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Review Article

Coronary artery disease in dialysis patients: What is the optimal therapy?

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ABSTRACT

Coronary artery disease (CAD) carries a high risk of mortality in dialysis patients. End-stage renal disease is considered to increase the vulnerability of patients with atherosclerosis superimposed on artery calcification. Recently, an increasing prevalence of CAD in dialysis patients has been attributed to a lack of effective prevention and treatment. Further studies have shown that optimal therapies for CAD in dialysis patients remain neglected and unclarified. These therapies include correction of anemia, control of blood pressure, and antiplatelet therapy. Because of bleeding tendencies in dialysis patients, the benefits of antiplatelet therapy and platelet glycoprotein IIb/IIIa inhibitors for treating CAD require more research. In addition, a meta-analysis of retrospective studies in 2012 showed that dialysis patients with CAD receiving coronary artery bypass surgery had a lower long-term mortality rate and fewer postoperative cardiac complications than those receiving percutaneous coronary angioplasty. A large randomized, long-term cohort study is necessary to confirm these issues.

1. Introduction

Coronary artery disease (CAD) in patients with end-stage renal disease (ESRD) contributes to high mortality, especially after acute myocardial infarction [1–3]. The development of ESRD further worsens the outcome of CAD, and the pathophysiology and course of CAD differ in the presence of ESRD, such as with advanced atherosclerosis superimposed on arterial calcification [4]. Coronary revascularization in dialysis patients with CAD is rarely reported and the optimal options are unclear [5].

2. Risk factors for CAD in dialysis patients

The traditional risk factors for CAD in dialysis patients are hypertension, diabetes, hyperlipidemia, left ventricular hypertrophy, aging, smoking, and lack of physical activity [6–9]. Nontraditional risk factors are uremic toxins, chronic inflammation, and abnormal metabolism of calcium and phosphorus, which increase the development of atherosclerosis and even calcification of the arteries [10–12]. Therefore, prevention and therapy for CAD in dialysis patients still require further clarification.

3. Diagnostic tools for dialysis patients with CAD

In addition to patient history and physical examination, other commonly used noninvasive examinations are resting electrocardiography, exercise electrocardiography, dobutamine stress echocardiography, adenosine- or dipyridamole-induced echocardiography, exercise-induced stress nuclear scintigraphy, and vasodilation by adenosine or dipyridamole-induced stress nuclear scintigraphy. Of these, dobutamine stress echocardiography has the highest sensitivity for CAD in patients with ESRD [13]. Furthermore, if CAD is highly suspected in dialysis patients, invasive procedures such as coronary angiography and coronary revascularization should be done.

4. Medication for dialysis patients with CAD

4.1. Correction of anemia

Using erythropoiesis-stimulating agents and iron therapy, the target level of plasma hemoglobin should be maintained in the range of 11–12 g/dL in dialysis patients [14,15]. Because higher hemoglobin levels could lead to a higher mortality rate, it is

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recommended that the plasma hemoglobin level is maintained at ≤13 g/dL in dialysis patients [14,15].

4.2. Therapy guidelines for blood pressure, blood glucose, and blood lipids

Hypertension in dialysis patients should first be controlled by removing excess body water. Moreover, if necessary, antihypertensive drugs should be given to treat and prevent worsening of CAD caused by long-term hypertension [15]. Beta-blockers can reduce the incidence of arrhythmias and slow CAD progression, particularly by reducing the incidence of myocardial infarction [10]. Nitrates and calcium channel blockers cause vasodilation and reduce angina. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers are also recommended for the treatment of CAD, especially to decrease the mass of the left ventricle without a higher statistical risk of hyperkalemia in dialysis patients and heart failure [15,16]. The 2005 Kidney Disease Outcome Quality Initiative (K/DOQI) guidelines recommend that blood pressure in dialysis patients should be maintained at less than 140/90 mmHg before dialysis and less than 130/80 mmHg after dialysis [15]. These guidelines also recommend that the level of glycosylated hemoglobin (HbA1c) should not be kept lower than 7.0% in dialysis patients with diabetes mellitus who have frequent episodes of hypoglycemia [15]. However, strict glycemic control may not benefit dialysis patients [17,18], as higher glucose and HbA1c levels are not associated with higher mortality in dialysis patients [18]. The clinician is encouraged to individualize glycemic targets based on the potential risks and benefits in diabetic patients undergoing dialysis [17]. The K/DOQI guidelines recommend that the level of low-density lipoprotein cholesterol should be less than 100 mg/dL and in dialysis patients with a high risk of CAD it should be maintained at less than 70 mg/dL [15].

4.3. Antiplatelet therapy

Because dialysis patients have an increased risk of bleeding and worsening arterial calcification, the benefits and safety of aspirin therapy for CAD in dialysis patients remain unclarified. The use of aspirin to decrease the risk of cardiovascular disease was not supported in a study of 28,320 randomly selected dialysis patients [19], but this needs to be further investigated with randomized controlled trials. Because of these concerns, the 2005 K/DOQI guidelines recommend that aspirin treatment be based on the risk and benefits of individual cardiovascular diseases [15]. If necessary, aspirin in low doses (81 mg/day) may be safe in dialysis patients with CAD [15,20]. In addition, aspirin may be beneficial only in dialysis patients with acute coronary syndrome (ACS) [20,21].

4.4. Fibrinolytic agents, heparin, and platelet glycoprotein IIb/IIIa inhibitors

There is a lack of favorable evidence for fibrinolytic agents, high-dose heparin, and platelet glycoprotein IIb/IIIa inhibitors to treat ACS in dialysis patients [22] and these treatments could result in significant bleeding [23,24]. Because of this bleeding risk, ESRD patients are excluded from clinical trials assessing the efficacy of platelet glycoprotein IIb/IIIa inhibitors [20]. If it is necessary to use platelet glycoprotein IIb/IIIa inhibitors and there are no contraindications, then abciximab and tirofiban are preferred, because abciximab requires no dosing changes in dialysis patients and dialysis-specific dosing recommendations are available for tirofiban [24,25]. In contrast, eptifibatide (platelet glycoprotein IIb/IIIa inhibitors) and enoxaparin (low molecular weight heparin) are contraindicated in dialysis patients and are significantly associated with an increased risk of in-hospital major bleeding [26].

5. Invasive management of CAD in dialysis patients

5.1. Appropriate therapies for coronary revascularization

Dialysis patients with unstable CAD and ACS and a poor response to medication may need to undergo coronary revascularization, such as coronary artery bypass grafting (CABG) or percutaneous coronary angioplasty (PTCA). Table 1 compares the survival rates and the incidence of cardiac events in several studies of dialysis patients with CAD undergoing PTCA and CABG. Early, small, retrospective studies showed no difference in the mortality of dialysis patients receiving CABG and PTCA [27–30]. However, recent retrospective studies reported higher survival rates in dialysis patients undergoing CABG than PTCA [31–34]. Two studies from the US Renal Data System database showed that dialysis patients had a better survival rate after CABG than PTCA [35,36]. Results of most studies indicated a lower incidence of cardiac events after CABG than PTCA [19,27,37]. These studies showed that dialysis patients had a lower incidence of restenosis and postoperative heart disease after CABG. Because of the low death rate after CABG surgery, dialysis patients with serious CAD could undergo this procedure [38]. The comparative survival of dialysis patients with diabetes undergoing CABG and PTCA treatment is unclear, because few studies have examined this issue. Barsness et al reported that there was no significant difference in survival rate after CABG and PTCA in a 5-year longitudinal study of dialysis patients with diabetes [30]. However, in a 5-year retrospective analysis from the US Renal Data System database, Herzog et al showed that dialysis patients with diabetes had better survival rates after CABG than PTCA [35]. A meta-analysis in 2012 showed that dialysis patients had lower long-term mortality rate and a lower rate of cardiac events after CABG than patients with PTCA, but large, randomized cohort studies are still needed [39]. In short, the optimal therapy for coronary revascularization in dialysis patients could depend on the severity of CAD in an individual patient and the skill of the surgeon.

5.2. Choice of coronary stent

The prognosis according to stent type in dialysis patients is not clear. Although there have been no randomized prospective studies, several studies have shown that the rate of coronary restenosis and revascularization was reduced in dialysis patients with CAD who received drug-eluting stents (DESs) compared with bare metal stents (BMSs) [40–42]. A comparison of the clinical benefits in dialysis patients with CAD undergoing coronary stenting and CABG is presented in Table 2. The survival of dialysis patients with coronary stenting compared with CABG remains unclear. Two small recent studies showed no difference between coronary stenting and CABG in dialysis patients [43,44]. However, a large-population analysis from the US Renal Data System database in 2002 showed that dialysis patients undergoing CABG had a higher survival rate than those receiving coronary stenting [35]. However, this study was a retrospective analysis, and more clinical random allocation studies are needed to confirm the benefits of both procedures. Comparative outcomes of DESs and CABG in dialysis patients are also indefinite because of a lack of clinical studies. One 5-year retrospective study indicated similar survival outcomes in dialysis patients who had DESs and CABG [45]. However, a 2-year longitudinal study reported a better survival rate with CABG than DESs in dialysis patients [46]. The AHA/ACC guidelines state that aspirin and either clopidogrel or prasugrel should be given for at least 12 months after patients with ACS

Table 1
Comparative outcome of survival rate and cardiac event-free survival rate between dialysis patients with CAD receiving PTCA and CABG.

Author (year)	Design	Years	Group: Number	Diseased vessels	Outcome	Cardiac event-free incidence
Barsness et al (1997) [30]	Prospective	5	Diabetes: PTCA: 144 CABG: 626 Non-diabetes: PTCA: 560 CABG: 1890	Diabetes: PTCA: 22% triple vessel CABG: 71% triple vessel Non-diabetes: PTCA: 19% triple vessel CABG: 60% triple vessel	Five-year survival: $P = NS$ PTCA: 76% CABG: 74% Five-year survival: $P = NS$ PTCA: 88% CABG: 86%	ND
Simsir et al (1998) [29]	Retrospective	1.5	PTCA: 19 CABG: 22	ND	1.5-Year survival: $P = NS$ PTCA: 69%. CABG: 67%	1.5-Year cardiac event-free survival: $P < 0.05$ PTCA: 40% CABG: 87%
Herzog et al (1999) [36]	Retrospective	10	PTCA: 6887 CABG: 7419	ND	Two-year survival: $P = 0.04$ PTCA: 52.9% CABG: 56.9%	ND
Agirbasli et al (2000) [28]	Retrospective	10	PTCA: 122 CABG: 130	PTCA: 27% triple vessel CABG: 56% triple vessel	One-year mortality: $P = NS$ PTCA: 23% CABG: 27%	ND
Chertow et al (2000) [34]	Retrospective	1	PTCA: 46 CABG: 29	ND	One-year survival: $P = 0.03$ PTCA: 54% CABG: 69%	ND
Szczech et al (2001) [33]	Retrospective	3	PTCA: 163 CABG: 244	PTCA: 11.1% triple vessel CABG: 63.1% triple vessel	Three-year survival: $P < 0.05$ PTCA: 46.1% CABG: 65.9%	ND
Ivens et al (2001) [27]	Retrospective	2	PTCA: 40 CABG: 65	PTCA: 40% triple vessel CABG: 62% triple vessel	One- and two-year survival: $P = NS$ PTCA: 95% and 82% CABG: 93% and 86%	One- and two-year cardiac event-free survival: $P < 0.001$ PTCA: 54% and 29% CABG: 94% and 90%
Baldovinos et al (2002) [32]	Retrospective	3	PTCA: 28 CABG: 23	ND	Two-year survival: $P < 0.05$ PTCA: 69% CABG: 82%	ND
Hemmelgarn et al (2004) [31]	Retrospective	8	PTCA: 147 CABG: 153	PTCA: 48.3% triple vessel CABG: 56.2% triple vessel	Eight-year survival: $P = 0.003$ PTCA: 41.2% CABG: 44.8%	ND
Fujimoto (2007) [37]	Retrospective	5	PTCA: 81 CABG: 64	ND	One- and five-year survival: $P = 0.0065$ PTCA: 93.8% and 66.6% CABG: 76.0% and 44.8%	One- and five-year cardiac event-free survival: $P < 0.001$ PTCA: 63.7% and 34.7% CABG: 83.2% and 66.8%

CABG = coronary artery bypass graft; CAD = coronary artery disease; ND = no data; NS = not significant; PTCA = percutaneous coronary angioplasty.

receive a BMS or DES [47]. However, the bleeding risk with dual antiplatelet therapy in dialysis patients should be considered. The ideal duration of this therapy is not known because of a lack of randomized trials.

6. Summary

The optimal therapies for CAD in dialysis patients include correction of anemia (11–12 g/dL) to reduce hypoxia, maintaining

Table 2
Comparative outcome of survival rate and cardiac event-free survival rate between dialysis patients with CAD receiving coronary stenting and CABG.

Author (year)	Design	Years	Group: Number	Diseased vessels	Outcome	Cardiac event-free incidence
Herzog et al (2002) [35]	Retrospective	4	PTCA: 9116 Stent: 4280 CABG: 6668	ND	Two-year survival: $P < 0.0001$ PTCA: 48.2% Stent: 48.4% CABG: 56.4% *In diabetes, relative mortality of CABG versus PTCA was 0.81 ($P < 0.0001$) *In diabetes, relative mortality of stent versus PTCA was 0.99 ($P > 0.05$)	* In diabetes, relative cardiac mortality of CABG versus PTCA was 0.71 ($P < 0.0001$) * In diabetes, relative cardiac mortality of stent versus PTCA was 0.99 ($P > 0.05$)
Manabe et al (2009) [44]	Retrospective	3	Stent: 12 CABG: 28	Stent : 22.2% triple vessel CABG: 75% triple vessel	Two-year survival: NS, $P = 0.41$ Stent: 73.9% CABG: 94.1%	Two-year cardiac event-free: $P = 0.001$ Stent: 37.1% CABG: 85.9%
Sunagawa et al (2010) [46]	Prospective	2	DES: 75 CABG: 29	ND	2-year survival: $P = 0.0271$ DES: 67.6% CABG: 84.0%	Two-year cardiac event-free: $P < 0.0001$ DES: 31.5% CABG: 75.8%
Terazawa et al 2012 [45]	Retrospective	5	DES: 67 CABG: 58	Stent: 6% triple vessel CABG: 67% triple vessel	One- and five-year survival: NS, $P = 0.202$ DES: 88.2% and 61.7% CABG: 84.2% and 56.2%	One- and five-year cardiac event-free: $P < 0.001$ DES: 63.0% and 0% CABG: 76.6% and 48.6%
Yeates et al 2012 [43]	Prospective	2	Stent: 31 CABG: 24	ND	One-year mortality: NS, $P = 0.28$ Stent: 6% CABG: 29%	ND

CABG = coronary artery bypass graft; CAD = coronary artery disease; DES = drug-eluting stents; PTCA = percutaneous coronary angioplasty; ND = no data; NS = not significant.

blood pressure less than 140/90 mmHg before dialysis and 130/80 mmHg after dialysis, controlling low-density lipoprotein cholesterol level at less than 100 mg/dL, antiplatelet therapy if there are no clinical contraindications, and coronary revascularization if dialysis patients have unstable CAD or ACS. A meta-analysis study in 2012 showed that dialysis patients have a lower long-term mortality rate and fewer cardiac events after CABG than PTCA, but this merits investigation in large, randomized cohort studies.

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