

Percutaneous coronary intervention using second generation drug-eluting stents vs coronary artery bypass graft in left main coronary artery and multivessel coronary artery disease

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Heart disease remains the leading cause of death in both men and women globally as per the CDC - with coronary artery disease (CAD) being the most common type of heart disease. Coronary artery disease (CAD) is responsible for killing 360,900 people in 2019 with 18.2 million adults above the age of 20 currently diagnosed in the United States.¹ However, mortality rates secondary to CAD have reduced an approximate 30% over the past 20 years due to various factors including earlier identification, increased awareness/education and improved medical therapy/technology.²

Although medication therapy is a commonly used treatment option for patients with CAD, especially for those diagnosed with stable coronary artery disease (SCAD), percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) have both been proven as the superior option in reducing angina frequency, increasing exercise capacity and improving quality of life based on short and long term follow-up studies.³ One study concluded that when comparing primary end-point events which included composite of death, myocardial infarction or urgent revascularization, PCI was almost three times safer than medication therapy alone (4.3% PCI vs 12.7% medical-therapy). The safety of PCI was also attributed to a lower rate of revascularization in the PCI group with a hazard ratio of 1.6% compared to 11.1% in the medical-therapy group.⁴ A follow up study was additionally able to demonstrate that within a three year timeframe, PCI was the more economically attractive option when compared with medication therapy alone.⁵

Studies that have compared medical-therapy to CABG are even more convincing; meta-analyses of seven RCTs comparing CABG to medical-therapy alone showed significantly lower all-cause mortality. A group that had undergone 5 years of medical therapy was found to have an all-cause mortality rate of 15.8%, compared to the all-cause mortality rate of 10.2% of the

CABG group. Similar trends were also found in groups that had experienced 7 and 10 years of medical therapy, coinciding with all-cause mortality rates of 21.7% and 30.5% respectively, versus the CABG group's 15.8% and 30.5% all-cause mortality rate. Additionally, the CABG group had a significantly lower all-cause mortality percentage of 10.2% vs the 15.8% of medical therapy at 5 years, 15.8% vs 21.7% at 7 years and 26.4% vs 30.5% at 10 years.⁶

The comparison of efficacy and end-point values between PCI and CABG is more complex. PCI was originally introduced in 1977 as a single vessel revascularization procedure and historically could not compete against CABG as the gold standard of treatment for patients with LMCA or three-vessel CAD.⁷ Most major studies that compared PCI to CABG amongst this population group demonstrated better outcomes for CABG, but many of these studies used older generations of stents as the comparative benchmark.

Stent technology has developed significantly over the past four decades, since initial PCI treatment involved the use of bare-metal stents (BMS) without any drug-eluting properties. With these improvements in technology as outlined in **Figure 1**, use of PCI has been progressively increasing for the treatment of more complex lesions. Everolimus, Biolimus and Zotarolimus eluting stents were introduced in 2008 have since replaced Paclitaxel and Sirolimus eluting stents (the first generation of drug-eluting stents), demonstrating lower rates of revascularization and stent thrombosis.⁷ Interestingly, a large meta-analysis from 2014 that included 100 RCTs and 93,553 patients demonstrated that early-generation DES (drug-eluting stents), BMS and balloon angioplasty was unable to achieve superiority over medication-therapy alone whereas newer generation DES (Everolimus, Zotarolimus) were associated with improved survival rates.⁸ Although this resurfaces the historical debate between early iterations of PCI and medication therapy, the focus of this article is to refresh readers on the decision making process behind PCI

and CABG for patients and to determine whether the newer generation DES are capable of challenging CABG for the gold standard of surgical therapy in patients with LMCA and three-vessel CAD. It is worth noting that the delay in this comparison, given that 2nd generation DES was introduced in 2008, is due to the long-term follow-up studies that are required to obtain data that will achieve clinical applicability.

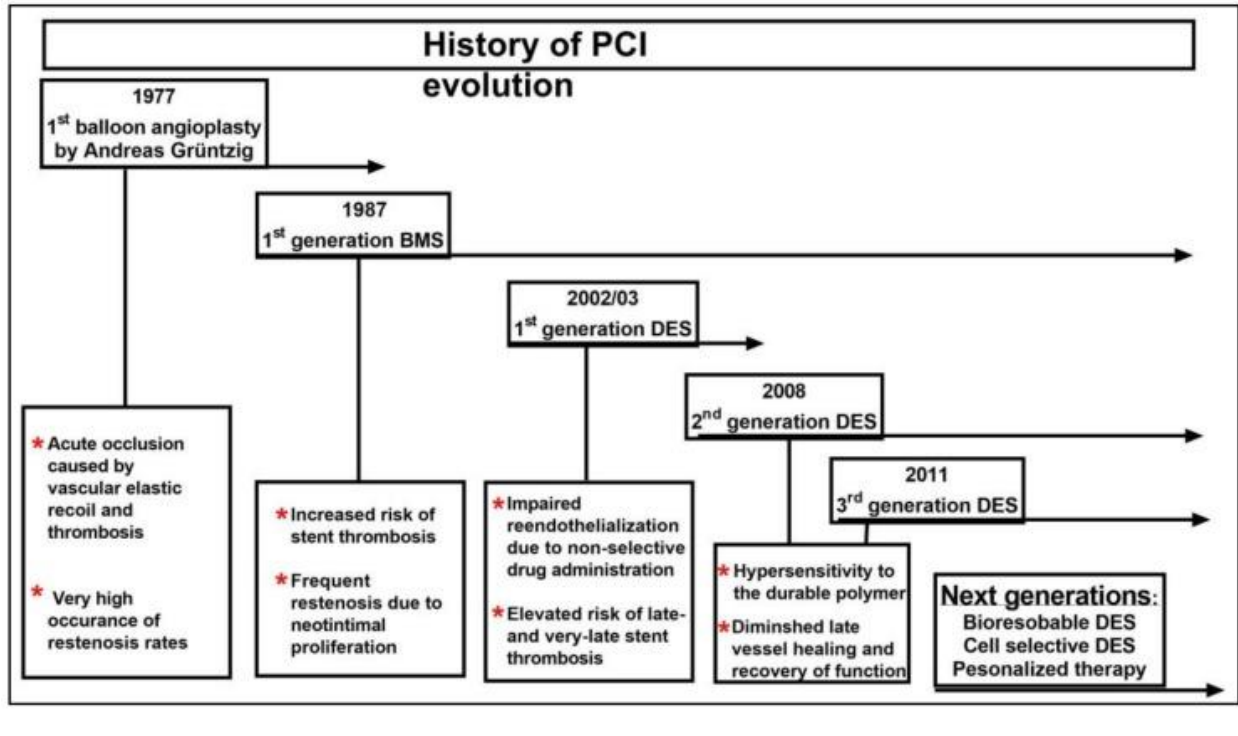


Figure 1. History of PCI evolution

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SYNTAX Score

Before comparing the two procedures, it is important to understand the standard process of decision making behind choosing PCI and CABG. The most recent ESC/EACTS guideline for myocardial revascularization recommends using the SYNTAX score to determine the anatomical complexity of the lesion before choosing between PCI and CABG.⁹ SYNTAX score, or

“Synergy between PCI with Taxus and Cardiac Surgery” score, is an angiographic scoring tool created to determine the anatomical complexity of CAD, including variables such as dominance (left or right), number of lesions, segments involved per lesion, total occlusion, trifurcation, bifurcation, aorto-ostial lesion, severe tortuosity, length >20mm, heavy calcification, thrombus and diffuse disease/small vessels.¹⁰ This calculation tool was then used in a validation RCT to compare outcomes between paclitaxel-eluting stents to CABG in patients with LMCA and/or three-vessel disease. The study determined that higher SYNTAX scores were associated with a higher 1-year rate of major cardiac and cerebrovascular events in 903 patients who underwent PCI when compared with CABG. The study found no correlation in cardiac and cardiovascular risk to SYNTAX scores in patients that underwent CABG.¹¹ The range of values in this study were then stratified in a follow-up study, with each group representing a prediction value for a major cardiac event following PCI. Low risk was defined as <16 points, intermediate risk as 16-22 points and high risk as >22 points, as shown in Table 1.¹² Overall, the study suggests that patients with either LMCA or three-vessel disease and/or fall under the high-risk category using the SYNTAX calculator would find most benefit with undergoing CABG over PCI due to this increased risk. However, as mentioned previously, this study explicitly focuses on patients that received paclitaxel eluting stents, which have since been replaced with everolimus, zotarolimus or biolimus eluting stents as the standard of care.

Table 1: Major adverse cardiac events following PCI at 14 months (median time)	
Syntax Score	Major adverse cardiac event rate
Low; ≤16	7.5%
Intermediate; 16-22	9.9%
High; >22	21.6%

Three-Vessel Disease:

The subgroup analysis of the SYNTAX trial for patients with three-vessel disease showed that 19.2% of patients that underwent PCI with paclitaxel-eluting stents had a cardiac or cerebrovascular event after 12 months, as opposed to the 11.5% in the CABG group. The percentage of repeat revascularizations was also noteworthy; 14.6% of patients in the PCI group needed to undergo revascularization versus 5.5% of the CABG group requiring revascularization.. The rate of all-cause mortality was similar between the two groups, but did not reach statistical significance (8.0% PCI and 6.6% CABG).¹¹ Another study that was released later that year supported this finding - three-year follow up of 3720 patients from a single institution concluded that patients who received either sirolimus or paclitaxel eluting stents had significantly higher rates of revascularization (17.6% PCI and 4.2% CABG), myocardial infarction (HR: 1.65 in PCI) and all-cause mortality (HR: 1.62 in PCI) than the CABG group at the 36-month mark. Although stroke rates were found to be higher in the CABG group, the study attributed this outcome to the older age demographic in the CABG group with a higher prevalence of peripheral vascular disease.¹³ A different study performed in 2008 was able to demonstrate higher survival rates for patients who underwent CABG at 94% v.s. 92.7% PCI (Sirolimus and Paclitaxel) in an 18-month timeframe. Additionally, freedom from myocardial infarction was also superior at 92.1% for CABG and 80.7% for PCI.¹⁴

In comparison, more recent studies such as the BEST trial conducted a randomized noninferiority trial with 438 patients that were assigned PCI with everolimus-eluting stents (438 PCI, 442 CABG). However, even with the newer generation everolimus eluting stents, the PCI group was unable to demonstrate up to the standards of CABG when comparing primary endpoints at 2 years. Additionally, a pooled data follow-up performed at a median of 4.6 years

showed a significant increase in primary endpoints for the PCI group in regards to death, myocardial infarction and target-vessel revascularization. The PCI group reached a primary endpoint of 11% v.s. 7.9% in the CABG group at 2 years, and 15.3% and 10.6% respectively, in the follow-up study (long-term, unknown length). The study goes further to discuss that in contrast to previous RCTs and meta-analyses that demonstrated higher rates of stroke in the CABG group, the stroke rate in this study was not significantly different between the two groups.¹⁵

Table 2: Outcomes in three-vessel disease		
Study	Type of DES	Overall outcome
SYNTAX trial, 2009 ¹¹	Paclitaxel	Patients that underwent PCI have a higher cardiac or cerebrovascular risk than CABG after 12 months
Li Y et al. 2009 ¹³	Sirolimus or Paclitaxel	PCI had significantly higher rates of revascularization and all-cause mortality than CABG after 36 months
Hannan EL et al. 2008 ¹⁴	Sirolimus or Paclitaxel	PCI had lower survival rates than CABG after 18 months
BEST trial, 2015 ¹⁵	Everolimus	PCI was unable to prove noninferiority based on death, MI, revascularization

Left Main Coronary Artery

As mentioned above, noninferiority was not achieved within the LMCA cohort in the SYNTAX trial. The rate of revascularization among patients in the PCI group was 11.8% vs 6.5% in the CABG group at 12 months, although there was a higher rate of stroke in the CABG group at 2.7% vs 0.3% in the PCI group. Interestingly, the rate of major adverse cardiac or

cerebrovascular events was similar in both the PCI and CABG group, but it did not reach statistical significance and thus did not prove noninferiority of PCI.¹¹

Additionally, a RCT of 201 patients demonstrated that in patients with LMCA CAD, those who underwent PCI using sirolimus-eluting stents were unable to achieve noninferiority to those who underwent CABG in regards to major adverse cardiac events and repeat revascularizations. Although the combined rates for death and myocardial infarction were lower in the PCI group (5.0% PCI vs 7.9% surgery), the primary endpoint was reached in 13.9% for those in the CABG group and 19% in the PCI group, thus proving superiority of CABG.¹⁶

However, the results of the newer-generation stents used in LMCA disease are slightly more promising. One of the largest RCTs performed since the SYNTAX trial was the EXCEL trial conducted in 2016, which exclusively used everolimus-eluting stents in 948 patients (957 in the CABG group) and found that the primary end-point composite of all-cause mortality, stroke and myocardial infarction for patients was reached in 15.4% of patients in the PCI group and 14.7% in the CABG group within a 3-year timeframe. Additionally, the secondary end-point of death, stroke, MI at 30 days was lower in the PCI group, reaching 4.9%, as opposed to the CABG group's 7.9%. The study was successfully able to conclude that PCI with everolimus-eluting stents are noninferior to CABG within a 3-year period.¹⁷ The recent, five-year follow up study done in 2018 was also able to reach noninferiority for PCI patients with everolimus-eluting stents, becoming one of the first studies to ever demonstrate noninferiority of PCI. However, the study explicitly mentions that all patients that underwent PCI in their study had a low to intermediate SYNTAX score.¹⁸

Another study conducted in 2017 was able to support this evidence - meta-analyses of 4 RCTs with a total of 4394 patients demonstrated near equivalent risk of all-cause mortality,

myocardial infarction between the two groups (HR: 1.06). Similar to the EXCEL trial, the meta-analyses only included patients of low to intermediate complexity CAD as per the SYNTAX score when reaching this conclusion.¹⁹

There is contradictory evidence, however, as the NOBLE study performed the same year as the EXCEL trial was unable to reach similar results. The study randomly assigned 598 patients with LMCA disease to undergo PCI with biolimus-eluting stents. The 5-year estimates of major adverse cardiac or cerebrovascular events was 29% for PCI and 19% for CABG, exceeding the limit to prove noninferiority. Additionally, all-cause mortality, non-procedural myocardial infarction, revascularization and stroke rates were all found to be higher in the PCI group after 5 years. Unlike the previous two studies, this data could not support any form of noninferiority in the PCI group, regardless of SYNTAX score.²⁰

Table 3: Outcomes in LMCA disease		
Study	Type of DES	Overall Outcome
SYNTAX trial, 2009 ¹¹	Paclitaxel	PCI had higher rates of revascularization, but CABG had higher rates of stroke after 12 months
Boudriot H et al. 2010 ¹⁶	Sirolimus	PCI unable to reach noninferiority to CABG when comparing major adverse cardiac events and revascularizations
EXCEL, 2016 ¹⁷⁻¹⁸	Everolimus	PCI noninferior to CABG when comparing all-cause mortality, stroke and MI after 3 years
Giacoppo D et al. 2017 ¹⁹	Second-generation DES	PCI noninferior to CABG when comparing all-cause

		mortality and MI
NOBLE, 2016 ²⁰	Biolimus	PCI unable to reach noninferiority to CABG when comparing major adverse cardiac or cerebrovascular events, all-cause mortality and revascularization after 5 years

Diabetes

There are limited studies that perform data-driven subgroup analyses of comorbidities in CAD patients. One RCT comparing CABG to PCI with first-generation stents proved that for patients with diabetes and three-vessel disease, the primary outcome (all-cause mortality, nonfatal MI, nonfatal stroke) occurred more frequently in the PCI group after 5 years, with 26.6% for the PCI group v.s. 18.7% in the CABG group.²¹ A newer meta-analysis using everolimus-eluting stents found that the PCI group was associated with a lower risk of all-cause mortality (HR: 0.58) but a higher risk of MI (HR: 2.44) within the 30 day timeframe. All-cause mortality between the two groups became similar in the long-term data-pool, although the risk of MI remained higher in the PCI group.²²

Table 4: Outcomes in patients with Diabetes and Three-vessel disease		
Study	Type of DES	Overall Outcome
FREEDOM, 2012 ²¹	First-generation DES	PCI unable to reach noninferiority to CABG when comparing all-cause mortality, nonfatal MI and nonfatal stroke after 5 years
Bangalore S et al. 2015 ²²	Everolimus	PCI has lower risk of all-cause mortality but a higher risk of MI than CABG in 30 day timeframe; mortality equalized in long-term, MI

		remained higher in PCI
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Stent Thrombosis vs. Graft occlusion

Aside from comparing primary end-points, an additional factor must be considered, such as the mortality risk in postoperative complications. Stent thrombosis is a dangerous complication that involves restenosis of the lumen created by the stent, often resulting in acute coronary syndrome. Pathogenesis of stent thrombosis additionally comes from multiple etiologies, as shown in Figure 2. Graft occlusion is a similar postoperative complication where the newly grafted vessels from the CABG procedure restenose due to various factors. However, one study found that stent thrombosis is a more severe complication with deadlier consequences - stent thrombosis was found to have higher rates of in-hospital mortality, major bleeding and major adverse cardiac events within a 30-day period than graft occlusions.²³ There is additional data in the SYNTAX trial 5-year follow up that demonstrates that stent thrombosis occurred more frequently, reaching 5.2% of the PCI group, compared to 3.6% in the CABG group.²⁴ However, recent studies have shown that newer-generation stents have a significantly lower risk of subacute and late stent thrombosis than BMS and older-generation DES, which may be promising news.

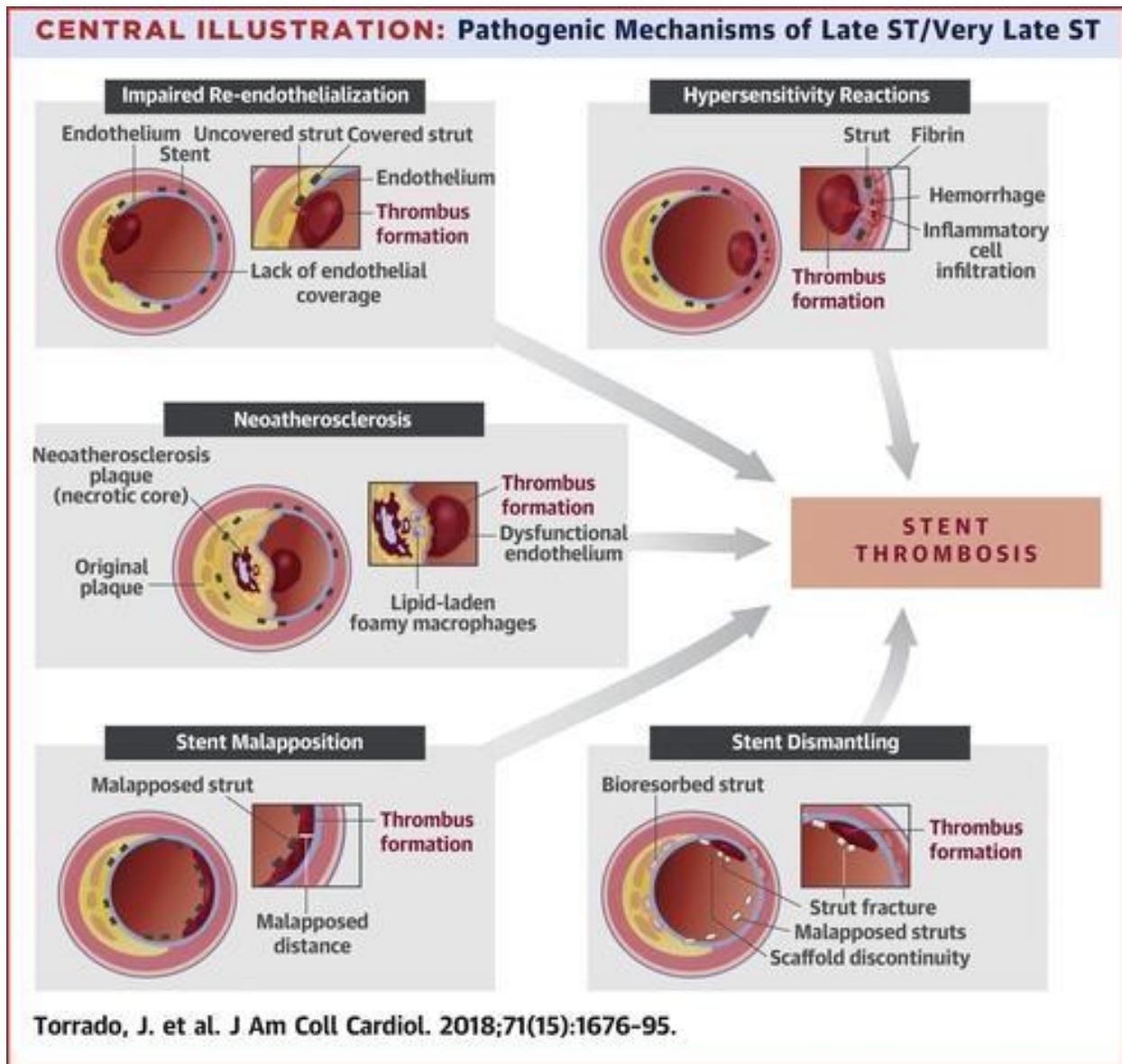


Figure 2. Pathogenesis of stent thrombosis

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The final verdict

Compared to BMS and first-generation DES, newer generation stents have come a long way in improving overall end-point outcomes for patients with CAD. However, ideal treatment plans remain dependent on various factors such as anatomical complexity, comorbidities,

surgeon's expertise and patient preference. Although there is some data that suggests that PCI with newer-generation drug eluting stents may be noninferior and in some endpoints, superior to CABG, there is limited evidence that supports this conclusion.^{17-19,22} Currently, the studies remain divided in the impact of newer-generation PCIs, and 10-year follow up studies may be required to further validate noninferiority before it can be applied clinically for complex lesions, including LMCA CAD and three-vessel CAD. However, even several studies that have demonstrated noninferiority of second-generation stents in treating LMCA and three-vessel disease is an improvement over the near unanimous data pool of first-generation stents that suggest superiority of CABG. Stent technology has come a long way over the past 40 years and advancements in stent structure, material and drugs continue to reach new milestones. PCI may soon reach a point where data may become more definitive with the help of newer research.

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