



ANTI-PLATELETS REGIMEN AND PATENCY OF VENOUS GRAFTS IN DIABETIC SEPTUAGENARIANS

Sharjeel Abbas^a, Waseem Riaz^{b*}, Ahmad Shahbaz^b, Saman Sarwar^c

ABSTRACT

BACKGROUND: Patency of venous graft to left anterior descending artery is of prime importance for healthy living of diabetic patients >70 years of age, maintained by antiplatelet or anticoagulant therapy. Whether Aspirin plus Clopidogrel therapy is better in certain situations than only Clopidogrel is not well established.

MATERIAL AND METHODS: This study was conducted at Outpatient Department of Punjab Institute of Cardiology Lahore Pakistan from March 2012 to February 2018. All patients were known to have Type II diabetes mellitus, who under-went Coronary Artery Bypass Grafting (CABG). The age at operation was ≥ 70 years. The patients were divided into two groups. Group A patients received Aspirin (75mg) and Clopidogrel (75mg); Group B patients were prescribed only Clopidogrel (75mg). At Completion of 2 years post CABG, CT coronary Angiography was done and Echo findings were noted and compared among both groups.

RESULTS: A total of 51 patients were studied. Mean age was 73.14 ± 1.887 years and 27 were male. Out of these 51 patients, 33 were in Group A (Aspirin + Clopidogrel) and 18 were in Group B (only Clopidogrel). At 2 years follow up, more than moderate (>40%) stenosis of venous grafts was observed in 4 (12.1%) patients in group A and 2 (11.1%) in group B with no statistically significant difference.

CONCLUSION: Both Aspirin + Clopidogrel and Clopidogrel-only antiplatelet regimens are equally effective

INTRODUCTION

Symptomatic improvement is also important in addition to outcome parameters like long term mortality, especially so, in elderly population undergoing CABG. They carry various comorbidities which may impact adversely on outcomes, and Diabetes in one of them¹⁻³.

In septuagenarians, the elderly (variable definitions)⁴, with comorbidities like Diabetes Mellitus, the chances of sternal wound infection are increased due to osteoporosis⁵. Additionally, there is high likelihood of diffuse and complicated Coronary Artery Disease as well^{6,7}. The Ejection fraction may not be optimal⁸ or at times internal mammary artery is either not harvestable or not suitable to be used as graft due to variety of reasons⁹. These may be few of the reasons, why some surgeons may decide for the "all venous grafts". This may

be suggested due to unmatched population of ours when compared to Caucasians, with respect to different socio-ethno-economic status. Under such situations the old school still opts for total venous graft revascularization strategy.

Previously the reversed saphenous vein grafts (RSVG) were believed to become obstructed over a period of time, due to non-availability of antiplatelet/anticoagulant medications¹⁰. Aspirin usage has decreased the blockage rate substantially in early decade of this century, becoming standard regimen¹¹, but then the increased bleeding tendency and other contraindications to its use led to a search for other antiplatelet agents. Clopidogrel emerged as an additional treatment option for Dual Antiplatelet Therapy (DAPT), which not only decreased dosage of aspirin but also its tendency to induce bleeding and other related problems^{12,13}.

The patency of grafts, especially to left anterior descending artery is of paramount importance for the symptomatic improvement and survival of post-CABG patients.^{10,11,14,15} The evolution in recognizing the pathophysiology of graft occlusion and molecular basis of various medications that hinder the development of stenosis has provided the miraculous benefits to our patients. The patency rate became better for vein grafts¹⁰ comparative to

(J Cardiovasc Dis 2018;14(4):93 -99)

^aLUMHS, Jamshoro

^bPunjab Institute of Cardiology,
Lahore-Pakistan

^cServices Institute of Medical Sciences,
Lahore-Pakistan

* Corresponding author:
Email:riazwaseem6@gmail.com



the one few decades back, but a lot of improvement is still needed. Another group of patients are those who were not tolerant to aspirin¹². In these patients, Clopidogrel is advised by many physicians.

In recent times where post-CABG patients with “all vein grafts” are rarely encountered, one may seldom find good studies which compare benefits of various medications for such patients. Moreover, it is found that no study was performed prospectively to address the patency rate of venous grafts in patients where both Aspirin and Clopidogrel were used in combination to patients in whom Clopidogrel was utilized as only medicine to avoid certain complications of Aspirin.

These issues in combination draw our attention towards taking the benefit of this available population of post CABG patients operated at various Hospitals were put either on Aspirin+Clopidogrel based regimen or on Clopidogrel only based regimen by their concerned Cardiologist/Cardiac surgeon, and follow them in our OPD over a period of two years to detect the effects of various anti-platelets on venous graft to left anterior descending artery in our elderly diabetic post CABG population, a cohort which is not easy to find in modern times. As stated above the LAD is chosen for its anchor role in all previous and recent indications for CABG.

Keeping such rationale in mind, we conducted a study in our septatgenerian patients who underwent CABG with all venous grafts to find out the patency rate of RSVG-LAD graft 2 years after Coronary revascularization, when either DAPT or Clopidogrel was used.

MATERIAL AND METHODS:

The study was conducted at Outpatient Department (OPD) of Punjab Institute of Cardiology (PIC) Lahore Pakistan from March 2012 to February 2018. All consecutive patients >70 years of age, who had Type II diabetes mellitus, who had undergone elective On-Pump Cardiac Surgical Revascularization were enrolled. Patients who underwent emergency CABG were also included in the study. They all were prescribed different anti-platelet regimens by their treating physicians/surgeons, however they visited PIC surgical OPD for regular follow up to avail consultations and medications.

Patients who had incomplete revascularization, where LIMA was placed on LAD, where endarterectomy was performed, where sequential / jump grafts were used, who underwent additional

cardiac surgical procedures, who became symptomatic during the study period of 2 years post-operatively (NYHA-III and above), were excluded from the study.

We included patients >70 years of age and marked them as elderly population, with following justification. Pakistan being a third world country encounters myriad of deficiencies in health, education and economy. This is reflected partly through its lower average age when compared to Developed Countries. Surgeons while treating our patients give a slight leverage on age of approximately 10-15 years than that of Developed countries when it comes to certain recommended age limits for different cardiac surgical management, and CABG is not different. Whereas the world is watching CABG at 90 years of age, people in Pakistan do not show willingness for operation of their elderly patients if they cross 70 years, which may be due to various socioeconomic reasons. Keeping this in mind, most of the surgeons in Pakistan take 70 years of our patient as equivalent to 90 years of western person when it comes to upper limit of CABG, and mark them as elderly¹⁶. However, with increasing awareness and health of our patients, we are receiving elderly patients quite regularly for CABG, but as there is no particular registry system available in this country¹⁷, a scientific inference cannot be drawn.

The patients were divided into two groups. Group A patients received Aspirin (75mg) + Clopidogrel (75mg) and Group B patients were prescribed Clopidogrel (75mg) only as the patients had/were considered to have history of peptic ulcer disease; they were additionally placed on Proton Pump Inhibitors or H2-Receptor Blockers.

All patients were guided to be part of regular follow-up, with written and informed consent. A previous surgical record was noted from the Discharge summary of the operation. All patients had to undergo two scheduled Echocardiographies during study period; the first one at the first encounter in OPD (taken as control or baseline echocardiography) while the other was performed at the end of study. In each setting, the Echocardiography would find out any Segmental Wall Motion Abnormalities (SWMA), changes in LVEF, and left ventricular systolic (LVESD) and diastolic (LVEDD) dimensions. At completion of 2nd year post-CABG, Diagnostic Coronary Tomographic (CT) Coronary Angiography were performed to find out the status of Reversed saphenous vein graft (RSVG) anasto-



moses to left anterior descending artery; to find out status of Aorto-RSVG anastomosis, RSVG tube, RSVG-LAD anastomosis. The maximum narrowing in any of multiple views was categorized as mild if <40%, moderate if 41-70% and severe if >70% of luminal diameter.

A record was made for Demographic profile (age, sex), operative parameters (cardiopulmonary bypass time, cross clamp time, total operative time), postoperative echocardiographic findings (SWMA, LVEF, LVESD, LVEDD) at the time of discharge from hospital & at the end of 2nd year postoperatively, and CT Angiographic findings (status of Aorto-RSVG anastomosis, RSVG tube, RSVG-LAD anastomosis and severity of the stenosis if any).

The data was analyzed with the help of SPSS® (IBM 23v). The variables were analyzed qualitatively and quantitatively, with the help of frequency tables & Charts, chi-square tests, and Student-T test, or any other relevant statistical test where applicable. The p-value <0.05 was taken as significant.

RESULTS:

A total of 51 patients were available for analysis at the end of study period; 33 in Group A and 18 in Group B. Overall, mean age was 73.14 ± 1.887 years; the youngest patient was 70 years of age whereas the oldest one was 78 years of age, the median being 73. Twenty seven (52.9%) patients were male while 24 (47.1%) were females. In 43 patients 3 vessels were grafted whereas in 8 patients 2 vessels were bypassed. The average duration of operation was 139.69 minutes, with median of 120 minutes; the average bypass time being 67.80 minutes, and median was 65 minutes; average Cross clamp time was 37.06 minutes, median being 36 minutes. Total ICU stay was 1.22 days on average (40 patients had 1 day stay) while total Hospital stay averaged 6.96 days (27 patients stayed for 7 days). The Control Echocardiographic findings were as follows; SWMA (Anterior wall 8 patients, Anterior & Lateral Walls 33 patients, Anterior and Inferior Walls 3 patients, Anterior & Basal Walls 7 patients); LVEF (40% in 16 patients, 41-50% in 34 patients, >51% in 1 patient). The Echocardiographic findings at the end of 2nd post-operative year were as below; SWMA (No Anomaly observed in 46 patients, Anterior wall 1 patient, Lateral wall in 3 patients, Inferior wall in 1 patient; LVEF (40% in 13 patients, 41-50% in 37 patients, >51% in 1 patient). The CT angiography findings at the end of 2nd postoperative year revealed more than moderate (>40%) stenosis of venous grafts

in 4 (12.1%) patients in group A and 2 (11.1%) in group B with no statistically significant difference.

Table 1: Baseline characteristics of all patients

	Group A	Group B	p-value
Age (yrs)			0.498
1. Mean	73.30±2.172y	72.83±1.20y	
2. Median	73y	73y	
3. Mode	72y	74y	
4. Minimum	70y	71y	
5. Maximum	78y	74y	
Gender			0.396
• Male	19	08	
• Females	14	10	
Number of Grafts Placed			0.233
1. Single	00	00	
2. Double	07	01	
3. Tripple	26	17	
Total Operation Time	114.5±32.122 Min	174.44±18.059 Min	0.000
CPB Time	63.55±9.728 Min	75.61±6.363 Min	0.000
Cross Clamp Time	36.45±7.977 Min	38.17±6.051 Min	0.833
ICU Stay	1.15±0.364 Days	1.33±0.485 Days	0.164
• 1 day	28	12	
• 2 days	05	06	
Hospital Stay	6.79±0.696 Days	7.28±0.575 Days	0.016
• 6 days	12	01	
• 7 days	16	11	
• 8 days	05	06	
Control EchoCardioGraphic Findings			
SWMA			0.812
• Anterior Wall Hypokinesia	04	04	
• Antero-Lateral Hypokinesia	22	11	
• Antero-Inferior Hypokinesia	02	01	
• Antero-Basal Hypokinesia	05	02	
LVEF	44.67±4.105%	42.78±2.557%	0.255
• 40%	08	08	
• 45%	25	10	
LVESD	33.0±2.318mm	32.83±2.149mm	0.906
LVEDD	50.73±1.232mm	50.33±0.485mm	0.150
EchoCardioGraphic Findings at End of 2nd Postoperative year			
SWMA			0.132
• None	29	17	
• Anterior	01	00	
• Lateral	03	00	
• Inferior	00	01	
LVEF	44.33±3.149%	44±3.125%	0.626
• 40%	08	05	
• 42%	00	01	
• 44%	01	00	
• 45%	21	10	
• 50%	02	02	
• 54%	01	00	
LVESD	33.27±2.719mm	32.61±2.570mm	0.365
LVEDD	50.94±1.580mm	50.67±1.372mm	0.850
CT Angiographic Findings			
AA-RSVG Anastomosis			0.120
• No Stenosis	33	16	
• Stenosis	00	02	
1. Mild (<40%)	00	01	
2. Moderate (41-70%)	00	01	
RSVG tube Graft			0.591
• No Narrowing	28	15	
• Narrowing	05	03	
1. Mild (<40%)	03	02	
2. Moderate (41-70%)	01	01	
3. Severe (>71%)	01	00	
RSVG-LAD Anastomosis			0.414
• No Narrowing	31	18	
• Moderate Narrowing (41-70%)	02	00	

AA-RSVG=Ascending Aorta anastomosis to Reversed Saphenous vein Graft
 RSV=Reversed Saphenous Vein
 RSVG-LAD=Reversed Saphenous Vein Graft anastomosis to Left Anterior Descending Artery
 SWMA=Segmental Wall Motion Anomalies
 LVEF=Left Ventricular Ejection Fraction
 LVESD=Left Ventricular End Systolic Dimension
 LVEDD=Left Ventricular End Diastolic Dimension



Table 2: Results of comparison between two Groups after applying Mann-Whitney U test

	Z-Value	P-test
AA-RSVG Anastomosis		
• Classification of disease (Yes/No)	-1.934	0.053
• severity of disease (No/Mild/Moderate/Severe)	-1.934	0.053
RSV Tube Graft		
• Classification of disease (Yes/No)	-0.141	0.888
• severity of disease (No/Mild/Moderate/Severe)	-0.109	0.913
RSVG-LAD Anastomosis		
• Classification of disease (Yes/No)	-1.055	0.291
• severity of disease (No/Mild/Moderate/Severe)	-1.055	0.291
Control EchoCardiographic Findings		
• SWMA	-0.835	0.404
• LVEF	-1.649	0.099
• LVESD	-0.419	0.623
• LVEDD	-1.674	0.094
Echocardiographic Findings at end of 2 nd year post-CABG		
• SWMA	-0.669	0.504
• LVEF	-0.272	0.786
• LVESD	-0.965	0.335
• LVEDD	-0.629	0.529

AA-RSVG=Ascending Aorta anastomosis to Reversed Saphenous vein Graft
 RSV=Reversed Saphenous Vein
 RSVG-LAD=Reversed Saphenous Vein Graft anastomosis to Left Anterior Descending Artery
 SWMA=Segmental Wall Motion Anomalies
 LVEF=Left Ventricular Ejection Fraction
 LVESD=Left Ventricular End Systolic Dimension
 LVEDD=Left Ventricular End Diastolic Dimension

Ascending Aortic-RSVG Anastomosis status was as under:
 No Stenosis in 49 patients, 1 patient had mild stenosis while another had moderate stenosis.
 RSVG Conduit Status was as under:
 43 patients had patent RSVG, 5 patients had Mild disease, 2 patients had moderate & 1 patient had severe disease.
 RSVG-LAD Anastomosis status was as under:
 49 patients had no disease whereas 2 patients had moderate stenosis).²

More specific data based on individual group findings/characteristics/variables is shown in Table: 1. The data showed mostly no significant difference between two groups, except in Total operative time and CPB time. None of the Groups have higher frequency of venous Graft failure when results were compared using Mann-Whitney U Test (Table 2), where the p-value remained insignificant (>0.05).

DISCUSSION:

This study showed that Dual anti-platelet therapy (DAPT) or only Clopidogrel are equally effective to maintain the patency of Saphenous vein graft to LAD at 2 years of follow up. Worldwide, there is increasing awareness and trust of general population regarding benefits of CABG. However,

the average age of our population is 66 years (Median 22.5 years) as compared to 80.1 years (Median 45.9 years) in Germany whereas in USA average age is 78.4 years (Median 37.6 years), it is difficult to follow the same treatment criteria based on age in our population¹⁸.

Another challenge is lack of effective Data Registry system / Data Base System, like STS¹⁹ model in Pakistan. In addition, the CABG is performed in high numbers at Private Hospital, which may have billing system but no surgical data recording. Most of the surgical revascularization provided to our patients is merely based on agreement between the patient and his surgeon, and infrequently by a proper heart team approach.

It may be appreciated that the indications of CABG treatment are variable in our environment, and the reasons to bypass completely or incompletely, with venous or arterial or even total arterial grafts also varied, due to the incomplete data provided on discharge slips of our patients. Thus the management pattern can not reflect the same results as are obvious in Developed countries.

With advancing medical knowledge, the ratio of ageing population is on the rise. Advancing age brings a lot of health related issues, among which ischemic heart disease (IHD) makes its place in top 3, affecting >15.5% of population¹⁸, having both adverse morbidity and mortality. IHD can be treated medically or with interventions (PCI or CABG). Surgical intervention can be performed with Total Arterial Revascularization, Arterio-venous Revascularization or rarely Total Venous Revascularization.

The disadvantage with classically used saphenous vein grafts is decreasing patency rate over time. The underlying mechanism is multifactorial (for example high arterial blood flow pressure causing intimal hyperplasia and thrombosis, or harvest related injury)³. One year after surgical revascularization 10-20% of grafted veins are occluded^{7,11}. Following that each year 1-2% occlusion rate is observed^{2,3,7,11}. From 6th postoperative year occlusion rate rise to 4-5% per year^{10-13,20,21}. Thus a decade after CABG only 50-60% of saphenous vein grafts are patent^{10,14}. Moreover, only 50% of these are free of angiographic atherosclerotic lesions^{10,11,22}. Thus, in patients who undergo CABG it is highly recommended that whenever possible Left Internal Mammary Artery should be used as a graft to Left Anterior Descending Coronary artery (patency rate at 10 years reach 90%)^{10,11,22,23}. However, there appear certain situations when



LIMA grafting is not possible⁹, e.g. Osteoporosis, Subclavian artery occlusion, Extreme chest deformities, previous radiation to chest, Emergency CABG, damaged/non-graftable LIMA). Under these situations only venous grafts are placed and thus the patency of the graft is at risk. Here anti-platelet and/ or anticoagulant drugs are the mainstay of treatment.^{11,24} Aspirin, Clopidogrel and Ticagrelor, are few of the available anti-platelet drugs.

Aspirin is an antiplatelet medication, a cornerstone of treatment for all forms of IHD⁵. However it is weak antiplatelet agent and is poorly tolerated by many patients²⁵. Clinical data favors that low-dose Aspirin (75-150mg every day) is adequate for long term use. The higher dose is associated with risk of gastrointestinal bleeding¹⁵. Mark R. Nelson²⁶ et al, believed in marked risk of potentially life threatening bleeding in septuagenarians placed on even a low dose of Aspirin every day for Primary prevention. He believed that the risk is itself greater than the heart disease protection offered by the aspirin based therapy. Moreover, Aspirin should not be prescribed^{7,16-18} if the patient has hemophilia, vitamin K deficiency, low platelet counts, recent history of stomach or intestinal bleeding, aspirin sensitive asthma, nasal polyps or when allergic to NSAID. Clopidogrel (another Antiplatelet agent) has been shown to improve outcomes in patients with ischemic heart disease across a variety of syndromes. Current guidelines²² recommend that Dual Antiplatelet therapy (DAPT) with Aspirin and ADP receptor antagonist be used for percutaneous interventions of coronary arteries. Aspirin resistance is seen in early period after CABG (1%-61%)²⁷, thus use of DAPT has become more common. Surprisingly less is known about the duration and effect of DAPT on graft patency, clinical outcomes and mortality. There may be increased chances of bleeding with such dual drug regimen, which requires a tradeoff between decreasing ischemic risk and stent thrombosis with an increased bleeding risk. Thus use of DAPT needs selective assessment of risk benefit equation for each patients¹⁰⁻¹⁸.

One may draw an inference from above evidence and discussion that our post-CABG patients may not be prescribed Aspirin based therapy, which however is not true. One may address the risk to benefit ratio individualized to each patient, and this is where no consensus exists. This enabled us to look at the differences in benefits among septuagenarian patients who either were prescribed by their physicians/surgeons Aspirin+Clopidogrel or Clopidogrel alone; the primary aim was directed

and confined towards patency of venous grafts to left anterior descending artery.

In view of small sample size, we used Mann Whitney U-Test to compare 2 Groups.(Table-2) None of the Groups had higher frequency of venous Graft failure when results were compared; p-value remained insignificant (>0.05).

As we have excluded most of the risk factors associated with the early graft failure, except age and Diabetes Mellitus, it appears that in such population giving either DAPT or Clopidogrel appears to have no significant impact on patency of Venous graft to LAD territory.

In a study on 249 patients by Zhang et al¹⁰, it was found by CT Angiography that Saphenous vein graft patency remained 91.6% at 3rd Postoperative month in patient Group who were treated with Aspirin and Clopidogrel both. Gao et al¹⁴ performed CT angiography at 1 and 12 months post CABG. The Graft patency in their study on 197 patients appeared 93.5% at 1 year post-CABG for patients who received Clopidogrel alone, whereas it was 96.3% in combination group. A Meta-Analysis¹⁵ of 16 original articles with a total number of included patients being 3133, an Angiography was performed at 10.4 months on the average. Though there was a significant advantage noted for the combined therapy group in all patients, there appeared insignificant results when subgroup Analysis was performed for SVG. A Subgroup analysis of ROOBY Trial²⁰ assessed Graft status with Angiography after 1 year of Post-CABG treatment. There appears no significant difference in Clopidogrel and no Clopidogrel group of medications. They concluded that use of Clopidogrel does not translate to improved graft patency.

We assessed venous graft patency at 2 years. Additionally our SVG graft was placed on LAD territory in patients who were not only elderly but were also Type 2 Diabetics, making this quite a unique group of patients. It may not be reflecting the same outcomes as described in previous studies. However, it was found that the patency of RSVG-LAD graft as assessed by disease free status is 78.4% at the end of 2nd postoperative year in both groups and the p value was non-significant (p=0.934).

The study concludes no difference in the patency of venous grafts in Diabetic patients over 70 years of age, whether Aspirin+Clopidogrel or Clopidogrel alone was used for 2 years post CABG. However, this is small study and ,meaningful conclusion cannot be drawn from this study. It is



proposed that in our population epidemiologists, cardiologists and cardiac surgeons should take an endeavor prospectively, to find out the advantage of one treatment regimen over other.

Author's Contribution

SA: Conducted the study and wrote the article.
WR: Re-analyzed data, reviewed and corrected the article.
AS & SS: Helped in conducting the study

REFERENCES

- 1.Spencer. Bureau of the Census: Projections of the population of the United States, by age, sex and race; 1988–2080. *CurrPopul Rep Ser* 1980; 1018:1988–2080. 1989;1018:25.
- 2.Peterson ED, Jollis JG, Bebczuk JD, DeLong ER, Muhlbaier LH, Mark DB et al. Changes in mortality after myocardial revascularization in the elderly. The national Medicare experience. *Ann Intern Med* 1994;121:919–27.
- 3.Baig K, Harling L, Papanikitas J, Attaran S, Ashrafian H, Casula R, Athanasiou T. Does coronary artery bypass grafting improve quality of life in elderly patients? *Interactive Cardiovascular and Thoracic Surgery*. 2013;542–553.
- 4.Rocha AS, Pittella FJ, Lorenzo AR, Barzan V, Colafranceschi AS, Brito JO, Mattos MA, Silva PR. Age influences outcomes in 70-year or older patients undergoing isolated coronary artery bypass graft surgery. *Rev Bras Cir Cardiovasc* 2012;27(1):45-51
- 5.Braxton JH, Marrin CA, McGrath PD, Morton JR, Norotsky M, Charlesworth DC, et al. 10-year follow-up of patients with and without mediastinitis. *SeminThoracCardiovascSurg* 2004; 16:70–76.
- 6.Norhammar A, Malmberg K, Diderholm E, Lagerqvist B, Lindahl B, Rydén L, et al. Diabetes mellitus: the major risk factor in unstable coronary artery disease even after consideration of the extent of coronary artery disease and benefits of revascularization. *J Am Coll Cardiol*. 2004;43:585–591.
- 7.Paneni F, Beckman JA, Creager MA, Cosentino F. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: Part I. *Eur Heart J*. 2013 Aug;34(31):2436-43.
- 8.Boonman-de Winter LJ, Rutten FH, Cramer MJ, Landman MJ, Liem AH, Rutten GE et al. High prevalence of previously unknown heart failure and left ventricular dysfunction in patients with type 2 diabetes. *Diabetologia*. 2012;55(8):2154–62.
- 9.Bonacchi M, Battaglia F, Prifti E, Leacche M, Nathan NS, Sani G, Popoff G. Early and late outcome of skeletonised bilateral internalmammary arteries anastomosed to the left coronary system. *Heart*. 2005 Feb; 91(2): 195–202.
- 10.Gao G, Zheng Z, Pi Y, Lu B, Lu J, Hu S.. Aspirin Plus Clopidogrel Therapy Increases Early Venous Graft Patency After Coronary Artery Bypass Surgery. *J Am Coll Cardiol*. 2010 Nov;56(20):1639–43.
- 11.Gaudino M, Antoniadou C, Benedetto U, Deb S, Di Franco A, Di Giammarco G et al. Mechanisms, Consequences, and Prevention of Coronary Graft Failure. *Circulation*. 2017;136(18):1749–64.
- 12.Van Diepen S, Fuster V, Verma S, Hamza TH, Siami FS, Goodman SG et al. Dual Antiplatelet Therapy Versus Aspirin Monotherapy in Diabetics With Multivessel Disease Undergoing CABG. *J Am Coll Cardiol*. 2017 Jan;69(2):119–27.
- 13.Hoxha A, Shehu S, Deveja R, Qirjazi T. Impact of Clopidogrel Loading for Coronarography on Bleeding After Urgent First Time CABG. *Med Arch*. 2018 Nov;72(3):319.
- 14.Gao C, Ren C, Li D, Li L. Clopidogrel and Aspirin Versus Clopidogrel Alone on Graft Patency After Coronary Artery Bypass Grafting. *Ann Thorac Surg*. 2009;88(1):59–62.
- 15.Chakos A, Jbara D, Singh K, Yan TD, Tian DH. Network meta-analysis of antiplatelet therapy following coronary artery bypass grafting (CABG): none versus one versus two antiplatelet agents. *Ann Cardiothorac Surg*. 2018 Sep;7(5):577–85.
- 16.Dar MI, Dar AH, Almani K, Atta-ul-Mannan, Khan AQ, Rizwani GH, Ahmad M. Coronary artery bypass surgery in old age group: Is age itself a barrier? *J Pak Med Assoc*. 2009;59(9):587-89.
- 17.Badar F. Response to Comments on Suhail Anwar. The role of a cancer registry in a health-care system. *J Pak Med Assoc*. 2018 Aug;68(8):1279.
- 18.Country Meters. <https://countrymeters.info>.
- 19.STS National Database. <https://www.sts.org/registries-research-center/sts-national-database>
- 20.Ebrahimi R, Bakaeen FG, Uberoi A, Ardehali A, Baltz JH, Hattler B, et al. Effect of clopidogrel use post coronary artery bypass surgery on graft patency. *Ann Thorac Surg*. 2014 Jan;97(1):15–21.
- 21.Verma S, Goodman SG, Mehta SR, Latter DA, Ruel M, Gupta M, et al. Should dual antiplatelet therapy be used in patients following coronary artery bypass surgery? A meta-analysis of randomized controlled trials. *BMC Surg*. 2015 Dec;15(1):112.
- 22.Sousa-Uva M, Head SJ, Milojevic M, Collet J-P, Landoni G, Castella M, et al. 2017 EACTS Guidelines on perioperative medication in adult cardiac surgery. *Eur J Cardiothorac Surg*. 2018 Jan 1;53(1):5-33.
- 23.Gulizia MM, Colivicchi F, Abrignani MG, Ambrosetti M, Aspromonte N, Barile G, et al. Consensus Document AN-



MCO/ANCE/ARCA/GICR-IACPR/GISE/SICOA: Long-term Antiplatelet Therapy in Patients with Coronary Artery Disease. *Eur Heart J Suppl.* 2018 May;20:F1–74.

24. Höfer S, Kullich W, Graninger U, Brandt D, Gaßner A, Klicpera M, et al. Cardiac rehabilitation in Austria: short term quality of life improvements in patients with heart disease. *Wien Klin Wochenschr.* 2006 Dec;118:744–53.

25. Deo S V, Dunlay SM, Shah IK, Altarabsheh SE, Erwin PJ, Boilson BA, et al. Dual anti-platelet therapy after coronary

artery bypass grafting: is there any benefit? A systematic review and meta-analysis. *J Card Surg.* 2013 Mar;28(2):109–16.

26. Woods RL, Tonkin AM, Nelson MR, Britt HC, Reid CM. Should aspirin be used for the primary prevention of cardiovascular disease in people with diabetes? *Med J Aust.* 2009 Jun;190(11):614–5.

27. Al Jaaly E, Zakkar M, Pufulete M, Ciulli F, Angelini GD. Dual antiplatelet therapy after coronary artery bypass grafting: Do we have a consensus? *Rev Artic J Integr Cardiol J Integr Cardiol.* 2015;1(4):90–3.