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Revascularization in complex multivessel coronary artery disease after FREEDOM

Is there an indication for PCI and drug-eluting stents?

Introduction

Diabetes mellitus is a highly prevalent metabolic disorder that imposes a substantial burden of cardiovascular morbidity and mortality. Currently, 220 million people worldwide have diabetes, with an expected increase to 360 million by 2030 [1]. Diabetic patients are prone to develop atherosclerotic disease and have a 2- to 4-fold higher likelihood of developing coronary artery disease (CAD) compared with nondiabetic individuals [2]. Characteristics of CAD among diabetic patients with implications for treatment include a higher burden of atherosclerosis, diffuse, frequently multifocal disease, a higher incidence of vulnerable, rupture-prone lesions, accelerated disease progression [3], and a greater risk of neointimal hyperplasia [4]. Myocardial revascularization is an important therapeutic intervention for the improvement of symptomatic status and prognosis, particularly in diabetic patients. Although diabetes affects about 5 % of the general adult population, diabetic patients account for 20–35 % of patients referred for myocardial revascularization [5]. Defining the optimal revascularization strategy in patients with diabetes has been the subject of intensive research. Coronary artery bypass surgery (CABG) is in general considered the preferred option in diabetic patients with complex disease as it provides more complete revascularization and confers a higher degree of protection against adverse events related to disease progression; however, owing to advances in stent technology, which have improved the safety and efficacy of percutaneous coronary interventions (PCIs), coronary stenting is increasingly appreciated as a valuable alternative to CABG in appropriately selected patients. This review article aims to summarize indications for myocardial revascularization across the spectrum of clinical presentations and to critically discuss current evidence and future perspectives regarding the value of each revascularization mode (CABG vs. PCI) in patients with diabetes.

Overview of the pathobiological role of diabetes in atherosclerosis

Diabetes promotes atherosclerosis and its thrombotic complications via pathobiological pathways affecting endothelial, inflammatory, vascular smooth muscle cell, and platelet function [6]. Briefly, metabolic derangements occurring in diabetes including hyperglycemia, altered fatty acid metabolism, and insulin resistance mediate abnormalities in endothelial cell function by attenuating the synthesis and promoting the degradation of nitric oxide; along with increased formation of vasoconstrictor prostanoids and endothelin, this results in endothelial dysfunction – a key step of atherogenesis [3]. The activation of inflammatory pathways, induced by advanced glycation end products, promotes the production of pro-inflammatory cytokines and growth factors, which in turn affect smooth muscle cell migration and phenotypic differentiation. Moreover, the augmented production of pro-inflammatory mediators and adhesion molecules enhances platelet adhesion, activation, and aggregation, and, along with the marked down-regulation of endogenous antithrombotic factors, favors a pro-thrombotic milieu [6]. Diabetic dyslipidemia also contributes greatly to the cumulative pro-atherogenic effects of diabetes on the coronary vasculature. Together, these mechanisms result in accelerated atherosclerosis with a typically large plaque burden, dictating aggressive measures for disease management for primary and secondary prevention.

Revascularization in diabetic patients with acute coronary syndromes

Diabetic patients presenting with acute coronary syndromes (ACS) have a worse prognosis, and at the same time benefit more from revascularization, compared with nondiabetic patients. PCI using new-generation drug-eluting stents (DES) play a prominent role in the management of diabetic patients with ACS [5]. The FRICS II [7] and TACTICS-TIMI 18 trials [8] showed greater benefit in diabetic compared with nondiabetic patients with regard to the relative and absolute risk reduction for death, MI or

Tab. 1 Summary of selected randomized trials comparing PCI vs CABG in diabetic patients

	Enrollment period (publication)	Patient profile	Stent used	N	Follow-up (years)	Primary endpoint	Outcome (CABG vs. PCI)	Secondary endpoints (CABG vs. PCI)
BARI (diabetic group)	1988–1991 (2007)	Symptomatic multivessel CAD	Balloon angioplasty	CABG: 180 PTCA: 173	10	All-cause death	CABG better 42.2 vs. 54.5 %; $p = 0.025$	MI: 52.8 vs. 58.6 %; $p = 0.28$ Revascularization: 18.3 vs. 79.7 %; *p*: NR
FREEDOM	2005–2010 (2012)	Diabetes and multivessel CAD	TAXUS PES or CYPHER SES	CABG: 947 PCI: 953	5	All-cause death, MI or stroke	CABG better 18.7 vs. 26.6 %; $p = 0.005$	Death: 10.9 vs. 16.3 %; $p = 0.049$ MI: 6 vs. 13.9 %; $p < 0.001$ Stroke: 5.2 vs. 2.4 %; $p = 0.03$
SYNTAX (diabetic group, 5-y outcomes)	2005–2007 (2013)	Diabetes with left main and/or 3-vessel CAD	TAXUS PES	CABG: 221 PCI: 231	5	Death, MI, stroke, or repeat revascularization	CABG better 29 vs. 46.5 % $p < 0.001$	Mortality: 12.9 vs. 19.5 %; $p = 0.07$ MI: 5.4 vs. 9 %; $p = 0.20$ Stroke: 4.7 vs. 3 %; $p = 0.34$ Revascularization: 14.6 vs. 35.3 %; $p < 0.001$
CARDia	2002–2007 (2010)	Diabetes and multivessel CAD or complex single-vessel disease	BMS (31 %) or CYPHER SES (69 %)	CABG: 254 PCI: 256	1	Death, MI or stroke	No difference 10.5 vs. 13 %; $p = 0.39$	Mortality: 3.2 vs. 3.2 %; $p = 0.97$ MI: 5.7 vs. 9.8 %; $p = 0.09$ Stroke: 2.8 vs. 0.4 %; $p = 0.07$ Revascularization: 2 vs. 11.8 %; $p < 0.001$
VA-CARDS	2006–2010 (2013)	Diabetes and multivessel CAD or isolated proximal LAD disease	Early-generation DES (55 %) New-generation DES (20 %) Mixed DES	CABG: 97 PCI: 101	2	Death or MI	18.4 vs. 25.3 % *p*: NR	Mortality: 5 vs. 21 %; *p*: NR MI: 15 vs. 6.2 %; *p*: NR Stroke: 1.2 vs. 1 %; *p*: NR Revascularization: 19.5 vs. 18.5 %; *p*: NR

BARI Bypass Angioplasty Revascularization Investigation, *BMS* bare metal stent, *CABG* coronary artery bypass graft, *CAD* coronary artery disease, *CARDia* Coronary Artery Revascularization in Diabetes, *DES* drug-eluting stents, *FREEDOM* Future REvascularization Evaluation in patients with Diabetes Mellitus, *LAD* left anterior descending artery, *MI* myocardial infarction, *NR* not reported, *PCI* percutaneous coronary intervention, *PES* paclitaxel-eluting stent, *PTCA* percutaneous transluminal coronary angioplasty, *SES* sirolimus-eluting stent, *SYNTAX* TAXUS Drug-Eluting Stent Versus Coronary Artery Bypass Surgery for the Treatment of Narrowed Arteries, *VA-CARDS* Veterans Affairs Coronary Artery Revascularization in Diabetes Study

re-hospitalization for ACS. In patients with NSTE-ACS, diabetes is an independent risk factor portending a worse prognosis and an invasive strategy is recommended over non-invasive management in the European Society of Cardiology (ESC) guidelines on non-ST-segment elevation acute coronary syndromes (class IA) [9]. In patients presenting with ST-segment elevation myocardial infarction (STEMI), primary PCI (if feasible within the recommended time limits) is recommended over fibrinolysis for the treatment of the culprit lesion and the restoration of blood flow (class IA) [5]; in the presence of the remaining obstructive lesions, persistent symptoms, evidence of ischemia, and individual patient characteristics should determine the need for and the timing of a staged PCI procedure, or possibly CABG in selected cases with complex anatomy and an acceptable surgical risk.

Rationale for myocardial revascularization in diabetic patients with stable CAD

For diabetic patients with chronic, stable CAD and multivessel disease, revascularization in addition to guideline-based medical treatment should be evaluated, with the objective of reducing symptoms and cardiovascular events. The appropriateness of myocardial revascularization was addressed in the BARI 2D trial [10], which randomized 2,368 diabetic patients to medical therapy alone or combined with myocardial revascularization; the mode of revascularization, i.e., PCI or CABG, was determined in a nonrandomized fashion by the treating physician. Although patients were recruited at 49 sites between 2001 and 2005, the enrolment target of 2,800 patients was not met and the follow-up had to be extended by 1.5 years to 5.3 years. Patients with left main disease, those who were unstable and required immediate revascularization, and patients with creatinine values > 2.0 mg/dl or moderate to severe heart failure were excluded. PCI included bare metal stents (BMS) in two thirds or DES in one third of patients (exclusively early-generation DES). At 5 years, there was no difference regarding mortality or major adverse cardiac or cerebrovascular events (MACCE; a composite of death, myocardial infarction [MI] or stroke) between the two groups. MACCE occurred less frequently in the CABG stratum in patients treated surgically vs. medical therapy alone (driven by a reduction in myocardial infarction), whereas no difference was observed in the PCI treatment arm; this difference needs to be viewed in light of angiographically more extensive disease in patients included in the CABG stratum. One notable finding is that revascularization (by either

mode) resulted in lower rates of worsening or new angina and a reduced need for subsequent revascularization compared with medical therapy alone [10]. Along the same lines, in the diabetic subgroup of the COURAGE trial (including 34 % of all 2,287 patients) the composite endpoint of death or MI did not differ in patients randomized to medical therapy vs. PCI, whereas subsequent revascularization was reduced in patients treated with PCI [11]. Collectively, based on available evidence, revascularization is recommended for diabetic patients with persistent symptoms despite medical therapy, evidence of ischemia, and multivessel disease to reduce cardiovascular events [5]. It provides superior, sustainable effects for better control of angina symptoms, improved quality of life, greater reduction of ischemia, and reduced need for repeat revascularization compared with medical therapy alone.

CABG vs. PCI in diabetic patients with stable, multivessel disease

Summary of available evidence

Most randomized trial data comparing CABG vs. PCI in diabetic patients represent pre-specified subgroup analyses, with only a few dedicated trials performed in diabetic populations (**Tab. 1**). Current recommendations have been largely based on the results of the Future REvascularization Evaluation in patients with Diabetes Mellitus (FREEDOM) trial [12], the diabetic sub-study of the SYNTAX trial [13], and meta-analyses of available trials [14]. The FREEDOM randomized trial compared CABG vs. PCI using early-generation DES (94 %) in diabetic patients undergoing elective revascularization for multivessel disease without left main coronary stenosis. The study population was derived from 33,966 screened patients, 3,309 of whom were considered eligible and 1,900 patients (6 %) finally enrolled. The mean age was 63 years, 71 % were men and 83 % of patients had three-vessel disease. The mean SYNTAX score amounted to 26 ± 9. Within a 5-year follow-up, the trial reported higher rates of the primary

Abstract · Zusammenfassung

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Revascularization in complex multivessel coronary artery disease after FREEDOM. Is there an indication for PCI and drug-eluting stents?

Abstract

Diabetes mellitus is a highly prevalent metabolic disorder frequently associated with the development of coronary atherosclerosis. Myocardial revascularization assumes a central role in the treatment of diabetic patients with coronary artery disease. Although coronary artery bypass grafting (CABG) is in principle the revascularization modality of choice in diabetic patients with complex, multivessel disease, percutaneous coronary interventions (PCI) using new-generation drug-eluting stents (DES) remain a valuable treatment option for properly selected diabetic patients. Defining the appropriate revascularization strategy is often a challenging task that requires tailored approaches, accounting for individual patient surgical risk, anatomical configurations, and the technical feasibility of each procedure in addition to careful judgment of the possible benefits and risks inherent to PCI and CABG. Evidence is building that advances in DES technology may mitigate at least in part some of the adverse vascular effects of diabetes; whether this may translate to PCI outcomes comparable with those achieved by CABG is under investigation in randomized trials currently underway. This review article summarizes the indications for myocardial revascularization across the spectrum of clinical presentations and critically discusses current evidence and future perspectives regarding the value of each revascularization mode (CABG vs. PCI) in patients with diabetes.

Keywords

Diabetes mellitus · Myocardial revascularization · Coronary artery disease · Coronary artery bypass grafting · Percutaneous coronary interventions

Revaskularisation bei komplexen koronaren Mehrgefäßerkrankungen nach FREEDOM. Gibt es eine Indikation für PCI und medikamentenbeschichtete Stents?

Zusammenfassung

Diabetes mellitus ist eine stark verbreitete metabolische Erkrankung, die häufig mit der Entwicklung koronarer Atherosklerose in Zusammenhang steht. Myokardiale Revaskularisation spielt bei der Behandlung von Patienten mit Diabetes mit einer koronaren Arterienerkrankung (CAD, coronary artery disease) eine große Rolle. Obwohl eine Koronararterienbypassoperation (CABG, coronary artery bypass grafting) bei Patienten mit Diabetes mit komplexen Mehrgefäßerkrankungen grundsätzlich die Revaskularisationsart der Wahl ist, bleiben perkutane Koronarinterventionen (PCI, percutaneous coronary interventions), die medikamentenbeschichtete Stents der neuen Generation einsetzen, eine nützliche Behandlungsoption für passend ausgewählte Patienten mit Diabetes. Die angemessene Revaskularisationsstrategie zu definieren ist oft eine herausfordernde Aufgabe, die maßgeschneiderter Ansätze bedarf, die das Operationsrisiko des einzelnen Patienten, seine anatomischen Gegebenheiten und die technische Machbarkeit jedes Eingriffs zusätzlich zur sorgfältigen Beurteilung der möglichen Vorteile und Risiken einbezieht, die mit PCI und CABG einhergehen. Es mehren sich die Belege, dass Verbesserungen in der DES-Technologie mindestens teilweise einige der vaskulären Begleiterscheinungen von Diabetes abschwächen können; ob sich dies auf die PCI-Ergebnisse übertragen lässt, die mit denen vergleichbar sind, die durch CABG erreicht werden, wird derzeit in randomisierten Test untersucht. Dieser Überblick fasst die Indikationen für myokardiale Revaskularisation über das Spektrum klinischer Erscheinungsformen zusammen und erörtert die aktuellen Nachweise und Zukunftsaussichten in Hinblick auf den Wert jeder Art der Revaskularisation (CABG vs. PCI) bei Patienten mit Diabetes kritisch.

Schlüsselwörter

Diabetes mellitus · Myokardiale Revaskularisation · Koronare Herzkrankheit · Koronararterienbypassoperation · perkutane Koronarinterventionen

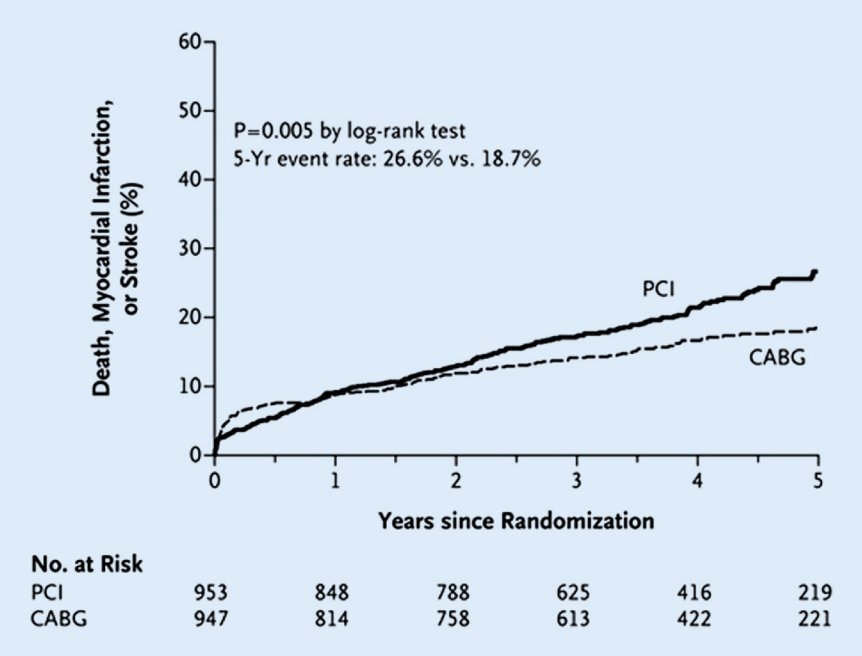

Fig. 1 ▲ Kaplan-Meier curves for the primary endpoint (all-cause death, myocardial infarction or stroke) in the Future REvascularization Evaluation in patients with Diabetes Mellitus (FREEDOM) trial. (Adapted from [12] with permission)

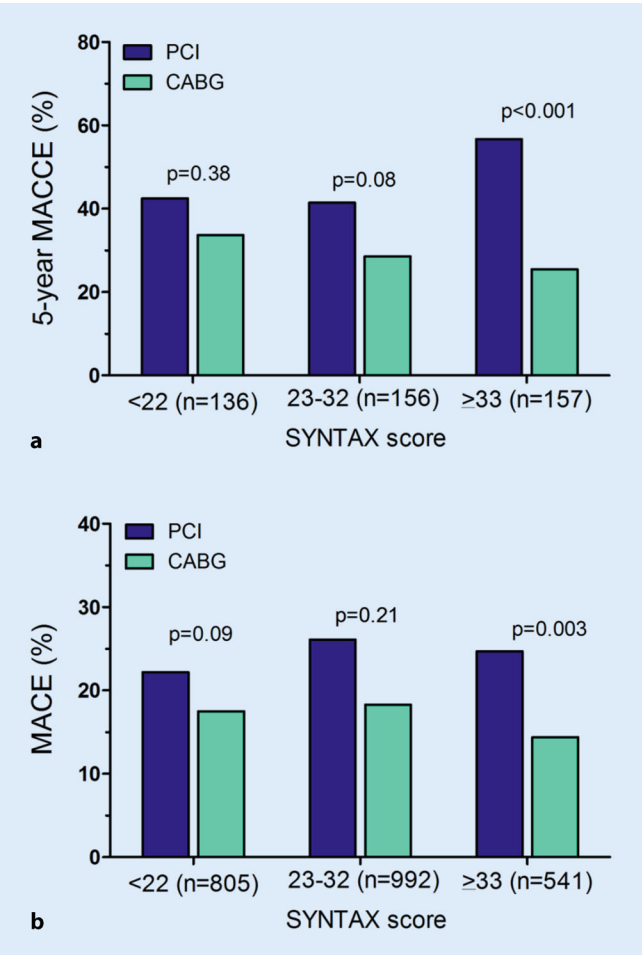

Fig. 2 ◀ **a** Five-year rates of major adverse cardiac or cerebrovascular events (*MACCE*), a composite of death, stroke, myocardial infarction, or repeat revascularization, in relation to TAXUS Drug-Eluting Stent Versus Coronary Artery Bypass Surgery for the Treatment of Narrowed Arteries (*SYNTAX*) scores in the diabetic sub-study of the SYNTAX trial. **b** Pooled analysis (random-effects model) of major adverse cardiac events (*MACE*), a composite of death, myocardial infarction, or repeat revascularization, from the SYNTAX and FREEDOM trials. Follow-up was 5 years for both trials

endpoint (a composite of death, myocardial infarction, and stroke) in patients treated with PCI, with divergence of the curves beginning at 2 years (**Fig. 1**; [12]). The difference in the primary endpoint was accompanied by a borderline reduction of all-cause mortality (p = 0.049), but a marked reduction in MI favoring CABG (p < 0.001). Conversely, the risk of stroke was doubled among patients allocated to CABG (p = 0.03), which was driven by both periprocedural and non-periprocedural events. CABG was superior to PCI across all pre-specified subgroups, the only exception being that patients recruited outside the USA (n = 1,130) versus those enrolled in the USA (n = 770) had a less pronounced benefit from CABG over PCI (p = 0.05 for interaction). Assessment of quality of life showed important and sustained improvements in health status with both PCI and CABG. During the first month, PCI resulted in more rapid improvement in quality of life, which was offset between 6 months and 2 years in favor of CABG, and was no longer different beyond 2 years.

Consistent results were reported in the diabetic sub-study of the TAXUS Drug-Eluting Stent Versus Coronary Artery Bypass Surgery for the Treatment of Narrowed Arteries (SYNTAX) trial assessing 454 diabetic patients with three-vessel CAD or left-main disease [13]; the study showed higher rates of the primary endpoint, MACCE (a composite of death, MI, stroke, or repeat revascularization), at 5 years for patients treated by means of PCI vs. CABG (46.5 vs. 29.0 %; p < 0.001), driven by higher rates of repeat revascularization (35.3 vs. 14.6 %; p < 0.001) with no significant difference in all-cause mortality (19.5 vs. 12.9 %; p = 0.07) or MI (9.0 vs. 5.4 %; p = 0.20; **Tab. 1**). More recently, in the randomized Coronary Artery Revascularization in Diabetes (CARDia) trial, PCI with BMS or DES was compared with CABG in 510 diabetic patients [15]. The study, which was underpowered for clinical outcomes, showed no difference in the primary endpoint of death, MI or stroke (13 vs. 10.5 %, p = 0.39), similar mortality (3.2 vs. 3.2 %, p = 0.97), but higher repeat

Tab. 2 Recommendations for myocardial revascularization in patients with diabetes according to the 2014 European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACTS) guidelines. Adapted from [5] with permission

Recommendations	Class	Level
In patients presenting with STEMI, primary PCI is recommended over fibrinolysis if it can be performed within recommended time limits	I	A
In patients with NSTE-ACS, an early invasive strategy is recommended over non-invasive management	I	A
In stable patients with multivessel CAD and/or evidence of ischemia, revascularization is indicated to reduce cardiac adverse events	I	B
In patients with stable multivessel CAD and an acceptable surgical risk, CABG is recommended over PCI	I	A
In patients with stable multivessel CAD and SYNTAX score ≤ 22, PCI should be considered as alternative to CABG	IIa	B
New-generation DES are recommended over BMS	I	A

BMS bare-metal stent, *CABG* coronary artery bypass grafting, *CAD* coronary artery disease, *DES* drug-eluting stent, *NSTE-ACS* non-ST-segment elevation acute coronary syndrome, *PCI* percutaneous coronary intervention, *STEMI* ST-segment elevation myocardial infarction

revascularization in patients treated with PCI (11.8 vs. 2 %, $p < 0.001$) [15].

The diabetic subgroup of the SYNTAX trial provided additional evidence with implications for decision-making in relation to angiographic disease complexity. In an analysis comparing patients across tertiles of SYNTAX scores, rates of MACCE did not differ in patients with low SYNTAX scores (≤ 22) treated with PCI or CABG, whereas PCI was associated with a higher risk in those with intermediate or high scores (23–32 or > 33), indicating a synergistic effect of anatomical disease complexity and diabetes on PCI outcomes (**Fig. 2a**) [13]. Although the FREEDOM trial reported the absence of a prognostic value of the SYNTAX score, a meta-analysis of the FREEDOM trial and the diabetic substudy of the SYNTAX trial confirmed differential results of PCI vs. CABG in diabetic patients in relation to different levels of the SYNTAX score (**Fig. 2b**) [14].

Current recommendations

According to available evidence, CABG is recommended over PCI for diabetic patients with multivessel disease and acceptable surgical risk, assuming class IA indication in current European guidelines [5]. Nonetheless, PCI should be considered as an alternative in patients with less complex multivessel disease, as quantified by SYNTAX scores ≤ 22 (class IIaB; **Tab. 2**).

Critical appraisal of the FREEDOM trial

Randomized controlled trials represent the most robust level of evidence for informed clinical practice. The FREEDOM trial is to our knowledge the only adequately powered randomized trial to date comparing PCI vs. CABG in diabetic patients and largely accounts for the class IA recommendation for CABG in the given clinical setting in current guidelines. However, some aspect of the trial methodology and reported results with implications for patient management deserve consideration. First, the analysis does not reflect current clinical practice, as first-generation DES, including the paclitaxel-eluting stents used in FREEDOM, are hardly used in contemporary practice. Thereby, the findings are only in part applicable to the current reality of new-generation DES. Second, the mortality benefit of CABG vs. PCI was marginal ($p = 0.049$) and therefore should be viewed as a hypothesis-generating finding, also considering that the trial was not powered for all-cause mortality, and was not driven by cardiovascular death, raising the question of mechanisms underlying the benefit of CABG. Moreover, event curves diverged only at 2 years, at which time an imbalance in the completeness of the ascertainment of vital status between the PCI and CABG groups emerged, and the mortality benefit was not apparent until 4–5 years after initial treatment. Third, the reported absence of a prognostic value of the SYNTAX score raises some concerns, given that:

1. Calculation of the SYNTAX score was not described in the trial's protocol.
2. It has not been clarified whether analyses were performed in a core lab to ensure reproducibility.
3. The SYNTAX score only became operational during the course of the trial.
4. Patients enrolled in the FREEDOM trial had preserved left ventricular ejection fraction (LVEF; mean 66 %, with only 2.5 % of patients with LVEF < 40 %) and low surgical risk (median European System for Cardiac Operative Risk Evaluation [EuroSCORE] 2.0). Therefore, findings cannot be directly extrapolated to patients with reduced systolic function, comorbidities such as renal insufficiency, or frailty. Depending on anatomical characteristics in addition to patient-specific factors that increase the surgical risk, PCI may be preferable in sicker patients owing to its less invasive nature; in such cases, optimal revascularization strategies should be defined on an individual basis by a multidisciplinary heart team.
5. The increased risk of stroke raises for CABG the question of treatment selection, particularly among elderly patients (> 75 years of age).

Advances in stent technology with potential implications for management of diabetic patients

Current guidelines regarding revascularization of diabetic patients are based exclusively on studies comparing CABG vs. early-generation DES. Compelling evidence, however, established that the transition from BMS to early- to new-generation DES has been associated with markedly improved efficacy and safety of PCI. In a network meta-analysis comparing revascularization versus medical therapy in patients with stable CAD, including 100 randomized trials and 262,090 patient-years of follow-up, new-generation DES, but not balloon angioplasty, BMS, or first-generation DES, resulted in a significant reduction in mortality compared with medical therapy alone [16]. This analysis is

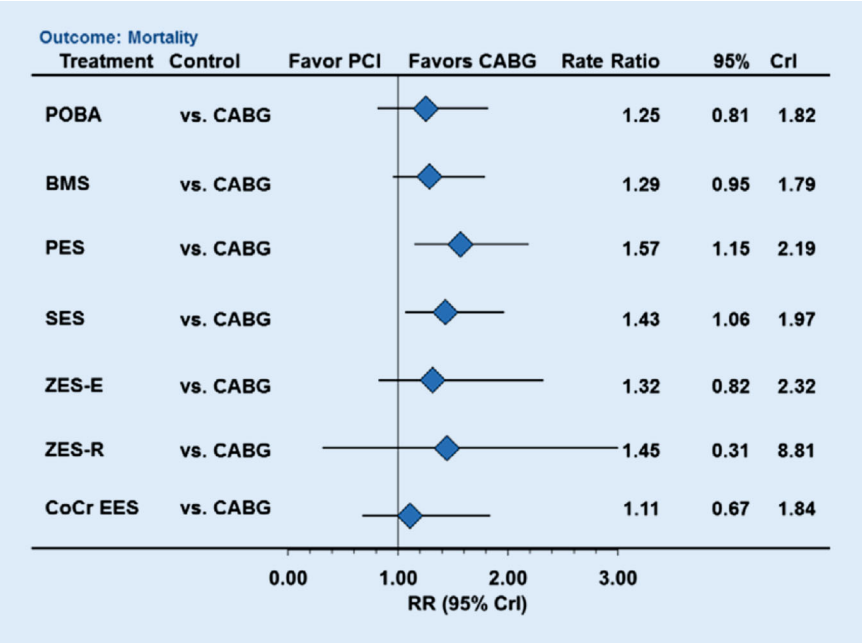

Fig. 3 ▲ Mixed treatment comparison analyses for coronary artery bypass graft surgery (*CABG*) vs. percutaneous coronary intervention (*PCI*) for all-cause mortality in diabetic patients in a meta-analysis including 68 randomized trials. *BMS* bare metal stent, *CoCr EES* cobalt-chromium everolimus-eluting stent, *CrI* credibility interval, *PES* paclitaxel-eluting stent, *POBA* plain old balloon angioplasty, *RR* rate ratio, *SES* sirolimus-eluting stent, *ZES-E* zotarolimus-eluting stent-endeavor, *ZES-R* zotarolimus-eluting stent-resolute. (Adapted with permission from [24])

consistent with studies demonstrating substantial reductions in cardiac mortality, myocardial infarction, and stent thrombosis with new-generation DES compared with earlier device types across a wide range of patient and lesion subsets [17–20]. A recent analysis of pooled data from several randomized trials demonstrated the consistent superiority of new-generation DES vs. early-generation DES across the spectrum of disease complexity, as assessed by the SYNTAX score [21] – a finding that may be particularly relevant for diabetic patients who typically harbor more advanced and complex disease. Collectively, this evidence regarding the improved efficacy and safety of new- vs. early-generation DES raises the potential that newer devices may compare more favorably with CABG in the treatment of patients with multivessel disease. Evidence from randomized trials to test this hypothesis is currently lacking. The Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease (BEST) trial, a prematurely terminated, underpowered randomized trial of patients (n = 880) treated with CABG or PCI using everolimus-eluting stents showed a higher rate of MACE (death, MI, or target-vessel revascularization) within 2 years in the PCI arm, driven by higher rates of MI and repeat revascularization, but – unlike the FREEDOM trial – with nondiffering mortality between the two treatment modes [22]. Moreover, an observational study assessing > 18,000 patients with multivessel CAD who underwent CABG or PCI with everolimus-eluting stents found fewer strokes but more frequent repeat revascularization procedures in the PCI group. Notably, and unlike previous evidence with early-generation DES, mortality did not differ in the two groups, and MI rates were more frequent with PCI only among patients who had not received complete revascularization [23]. Notwithstanding methodical considerations (underpowered randomized trial [22] and observational study [23]), these two investigations have yielded insights suggesting that incremental improvements in stent technologies might narrow the outcome gap between CABG and PCI, as was documented in earlier investigations using early-generation DES.

Of greater relevance to the treatment of diabetic populations, a network meta-analysis focusing on diabetic patients analyzed 42 trials with 22,844 patient-years of follow-up [24]. The study reported that the cobalt-chromium everolimus-eluting stent is superior to other DES and BMS with regard to efficacy (target-vessel revascularization) and safety (death, myocardial infarction, stent thrombosis). Because DES vary significantly in efficacy and safety, they cannot be considered a homogeneous group. These insights are important for the interpretation of the available randomized trial evidence, which compared CABG with early-generation DES in diabetic patients, including the FREEDOM trial [12]. Along these lines, a recent post hoc analysis pooling > 6,000 patients from four all-comers DES trials compared PCI outcomes in diabetic and nondiabetic patients. While MACE (cardiac death, MI, or target-lesion revascularization) within 2 years were more frequent in diabetic than in nondiabetic patients overall (p = 0.03), the difference was mitigated (p = 0.13) in a sensitivity analysis of patients treated with new-generation DES – a group that comprised 75 % of the pooled cohort [25]. Although these findings are hypothesis-generating, given the exploratory nature of the analysis, they do support the concept that new-generation DES may mitigate, at least in part, some of the adverse vascular effects of diabetes. Whether this translates to PCI outcomes comparable with those achieved by CABG remains to be determined in properly designed, adequately powered, randomized trials.

Emerging evidence supporting PCI in diabetic patients

A recent meta-analysis including 68 randomized trials that enrolled 24,015 diabetic patients demonstrated a reduced gap for cardiovascular events between CABG and PCI using new-generation DES, particularly using the

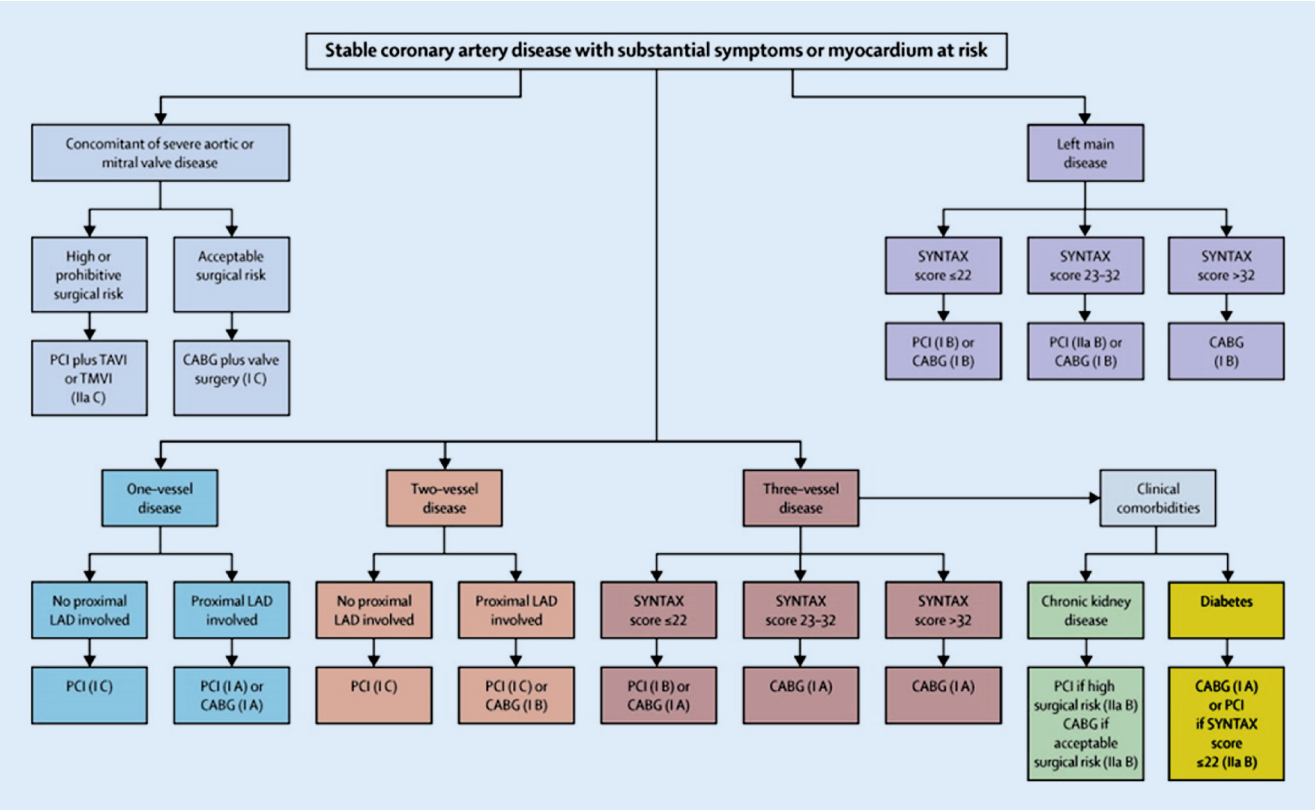

Fig. 4 ▲ Algorithm for revascularization across anatomical and clinical subsets in patients with stable coronary artery disease. Class recommendations are derived from European guidelines on myocardial revascularization and refer to patients with coronary artery disease with suitable coronary anatomy for either percutaneous coronary intervention (*PCI*) or coronary artery bypass graft (*CABG*) and low predicted surgical mortality. *LAD* left anterior descending artery, *TAVI* transcatheter aortic valve implantation, *TMVI* transcatheter mitral valve implantation. (Adapted with permission from [27])

cobalt-chromium everolimus-eluting stent – the current standard of care [26]. Although excess mortality was observed with PCI using early-generation sirolimus- or paclitaxel-eluting stents compared with CABG, this effect was attenuated with new-generation DES and mortality did not differ between patients treated with the everolimus-eluting stent and those treated with CABG (relative risk 1.11, 95 % confidence interval 0.67–1.84) (**Fig. 3**; [26]). Moreover, an observed greater need for repeat revascularization compared with CABG gradually decreased from balloon angioplasty to early-generation DES, and the difference was not significant with newer-generation DES. Although inherent limitations of nonrandomized comparisons apply, these provocative findings are in line with growing evidence in general (nondiabetic) populations, suggesting that PCI with everolimus-eluting stents might narrow or eliminate the superior performance of CABG in the setting of multivessel CAD.

Conclusions and future perspectives

Treatment of diabetic patients with coronary artery disease requires a multi-level approach, including optimal risk-factor modification, evidence-based medical therapies, and coronary revascularization. Current evidence, formed in large part by the FREEDOM trial, indicates that bypass surgery is in principle the revascularization modality of choice in diabetic patients with complex multivessel CAD. However, coronary stenting remains a valuable treatment option for diabetic patients with ischemic heart disease when selected properly. First, PCI is the first-line revascularization option for patients presenting with STEMI. Second, an early invasive strategy with PCI is indicated in the majority of patients with NSTE-ACS. Third, in patients with chronic, stable CAD, PCI using new-generation DES remains the primary modality for single- or two-vessel disease, and it can be considered an alternative to CABG in the setting of multivessel CAD with less complex disease (i. e., SYNTAX score ≤ 22) (**Fig. 4**; [27]). It is important to note that in certain cases, defining the appropriate revascularization strategy in diabetic patients remains a challenging task that requires tailored approaches, also accounting for individual patient surgical risk, focal vs. diffuse disease distribution, and the technical feasibility of each procedure (e.g., distal lesion localization precluding the confection of surgical anastomoses or excessive vessel tortuosity or calcification challenging complete revascularization by means of coronary stenting).

Preliminary evidence suggests that coronary interventions using newer de-

vices might compare more favorably with CABG, while retaining a reduced risk of stroke. Randomized trials are currently underway to address this issue. In the Effectiveness of Left Main Revascularization (EXCEL) trial (NCT01205776) 2,600 patients with left-main disease and SYNTAX score < 32 are planned to be randomized to PCI with everolimus-eluting stents vs. CABG; diabetic patients will be a pre-specified subgroup of the study. Furthermore, functional testing may assume a role by affirming the hemodynamic relevance of angiographic three-vessel disease or reclassifying some patients to single- or two-vessel disease, with implications for selection of the treatment mode. Along these lines, in the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) trial, only14 % of patients who underwent angiography also had functional three-vessel disease [28]. The FAME-3 trial (NCT02100722) is designed to test in 1,500 patients (including a diabetic subset) whether fractional flow reserve (FFR)-guided PCI in patients with multivessel CAD will result in similar outcomes to those with CABG.

Advances in stent technology have improved the performance of PCI for prevention of recurrent events related to culprit lesions treated during the index procedure (i.e., reduced in-stent restenosis and thrombosis). In addition, adherence to evidence-based medical therapies, including high-intensity statins (which halt plaque progression and stabilize high-risk lesions [29], with reversal of accelerated coronary atherosclerosis in diabetic patients [30]), holds promise in mitigating adverse events stemming from angiographically nonrelevant lesions that were not stented during index interventions in patients revascularized by means of PCI. A combined approach of highly efficient local interventions (PCI with new-generation devices) and systemic interventions (optimized, guideline-recommended secondary prevention therapies) may further improve outcomes in the high-risk population of diabetic patients with complex CAD.

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Compliance with ethical guidelines

Conflicts of interest. K. C. Koskinas and S. Windecker state that there are no conflicts of interest.

The accompanying manuscript does not include studies on humans or animals.

References

1. Shaw JE, Sicree RA, Zimmet PZ (2010) Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract 87:4–14
2. Aronson D, Edelman ER (2010) Revascularization for coronary artery disease in diabetes mellitus: angioplasty, stents and coronary artery bypass grafting. Rev Endocr Metab Disord 11:75–86
3. Libby P, Theroux P (2005) Pathophysiology of coronary artery disease. Circulation 111:3481–3488
4. Palmerini T, Dangas G, Mehran R et al (2010) Predictors and implications of stent thrombosis in non-ST-segment elevation acute coronary syndromes: the ACUITY Trial. Circ Cardiovasc Interv 4:577–584
5. Windecker S, Kolh P, Alfonso F et al (2014) 2014 ESC/EACTS guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J 35:2541–2619
6. Lüscher TF, Creager MA, Beckman JA, Cosentino F (2003) Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: Part II. Circulation 108:1655–1661
7. Cannon CP, Weintraub WS, Demopoulos LA et al (2001) Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. N Engl J Med 344:1879–1887
8. Lagerqvist B, Husted S, Kontny F et al (2006) 5-year outcomes in the FRISC-II randomised trial of an invasive vs. a non-invasive strategy in non-ST-elevation acute coronary syndrome: a follow-up study. Lancet 368:998–1004
9. Roffi M, Patrono C, Collet JP et al (2015) 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 37:267–315
10. Frye RL, August P, Brooks MM et al (2009) A randomized trial of therapies for type 2 diabetes and coronary artery disease. N Engl J Med 360:2503–2515
11. Boden WE, O'Rourke RA, Teo KK et al (2007) Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med 356:1503–1516
12. Farkouh ME, Domanski M, Sleeper LA et al (2012) FREEDOM Trial Investigators. Strategies for multivessel revascularization in patients with diabetes. N Engl J Med 367:2375–2384
13. Kappetein AP, Head SJ, Morice MC et al (2013) SYNTAX Investigators. Treatment of complex coronary artery disease in patients with diabetes: 5-year results comparing outcomes of bypass surgery and percutaneous coronary intervention in the SYNTAX trial. Eur J Cardiothorac Surg 43:1006–1011
14. Hakeem A, Garg N, Bhatti S, Rajpurohit N, Ahmed Z, Uretsky BF (2013) Effectiveness of percutaneous coronary intervention with drug-eluting stents compared with bypass surgery in diabetics with multivessel coronary disease: comprehensive systematic review and meta-analysis of randomized clinical data. J Am Heart Assoc 2:e000354
15. Kapur A, Hall RJ, Malik IS et al (2010) Randomized comparison of percutaneous coronary intervention with coronary artery bypass grafting in diabetic patients: 1-year results of the CARDia (Coronary Artery Revascularization in Diabetes) trial. J Am Coll Cardiol 55:432–440
16. Windecker S, Stortecky S, Stefanini GG et al (2014) Revascularisation versus medical treatment in patients with stable coronary artery disease: network meta-analysis. BMJ 348:g3859
17. Valgimigli M, Sabate M, Kaiser C et al (2014) Effects of cobalt-chromium everolimus eluting stents or bare metal stent on fatal and non-fatal cardiovascular events: patient level meta-analysis. BMJ 349:g6427
18. Palmerini T, Biondi-Zoccai G, Della Riva D et al (2012) Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. Lancet 379:1393–1402
19. Stefanini GG, Baber U, Windecker S et al (2013) Safety and efficacy of drug-eluting stents in women: a patient-level pooled analysis of randomised trials. Lancet 382:1879–1888
20. Mehilli J, Pache J, Abdel-Wahab M et al (2011) Drug-eluting vs. bare-metal stents in saphenous vein graft lesions (ISAR-CABG): a randomised controlled superiority trial. Lancet 378:1071–1078
21. Piccolo R, Pilgrim T, Heg D et al (2015) Comparative effectiveness and safety of new-generation versus early-generation drug-eluting stents according to complexity of coronary artery disease: a patient-level pooled analysis of 6,081 patients. JACC Cardiovasc Interv 8:1657–1666
22. Park SJ, Ahn JM, Kim YH et al (2015) Trial of everolimus-eluting stents or bypass surgery for coronary disease. N Engl J Med 372:1204–1212
23. Bangalore S, Guo Y, Samadashvili Z et al (2015) Everolimus-eluting stents or bypass surgery for multivessel coronary disease. N Engl J Med 372:1213–1222
24. Bangalore S, Kumar S, Fusaro M et al (2012) Outcomes with various drug eluting or bare metal stents in patients with diabetes mellitus: mixed treatment comparison analysis of 22,844 patient years of follow-up from randomised trials. BMJ 345:e5170
25. Koskinas KC, Siontis GC, Piccolo R et al (2016) Impact of diabetic status on outcomes following revascularization with drug-eluting stents in relation to coronary artery disease complexity. A

patient-level pooled analysis of 6,081 patients. Circ Cardiovasc Interv 9:e003255. doi: 10.1161/CIRCINTERVENTIONS.115.003255
26. Bangalore S, Toklu B, Feit F (2014) Outcomes with coronary artery bypass graft surgery versus percutaneous coronary intervention for patients with diabetes mellitus: can newer generation drug-eluting stents bridge the gap? Circ Cardiovasc Interv 7:518–525
27. Piccolo R, Piccolo R, Giustino G, Mehran R, Windecker S (2015) Stable coronary artery disease: revascularisation and invasive strategies. Lancet 386:702–713
28. Tonino PA, Fearon WF, De Bruyne B et al (2010) Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. J Am Coll Cardiol 55:2816–2821
29. Nicholls SJ, Ballantyne CM, Barter PJ et al (2011) Effect of two intensive statin regimens on progression of coronary disease. N Engl J Med 365:2078–2087
30. Stegman B, Puri R, Cho L et al (2014) High-intensity statin therapy alters the natural history of diabetic coronary atherosclerosis: insights from SATURN. Diabetes Care 37:3114–3120

Buchbesprechung

R. Kroidl, S. Schwarz, B. Lehnigk, J. Fritsch

Kursbuch Spiroergometrie

Klinik und Befundung verständlich gemacht

Thieme Georg Verlag 2015, 528 S., (ISBN 3-13-143443-0), 129.00 EUR

Das deutsche Standardwerk Kursbuch Spiroergometrie liegt nun in der 3. Auflage vor. Den Autoren Rolf F. Kroidl, Stefan Schwarz, Burghart Lehnigk und Jürgen Fritsch gelingt es, die Faszination für diese komplexe Untersuchungstechnik zu vermitteln und zugleich auch immer wieder ihre methodischen Grenzen aufzuzeigen. Das Lehrbuch ist im bewährten Kursformat aufgebaut und lehnt sich an die seit vielen Jahren angebotenen Spiroergometrie-Kurse der Autoren an.

Die Eingangskapitel zu technischen Grundlagen, Physiologie und technischer Durchführung sind verständlich und haben einen engen Praxisbezug. Im Folgenden vermitteln die Autoren eine Systematik und weisen damit gerade dem Anfänger einen Weg durch das Labyrinth der Messwerte und Grafiken. Dabei liegt ein Schwerpunkt auf der grafischen Auswertung. Dieser Ansatz hat einen hohen Praxisbezug, ist didaktisch wertvoll und hilft, Messfehler zu erkennen. Spezielle Fragestellungen wie präoperative Risikoabschätzung, pulmonale Hypertonie, Herzinsuffizienz, Herzklappenfehler und Spiroergometrie in der Begutachtung werden gesondert besprochen. Das Kapitel Standards bei der Durchführung der Spiroergometrie listet formale Kriterien wie Indikationen, Abbruchkriterien und apparative Voraussetzungen auf. Außerdem werden Einflussfaktoren wie Belastungsform, Belastungsdauer und die Befunddarstellung dargestellt. Die Kasuistiken und Fragen am Ende des Lehrbuches ermöglichen eine Lernkontrolle.

Das Buch stellt die gesamte Bandbreite der Untersuchungsmethode dar. Dabei ist es bemerkenswert, dass sowohl pneumologische, als auch kardiologische Aspekte gleichermaßen behandelt werden. So ist das Werk sowohl für den klinisch tätigen Arzt als auch für den niedergelassenen Kardiologen/Pneumologen von hohem praktischen Nutzen. Das graphisch hervorragend aufgearbeitete Buch ist in der aktuellen Auflage unter anderem um Kapitel zur klinisch immer häufiger relevanten Adipositas und zu der neuen Messtechnik der Inertgas-Rückatmungsmethode erweitert worden.

Das Kursbuch Spiroergometrie ist weiterhin das Standardwerk im deutschsprachigen Raum. Das bewährte Buchkonzept wurde beibehalten und um aktuelle Themen ergänzt. Es sei dem Anfänger als Lehrbuch und dem Fortgeschrittenen Untersucher als Nachschlagewerk empfohlen

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