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ORIGINAL RESEARCH

Bleeding in Patients with Atrial Fibrillation Plus Coronary Artery Disease under Triple anti-Coagulant Therapy

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Abstract: **Introduction:** Regarding scarce knowledge about bleeding in non-valvular atrial fibrillation (AF) patients with simultaneous coronary artery disease (CAD) under triple anti-coagulant therapy, this study was carried out to recognize the risk of hemorrhage and preventive programming. **Material and Methods:** In this performed prospective, 150 consecutive patients with non-valvular atrial fibrillation and concurrent coronary disease, candidate for triple therapy with Asprin 80 mg, Clopidogrel 75 mg and Rivaroxaban 15 mg (in Shohada, Loghman, Modarres, and Labafinezhad centers, in Tehran, Iran during Jan 2019 to Jan 2020 were enrolled and the incidence rate of bleeding and compliance were evaluated for one month. **Results:** The results in this study demonstrated that 87.3% had compliance and completely use three drugs. Bleeding occurred in 0.6% (4 patients), no major bleeding , only one minor bleeding as GIB, three minimal cases (totally 4 bleeding cases), 3 cases with epistaxis, 7 patients with ecchymosis, 6 subjects with hematuria, no one required discontinuation of drug. Diabetes mellitus, hypertension, female sex, older age, higher HASBLED Score, and higher CHADS-VASC Score were related to lack of compliance ($P < 0.05$). **Conclusion:** Incidence rate of bleeding in atrial fibrillation plus coronary concurrent patients, candidate for triple therapy with ASA, Clopidogrel and Rivaroxaban is low. Also the bleeding is minor and the compliance is high showing that majority of cases use routinely these triple therapy regimen.

Keywords: Atrial fibrillation; Bleeding; CAD; Compliance; Rivaroxaban

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1. Introduction

Atrial fibrillation (AF) is a common cardiac dysrhythmia seen in nearly one percent of the general population, six percent in elderly subjects, and nine percent in subjects aging from 80 to 89 years (1). Subjects with atrial fibrillation are at five-fold higher risk of cardiovascular events leading to mortality, morbidity, and health costs (1-3). Nearly 33 million AF cases are present worldwide (4) and it is responsible for seventy percent of non-valvular fibrillation cases (5). Vitamin-K antagonists such as warfarin are used for prevention of ischemic events and optimal doses lead to INR (international normalized ratio) range from 2 to 3 that is also accompanied with severe bleeding (6-8). Nowadays there are four types of Non-vitamin K antagonist (Non-VKA) anticoagulants with good efficacy but without need to INR assessment with lower interactions (6, 9, 10). Dabigatran, Rivaroxaban, Apixaban, and Edoxaban are these four approved therapeutics (5). Bleeding is main adverse effect due to anti-coagulants (11-14). Rivaroxaban is Xa factor inhibitor used for prevention of myocardial infarction in AF cases (11). But there is scarce data about the gastrointestinal bleeding in Iranian Rivaroxaban users as reported by Bigdeli and Sharif-Kashani (15). Regarding the role of cytochrome oxidase enzymes and genetic variations according to the ethnic differences, some various results for the users may be expected (10). The importance is higher in coronary artery disease cases for thromboembolism prevention in atrial fibrillation, artificial valve cases, and left ventricular systolic heart failure. These patients receive triple-therapy with addition of aspirin and P2Y12 receptor blocker and Rivaroxaban is the only approved case for addition to dual therapy (12-14). Regarding scarce knowledge about bleeding in AF patients with simultaneous CAD (coronary artery disease) under treatment with rivaroxaban beside other agents such as aspirin and Clopidogrel, this

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study was carried out to recognize the risk of hemorrhage and evaluating compliance of drugs.

2. Material and Methods

In this cohort 150 consecutive patients with non-valvular atrial fibrillation and concurrent coronary disease, candidate for triple therapy with Asprin 80 mg (ABIDI Co. Tehran, Iran), Clopidogrel 75 mg (ABIDI Co. Tehran, Iran), and Rivaroxaban 15 mg (ABIDI Co. Tehran, Iran) in Shohadaa, Loghman, Modarres, and Labafinezhad centers, in Tehran, Iran from Jan 2019 to Jan 2020 were enrolled.

The study was approved by local ethical committee in Shahid-Beheshti Medical Sciences University (Ethical code: IR.SBMU.RETECH.REC.1398.144). Inclusion criteria were established AF (atrial fibrillation) by electrocardiogram (ECG) and echocardiography, established coronary artery disease by EKG and angiography, and being candidate for triple therapy with ASA, Clopidogrel and Rivaroxaban. The exclucriteria were renal/hepatic failure, Rivaroxaban hypersensitivity, GFR (Glomerular filtration rate) under 30 ml/min, active bleeding, CHADS2-VASC scores of 0, and 1 in men and 0, 1, and 2 in women according to EHRA2018 and European Society of Cardiology (ESC) 2019. The informed consent form was received from participants.

At initiation of triple-therapy course the patients were enrolled and followed up till one month. The adverse effects and drug tolerance were fulfilled in periodical assessments. The cases were learned to attend if there were bleeding earlier than visits. The incidence rate of major/minor bleeding (by TIMI Bleeding Criteria as shown in Figure 1) and compliance rates were determined. Compliance was assessed by phone call and was defined as complete use of three drugs during whole times. Also in the bleeding cases the HASBLED scores were calculated and sub-analysis was done according to it. Follow-up was after one month. Smokers were whom smoke in last year (more than one pack / year). Diabetic cases were controlled patients with diabetes mellitus according to known history of hyperglycemia and diabetes therapeutics use.

Data analysis was done by SPSS version 21.0 software among 150 patients. The utilized tests for sub-Group analysis (assessment for background factors) in groups were Kolmogorov-Smirnov, Chi-Square, Exact-Fisher, and Independent-Sample-T and the P values under 0.05 were considered statistically significant.

3. Results

The mean age of the participants in this work was 40.69 ± 13.23 years. The mean age of the general population and urologists was 35.8 ± 13.7 and 45.6 ± 10.6, respectively (P=0.0001). 42.1% of the participants in the general population were under 30 years old (Table 1). 56.8% of the general population respondents in this study had a university degree (Table 2). Table 3 summarizes the prevalence of the educational priorities among urologists and the general population. In general, erectile dysfunction and STDs were the most mentioned diseases as an educational priority (Table 3). 49.3% of the urologists considered erectile dysfunction as an educational priority whereas 31% of the general population mentioned it as a priority (P=0.0001). STDs were an educational priority among 45.3% of urologists while 35% of the general population mentioned it as a priority (P=0.003). Urolithiasis was an educational priority for 40% of the specialists and 26.8% of the general population (P=0.0001). 37.3% of urologist participants and 29.8% of the general population mentioned prostate cancer as a priority (P=0.025). 37.3% of urologists also prioritized infertility while 17.8% of the general population considered infertility an educational priority (P=0.0001). BPH was taken into account as an educational priority by 34.5% of urology specialists and 23.0% of the general population (P=0.0001). Chronic prostatitis was considered an educational priority among 30.5% of urologists and 11.3% of the general population (P=0.0001).

4. Discussion

Among 150 cases, there were 96 patients (64%) with stable IHD, 37 subjects (24.6%) with unstable angina/non-STEMI (segment elevation myocardial infarction), and 17 cases (11.4%) with PRIMARY PCI (PPCI). The compliance rate was 87.3%. As demonstrated in Figure 2, there were no major bleeding cases. But one case with minor bleeding as GI Bleeding, three minimal cases (totally 4 bleeding cases), 3 cases with epistaxis, 7 patients with ecchymosis, 6 subjects with hematuria, and no one required discontinuation of drug. In second week, there was one minor GIB leading to 4 units of hemoglobin reduction that underwent endoscopy and received one unit of pack-cell with diagnosis of gastric ulcer. Also, the aspirin and (Non-Oral vitamin K antagonist) NOAC were discontinued for one week and also Clopidogrel was discontinued two days and then these were continued again and after one week aspirin and Apixaban were restarted. Among three minimal cases after endocolonoscopy there were two cases with hemorrhoid and one with erosion. In hemorrhoid cases the drugs was discontinued for one day and in erosion case the Clopidogrel was continued but aspirin and Rivaroxaban were discontinued for three days and then Rivaroxaban was replaced with Apixaban. The epistaxis, hematuria, and ecchymosis were controlled spontaneously, and drug was continued.

As shown in Table 1, the age, and HASBLED Scores were significantly differed between those with and without tolerance (P=0.001). But CHADS-VASC Scores were not differed by

Table 1: Age, HASBLED, and CHADS-VASC Scores and compliance.

Variable	With compliance	Without compliance	P Value
Age	57.1 ± 12.1	72.3 ± 9.3	0.001
HASBLED	1.4 ± 0.5	2.7 ± 1.3	0.001
CHADS-VASC	2.7 ± 1.4	2.8 ± 1.4	0.280

Table 2: Categorical variables by compliance.

Variable	With compliance	Without compliance	P Value
Male/female	107/24	11/8	0.032
Diabetes mellitus	31 (75.6%)	100 (91.7%)	0.008
Family history	38 (92.7%)	93 (85.3%)	> 0.05
Smoking	64 (92.8%)	67 (82.7%)	> 0.05

compliance (P=0.280). Compliance was assessed by phone call and was defined as complete use of three drugs during whole times.

As shown in Table 2, the female gender and diabetes mellitus were related to lack of compliance. But the family history and smoking were not related to the compliance (P > 0.05). As shown in Figure 3, the severity of involvement in angiography was not related to compliance (P > 0.05).

5. Discussion

Anti-coagulant prophylaxis is an important point in the AF patients and selection of the best drug with appropriate INR and lower adverse effect is the main goal. Totally 87 percent of subjects tolerated the triple therapy and completed the course. We had no major bleeding but there were some cases with minimal or minor bleedings. Some cases had hematuria, epistaxis, and ecchymosis without drug discontinuation. Higher HASBLED and age, and female sex and presence of diabetes mellitus history were related to lack of compliance. Older age and also diabetes mellitus are expected ones due to poly-pharmacy. Also, the female cases are more probable to discontinue the drugs because of fear of side effects. The association with higher HASBLED score can shows some clinical relevance for preventive programming.

Fang et al (16) assessed 13,559 cases under warfarin therapy and it was found that intra-cranial hemorrhage was main bleeding adverse effect in survived users. This matter shows the importance of alternative medications for warfarin as well as Rivaroxaban. Fox et al (17) reported lower cranial and gastrointestinal bleeding for Rivaroxaban versus warfarin. The rate of GI bleeding in their study was 3.2 percent for Rivaroxaban. In our study only there was one case with minor GI bleeding. Patel et al (18) assessed 7131 AF cases and it was found that Rivaroxaban had better emboli prevention effect versus warfarin. However, in the study only adverse effects were assessed and the efficacies were not evaluated.

Habert et al (19) reported higher rate of GI bleeding in Rivaroxaban versus warfarin cases but the fatal and cranial hemorrhage had lower in Rivaroxaban group. But in our study only there was one case with GI bleeding. Lip et al (5) reported same rate of GI bleeding in warfarin users and those that received Rivaroxaban. But in our study only one GI bleeding case was present and sub-analysis was impossible. Yao et al (20) reported the rate of GI bleeding in Rivaroxaban cases was 0.21 that was higher warfarin users. But in our GI safety was not common in Rivaroxaban user cases.

Vimalesvaran et al (21) reported in their review study that there is low risk of bleeding and mortality in Rivaroxaban users that is in congruence with our study. Mendoza-Sanchez and colleagues (22) reported better efficacy and lower adverse effects by Apixaban. Also, conversely they reported higher safety for warfarin versus Rivaroxaban. The cause of this difference may be type of used scorings by them. Coleman et al (23) assessed 5517 diabetic cases and found that warfarin and Rivaroxaban users had same side effect rates including major bleeding cases. But we observed only minor bleeding cases. Martinez et al (24) similarly reported good safety and low rate and severity of GI bleeding cases by Rivaroxaban as same as our study.

6. Conclusion

According to the obtained results, it may be concluded that the incidence of bleeding in atrial fibrillation plus coronary concurrent patients who are the candidate for triple therapy with ASA, Clopidogrel, and Rivaroxaban, is minimal. Furthermore, the compliance is good, and the majority of cases make routine use of these triple therapy regimens. Small sample size and high costs were among the main limitations in this study. Further studies with larger sample population and longer follow-up can develop more evidence on drug safety in AF cases using Rivaroxaban.

7. Appendix

7.1. Acknowledgements

None.

7.2. Author contribution

All the authors have the same contribution.

7.3. Funding/Support

None.

7.4. Conflict of interest

No conflict of interest.

References

1. Marini C, De Santis F, Sacco S, Russo T, Olivieri L, Totaro R, et al. Contribution of atrial fibrillation to incidence and outcome of ischemic stroke: results from a population-based study. Stroke. 2005;36(6):1115-9.
2. Savelieva I, Bajpai A, John Camm A. Stroke in atrial fibrillation: update on pathophysiology, new antithrombotic therapies, and evolution of procedures and devices. Annals of medicine. 2007;39(5):371-91.
3. Chobanian AV, Hill M. National Heart, Lung, and Blood Institute Workshop on Sodium and Blood Pressure: a critical review of current scientific evidence. Hypertension. 2000;35(4):858-63.
4. Rahman F, Kwan GF, Benjamin EJ. Global epidemiology of atrial fibrillation. Nature Reviews Cardiology. 2014;11(11):639.
5. Lip GY, Pan X, Kamble S, Kawabata H, Mardekian J, Masseria C, et al. Major bleeding risk among non-valvular atrial fibrillation patients initiated on apixaban, dabigatran, rivaroxaban or warfarin: a "real-world" observational study in the United States. International journal of clinical practice. 2016;70(9):752-63.
6. De Caterina R, Husted S, Wallentin L, Andreotti F, Arnesen H, Bachmann F, et al. Vitamin K antagonists in heart disease: current status and perspectives (Section III). Thromb Haemost. 2013;110(6):1087-107.
7. Zirlik A, Bode C. Vitamin K antagonists: relative strengths and weaknesses vs. direct oral anticoagulants for stroke prevention in patients with atrial fibrillation. Journal of thrombosis and thrombolysis. 2017;43(3):365-79.
8. Ogilvie IM, Newton N, Welner SA, Cowell W, Lip GY. Underuse of oral anticoagulants in atrial fibrillation: a systematic review. The American journal of medicine. 2010;123(7):638-45. e4.
9. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. The Lancet. 2014;383(9921):955-62.
10. Hylek EM, Ko D, Cove CL. Gaps in translation from trials to practice: non-vitamin K antagonist oral anticoagulants (NOACs) for stroke prevention in atrial fibrillation. Thrombosis and haemostasis. 2014;112(05):783-8.
11. Cheung K-S, Leung WK. Gastrointestinal bleeding in patients on novel oral anticoagulants: Risk, prevention and management. World journal of gastroenterology. 2017;23(11):1954.
12. Alirhayim Z. Restarting anticoagulation and outcomes after major gastrointestinal bleeding in atrial fibrillation: author reply. The American Journal of Cardiology. 2014;114(2):327.
13. Qureshi W, Mittal C, Patsias I, Garikapati K, Kuchipudi A, Cheema G, et al. Restarting anticoagulation and outcomes after major gastrointestinal bleeding in atrial fibrillation. The American Journal of Cardiology. 2014;113(4):662-8.
14. Wu H, Jing Q, Wang J, Guo X. Pantoprazole for the prevention of gastrointestinal bleeding in high-risk patients with acute coronary syndromes. Journal of critical care. 2011;26(4):434. e1-. e6.
15. Bikedli B, Sharif-Kashani B. Venous thromboembolism: a Persian Perspective to Prevention, Diagnosis, and Treatment. North American Thrombosis Forum 2010. 2012.
16. Fang MC, Go AS, Chang Y, Hylek EM, Henault LE, Jensvold NG, et al. Death and disability from warfarin-associated intracranial and extracranial hemorrhages. The American journal of medicine. 2007;120(8):700-5.
17. Fox KA, Piccini JP, Wojdyla D, Becker RC, Halperin JL, Nessel CC, et al. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment. European heart journal. 2011;32(19):2387-94.
18. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. New England Journal of Medicine. 2011;365(10):883-91.
19. Habert JS. Minimizing bleeding risk in patients receiving direct oral anticoagulants for stroke prevention. International journal of general medicine. 2016;9:337.
20. Yao X, Abraham NS, Sangaralingham LR, Bellolio MF, McBane RD, Shah ND, et al. Effectiveness and safety of dabigatran, rivaroxaban, and apixaban versus warfarin in nonvalvular atrial fibrillation. Journal of the American Heart Association. 2016;5(6):e003725.
21. Vimalesvaran K, Dockrill SJ, Gorog DA. Role of rivaroxaban in the management of atrial fibrillation: insights from clinical practice. Vascular Health and Risk Management. 2018;14:13.
22. Mendoza-Sanchez J, Silva F, Rangel L, Jaramillo L, Mendoza L, Garzon J, et al. Benefit, risk and cost of new oral anticoagulants and warfarin in atrial fibrillation; A multicriteria decision analysis. PlOS One.

2018;13(5):e0196361.
23. Coleman C, Bunz T, Eriksson D, Meinecke AK, Sood N. Effectiveness and safety of rivaroxaban vs warfarin in people with non-valvular atrial fibrillation and diabetes: an administrative claims database analysis. Diabetic Medicine. 2018;35(8):1105-10.
24. Martinez BK, Sood NA, Bunz TJ, Coleman CI. Effectiveness and safety of apixaban, dabigatran, and rivaroxaban versus warfarin in frail patients with nonvalvular atrial fibrillation. Journal of the American Heart Association. 2018;7(8):e008643.

Non-CABG Related Bleeding:

1. Major

- Any intracranial bleeding (excluding microhemorrhages <10 mm evident only on gradient-echo MRI)
- Clinically overt signs of hemorrhage associated with a drop in hemoglobin of ≥5 g/dL or a ≥15% absolute decrease in haematocrit
- Fatal bleeding (bleeding that directly results in death within 7 d)

2. Minor

- Clinically overt (including imaging), resulting in hemoglobin drop of 3 to <5 g/dL or ≥10% decrease in haematocrit
- No observed blood loss: ≥4 g/dL decrease in the haemoglobin concentration or ≥12% decrease in haematocrit
- Any overt sign of hemorrhage that meets one of the following criteria and does not meet criteria for a major or minor bleeding event, as defined above
  - Requiring intervention (medical practitioner-guided medical or surgical treatment to stop or treat bleeding, including temporarily or permanently discontinuing or changing the dose of a medication or study drug)
  - Leading to or prolonging hospitalization
  - Prompting evaluation (leading to an unscheduled visit to a healthcare professional and diagnostic testing, either laboratory or imaging)

3. Minimal

- Any overt bleeding event that does not meet the criteria above
- Any clinically overt sign of haemorrhage (including imaging) associated with a <3 g/dL decrease in haemoglobin concentration or <9% decrease in haematocrit

Bleeding in the Setting of CABG:

- Fatal bleeding (bleeding that directly results in death)
- Perioperative intracranial bleeding
- Reoperation after closure of the sternotomy incision for the purpose of controlling bleeding
- Transfusion of ≥5 U PRBCs or whole blood within a 48-h period; cell saver transfusion will not be counted in calculations of blood products.
- Chest tube output >2 L within a 24-h period

Figure 1: Diagram of TIMI Bleeding Criteria for bleeding measurement.

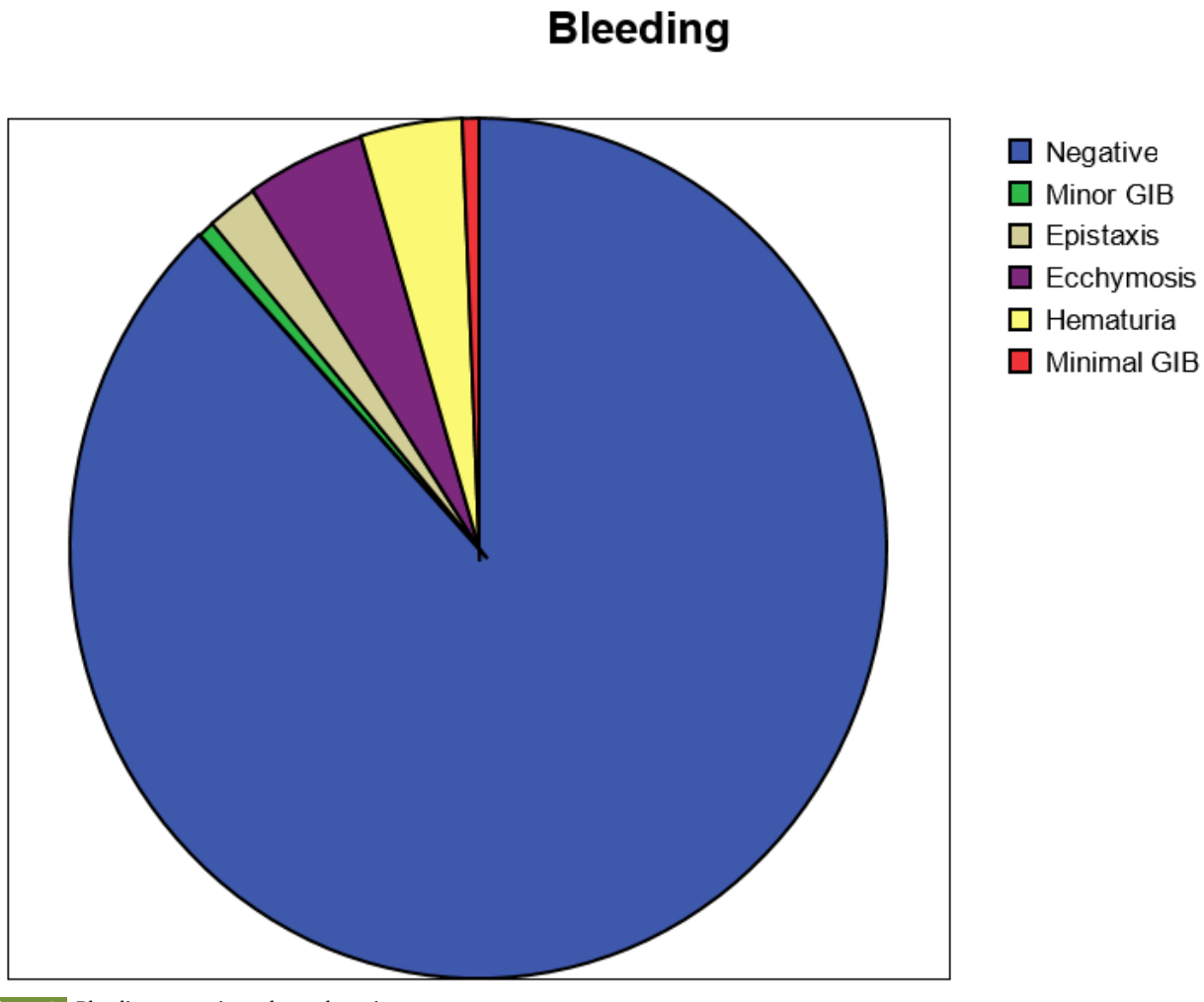

Figure 2: Bleeding events in understudy patients.

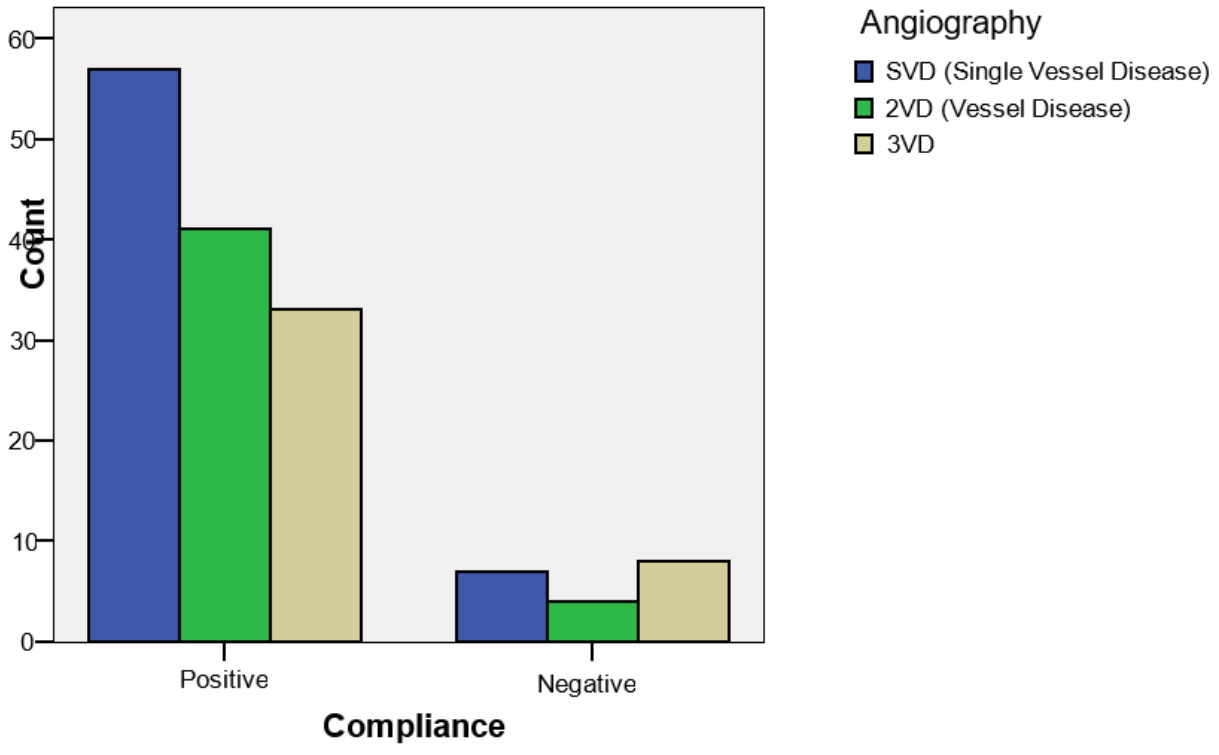

Figure 3: Angiography severity by compliance.