only predictor of patency (OR, 0.61; 95% CI, 0.40-0.94; Table 5). None of the variables were

TABLE 2. Perioperative characteristics

Variable	Total, N = 1422 No. (%)	Univariate analysis* OR	95% CI	P value
First 100 cases	90 (6)	0.92	0.53-1.60	.765
No. of anastomoses	3.7 ± 1.2	1.01	0.88-1.16	.853
Incomplete revascularization	187 (13)	0.89	0.57-1.39	.607
Conversion to CCAB	4 (0.3)	—	—	—
Operation time (min)	288 ± 72	1.13	1.01-1.27	.032
Conduit				
LITA	1365 (96)	Reference		
RITA	1083 (76)	1.04	0.73-1.48	.836
GEA	476 (33)	1.27	0.82-1.95	.285
SVG	586 (41)	1.68	1.17-2.43	.005
Radial artery	47 (3)	0.95	0.29-3.11	.936
Territory				
LAD	1400 (98)	Reference		
LCx	1237 (87)	1.20	0.87-1.65	.273
RCA	962 (68)	1.39	0.99-1.94	.056
Grafting technique				
Sequential graft	1076 (76)	0.80	0.61-1.04	.099
Composite graft	345 (24)	1.36	0.91-2.04	.128
Endarterectomy	31 (2)	2.23	0.65-7.68	.202
Proximal anastomotic devices	83 (5)	0.46	0.20-1.06	.068
Recipient coronary (N = 5262)				
Stenosis > 75%	3293 (63)	0.73	0.56-0.95	.019
Diameter < 1.5 mm	1860 (35)	1.61	1.25-2.09	<.001
<1.0 mm	21 (0.4)			
1.0 mm	2462 (47)			
1.5 mm	2613 (50)			
>1.5 mm	166 (3)			
Max CK-MB IU/L (N = 1402)	13 (8.6-24)†	1.02	1.00-1.03	.026
CK-MB > 50 IU/L	148 (10)	1.66	1.12-2.47	.012
Mortality				
Operative (within 30 d)	1 (0.1)			
In-hospital	5 (0.4)			

OR, Odds ratio; *CI*, confidence interval; *CCAB*, conventional coronary artery bypass; *LITA*, left internal thoracic artery; *RITA*, right internal thoracic artery; *GEA*, gastroepiploic artery; *SVG*, saphenous vein graft; *LAD*, left anterior descending; *LCx*, left circumflex; *RCA*, right coronary artery; *CK-MB*, creatine kinase-myocardial band isozyme. *Univariate analysis for graft occlusion. Estimates of naïve ORs by the GEEs. †Median (interquartile range).

associated with RITA graft failure. Smaller recipient coronary diameter (<1.5 mm) showed a trend to correlate with GEA graft and SVG failure (OR, 2.37 and 2.36; 95% CI, 1.08-5.20 and 1.32-4.19, respectively). Of note, the LCx system was a predictor of GEA graft failure (OR, 4.39; 95% CI, 1.66-11.61), whereas sequential graft was a protective factor for GEA graft patency (OR, 0.33; 95% CI, 0.15-0.70).

Patients Who Did Not Undergo Angiography

Among the patients who did not undergo postoperative angiography, all but 1 had no sign of ischemia during the hospital stay. One death occurred in a 69-year-old woman. Vasospasm of the radial artery graft was suspected to be the cause.

TABLE 3. Graft distribution and patency rate

Conduit	Territory	Total no.	FitzGibbon A	FitzGibbon B*	FitzGibbon O	Patency rate†
LITA	LAD	1925	1841	70 (13)	14	95.6%
	LCx	227	218	7 (1)	2	96.0%
	RCA	4	2	0	2	50.0%
	Total	2156	2061	77 (14)	18	95.6%
RITA	LAD	231	220	10 (1)	1	95.2%
	LCx	1145	1093	31 (3)	21	95.5%
	RCA	37	36	1	0	97.3%
	Total	1413	1349	42 (4)	22	95.5%
GEA	LAD	7	7	0	0	100%
	LCx	60	52	2	6	86.7%
	RCA	585	557	16 (3)	12	95.2%
	Total	652	616	18 (3)	18	94.5%
SVG	LAD	88	84	3	1	95.5%
	LCx	288	266	4	18	92.4%
	RCA	588	546	16 (1)	26	92.9%
	Total	964	896	23 (1)	45	92.9%
Radial artery	LAD	4	4	0	0	100%
	LCx	49	48	1	0	98.0%
	RCA	23	21	1	1	91.3%
	Total	76	73	2	1	96.1%

LITA, Left internal thoracic artery; *LAD*, left anterior descending; *LCx*, left circumflex; *RCA*, right coronary artery; *RITA*, right internal thoracic artery; *GEA*, gastroepiploic artery; *SVG*, saphenous vein graft. *Numbers in parentheses represent string sign. †FitzGibbon A.

Postangiography Outcomes

Eight patients (0.6%) experienced complications of postoperative angiography: limb thrombosis in 2 patients, ventricular arrhythmia in 1 patient, dissection of the aorta in 1 patient, transient ischemic attack in 2 patients, and cerebral infarction in 2 patients. The 2 patients with cerebral infarction showed neurologic dysfunction, but all 8 patients were discharged.

Of the 216 patients with at least 1 suboptimal graft (FitzGibbon B or O), 25 underwent repeated interventions as staged procedures (24 percutaneous coronary interventions and 1 surgery) after scintigraphy.

DISCUSSION

One of the possible drawbacks of OPCAB surgery is reduced patency compared with CCAB.[2,4,5] Graft failure is relevant to the clinical prognosis of patients undergoing CCAB,[6] and it is logical to think that this association may fit the OPCAB cohort. Many studies have been published concerning graft patency in CCAB. However, few reports have specifically dealt with this issue in OPCAB surgery.[17] In addition, the results from these studies should be interpreted cautiously, because few of them took clustering into account,[1,17] and the findings of most studies were derived from symptom-driven angiography.