Landmark Trials in Cardiology in 2017—Celebrating 40 Years of Angioplasty

Akshyaya Pradhan, DM, FAPSC¹ Pravesh Vishwakarma, DM¹ Rishi Sethi, FACC, FESC, FSCAI, FRCP¹

¹Department of Cardiology, King George's Medical University, Lucknow, Uttar Pradesh, India

Int J Angiol 2018;27:167–173.

Address for correspondence Akshyaya Pradhan, DM, FAPSC, Department of Cardiology, King George's Medical University, Shahmina Road Chowk, Lucknow 226003, UP, India (e-mail: akshyaya33@gmail.com).

Abstract

Keywords

- cardiogenic shock
- STEMI
- dual antiplatelet
- multivessel disease
- fractional flow reserve (FFR)
- rivaroxaban
- evolocumab

Cardiovascular (CV) diseases continue to be the leading cause of morbidity and mortality worldwide. Significant progress has been made in the management of coronary artery disease (CAD) and acute coronary syndrome (ACS) over the past 3 decades. The year 2017 marks 40th anniversary of the first coronary angioplasty performed by Andreas Gruentzig in the year 1977. Evidence-based medicine and research has been the key driving force of these positive outcomes. The year 2017 witnessed presentation of several landmark studies at major meetings and many of them getting published in literature simultaneously. These trials evaluated wide range of issues from novel percutaneous coronary intervention (PCI) strategies to newer drugs to innovative devices in management of CAD. We selectively discuss a few major landmark studies that have the potential to alter our daily practice in 2018.

Cardiovascular (CV) diseases continue to be the leading cause of morbidity and mortality worldwide. Parallel to its increased prevalence due to improved methods of diagnosis, significant progress has been made in the management of coronary artery disease (CAD) and acute coronary syndrome (ACS) over the past 3 decades too. Fortunately, the year 2017 marks 40th anniversary of the first coronary angioplasty performed by Andreas Gruentzig at University Hospital Zurich, Switzerland in the year 1977¹ (→Fig. 1). Since its inception, percutaneous coronary intervention (PCI) has now become the most commonly performed procedure worldwide.

Evidence-based medicine and research has been the key driving force of these positive outcomes. Development of clinical practice guidelines based on clinical research and implementation of protocols based on them have finally led to reduction in CAD mortality for the first time in decades. The year 2017 witnessed more than 100 randomized trials being presented at major meetings (American College of Cardiology [ACC], European Society of Cardiology [ESC], Transcatheter Cardiovascular Therapeutics [TCT], Society for Cardiovascular Angiography and Interventions [SCAI], percutaneous coronary revascularization [PCR], etc.) and many of them being published in literature too. We have selected a handful of them which have the potential to impact

our daily cardiology practice. It is noteworthy that trials and guidelines are not “Gospel truth” and are meant to guide the physician to adopt an individualized approach in his patient.

CULPRIT SHOCK

Cardiogenic shock in patients of ST-segment elevation myocardial infarction (STEMI) portends poor prognosis. There is unanimity among guidelines and consensus statements for complete revascularization in such a scenario although the evidence base is weak and is based on a single SHOCK trial done 20 years ago.² However, the data from recently presented CULPRIT SHOCK trial at TCT 2017 throw up more question than answers.

In CULPRIT SHOCK study, patients of ACS with multivessel disease and cardiogenic shock were randomized to a strategy of infarct artery PCI only with the option of additional staged revascularization of non-infarct artery versus an immediate complete revascularization all vessels.³ The primary endpoint of the study was a composite of death or renal failure leading to renal replacement therapy at 30 days. At study completion, the primary endpoint was observed less frequently (17% decrease) in culprit artery PCI only group as compared with the immediate multivessel PCI group [45.9%

Fig. 1 Andreas Gruentzig (1939–1985).

versus 55.4%, relative risk (RR), 0.83; $p = 0.01$]. The individual components of primary endpoint were also decreased in culprit only PCI group (RR of death in the culprit-lesion-only PCI group was 0.84; $p = 0.03$, and the RR of renal-replacement therapy in the same was 0.71; $p = 0.07$). Hence, the benefits were driven primarily by reduction in deaths. Surprisingly, despite the use of higher contrast amount of contrast medium in multivessel PCI group, the rates of renal replacement were no different between groups allaying fears of renal safety of such a strategy.

In STEMI without cardiogenic shock, the recent encouraging data from randomized studies and meta-analyses have favored a complete revascularization approach.⁴ However, in the presence of cardiogenic shock, all guidelines and conventions favored an approach of complete revascularization until now. But the results of current study argue against it. More importantly, it is distressful to see that despite major advances in PCI and pharmacotherapy over the past two decades from SHOCK study to CULPRIT-SHOCK study the mortality from cardiogenic shock is still in range of 45%.

COMPARE ACUTE

Multivessel disease is common in STEMI, and management of non-culprit/non-infarct-related arteries presents a therapeutic dilemma. Fractional flow reserve (FFR) is a novel pressure wire based method to evaluate physiological significance of coronary lesion and has proven to be quintessential tool in managing multivessel disease in chronic stable angina.⁵ Although, use of FFR in ACS has challenges of microvascular dysfunction and presence of stunned myocardium, DANAMI 3 PRIMULTI has shown that it is feasible to perform it after acute phase is over.⁶

COMPARE ACUTE trial ($n = 885$) utilized FFR in patients of STEMI with multivessel disease during primary PCI itself. Patients were randomized to receive FFR-guided complete revascularization approach versus a culprit lesion only PCI approach.⁷ FFR of non-infarct arteries were done in both groups, but were not used for decision making in “culprit

only” arm. The principal endpoint evaluated in the trial was a combination of death, nonfatal myocardial infarction (MI), revascularization, and cerebrovascular events at 12 months. At the culmination of study, the major adverse cardiovascular and cerebral events (MACCE) was significantly reduced in complete revascularization group as compared to culprit artery PCI only group (7.3% versus 20.5%; hazard ratio [HR] – 0.35; $p < 0.001$). Dissection of individual components of primary outcome revealed that the benefit was primarily derived from reduction of revascularization in multivessel PCI arm (5.1% versus 16.6%; HR – 0.32; $p < 0.001$). Interestingly, one third of these higher number procedures performed in “culprit only” group were for unstable angina, which is considered a soft endpoint by many critics. The study has multiple takeaways apart from the primary endpoint. First, approximately only 50% of lesions which were deemed significantly on conventional angiography were found to have an FFR < 0.80 . Second, majority (83%) of non-infarct artery PCI in complete revascularization arm were done at index PCI itself. Last but not the least, in contrast to DANAMI 3 PRIMULTI where FFR was done 2 days after index primary PCI, FFR was done during the setting of primary PCI itself.

DAPT-STEMI

Dual anti platelet therapy (DAPT) refers to combination of aspirin and a P2Y₁₂ inhibitor (usually clopidogrel) and it is the most vital antithrombotic measure following PCI. Not only DAPT reduces the risk of stent thrombosis, but also the benefits extend to attenuation of subsequent reinfarctions. There is a general agreement in favor of 1 year of DAPT post PCI in patients of STEMI.⁸ With advent of potent P2Y₁₂ inhibitors (prasugrel or ticagrelor), the bleeding risk with DAPT has potentially increased. One potential method for mitigating the bleeding risk can be shortening the duration of DAPT.

In the DAPT-STEMI trial ($n = 870$), STEMI patients were randomly assigned to short (6 month) versus a standard (12 month DAPT) after undergoing primary PCI with a zotarolimus-eluting stent.⁹ An additional requirement was an event-free 6 months period post index PCI (absence of any MI, stent thrombosis, target vessel or lesion revascularization, or stroke/bleeding requiring DAPT discontinuation). The primary outcome measure studied was the composite of death from any cause, MI, revascularization, stroke, and thrombolysis in myocardial infarction (TIMI) major bleeding at 18 months. At study conclusion, the events rates for 6-month versus 12-month DAPT were 4.8% versus 6.6% (HR = 0.73; 95% confidence interval [CI] – 0.41 to 1.27; $p = 0.26$; p -value for noninferiority = 0.004). The secondary outcomes evaluated (stent thrombosis and target vessel failure) were also not significantly different between the two DAPT regimens. The study outcomes demonstrate the safety (regarding ischemic end points) of a shorter DAPT regimen in STEMI and question the current dogma of 1 year of DAPT following PCI for STEMI. A noteworthy point is that diabetes and history of previous MI were both underrepresented in the study at 14 and 5%, respectively. Both of these are important predictors of stent thrombosis and figure as elements of the “DAPT

score,” which is used for predicting DAPT continuation beyond first year of PCI.¹⁰

Investigators in the REDUCE study went a step further and compared a 3 months DAPT following PCI in patients of ACS to the standard 12-month DAPT.¹¹ In the study, 1496 patients of ACS (almost half of them were STEMI) underwent implantation of COMBO dual therapy stent (polymer drug-eluting stent [DES] loaded with sirolimus as well as endothelium promoting anti CD34+ antibody). At the end of 12 months, there was no difference in MACCE rates between patients randomized to the short DAPT course and those to the longer DAPT duration (8.2 versus 8.4%; odds ratio: 0.97, 95% CI = 0.67–1.41; *p* noninferiority <0.001). The results reaffirm the possibility of a shorter DAPT regimen in ACS, which are in line with findings from DAPT STEMI study.

PRECISE-DAPT

The optimal duration of DAPT beyond first year of PCI is unknown. Previously published studies have demonstrated equivocal results. Guidelines advise an individualized approach and advocate the use of “DAPT score” or other prediction rules to balance the ischemic and bleeding risk.¹²

The PRECISE-DAPT score (► **Table 1**) was derived from large cohort of patients treated with varying duration of DAPT (mainly aspirin and clopidogrel) after coronary stenting.¹³ About 14,963 patients from eight large randomized clinical trials of DAPT following PCI were included, and all post discharge bleeding events (major or minor by TIMI definition) were analyzed. Using the Cox proportional regression method, multivariate predictors of bleeding were identified to formulate a score—PRECISE-DAPT (► **Table 1**). They use four continuous variables (age, hemoglobin, white cell count, and creatinine clearance) and one dichotomous variable—history of prior bleeding. When validated on patient cohorts derived from PLATO Trial and BERN PCI registry, the score demonstrated excellent c-statistic (0.7; 95% CI –0.65 to 0.74 and 0.66; 95% CI –0.61 to 0.71, respectively). A longer DAPT (12–14 months versus 3–6 months) duration significantly increased bleeding in patients at high risk (score > 25), but did not in those with lower bleeding risk profiles. As corollary to above-mentioned findings, significant ischemic benefit was only in low the bleeding risk group. The 2017 ESC/EACTS

Table 1 The PRECISE DAPT score for continuing Dual antiplatelet therapy beyond 1 year of PCI

PRECISE DAPT score
Variables used
<ul style="list-style-type: none"> • Age • Prior Bleeding • White blood count • Creatinine Clearance • Hemoglobin
Total score ranges 0–100
Score > 25—shorter DAPT
Score < 25—standard DAPT

Abbreviation: DAPT, dual antiplatelet therapy.

Consensus document on DAPT advocates use of PRECISE-DAPT score to decide DAPT durations following PCI.¹⁴

GEMINI ACS-1

Role of Novel Oral Anticoagulants (NOAC) in patients of ACS without atrial fibrillation is controversial. In the previously reported studies, with the addition of a NOAC to DAPT regimen, the bleeding risk outweighed ischemic benefits and consequently most trials of NOAC in ACS were terminated prematurely like REDEEM and APPRAISE-2. However, ATLAS ACS TIMI 2 trial did reveal ischemic benefits with low dose rivaroxaban in patients with a recent ACS albeit at the cost of doubling of bleeding events.¹⁵ To mitigate the excessive bleeding associated with the classical “triple therapy,” an approach of a “dual therapy” of NOAC plus single antiplatelet can be envisaged. However, feasibility of such a strategy of balancing bleeding with ischemic risk in patients of ACS is unknown.

GEMINI-ACS-1 trial tested the above-mentioned strategy in 3037 patients with a recent ACS (enrolled up to 10 days of the index event). Patients across the spectrum of ACS were randomized to receive either aspirin or low dose rivaroxaban (2.5 mg twice daily [BD]) on the background of a P2Y12 therapy.¹⁶ The goal was to assess rates of non-coronary artery bypass grafting (non-CABG)-related TIMI significant bleeding at 1 year in both arms. At a median follow-up of 291 days, the rates of bleeding were not different with either strategy. This was despite of the fact that 56% of background P2Y12 therapy comprised of ticagrelor. However, the trial was not directed at comparing the ischemic endpoints (including stent thrombosis) though they were similar in both arms.

TROPICAL ACS

Routine use of platelet function testing (PFT) to guide antiplatelet therapy has not been shown to be of benefit and is not advocated by guidelines either. It would be prudent enough to switch from a potent P2Y12 to clopidogrel after the acute phase of ACS. This strategy aims to ameliorate the long-term bleeding risk while preserving ischemic benefits in the early post ACS phase. The optimal timing and method of such a de-escalation maneuver is unknown. PFT can play a key role in selecting patients for de-escalation of DAPT and was studied recently in TROPICAL ACS trial.¹⁷

The study enrolled 2601 patients of ACS after PCI and randomized them to receive a standard DAPT regimen (aspirin plus uninterrupted prasugrel) for 12 months versus a “step down” regimen (► **Fig. 2**). Beyond 14 days, in the step down regimen PFT was utilized to decide the type of P2Y12 therapy. Those with high on clopidogrel platelet reactivity (>46 IU) were switched back to prasugrel, while those without were maintained on clopidogrel. The primary endpoint comprised of net clinical benefit, which was a composite of CV death, MI, stroke, or Bleeding Academic Research Consortium (BARC) bleeding grade >2. At study completion, events rates were 7% in the guided step down group versus 9% in the standard group

Fig. 2 De-escalation Strategy used in TROPICAL ACS study. Abbreviations: HPR-High on treatment platelet reactivity; based on Multiplate analyzer testing, value >46 U is positive according to consensus definition.

($p = 0.004$ for noninferiority, HR -0.81). The ischemic endpoint (combination risk of death, MI, or stroke) was also similar between groups as was BARC bleeding grade >2 . The study assures that a guided DAPT de-escalation approach is both feasible and safe.

SYNTAX II

In patients with multivessel disease, the choice between CABG and multi-vessel PCI has been a matter of debate for the past two decades. The last published SYNTAX I study failed to demonstrate the superiority of PCI over CABG in patients with multivessel disease even at 5-year follow-up.¹⁸ However, one of the major criticisms of the trial was the use of first-generation paclitaxel DES and underuse of contemporary PCI techniques such as physiological assessment and imaging. SYNTAX II score was derived from SYNTAX I study and combines clinical characteristics and anatomical syntax score to improve decision making about type of revascularization in multivessel PCI.¹⁹

The SYNTAX II study was designed to test whether incorporation of contemporary best PCI practices improves outcomes with PCI in multivessel disease.²⁰ In this open-labeled, multicenter and single-arm study, patients with three-vessel disease without significant left main disease were screened by local heart team. SYNTAX II score was then applied, and only those patients in whom the score projected similar mortality at 4 years by either PCI or CABG were enrolled ($n = 454$). Multivessel PCI was performed in accordance with principles enumerated in **Table 2** (Syntax II strategy). The primary outcome studied was the rate of MACCE at 1 year. The comparator arm was a pre-specified cohort of patients from prior published SYNTAX I trial, in which 4-year outcomes of PCI and CABG were at equipoise when evaluated with SYNTAX II score ($n = 643$). At 1 year, MACCE were significantly reduced in study cohort vis-a-vis the historical SYNTAX I cohort (10.6% versus 17.4%; HR -0.58 ; $p = 0.006$). This was attributed primarily to reduction

Table 2 The “Best of PCI” practices used in SYNTAX II study

Best PCI practices implemented in SYNTAX II trial
Heart team discussion
Syntax II score use
iFR/FFR to guide revascularization
Thin strut DES with bioresorbable polymer
IVUS use to optimize PCI results
Guideline directed medical therapy
CTO/bifurcation techniques as per current norms

Abbreviations: CTO, chronic total occlusion; DES, drug eluting stent; FFR, fractional flow reserve; iFR, instantaneous wave free ratio; IVUS, intravascular ultrasound; PCI, percutaneous coronary intervention.

in MI (73% ↓) and repeat revascularization (43% ↓). Definite stent thrombosis was also decreased in SYNTAX II trial (0.7% versus 2.6%; HR -0.26 ; $p = 0.045$). Physiological lesion assessment was done in 75% patients and post procedure IVUS in 84% patients. The study demonstrates improved outcomes of PCI in multivessel as a result of utilization of contemporary state-of-the-art scientific and evidence-based PCI (SYNTAX II strategy). Due to the nonrandomized design, a prospective randomized study with CABG as comparator will produce more meaningful and fruitful conclusions.

ORBITA

The benefits of PCI in chronic stable angina were questioned previously by studies such as COURAGE and subsequent meta-analysis based on them.²¹ Current guidelines recommend medical therapy as the first line treatment in stable angina. Although, there is no mortality benefit, PCI in stable angina is generally believed to offer superior symptomatic relief from angina.

ORBITA study randomized 230 patients of stable angina with at least one significant ($>70\%$) lesion in a single coronary artery to PCI versus a sham procedure (coronary angiography only).²² Optimal medical therapy was administered in both groups. The primary endpoint was change in exercise times on treadmill testing from baseline at 6 weeks. The secondary endpoints evaluated were Seattle angina questionnaire physical limitation and angina frequency from baseline. Prior to randomization, patients were given intensified guideline-directed medical therapy in both arms. At 6 weeks, there was no difference in increment in the treadmill exercise times from baseline (28.4 s versus 11.4 s; $p = 0.20$). The secondary endpoints were also not different after PCI versus medical therapy. The results of trial are surprising given the presence of angiographic severe stenosis. The trial also reaffirms the importance of sham procedures in cardiology after SIMPLICITY HTN 3 trial. The use of angiographic severity for decision making rather than relying on FFR/instantaneous wave free ratio (iFR), small sample size and short period of follow-up are major criticisms, which need to be addressed in further studies.

COMPASS

Aspirin is the backbone of pharmacotherapy for secondary prevention in chronic stable angina. NOAC have now proven their safety as well as efficacy in decreasing ischemic endpoints in atrial fibrillation, and now they are being tried in ACS too as previously alluded. Going a step further, their use was explored for decreasing ischemic events in setting of stable angina pectoris (SAP).

The COMPASS study tested the efficacy of rivaroxaban alone (5 mg BD) or low dose (2.5 mg BD) in combination with aspirin compared with aspirin monotherapy alone.²³ Over 27,000 patients of SAP were randomized to these three arms and had been followed up to a median of 23 months. There was an absolute 1.3% reduction in primary outcome of death, nonfatal MI, or stroke with rivaroxaban plus aspirin arm compared with aspirin alone leading to premature termination of study. Deaths were significantly decreased with rivaroxaban plus aspirin arm compared with aspirin alone (0.7% absolute decrease; HR -0.82; $p = 0.01$). These benefits were attained at the cost of absolute increase in bleeding events by 1.2%. Fortunately, the rate of fatal bleeding and intracranial hemorrhage was similar between both groups. There was no benefit with use of rivaroxaban alone in the study compared with aspirin monotherapy with respect to primary outcomes, and rather bleeding events were increased. These results mirror the ATLAS TIMI 2 ACS where low-dose rivaroxaban (2.5 mg BD) was able to achieve an equipoise between bleeding events and ischemic risk, but the 5-mg BD dose resulted in excess bleeding. Even with the low dose, the signals of excess bleeding in both this trial and GEMINI ACS are a cause of concern mandating further research before rivaroxaban becomes the workhorse anticoagulant.

FOURIER

Antibodies to proprotein convertase subtilisin kexin type 9 (PCSK-9) have emerged as an extremely effective class of lipid lowering drugs achieving lower lipid goals hitherto unseen.²⁴ Evolocumab, a fully humanized monoclonal antibody, has shown drastic reduction in low-density lipoprotein (LDL) levels by up to 60%. It was recently approved by the US Food and Drug Administration (USFDA) for treatment of familial hypercholesterolemia. However, long-term CV outcome studies with PCSK-9 inhibitors are lacking.

FOURIER was a randomized study of 27,564 patients with atherosclerotic CV disease on statin therapy whose LDL levels were higher than >70 mg%.²⁵ Patient received either placebo or evolucumab in two different doses (240 mg fortnightly or 420 mg monthly). The primary end point was combination of death, MI, stroke, revascularization, and hospitalization for unstable angina at 2.2 years. The results revealed that, compared with placebo arm, the primary event rate was significantly decreased in the evolucumab arm (11.3% versus 9.8%; HR -0.85; $p = < 0.001$). The secondary endpoint of death, MI, and stroke was also significantly reduced with the evolucumab therapy. The mean LDL level achieved was in range of 30 mg% (from a mean baseline LDL value of 92 mg%; almost 60% fall!). There was no signal of any major adverse events, and the

results were consistent across various study subgroups. The FOURIER study has filled the current void in PCSK-9 inhibitors data regarding CV outcomes. Despite spectacular success in lowering LDL to hitherto unseen levels, critics had questioned the safety and meaningful benefit of achieving such abysmally low LDL goals. Not only FOURIER puts an end to long-term safety concerns but adds to the growing chorus demanding further lowering of current LDL goal from 70 to 50 mg%.

CANTOS

Although, current therapeutic approaches for atherosclerosis are focused around lipid lowering, inflammation remains a key area of focus for further research. However, the hunt for the ideal anti-inflammatory agent is still on. Statins reduced highly sensitive C-reactive protein (hs-CRP) levels in JUPITER trial and improved outcomes. Canakinumab is a monoclonal antibody against interleukin-1 β and has potential anti-inflammatory effects. Currently, it is being used for rheumatologic disorders.

CANTOS trial evaluated canakinumab in 10,061 patient of prior MI with elevated hs-CRP levels (>2.0 mg/L).²⁶ Canakinumab was tested in three doses (50 mg, 150 mg, and 300 mg given every 3 monthly) versus placebo. Nonfatal MI, death and nonfatal stroke were analyzed during the study period. At 48 months, the primary event rates were decreased in all three-dose arms of drug compared with placebo. Unfortunately, only in the 150-mg dose arm, the results met the prespecified threshold for statistical significance. Secondary endpoint which also included urgent hospitalization for unstable angina was also significantly reduced with the 150-mg dose. Although, fatal infections increased with the drug, the death from any cause was no different vis-à-vis placebo.

DEFINE FLAIR and SWEDEHEART

FFR has emerged as the gold standard for assessing physiological significance of coronary lesions. However, the dependence on adenosine for maximal hyperemia poses logistic and safety issues at time. iFR is a pressure-derived index that is obtained without vasodilators and has been shown comparable to FFR in various studies. Two studies evaluated the role of iFR-based revascularization on patient outcomes.

DEFINE FLAIR was a randomized study to show noninferiority of an iFR-guided revascularization compared with a FFR-guided strategy. It enrolled 2,492 patients with CAD and need for physiology assessment (40–70% stenosis on angiography) and randomized them to either of the two approaches.²⁷ At 1 year, there was no difference in major adverse cardiac event (MACE) rate between iFR- and FFR-guided groups (6.8% versus 7.0%; HR 0.95; $p = 0.78$; p non-inferiority <0.001). As expected, the procedural times were trimmed, and procedural symptoms were fewer in the iFR group. Interestingly, difference in the individual endpoints of MACE were also unremarkable between groups. Majority (80%) of patients in the study were of SAP.

On a similar note, iFR-SWEDEHEART enrolled 2037 patients of CAD to receive FFR- or iFR-guided decision

making in a randomized manner.²⁸ The proportion of stable CAD was less (60%) compared with previous study. The study used the standard primary endpoint of MACE (combination of death, MI, or unplanned revascularization). Data analysis at 12 months revealed that primary event rates were similar between iFR- and FFR-guided cohorts (6.7% versus 6.1%; HR = 1.12; $p = 0.53$; p noninferiority = 0.007). Neither the results differed between the two strategies on subgroup analysis, nor they were altered when individual endpoint of MACE were analyzed. However, chest discomfort reported by patients was significantly higher in the FFR group, which was anticipated priori. Collectively, these two studies have established iFR as a suitable alternate to FFR for physiological assessment in catheterization laboratory.

SURTAVI

The year 2017 witnessed another landmark clinical trial SURTAVI seeking safety and efficacy of transcatheter aortic valve replacement (TAVR) in patients with severe symptomatic aortic stenosis (AS) with intermediate surgical risk. PARTNER A, PARTNER B, and core valve high-risk study have already established TAVR as an acceptable alternative to surgical aortic valve replacement (SAVR) in patients who are either not candidate for surgery or at high risk.²⁹

SURTAVI, conducted at 87 centers, randomized 1,660 patients at intermediate risk for surgical complications ($4.5 \pm 1.6\%$ Society of Thoracic Surgeons-predicted risk of mortality [STS-PROM] score) to either SAVR or TAVR and assessed for a primary composite outcome of all-cause mortality or disabling stroke.³⁰ This is the first study to evaluate outcomes with the self-expanding CoreValve and the new Evolut-R bioprosthesis valves, used in 84 and 16% of TAVR patients, respectively. At 24 months, the primary outcome was met in 12.6% of patients randomized to TAVR versus 14.0% of patients randomized to SAVR (criteria for noninferiority of TAVR were met), with similar rates of both stroke and all-cause mortality in both groups. Though not a primary outcome, SAVR was associated with a marginal absolute 2.2% increase in perioperative stroke rates, while TAVR was associated with a 3.5% absolute increase in hospitalizations related to aortic valvular disease at 2 years. Echocardiographically, TAVR worked better with a statistically superior valve orifice and lower mean gradients than with surgery at all time points. Moderate-to-severe paravalvular leakage was more common with TAVR than with SAVR, occurring in 5.4 versus 0.4% of patients, respectively, and pacemaker implantation was more common with TAVR. In contrast, SAVR was associated with more acute kidney injury, atrial fibrillation, and transfusions. It is noteworthy that SURTAVI has by far the best surgical outcomes seen in any of the randomized trials, and TAVR proved itself equivalent. Current ACC/AHA guidelines give class IIa recommendation to TAVR in symptomatic, severe AS in intermediate surgical risk patients based on results of PARTNER 2 trial.³¹ Results of SURTAVI substantiate the evidence provided by the PARTNER 2, and an upward shift in class of recommendation can be expected for intermediate surgical risk patients.

Conclusion

In the year 2017, many important studies made their way into the literature. The list is exhaustive, and we discussed only a handful of them, which were deemed game changers to the best of our knowledge.

Multivessel disease remained the pot boiler in STEMI discussions. While the CULPRIT SHOCK study questioned the long held dogma that complete revascularization is the need of the hour in STEMI with cardiogenic shock, whereas COMPARE ACUTE revealed that use of FFR in acute STEMI was feasible and helped in decision making.

More pharmacotherapy trials in CAD made way into headlines this year than any previous one. DAPT-STEMI and REDUCE demonstrated the feasibility of DAPT withdrawal before completion of a year of STEMI/ACS. PRECISE-DAPT study gave us a score to selected low-risk patients in whom DAPT can be safely curtailed at 1-year post PCI. GEMINI ACS revealed the safety of using a low-dose rivaroxaban in ACS. TROPICAL ACS used a novel DAPT de-escalation regimen in ACS to decrease bleeding with success. COMPASS demonstrated ischemic benefits of low-dose rivaroxaban and aspirin in stable CAD subjects.

PCSK-9 inhibitors finally got their due when FOURIER established significant decrease in long-term CV outcomes with evolocumab. Inflammatory hypothesis of CAD was rekindled by CANTOS trial where canakinumab decreased long-term CV outcomes.

TAVR got a shot in the arm with SURTAVI extending benefits to even intermediate-risk patients. Benefits of PCI in stable angina were again questioned by ORBITA, which showed no added symptomatic relief with PCI in short term despite presence of significant stenosis on angiogram.

The rapid and versatile pace of research has helped to improve the outcomes to CAD in recent years. What was started by Andreas Gruentzig 40 years ago as an experimental treatment of CAD has now become the most frequently performed procedure worldwide and has revolutionized the way we managed CAD. Despite the colorful picture depicted by these positive studies, there is a huge unmet need in CAD especially in low and middle income countries. However, as students of science and active researchers, we pledge to continue the war against the Tsunami of CAD undeterred by small failures.

“However difficult life may seem, there is always something you can do and succeed at. It matters that you don’t give up.”

- Stephen Hawkins (1942–2018)

Conflicts of Interest
None.

References

- 1 Byrne RA, Stone GW, Ormiston J, Kastrati A. Coronary balloon angioplasty, stents, and scaffolds. *Lancet* 2017;390(10096): 781–792
- 2 Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock.

- SHOCK investigators. Should we emergently revascularize occluded coronaries for cardiogenic shock. *N Engl J Med* 1999; 341(09):625–634
- 3 Thiele H, Akin I, Sandri M, et al. Investigators C-S. PCI strategies in patients with acute myocardial infarction and cardiogenic shock. *N Engl J Med* 2017;377:2419–2432
 - 4 Elgendy IY, Mahmoud AN, Kumbhani DJ, Bhatt DL, Bavry AA. Complete or culprit-only revascularization for patients with multivessel coronary artery disease undergoing percutaneous coronary intervention: a pairwise and network meta-analysis of randomized trials. *JACC Cardiovasc Interv* 2017;10(04):315–324
 - 5 Pijls NH, van Schaardenburgh P, Manoharan G, et al. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study. *J Am Coll Cardiol* 2007;49(21): 2105–2111
 - 6 Engström T, Kelbæk H, Helqvist S, et al; DANAMI-3–PRIMULTI Investigators. Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3–PRIMULTI): an open-label, randomised controlled trial. *Lancet* 2015;386(9994):665–671
 - 7 Smits PC, Abdel-Wahab M, Neumann FJ, et al; Compare-Acute Investigators. Fractional flow reserve-guided multivessel angioplasty in myocardial infarction. *N Engl J Med* 2017;376(13): 1234–1244
 - 8 O’Gara PT, Kushner FG, Ascheim DD, et al; American College of Emergency Physicians; Society for Cardiovascular Angiography and Interventions. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013;61(04):e78–e140
 - 9 DAPT-Clinical trial results. Available from URL http://www.clinicaltrialresults.org/slides/TCT2017/DAPT-STEMI_kedhi. Accessed March 28, 2018
 - 10 Yeh RW, Secemsky EA, Kereiakes DJ. DAPT Study Investigators. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year a year of percutaneous coronary intervention. *JAMA* 2016;315(16):1735–1749
 - 11 Suryapranata H. REDUCE: A randomized trial of 3-month vs 12-month DAPT after implantation of a bioabsorbable polymer-based metallic des with a luminal CD34+ antibody coating in patients with ACS. Presented at: Transcatheter cardiovascular therapeutics scientific symposium, October 30–November 2, 2017. Denver, CO
 - 12 Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2016;68(10): 1082–1115
 - 13 Costa F, van Klaveren D, James S, et al; PRECISE-DAPT Study Investigators. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. *Lancet* 2017;389(10073):1025–1034
 - 14 Valgimigli M, Bueno H, Byrne RA, et al; ESC Scientific Document Group; ESC Committee for Practice Guidelines (CPG); ESC National Cardiac Societies. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the task force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2018;39(03):213–260
 - 15 Mega JL, Braunwald E, Wiviott SD, et al; ATLAS ACS 2–TIMI 51 Investigators. Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med* 2012;366(01):9–19
 - 16 Ohman EM, Roe MT, Steg PG, et al. Clinically significant bleeding with low-dose rivaroxaban versus aspirin, in addition to P2Y12 inhibition, in acute coronary syndromes (GEMINI-ACS-1): a double-blind, multicentre, randomised trial. *Lancet* 2017;389(10081):1799–1808
 - 17 Sibbing D, Aradi D, Jacobshagen C, et al; TROPICAL-ACS Investigators. Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomised, open-label, multicentre trial. *Lancet* 2017;390(10104):1747–1757
 - 18 Mohr FW, Morice MC, Kappetein AP, et al. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet* 2013;381(9867):629–638
 - 19 Farooq V, van Klaveren D, Steyerberg EW, et al. Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. *Lancet* 2013;381(9867):639–650
 - 20 Escaned J, Collet C, Ryan N, et al. Clinical outcomes of state-of-the-art percutaneous coronary revascularization in patients with de novo three vessel disease: 1-year results of the SYNTAX II study. *Eur Heart J* 2017;38(42):3124–3134
 - 21 Stergiopoulos K, Boden WE, Hartigan P, et al. Percutaneous coronary intervention outcomes in patients with stable obstructive coronary artery disease and myocardial ischemia: a collaborative meta-analysis of contemporary randomized clinical trials. *JAMA Intern Med* 2014;174(02):232–240
 - 22 Al-Lamee R, Thompson D, Dehbi HM, et al; ORBITA investigators. Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial. *Lancet* 2018;391(10115):31–40
 - 23 Eikelboom JW, Connolly SJ, Bosch J, et al; COMPASS Investigators. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med* 2017;377(14):1319–1330
 - 24 Raal FJ, Stein EA, Dufour R, et al; RUTHERFORD-2 Investigators. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. *Lancet* 2015;385(9965): 331–340
 - 25 Sabatine MS, Giugliano RP, Keech AC, et al; FOURIER Steering Committee and Investigators. Evolocumab and clinical outcomes with cardiovascular disease. *N Engl J Med* 2017;376(18): 1713–1722
 - 26 Ridker PM, Everett BM, Thuren T, et al; CANTOS Trial Group. Anti-inflammatory therapy with canakinumab in atherosclerotic disease. *N Engl J Med* 2017;377(12):1119–1131
 - 27 Davies JE, Sen S, Dehbi HM, et al. Use of the instantaneous wave-free ratio or fractional flow reserve in PCI. *N Engl J Med* 2017;376(19):1824–1834
 - 28 Götzberg M, Christiansen EH, Gudmundsdottir JJ, et al; iFR-SWE-DEHEART Investigators. Instantaneous wave-free ratio versus fractional flow reserve to guide PCI. *N Engl J Med* 2017;376(19):1813–1823
 - 29 Reardon MJ, Adams DH, Kleiman NS, et al. 2-Year outcomes in patients undergoing surgical or self-expanding transcatheter aortic valve replacement. *J Am Coll Cardiol* 2015;66:121–131
 - 30 Reardon MJ, Van Mieghem NM, Popma JJ, et al; SURTAVI Investigators. Surgical or transcatheter aortic valve replacement in intermediate risk patients. *N Engl J Med* 2017;376(14):1321–1331
 - 31 Nishamura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. *J Am Coll Cardiol* 2017;70(02): 252–289