

# Debate – from SYNTAX to FREEDOM and STICH: PCI is moving to centre stage

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## Summary

Myocardial revascularisation by means of percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) has an established role for the treatment of coronary artery disease. During the past years, the introduction of new-generation drug-eluting stents and improvements pharmacological therapy allowed for an increasing adoption of PCI for myocardial revascularisation. This review summarises the evidence on the role of PCI among patients with multivessel or left main coronary artery disease as well as among those with diabetes or left ventricular dysfunction.

Key words: PCI; CABG; myocardial revascularisation; stent



## Introduction

Introduced 40 years ago, percutaneous coronary intervention (PCI) has become the most frequently performed procedure for myocardial revascularisation, being preferred for more than three-quarters of patients [1]. Although the preferential use of PCI in lieu of conservative medical therapy in the setting of acute coronary syndromes is supported by several randomised trials and meta-analyses, the role of PCI for revascularisation in patients with stable coronary artery disease (CAD) still remains a matter of debate. Direct evidence from randomised trials failed to show a clear survival benefit over medical therapy for PCI in stable CAD [2], whereas a network meta-analysis of 100 randomised trials suggested that PCI with new-generation drug-eluting stents (DESs) reduces the risk of all-cause mortality compared with medical therapy, rivalling outcomes of coronary artery bypass grafting (CABG) [3]. In this article, we review the role of PCI and CABG as revascularisation modalities for patients with multivessel or left main CAD, and those with more challenging conditions such as ischaemic cardiomyopathy and diabetes.

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## Multivessel coronary artery disease

The choice of revascularisation modality (either PCI or CABG) finds broad agreement among cardiovascular surgeons and interventional cardiologists in most patients encountered in routine clinical practice. In an observational study, of 1943653 patients >65 years of age with two- or three-vessel CAD who had undergone either PCI or CABG between 2004 and 2008, the vast majority of patients had a clear indication for one particular revascularisation procedure, leaving only 189793 patients, or approximately 10%, for the purpose of a comparative analysis [4].

In the DES era, several trials compared PCI with surgical revascularisation in patients with multivessel CAD [5–8]. The Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery (SYNTAX) trial randomised 1800 patients with left main and/or three-vessel CAD to either PCI with the early-generation paclitaxel-eluting stent or CABG [5]. At 5 years, CABG was associated with a lower risk of the primary endpoint of major adverse cardiovascular and cerebrovascular events (26.9 vs 37.3%), mainly driven by lower rates of repeat revascularisation and myocardial infarction. An important feature of the SYNTAX trial was the stratification according to the SYNTAX score, which classifies anatomical complexity of CAD as low ( $\leq 22$ ), intermediate (23–32) and severe ( $> 32$ ). Overall, the prognostically relevant composite endpoint of death, stroke, or myocardial infarction was not significantly different between CABG and PCI in low (14.9 vs 16.1%,  $p = 0.81$ ) and intermediate (18.0 vs 20.7%,  $p = 0.42$ ) SYNTAX score risk categories, whereas there was a clear advantage for CABG in patients with a high SYNTAX score (17.1 vs 26.1%,  $p = 0.007$ ) [9]. To overcome the limitations inherent to the SYNTAX score, which is based on anatomical criteria only, a newer clinical tool, the SYNTAX score II, has been developed on the basis of a combination of anatomical and clinical factors (age,

creatinine clearance, left ventricular ejection fraction, left main disease, sex, chronic obstructive pulmonary disease and peripheral vascular disease) [10]. The goal of the SYNTAX score II is to help decision-making in the heart team by providing the risk of 4-year mortality associated with PCI and CABG. However, it is important to emphasise that a prospective, external clinical validation of the SYNTAX score II is still lacking.

More recently, the BEST (Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease) trial compared PCI with use of the new generation, everolimus-eluting stent with CABG in the setting of multivessel CAD [11]. This trial was prematurely terminated because of slow enrolment and included approximately half of the patients originally planned (880 out of 1776 or 49.5%). Although PCI was found inferior to CABG for the primary endpoint of death, myocardial infarction, or target-vessel revascularisation (17 vs 11%,  $p = 0.04$ ), the rates of the composite of death, myocardial infarction, or stroke was similar (13.4 vs 10.2% with PCI and CABG, respectively,  $p = 0.27$ ). In a pooled analysis of the SYNTAX and BEST trials, CABG was associated with a reduced risk of mortality among nondiabetic patients with multivessel disease (6.7 vs 10.0%,  $p = 0.037$ ) in the overall population [12]. Of note, the two strategies showed similar rates of mortality in patients with low SYNTAX score (7.5 vs 6.0% with PCI and CABG, respectively,  $p = 0.66$ ) [12].

A large, propensity-score-matched comparison between new-generation, everolimus-eluting stents and CABG in 18 446 patients from the New York State Registry suggested that PCI is associated with a similar risk of mortality (3.1 vs 2.9% per year,  $p = 0.50$ ) [13]. Interestingly, although PCI was associated with a higher risk of myocardial infarction (1.9 vs 1.1% per year,  $p < 0.001$ ), this was mainly confined to patients with incomplete revascularisation, which was more frequent among PCI-treated patients [13]. Collectively, data from the New York Registry showed a progressive reduction in the risk of mortality associated with PCI compared with CABG, through the development of PCI techniques from balloon angioplasty over bare-metal stents and early-generation DESs to new-generation DESs [14].

### Left main coronary artery disease

Left main disease is observed in approximately 5–10% of patients undergoing diagnostic coronary angiography [15]. In view of the large myocardial area at risk,

a significant stenosis of the left main coronary artery confers a mortality rate of more than 50% at 5 years if left untreated [16]. Although CABG historically represented the cornerstone of revascularisation for left main disease, PCI has been increasingly adopted in clinical practice, particularly in favourable anatomical settings. Data from the IRIS-MAIN (Interventional Research Incorporation Society-Left MAIN Revascularization) registry showed a progressive use of PCI in patients with left main disease, which progressively increased from 25% in period between 1995 and 2002 to 61% between 2007 and 2013 [17].

Among 705 patients with left main disease enrolled in the SYNTAX trial, the 5-year rates of death (14.6 vs 12.8%,  $p = 0.53$ ) and myocardial infarction (4.8 vs 8.2%,  $p = 0.10$ ) were not different between the two revascularisation modalities, whereas CABG had a higher rate of stroke (4.3 vs 1.5%,  $p = 0.03$ ) and a lower risk of repeat revascularisation (15.5 vs 26.7%,  $p < 0.001$ ); there was no significant difference in the overall rate of major adverse cardiovascular and cerebrovascular events (13.6 vs 15.8%,  $p = 0.44$ ) [18]. In the lower (0–22) and intermediate (23–32) SYNTAX score tertiles, PCI was associated with superior outcomes compared with CABG, whereas in patients with SYNTAX scores  $> 32$  CABG was associated with a numerically lower mortality rate (14.1 vs 20.9%,  $P = 0.11$ ) and a significantly reduced need for repeat revascularisation (11.6 vs 34.1%,  $p < 0.001$ ) [18]. Similar findings were reported by the Premier of Randomized Comparison of Bypass Surgery vs Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease (PRECOMBAT) trial that included 600 patients with left main disease, who were randomly assigned to treatment with early-generation sirolimus-eluting stents or CABG [19]. In the PRECOMBAT trial, there was no difference between CABG and PCI in terms of major adverse cardiovascular and cerebrovascular events at 5-year follow-up (17.5 vs 14.3%,  $p = 0.26$ ), although PCI was associated with an increased rate of ischaemia-driven target-vessel revascularisation (11.4 vs 5.5%,  $p = 0.01$ ) [19].

Recently, the results of two dedicated, randomised trials testing the hypothesis of noninferiority between new generation DESs and CABG in the setting of left main disease were reported: the Evaluation of the Xience Everolimus-Eluting Stent Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularisation (EXCEL) and the Nordic-Baltic-British Left Main Revascularisation Study (NOBLE) trials [20, 21]. In the EXCEL trial, 1905 patients with left main disease and a SYNTAX score of  $\leq 32$  were randomly assigned to PCI with new-generation DESs (everolimus-eluting stents) or CABG and followed up for 3 years [20].

The primary endpoint, a composite of death, myocardial infarction or stroke, occurred at similar rates with PCI and CABG (15.4 vs 14.5%,  $p = 0.98$ ). Importantly, there was no significant difference in the rates of individual endpoints including mortality (8.2 vs 5.9%,  $p = 0.11$ ), myocardial infarction (8.0 vs 8.3%,  $p = 0.64$ ), and stroke (2.3 vs 2.9%,  $p = 0.37$ ). Although the overall results of the EXCEL trial suggest equipoise between the two techniques, PCI had better results, particularly in the early period after intervention, whereas CABG showed a trend toward improved late outcomes. Indeed, periprocedural myocardial infarction was significantly lower among patients assigned to PCI as compared with CABG (3.8 vs 6.0%,  $p = 0.03$ ), whereas subsequent spontaneous events tended to be more frequent with PCI (4.3 vs 2.7%,  $p = 0.07$ ). These data are of importance because the EXCEL trial used a high threshold for the definition of periprocedural myocardial infarction, including only large, periprocedural events – specifically those with a more than 10-fold elevation in cardiac biomarkers (or 5-fold plus additional evidence of ischaemia). Definite stent thrombosis or symptomatic graft occlusion was significantly lower among patients allocated to PCI compared with CABG (0.7 vs 5.4%,  $p < 0.001$ ) [20]. This finding is noteworthy as it is at variance with the SYNTAX trial, in which the composite of stent thrombosis and graft occlusion occurred at similar rates for patients treated with PCI and CABG (5.1 vs 4.4%,  $p = 0.70$ ) [18]. Periprocedural events in the EXCEL trial were carefully assessed and allowed a more comprehensive evaluation of the two techniques regarding early adverse events. PCI offered several advantages over CABG within the first 30 days in terms of risk of stroke (0.6 vs 1.3%,  $p = 0.16$ ), major and minor bleeding (3.7 vs 8.9%,  $p < 0.001$ ), major arrhythmias (2.1 vs 16.1%,  $p < 0.001$ ), renal failure (0.6 vs 2.5%,  $p < 0.001$ ), and prolonged intubation (0.4 vs 2.9%,  $p < 0.001$ ) [20]. In the NOBLE trial, 1201 patients with left main disease were randomly allocated to PCI with predominantly new-generation DESs or CABG and were followed up for a median period of 3.1 years [21]. The primary endpoint, the rate of major adverse cardiovascular and cerebrovascular events, was significantly increased for PCI compared with CABG (29 vs 19%,  $p = 0.0066$ ) owing to a higher risk of nonprocedural myocardial infarction (7 vs 2%,  $p = 0.004$ ) and repeat revascularisation (16 vs 10%,  $p = 0.032$ ). Notably, periprocedural events, in particular myocardial infarction, were not included in the definition of myocardial infarction in the trial and were assessable in only 45% of patients [21]. In addition, at variance with all other trials, the rate of stroke in NOBLE was unexpectedly higher among patients assigned to PCI and this probably represents a chance finding.

## Ischaemic cardiomyopathy and diabetes

Ischaemic cardiomyopathy with left ventricular dysfunction and CAD represents a high-risk condition with a survival rate of less than 50% at 10 years. The Surgical Treatment for Ischemic Heart Failure Extension Study (STICH) trial randomised 1212 patients with CAD and a left ventricular ejection fraction of  $\leq 35\%$  to CABG or medical therapy [22]. At 10-year follow-up, CABG conferred a significant benefit in terms of the primary endpoint of all-cause mortality (58.9 vs 66.1%,  $p = 0.02$ ), mainly due to a reduction in cardiovascular mortality (40.5 vs 49.3%,  $p = 0.006$ ) [22]. Although there is a lack of clinical trials comparing PCI with medical therapy in patients with left ventricular dysfunction, a propensity-matched analysis from the New York State Registry, including 2126 patients with multivessel CAD and a left ventricular ejection fraction of  $\leq 35\%$ , revealed a similar risk of all-cause mortality between PCI with use of everolimus-eluting stents and CABG (25.2 vs 21.0%,  $p = 0.91$ ) [23]. Of note, PCI was associated with a 2-fold higher risk of myocardial infarction and a 43% relative reduction in the risk of stroke [23].

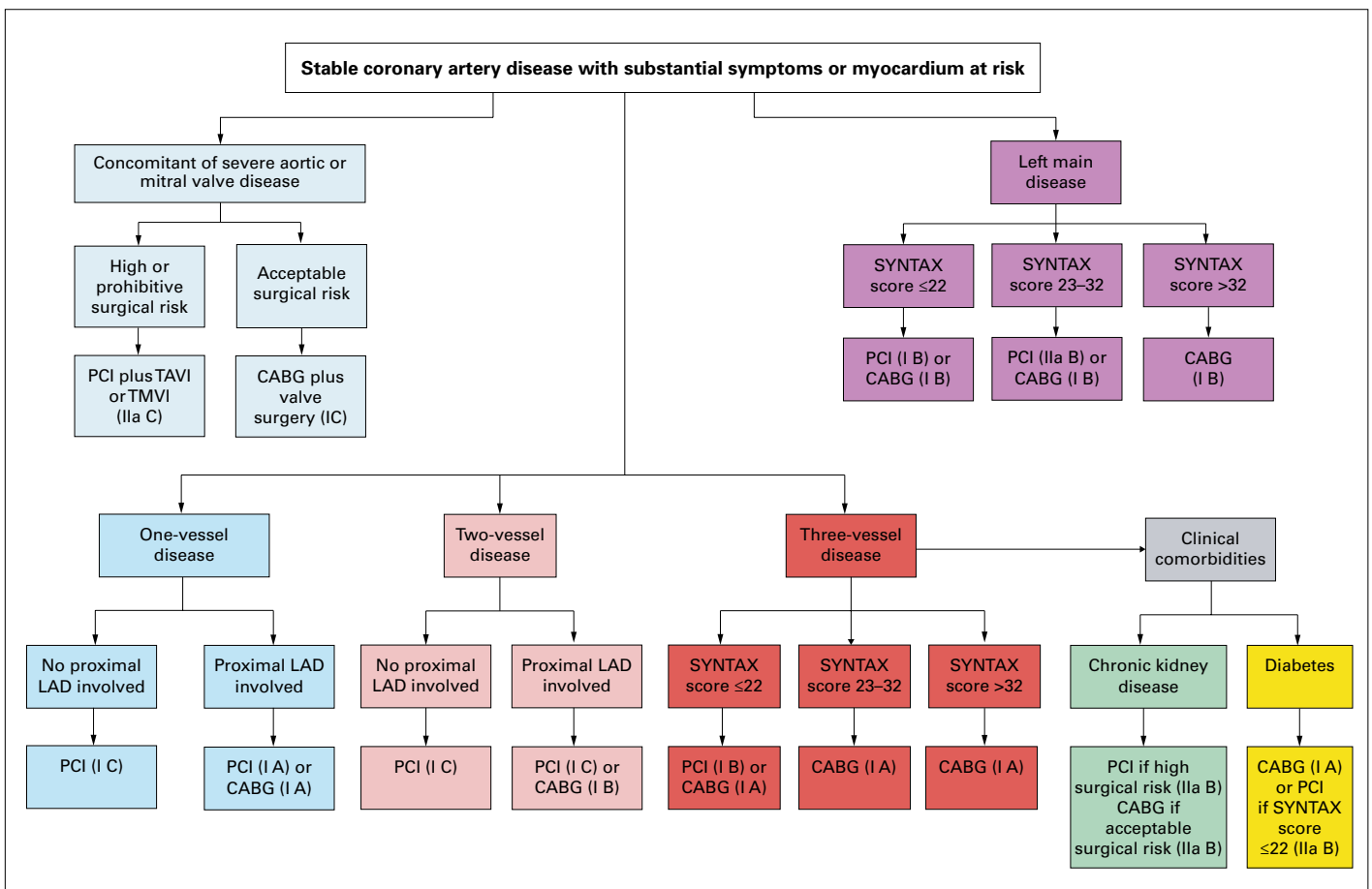
Diabetes mellitus is a common clinical condition and a serious global health problem [24]. During the last two decades, the incidence and prevalence of diabetes have grown at exponential rates worldwide, and by 2035, the global prevalence is expected to further increase by more than 50% compared with current estimates. In the Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial, the largest randomised study in patients with diabetes, PCI with use of early-generation DESs was compared with CABG in patients undergoing elective revascularisation for multivessel CAD [8]. Out of 33966 patients screened, 1900 patients (6%) with a mean age of 63 years and a mean SYNTAX score of  $26 \pm 9$  were enrolled [8]. CABG significantly reduced the risk of the primary endpoint of death, myocardial infarction or stroke compared with PCI (18.7 vs 26.6%,  $p = 0.005$ ), with divergence of the Kaplan-Meier curves starting at 2 years [8]. There was a markedly lower rate of myocardial infarction in the CABG group (6.0 vs 13.9%,  $p < 0.001$ ), whereas rates of stroke were doubled compared with PCI (5.2 vs 2.4%,  $p = 0.03$ ). Cardiovascular mortality did not significantly differ between PCI and CABG (10.9 vs 6.8%,  $p = 0.12$ ) [8]. In a meta-analysis of four randomised trials including 3052 diabetic patients, Hakeem and colleagues found that PCI compared with CABG had a similar risk of major adverse cardiovascular and cerebrovascular events in patients with lower (relative risk [RR] 1.27, 95% confidence interval [CI] 0.96–1.68) and

intermediate (RR 1.32, 95% CI 0.86–2.02) SYNTAX scores (0–32), but a higher risk (RR 1.73, 95% CI 1.21–2.46) in the group with high SYNTAX score of >32 [25].

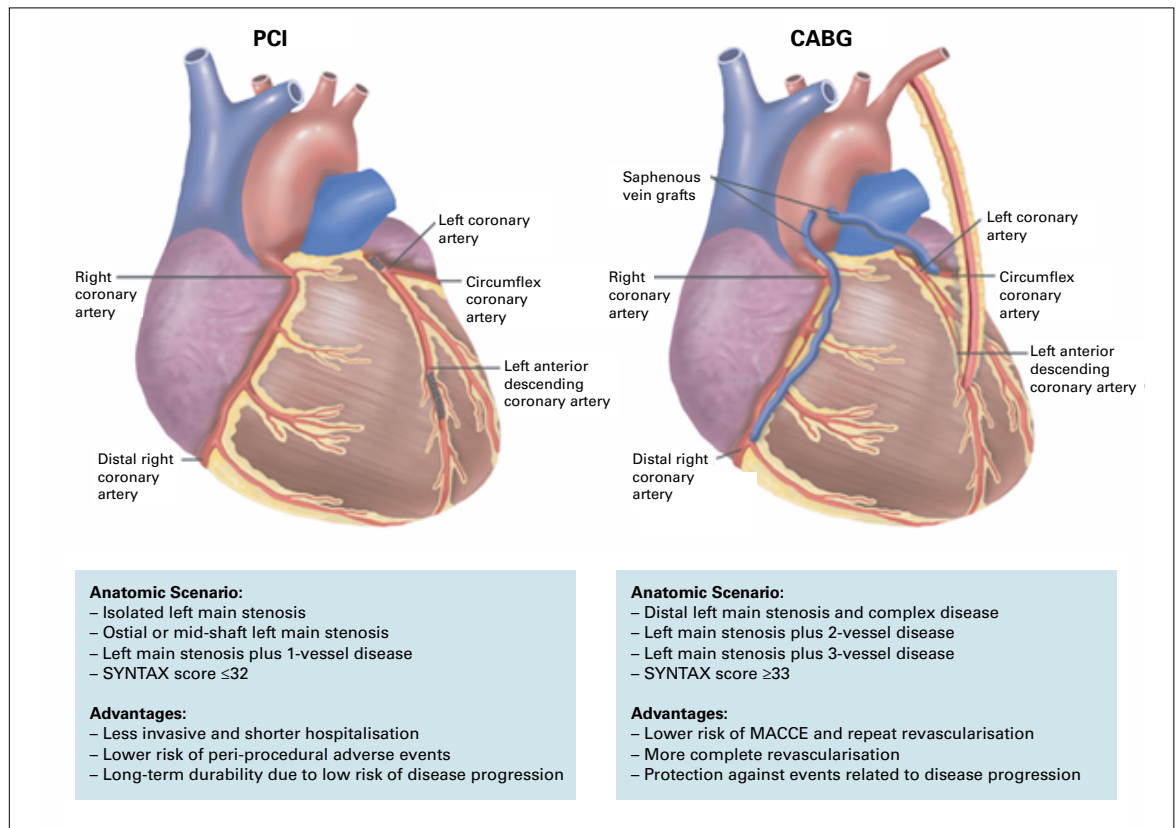
### Conclusions

Current recommendations for revascularisation by means of PCI and CABG for patients with stable CAD are summarised in figure 1 [26, 27]. Available data suggest that PCI and CABG have a similar effect on survival in patients with multivessel CAD, particularly those with lower anatomic complexity (SYNTAX score <22). CABG provides better protection from the clinical implications of atherosclerosis progression, as evidenced by a decreased need of repeat revascularisation as well as a lower risk of spontaneous myocardial infarction. Notwithstanding, CABG is associated with a nearly 3-fold increased risk of stroke [28]. Currently, the use of fractional flow reserve (FFR) to detect of func-

tionally significant lesions in patients with multivessel CAD is being investigated in the FAME-3 trial, which will randomly assign 1500 patients to FFR-guided PCI or CABG [29]. Among patients with left main CAD, PCI is a valid alternative to CABG for patients with isolated left main stenosis as well as those with lesions at the ostium or within the shaft and in patients with a SYNTAX score ≤32. Conversely CABG remains the therapy of choice in more complex anatomical scenarios, including distal left main stenosis with two- and three-vessel disease, as well as for patients with a SYNTAX score ≥33 (fig. 2) [30]. Notably, long-term (5-year) follow-up data from the SYNTAX and NOBLE trials are eagerly expected and will further inform decision-making in the setting of left main disease. Patients with ischaemic cardiomyopathy should be considered for revascularisation in addition to evidence-based medical therapy, and the choice of CABG or PCI should be made on an individual basis, and take



**Figure 1:** Algorithm for revascularisation across anatomical and clinical subsets in patients with coronary artery disease. Class and level of evidence recommendations are derived from the guidelines of the European Society of Cardiology on myocardial revascularisation and refer to patients with stable coronary artery disease with coronary anatomy suitable for either percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) and low predicted surgical mortality. TAVI = transcatheter aortic valve implantation; TMVI = transcatheter mitral valve; LAD = left anterior descending artery. Adapted, with permission from Elsevier, from Piccolo et al. [27].



**Figure 2:** PCI versus CABG in patients with left main coronary artery disease. CABG = coronary artery bypass grafting; MACCE = major adverse cardiovascular and cerebrovascular events; PCI = percutaneous coronary intervention; SYNTAX = Synergy Between PCI With TAXUS and Cardiac Surgery trial. Reproduced, with permission from Elsevier, from Piccolo and Windecker [30].

into account anatomic suitability and risk profile. In this respect, the role of the heart team and patient involvement are essential for personalised decision making.

Revascularisation in diabetic patients remains challenging owing to the frequent presence of extensive and diffuse CAD and high propensity to disease progression. New-generation DESs have improved outcomes in diabetic patients undergoing PCI given the more effective prevention of restenosis [31]. However, the threshold for considering CABG instead of PCI among diabetic patients with multivessel CAD should be lower than in nondiabetic patients (fig. 1) [26, 27]. During the past four decades, the continuous improvement in PCI resulted in better clinical outcomes, as

shown by several lines of evidence including observational and randomised data. As such, PCI is currently the preferred revascularisation modality among patients with CAD, including those with multivessel disease.

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#### References

The full list of references is included in the online version of the article at [www.cardiovascmed.ch](http://www.cardiovascmed.ch) (DOI <https://doi.org/10.4414/cvm.2018.14546>).

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