ECRONICON OPEN ACCESS

EC CARDIOLOGY
Research Article

Cost Effective Analysis of the Use of Computed Tomography Fractional Flow Reserve for Diagnosis and Improvement of Clinical Outcomes in First Time Coronary Artery Disease Compared to Invasive Coronary Angiography

Narendra Kumar[1]*#, Madhan Kumar Ranganathan[2#], Cyril James[3], Ahmad Zakariya[4], Manish Barman[5], Swaroop Varghese[6] and Shaimaa Mustafa[7]

[1]Department of Cardiology, Manchester University NHS Foundation Trust, Oxford Road, Manchester, UK

[2]BronxCare Health System, Bronx, New York, NY, USA

[3] Wexford General Hospital, Wexford, Ireland

[4]Northern Devon Healthcare NHS Trust, Raleigh Park, Barnstaple, Devon, UK

[5] Hamad Medical Corporation, Qatar. and Weill Cornell Medicine University, Qatar

[6] Harz Hospital Quedlinburg, Ditfurter Weg 24, Quedlinburg. Germany

[7]Assistant Professor of Cardiovascular Medicine, Faculty of Medicine, Benha University, Egypt

#Narendra Kumar and Madhan Kumar have contributed equally to the manuscript

***Corresponding Author:** Narendra Kumar, Department of Cardiology, Manchester University NHS Foundation Trust, Oxford Road, Manchester, UK.

Received: July 04, 2019; **Pubished:** August 06, 2019

Abstract

Introduction: Globally cardiovascular disease is a leading cause of morbidity and mortality. Invasive angiography fractional flow reserve estimation (FFR-I) remains the gold standard to diagnose and determine the prognosis of coronary artery disease (CAD). However, fractional flow reserve estimation using Computed tomography scan (FFR-CT) is gaining prominence for diagnosis of CAD. This study aims to determine the cost-effective analysis (CEA) of FFR-CT to diagnose CAD.

Methods and Analysis: After careful screening with aid of the inclusion and exclusion criteria for systemic review and meta-analysis, for estimating the diagnostic efficiency for FFR-CT, clinical data of patients were selected. The data of clinical outcome of from the literature was used for estimating the costs and outcomes of 4 clinical pathways: (1) Usual care with invasive coronary angiography (CA-I) and visual guided further interventional management, (2) CA- I and FFR-I and guided further interventional treatment (3) CA-CT and CA-I guided further invasive management (4) CA-CT, FFR-CT, CA-I guided further Interventional treatment.

Results: Among the 5 selected studies having 914 patient's clinical data was chosen for further statistical analysis. The first pathway had the highest cost with maximum annual death/adverse coronary event. The cost FFR-CT was US $ 7,126 with expected QALYs of 0.813 while usual care using invasive coronary angiography costed US $ 17,993 with expected 0.716 QALYs. had lower costs per patient correctly diagnosed.

Conclusion: Use of non-invasive computed tomography FFR and coronary angiography to select patients for CA-I and further interventional management may not only reduce costs but also improve clinical outcomes for coronary artery disease patients.

Keywords: *Angiography; Computed Tomography; Computed Tomography-Fractional Flow Reserve; Coronary Artery Disease; Fractional Flow Reserve; Cost Effective Analysis*

Introduction

Cardiovascular disease remains a major burden for morbidity and mortality in all parts of world. In USA and Europe, the costs associated with coronary artery disease (CAD) burden are expected to be as high as 156 and 49 billion Euros respectively [1,2]. Cardiac imaging tools and techniques have undergone tremendous change since introduction of invasive coronary angiography (CA-I) in late 1950s to computed tomography angiography (CA-CT) in recent decades. These techniques are performed to identify the hemodynamically significant stenosis of the coronary vessels to determine the prognosis of cardiovascular events in future [3].

FFR estimation not only increases event-free survival, decreases unnecessary revascularization but also significantly reduces the overall healthcare expenditure [4,5]. Several studies have supported the role of fractional flow reserve estimation using computed tomography (FFR-CT) to determine the severity and extent of coronary atherosclerosis to determine a patient's prognosis [6-8]. Till date, there are inconclusive data regarding the cost effective analysis of FFR-CT for diagnosis of CAD while being compared to usual care of invasive CA. Earlier published studies were composed of either single-center studies or limited multi-centric studies limited to regional geographies [9-11]. Moreover, none of the studies which have systematically evaluated the CEA of this technique using the latest data available till August 2018. Thus, a cost effective analysis is done to answer the important question.

Methods and Analysis

The focus of the research was a recent systemic review and meta-analysis for which a cross-searching Medline and CENTRAL databases, using the terms "computed tomography" or "CT" and "fractional flow reserve" or "FFR" were conducted, and only English publications were included with human participants of all age till 14 August 2018. Then a systemic review and meta-analysis was conducted of the selected patients for diagnostic efficacy of FFR-CT for first-time diagnosis of CAD. The aim of the current study is to determine CEA of such patients who meet the above criteria for diagnosis and improvement of clinical outcomes in such CAD patients using FFR-CT vs usual care of CA-I.

Data from selected total of 296 patients having suspected CAD and soon to undergo CA-I was selected and divided into four hypothetical diagnostics cum treatment pathways (as below) on the basis of patient-specific data from this study:

- **Pathway 1:** Usual care with CA-I: All patients undergo CA-I as scheduled and ones with ≥ 50% narrowing by visual assessment of CA-I images are subjected to interventional treatment.
- **Pathway 2:** CA- I and FFR-I: All patients undergo CA-I as planned and ones with ≥ 50% narrowing undergo FFR-I, which if ≥ 80 are subjected to interventional treatment.
- **Pathway 3:** CA-CT and CA-I: All patients undergo CA-CT as planned before and ones ≥ 50% narrowing undergo CA-I. Those with ≥ 50% stenosis by visual assessment of the angiogram are planned for interventional treatment.
- **Pathway 4:** CA-CT, FFR-CT, CA-I: All patients undergo CA-CT and ones with ≥ 50% narrowing undergo FFR-CT, which if ≥ 80 are subjected to CA-I. Interventional treatment is performed after the visual diagnosis of narrowing.

Each pathway analysis consisted of summing up of individual procedure, and test mentioned for all patients as described for all patients in the pathway and divided by total no. of patients yielding per patient's average cost.

Cost estimation

Costs for each strategy included the initial procedure cost and also included the later costs for a single year follow up. Index procedure was calculated from actual resource consumption by determining number of regular wires, guiding catheters, balloon dilatation catheters, pressure wires, antiplatelet therapy, stents, contrast media, adenosine, and number of days admitted in medical center for each of patient's index procedure. They were multiplied by the cost of each resource in US dollars using a recent publication data [12]. The cost of a medical center admission day was estimated to be for patients initially admitted at a hospital with an acute coronary syndrome before their index procedure and therefore likely to be in a coronary care unit as shown in figure 3 and a step-down or telemetry bed and for other patients on the basis of the cost for a hospital bed. These costs were applied only to the index hospitalization. The costs of the other resources were obtained from a US participating sites mentioned in references. Laboratory time costs and personnel costs were excluded because they were similar between the comparison modalities [4]. The national mean reimbursement rate was calculated by Medicare for each event and then averaged the national Medicare physician reimbursement rate for different interventions were also added.

The incremental cost-effectiveness of ratio (ICER) of FFR-CT versus usual care was calculated as following:

$$\frac{[\text{cost}_{\text{FFR-CT}}(t) - \text{cost}_{\text{usual care}}(t)]}{[\text{life-years}_{\text{FFR-CT}}(t) - \text{life-years}_{\text{usual care}}(t)]}$$

With cost (t) representing the cumulative medical cost up to a specified time (t) which is one year for current study during follow-up, and life-years (t) representing the area under the survival curve up to that time as shown in figure 6.

Indirect costs coming out of productivity losses were presumed to be captured by ICER's denominator. Thus, they were not included in the ICER's numerator [13]. With aid of using the consumer price index, all costs were converted to 2016 US dollars [14-16]. Due to non-availability of Medicare payment for the FFR procedures, it's pricing was simulated by adding up the costs of the material used as listed earlier [4] and the Medicare average national physician payment assigned to the CPT codes of the test [17]. Figure 4 shows the procedural costs used in current study. Future event rates for the effectiveness criterion is achieved by the detection of a stenosis ≥ 50% in coronary vessels combined with an FFR ≤ 80 % which is acceptable as significant CAD [18-21]. All the calculation done above, which are summarized in figures are based on assumption that even if computed tomography or invasive procedure is used for coronary angiography and FFR estimation, the reference tests have 100% diagnostic accuracy.

Health utilities and outcomes

As is conventional in cost-effectiveness analyses, Quality of Life was captured as health utility in the model whose values were on a scale of 0 to 1. Perfect health represented by 1 and death represented by 0.

Results

Total of 5 studies that enrolled 296 patients were included in this current review whose details are discussed in pathways as mentioned earlier. The mean per patient cost under each pathway is shown in figure 2. Using ICER calculations, use of FFR-CT is more effective and less expensive. The first pathway had the highest cost with maximum annual death/adverse coronary event. The cost FFR-CT was US $ 7,126 with expected QALYs of 0.813 as shown in figure 1. The usual care using CA-I costed US $ 17,993 with expected 0.716 QALYs as shown in figure 2. By using the ICER formula various results were obtained as show in figure 3. However, the cost components of the various diagnostic cum treatment pathways is shown in figure 4. The outline of all four pathways which were selected for various strategies for all chosen patients for the studies are shown in figure 5. Combined per patient cost with annual event rate were plotted on Y axis and X axis respectively to do the sensitivity analysis. That clearly shows pathway 1 is associated with highest costs and also maximum event rate. The second pathway is associated with lowest cost but had similar event rate as pathway four. After calculation of values, finally the cost-effectiveness plane was drawn as shown in figure 7. It shows use of FFR either with CT or invasive angiography bring cost reduction to the procedure costs and events rate which is applicable for pathway 2 and 4.

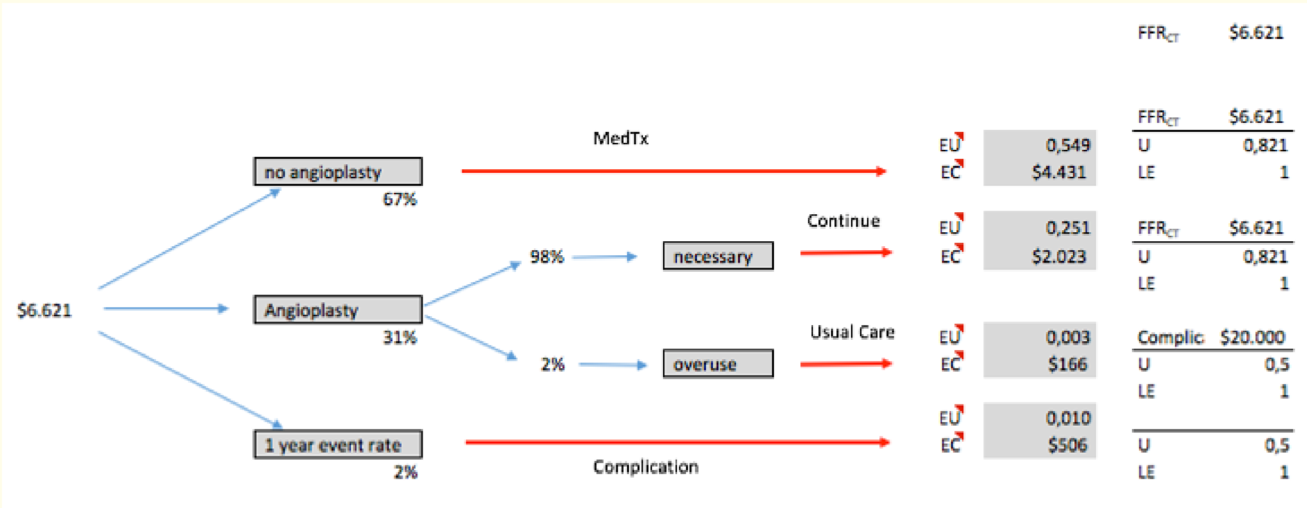

__Figure 1:__ Calculation of cost and outcomes for treatment, QALYs for FFR-CT use.

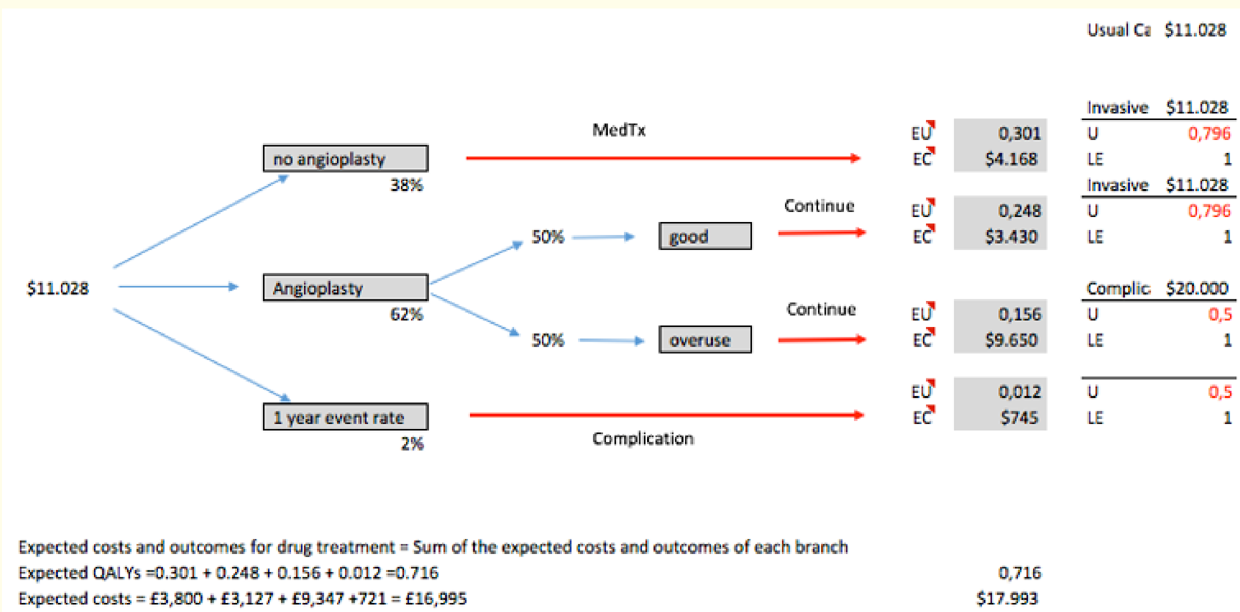

__Figure 2:__ Calculation of cost and outcomes for treatment, QALYs for usual care.

Inputs:	
FFR_{CT}	$6.621
Usual Care	$11.028
Complication	$20.000

Strategy	Cost	Incremental cost	Effect	Incremental effect	C/E	ICER
Usual care	$17.993	£0	0,72		$25.132	
FFR_{CT}	$7.126	-$10.867	0,81	0,10	$8.766	-$112.078

Sensitivity analysis

		Usual Care				
	-$112.078	$7.000	$8.000	$9.000	$10.053	$12.000
FFR-CT	$4.000	-$96.571	-$107.132	-$117.692	-$128.813	-$149.375
	$5.000	-$86.258	-$96.818	-$107.379	-$118.500	-$139.061
	$6.621	-$69.540	-$80.101	-$90.661	-$101.782	-$122.344
	$8.000	-$55.318	-$65.879	-$76.439	-$87.560	-$108.122
	$10.000	-$34.692	-$45.252	-$55.813	-$66.933	-$87.495

Figure 3: *Calculation of Incremental cost-effective ratio (ICER). Refer to manuscript for details.*

Costs Components	Procedure fee	Device cost	Hospital stay: Per night	Hospital stay: Avg nights	Hospital stay: Total	Total costs
Angio	$420	$60	$1.500	1	$2.100	$2.580
Percutaneous coronary intervention -1 vessel	$2.550	$5.789	$1.500	2	$3.000	$11.339
Percutaneous coronary intervention -2 vessel	$2.550	$9.802	$1.500	2	$3.000	$15.352
Percutaneous coronary intervention -3 vessel	$2.550	$13.815	$1.500	2	$3.000	$19.365
cCoronary CT angiography	$400	–	–	-	–	$400
FFR	$42	$1.800	–	-	–	$1.842
Price FFRct	–	$2.000	–	-	–	$2.000

Pathways	CAG visual	CA-I & FFR-CT	CA-CT & CA-I	[illegible]
No. of patients undergoing CAG (per 100 pts)	100	100	75	38
No. of patients undergoing PCI (per 100 pts)	62%	29%	54%	33%
Vessels treated by PCI (per 100 pts)	80	37	72	48
Costs per patient	$11.028	$2.246	$9.779	$6.621
1 year event rate	2,4%	1,9%	2,2%	1,9%

Figure 4: *Cost components of different diagnostic cum treatment pathways (Kindly refer to excel sheet for original quality).*

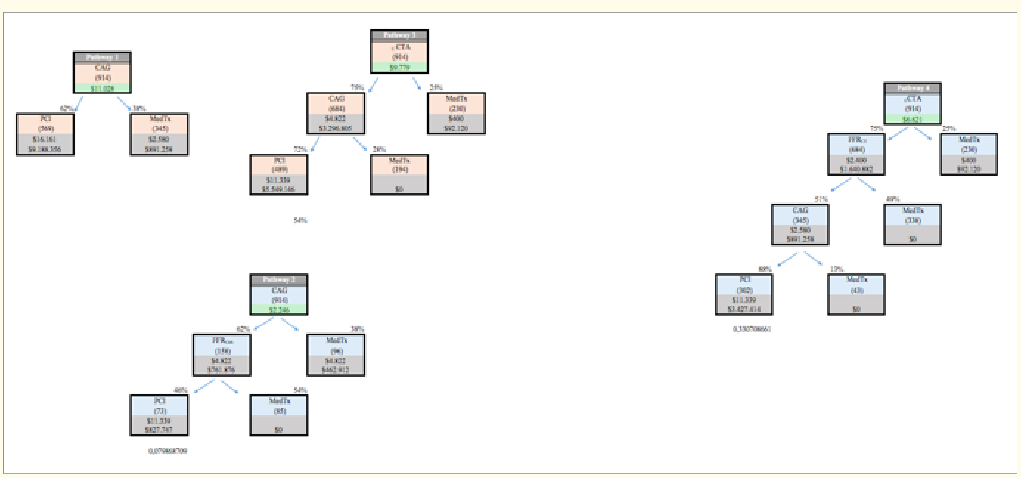

Figure 5: *The outline of four pathways selected for diagnostic/treatment strategies applied to 916 patients during this study. (kindly refer to attached excel sheet for better quality).*

Figure 6: *Combined cost and annual event rate. Numbers 1 to 4 refer to the pathways as described in manuscript.*

Figure 7: *The cost-effectiveness plane to determine cost to effective ratio.*

Discussion

Coronary imaging is an important tool for diagnosis and management for such diseases. The fractional flow reserve (FFR) measurement is the current standard for the functional assessment of lesion severity to diagnose the CAD. Computation of FFR from computed tomography angiography provides an important non-invasive tool to identify coronary artery stenosis [25]. The use of CA-I using FFR to identify lesion-specific ischemia and guide coronary intervention is now well-established. This not only improves patient outcome but also reduces costs in the current economic context, thus maintaining a healthy balance between economic sustainability with high quality of related medical standards. The further interventional management of coronary lesions when FFR ≤ 0.80 tends to improve clinical outcomes compared with usual therapy [22]. Therefore, in the following study we estimated the costs of the 2 different strategies i.e. CA-I and CA-CT relative to their efficacy conserving their respective FFR for tow purpose. Firstly, to correctly diagnose the presence of significant CAD that maybe causing the relevant ischemia and secondly for obtaining complete anatomical details of the affected or involved coronary vasculature causing myocardial ischemia. Especially, the CEA of both strategies were compared after its application to patient populations with entirely different CAD pre-test expectations. Finally, the cost effectiveness ratios of the 2 strategies were calculated for the individual health care systems.

The practice guidelines from American Heart Association and European Society of Cardiology recommend CA-I FFR as the standard to assess the hemodynamic importance a coronary lesion and to aid in planning future clinical pathway [23,24]. Ground reality checks using parameters of time and safety issues, limit its wider application. FFR-CT has a huge potential role in such cases to not only improve clinical outcomes but also decrease overall expenditure.

When the values of FFR are on extremes i.e. very high or very low, it is easy to make decisions regarding the future course of a patient, but main confusion tends to happen when such values are intermediate. In such kind of cases, this study seems helpful to follow which pathway especially with due consideration to CEA. This study also finds support from US and Japanese study [9,11].

Ethics and Dissemination

This cost-effective analysis required no ethical approval. This study for peer review journal was conducted to guide healthcare practices and policies of clinicians and researchers.

Strengths and Limitations of this Study

- Non-invasive CA-CT and FFR-CT can diagnose more accurately with lower cost per patient than traditional CA-I and associated FFR estimation.
- The study may help key decision makers to make better and efficient use of available technology about a not so well researched topic at reducing coronary artery intervention.
- This study excluded patients with active ischemia or ones who already underwent intervention. Thus, the results of this study may not apply to them.
- This is a simulation of possible costs and benefits using FFR-CT rather than in true clinical practice.

Conclusions

Analysis of data from the summarized data suggests that utilization of non-invasive CA-CT and FFR-CT for clinical decision making may improve clinical outcomes and reduce costs by precisely identifying patients for invasive coronary angiography and further Interventional treatment.

Contributors

All group members have equally contributed in conceptualizing, designing the study, conducting comprehensive literature searches, data accumulation and statistical analysis for the work.

Funding

No grants were received for this research from any funding agency.

Competing Interests

None declared. Provenance and peer review Not commissioned; externally peer reviewed.

Bibliography

1. Allender S., *et al*. "Patterns of coronary heart disease mortality over the 20(th) century in England and Wales: Possible plateaus in the rate of decline". *BMC Public Health* 8 (2008): 148.

2. Writing Group M., *et al*. "Heart Disease and Stroke Statistics-2012 Update: A Report From the American Heart Association". *Circulation* 125.1 (2012): e2-e220.

3. Schoenhagen P., *et al*. "Coronary CT Angiography and Comparative Effectiveness Research Prognostic Value of Atherosclerotic Disease Burden in Appropriately Indicated Clinical Examinations". *JACC: Cardiovascular Imaging* 4.5 (2011): 492-495.

4. Fearon WF., *et al*. "Economic evaluation of fractional flow reserve-guided percutaneous coronary intervention in patients with multivessel disease". *Circulation* 122.24 (2010): 2545-2550.

5. Pijls NH., *et al*. "Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease: 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study". *Journal of the American College of Cardiology* 56.3 (2010): 177-184.

6. Min JK., *et al*. "Prognostic value of multidetector coronary computed tomographic angiography for prediction of all-cause mortality". *Journal of the American College of Cardiology* 50.12 (2007): 1161-1170.

7. Carrigan TP., *et al*. "Prognostic utility of 64-slice computed tomography in patients with suspected but no documented coronary artery disease". *European Heart Journal* 30.3 (2009): 362-371.

8. Hadamitzky M., *et al*. "Prognostic value of coronary computed tomographic angiography for prediction of cardiac events in patients with suspected coronary artery disease". *JACC Cardiovascular Imaging* 2.4 (2009): 404-411.

9. Kimura T., *et al*. "Cost analysis of non-invasive fractional flow reserve derived from coronary computed tomographic angiography in Japan". *Cardiovascular Intervention and Therapeutics* 30.1 (2015): 38-44.

10. Min JK., *et al*. "Rationale and design of the DeFACTO (Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography) study". *Journal of Cardiovascular Computed Tomography* 5.5 (2011): 301-309.

11. Hlatky MA., *et al*. "Projected costs and consequences of computed tomography-determined fractional flow reserve". *Clinical Cardiology* 36.12 (2013): 743-748.

12. Centers for Medicare and Medicaid Services. CMS programs and information.

13. Siegel JE., *et al*. "Recommendations for reporting cost-effectiveness analyses". *Journal of the American Medical Association* 276.16 (1996): 1339-1341.

14. Kaufmann S and Valderrama MT. "The role of credit aggregates and asset prices in the transmission mechanism: A comparison between the euro area and the USA". *The Manchester School* 78.4 (2010): 345-377.

15. Dittmar RD., *et al*. "Inflation persistence and flexible prices". *International Economic Review* 46.1 (2005): 245-261.

16. Goodhart C. "What weight should be given to asset prices in the measurement of inflation?" *The Economic Journal* 111.472 (2001): 335-356.

17. Procedural Reinbursement Guide Medicare (2012).

18. Pijls NH., *et al*. "Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study". *Journal of the American College of Cardiology* 49.21 (2007): 2105-2111.

19. Tonino PA., *et al*. "Fractional flow reserve versus angiography for guiding percutaneous coronary intervention". *The New England Journal of Medicine* 360.3 (2009): 213-224.

20. Tonino PA., *et al*. "Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation". *Journal of the American College of Cardiology* 55.25 (2010): 2816-2821.

21. Stone GW., *et al*. "A prospective natural-history study of coronary atherosclerosis". *The New England Journal of Medicine* 364.3 (2011): 226-235.

22. Fearon WF., *et al*. "Cost-effectiveness of percutaneous coronary intervention in patients with stable coronary artery disease and abnormal fractional flow reserve". *Circulation* 128.12 (2013): 1335-1340.

23. Wijns W., *et al*. "Guidelines on myocardial revascularization". *European Heart Journal* 31.20 (2010): 2501-2555.

24. Levine GN., *et al*. "2011 ACCF/AHA/SCAI Guideline for percutaneous coronary intervention". *Circulation* 124.23 (2011): 2574-2609.

25. Kumar N., *et al*. "Systemic review and meta-analysis of diagnostic efficacy of fractional flow reserve using computed tomography angiography for first-time diagnosis of coronary artery disease". *Research in Cardiovascular Medicine* 7.4 (2018): 159-164.

Volume 6 Issue 9 September 2019