



## Do practice gaps exist in evidence-based medication prescription at hospital discharge in patients undergoing coronary artery bypass surgery & coronary angioplasty?

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**Background & objectives:** Prescription patterns of guideline-directed medical therapy (GDMT) after coronary artery bypass surgery [coronary artery bypass graft (CABG)] and percutaneous coronary intervention (PCI) at hospital discharge are often not optimal. In view of scarce data from the developing world, a retrospective analysis of medication advice to patients following CABG and PCI was conducted.

**Methods:** Records of 5948 patients (post-PCI: 5152, post-CABG: 796) who underwent revascularization from 2010 to 2014 at a single tertiary care centre in north India were analyzed.

**Results:** While age and gender distributions were similar, diabetes and stable angina were more frequent in CABG group. Prescription rates for aspirin 100 per cent versus 98.2 per cent were similar, while beta-blockers (BBs, 95.2 vs 90%), statins (98.2 vs 91.6%), angiotensin-converting enzyme inhibitors (89.4 vs 41.4%), nitrates (51.2 vs 1.1%) and calcium channel blockers (6.6 vs 1.6%) were more frequently prescribed following PCI. Despite similar baseline left ventricular ejection fraction (48.1 vs 51.1%), diuretics were prescribed almost universally post-CABG (98.2 vs 10.9%,  $P<0.001$ ). Nearly all (94.4%) post-CABG patients received a prescription for clopidogrel. Patients undergoing PCI were much more likely to receive higher statin dose; 40-80 mg atorvastatin (72 vs <1%,  $P<0.001$ ) and a higher dose of BB.

**Interpretation & conclusions:** Significant differences in prescription of GDMT between PCI and CABG patients existed at hospital discharge. A substantial proportion of post-CABG patients did not receive BB and/or statins. These patients were also less likely to receive high-dose statin or optimal BB dose and more likely to routinely receive clopidogrel and diuretics. Such deviations from GDMT need to be rectified to improve quality of cardiac care after coronary revascularization.

**Key words** Coronary artery bypass graft - guideline-directed medical therapy - hospital discharge - percutaneous coronary intervention - prescription

Guideline-directed medical therapy (GDMT) should be routinely recommended after coronary

artery bypass graft (CABG) as well as percutaneous coronary intervention (PCI) because despite successful

coronary revascularization, the underlying process of coronary atherosclerosis remains unaffected. According to the 2011 American Heart Association (AHA)/American College of Cardiology Foundation (ACCF) guidelines for secondary prevention and risk reduction therapy for patients with coronary disease and the 2011 ACC/ACCF guidelines for those undergoing CABG/PCI, recommended drugs include optimal doses of antiplatelet drugs, beta-blockers (BBs), angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin II receptor blockers (ARBs) and lipid-lowering drugs<sup>1-3</sup>. Various updated guidelines including the 2014 European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Guidelines on myocardial revascularization<sup>4</sup>, the 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction<sup>5</sup> and the ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation<sup>6</sup> have also summarized that whenever indicated, optimal doses of these drugs are essential in patients with stable or unstable coronary artery disease (CAD). Although the use of medications in patients following PCI is largely evidence based, use of these drugs following successful CABG often deviates from GDMT and represents an important area of unmet need. In a review of randomized controlled trials assessing medical therapy in post-CABG patients, Okrainec *et al*<sup>7</sup> concluded that while use of aspirin and anti-lipid agents was beneficial, current data did not support the use of BBs, calcium channel blockers (CCBs) and nitrates and more studies were needed to assess the routine use of ACEI after CABG. In a large population-based series of 2500 post-CABG survivors, Bradshaw *et al*<sup>8</sup> reported that deficiencies existed in the use of recommended medications after CABG. Belcher *et al*<sup>9</sup> studied pharmacological secondary prevention strategies at one year following CABG and observed that apart from statins, secondary prevention measures were poorly applied in these patients. Under-usage of drugs recommended for secondary prevention may result from non-compliance, lack of patient education regarding drug-related benefits or belief that drugs may not be required once a coronary obstruction has been treated mechanically. Another important and often unrecognized reason for under-usage of secondary prevention strategies in this subset of patients is the lack of prescription of GDMT at hospital discharge. Despite evidence supporting the use of aspirin, BB, ACEI and lipid-lowering therapies in appropriate patients, adoption of these secondary prevention measures

after CABG has been inconsistent and lagged behind PCI. In the absence of specific contraindications, aspirin, BB, lipid-lowering drugs and ACEI should be prescribed to all patients following CABG. In a clinical review assessing under-prescribing and non-adherence to medication guidelines in post-CABG patients, Sengstock *et al*<sup>10</sup> summarized that healthcare providers should ensure that all patients are prescribed appropriate medications at discharge and patients should be motivated to continue long-term use of these medications. Williams *et al*<sup>11</sup> reported more effective implementation of such measures by a continuous quality improvement programme focussed to improve the prescription of these secondary prevention drugs at discharge in post-CABG patients.

Such deficiencies in implementing evidence-based medication prescription with resultant lack of GDMT at hospital discharge represent an important correctable component of the adequacy of quality healthcare. Despite published guidelines recommending various secondary prevention strategies following PCI and CABG, only a few studies have directly compared the rate of medication use following both<sup>12,13</sup>. Hiratzka *et al*<sup>12</sup> analyzed compliance with hospital discharge prescriptions of aspirin, BB, ACEI and lipid-lowering drugs and reported significantly lower prescription rates of all drugs as compared to PCI. The study further emphasized the importance of timely institution of effective secondary prevention measures at discharge following revascularization in patients with CAD. In a comparative study assessing the use of secondary preventive medicines in post-CABG and post-PCI patients, Hlatky *et al*<sup>13</sup> reported lower prescription rates at discharge and lower adherence rates assessed by medication possession ratio at one year in those undergoing CABG.

Such data assume greater relevance in the Indian population which is often prone to develop CAD at a younger age as compared to Western counterparts with the extent of disease being more progressive and relentless<sup>14,15</sup>. Therefore, this retrospective analysis was carried out to assess if prescription of GDMT at hospital discharge was any different between patients following CABG and PCI over a duration of four years and whether the prescription pattern demonstrated any change over the years.

### Material & Methods

This study was conducted in the department of Cardiology, Sanjay Gandhi Postgraduate Institute of

Medical Sciences, Lucknow, India. The prescription patterns of patients with CAD following CABG and PCI at discharge were assessed against the recommendations from the latest available guidelines for patients undergoing myocardial revascularization: 2014 ESC/EACTS Guidelines on myocardial revascularization<sup>4</sup>, 2011 ACCF/AHA/Society of Cardiovascular Angiography and Interventions guidelines for percutaneous coronary interventions<sup>3</sup> and 2011 ACCF/AHA guideline for CABG surgery<sup>2</sup>.

The study was approved by the institutional ethics committee. Case record files and discharge records of consecutive patients with CAD who underwent revascularization either in the form of CABG or PCI in the preceding 44 months (from 2010 to 2014) were analyzed. Capture data included demographic characteristics, comorbidities and types of medication (with dosages) prescribed at discharge. Medications of interest included aspirin, clopidogrel, BB, ACEIs, ARBs, statins, diuretics and any others. Patients who did not undergo revascularization or died during the hospital stay (therefore, precluding analysis of drug prescription at discharge) were excluded.

**Statistical analysis:** The data were analyzed using SPSS 16 statistical software (SPSS Inc., Chicago, Illinois, USA). All continuous variables were expressed as mean±standard deviation and categorical variables as number (percentage). The proportions of categorical variables were compared using Pearson Chi-square test for statistical significance under cross-tabulation analysis tool. Student's *t* test was used to compare means between groups. The calculated power of the study for the given sample size (group 1, n=5152 and group 2, n=796) was 99.8 per cent for  $\alpha=0.05$  (PASS 11 software, NCSS, USA).

## Results

Records of 5948 patients (mean age 59.9±9.2 yr, range 27-82) comprising 4827 males (81.2%) and 1121 females (18.1%) were analyzed. Of these, 5152 (86.5%) had undergone PCI while 796 (13.5%) had undergone CABG. The year-wise distribution of patients undergoing PCI/CABG is depicted in Table I.

The demographics of the patient cohort are depicted in Table II. There was no significant difference in the two groups in terms of age or gender distribution. Patients undergoing CABG more frequently had diabetes and more commonly presented with stable angina unlike in the PCI group where acute coronary

**Table I.** Year-wise distribution of patients undergone percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG)

Year	PCI, n (%)	CABG, n (%)
2010	1357 (92.1)	117 (7.9)
2011	914 (81.6)	205 (18.4)
2012	963 (85.9)	158 (14.1)
2013	1200 (83.1)	244 (16.9)
2014	718 (90.8)	72 (9.2)
Total	5152 (86.5)	796 (13.5)

**Table II.** Demographic and clinical characteristics of patients undergone percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG)

Parameter	PCI group (n=5152)	CABG group (n=796)
Age (yr)	57.8±9.5	60±8.2
Males	4266 (82.8)	640 (80.5)
Diabetes mellitus	1607 (31.2)	299 (37.6)
Hypertension	222 (43.1)	359 (45.1)
Smoking/tobacco use	1412 (27.4)	248 (31.2)
Chronic stable angina	2504 (48.6)***	519 (65.2)
Acute coronary syndrome	2648 (51.4)***	277 (34.8)
Left ventricular ejection fraction (%)	48.1±8.7	51.1±7.6
Total cholesterol (mg/dl)	132±10.6	136±12.8
LDL cholesterol (mg/dl)	82±14.4	79±15.8
HDL cholesterol (mg/dl)	32±8.2	39±10.4
Creatinine (>1.5 mg/dl)	453 (8.8)***	26 (3.3)

\*\*\* $P<0.001$  compared to CABG group. Data are presented as mean±SD or as n (%). LDL, low-density lipoprotein; HDL, high-density lipoprotein; SD, standard deviation

syndrome (ACS) was more often the presenting feature. Prevalence of hypertension, tobacco use, mean left ventricular ejection fraction (LVEF) and lipid profiles were comparable between the two groups (Table II). The proportion of patients with serum creatinine >1.5 mg/dl was significantly ( $P<0.001$ ) more frequent in the PCI group.

**Medication prescription at discharge:** Medications prescribed at discharge in patients undergoing PCI and CABG are presented in Table III. Newer antiplatelet agents, prasugrel and ticagrelor, were prescribed only in the post-PCI group (overall usage 11.2%). Overall, ramipril was the most common ACEI prescribed, while amongst ARBs, the most frequently used were losartan

**Table III.** Prescription rates of medications at discharge

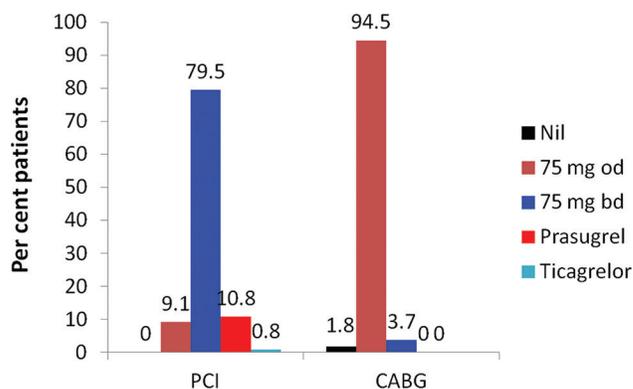
Medication	PCI group (n=5152)	CABG group (n=796)
Aspirin	5152 (100)	782 (98.2)
Thienopyridines	5152 (100)**	752 (94.4)
Beta-blockers	4905 (95.2)**	716 (90.0)
Statin	5059 (98.2)**	729 (91.6)
Atorvastatin	4256 (82.6)	742 (93.2)
Rosuvastatin	896 (17.4)	54 (6.8)
ACEI	4606 (89.4)**	330 (41.4)
Nitrates	2638 (51.2)***	9 (1.1)
CCB	340 (6.6)**	13 (1.6)
Diuretics	562 (10.9)***	782 (98.2)
ARB	134 (2.6)	14 (1.7)

*P* \*\*<0.01, \*\*\*<0.001 compared to CABG group. Data are presented as n (%). PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; ACEI, angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker; ARB, angiotensin receptor blocker; NS, not significant

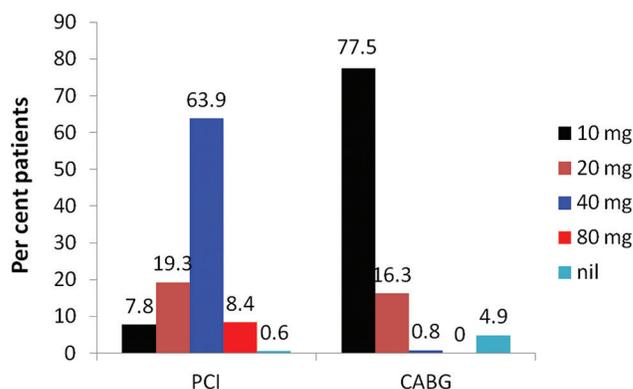
followed by telmisartan and olmesartan. Diuretics were almost universally prescribed at discharge following CABG, irrespective of baseline LVEF.

**Drug doses:** Aspirin 150 mg was the most frequent dose prescribed both in the CABG and PCI groups (91.2 vs 92.2%). Aspirin 300 mg was only prescribed in the PCI group (4.6 vs 0%, *P*<0.01) while a dose of 75 mg aspirin was used in 3.2 per cent of PCI versus 6.8 per cent of CABG. Clopidogrel (75 mg bd) was the most commonly used dose post-PCI (79.5%) while it was prescribed in only 3.7 per cent of those who underwent CABG (*P*<0.001). A dose of 75 mg od was more frequently prescribed in the CABG group (94.5 vs 9.1%, *P*<0.001) in the PCI group (Fig. 1). Further 98.2 per cent of post-CABG patients received a prescription for clopidogrel (either 75 mg od or 75 mg bd) in addition to aspirin.

Prescription of BB (50 mg dose) was more common post-PCI (79.2 vs 46.1%, *P*<0.001) while 25 mg was more frequently prescribed post-CABG (45.3 vs 14.1%, *P*<0.01). Metoprolol was the most commonly prescribed BB (98.3% in post-PCI group and 94.2% in post-CABG group), while atenolol was prescribed in 1.24 per cent amongst post-PCI patients and in 5.8 per cent in post-CABG patients. Carvedilol and nebivolol were prescribed only in post-PCI patients (0.3 and 0.2%, respectively).



**Fig. 1.** Percentage of patients prescribed various antiplatelet drugs at discharge after percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG). Od, once a day; bd, twice a day of Clopidogrel.



**Fig. 2.** Distribution of atorvastatin doses prescribed at discharge after percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG).

Patients undergoing PCI were much more likely to receive higher statin dose; 40 mg atorvastatin (63.9 vs 0.8%, *P*<0.001) and 80 mg atorvastatin (8.4 vs 0%) in PCI and CABG group, respectively. A dose of 10 mg atorvastatin was used more commonly after CABG (7.8 vs 77.5% for PCI and CABG, respectively, *P*<0.001), while 20 mg was used equally frequently in both PCI and CABG (19.3 vs 16.3%, respectively) (Fig. 2). Nearly five per cent in the CABG group and 0.4 per cent in the PCI group failed to receive a prescription of statin at discharge. Amongst post-PCI patients, the most frequently used dose of ACEI at discharge was 5 mg (69.4%), followed by 2.5 mg (29.1%), while 10 mg was prescribed in 2.4 per cent patients. In contrast, in the CABG group, the most frequently prescribed dose was 2.5 mg (72.2%) followed by 5 mg (20.6%) and 10 mg (7.1%).

*Temporal trends of drug use in the percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) groups:* All patients in the PCI

**Table IV.** Year-wise trends in medications prescribed at discharge

Medication	PCI group (n=5152)					CABG group (n=796)				
	2010	2011	2012	2013	2014	2010	2011	2012	2013	2014
Aspirin	100	100	100	100	100	94.5	97.8	100	100	100
Clopidogrel	100	100	100	100	100	98.2	99.0	97.8	96.9	91.2
Beta-blockers	97.1	98.6	97.5	98.6	92.1	91.8	98.4	94.4	96.9	89.2
Statin	99.6	100	98.7	97.6	98.2	80.0	98.4	99.3	94.4	86.2
Atorvastatin	96.8	94	77.7	63.1	64.3	98.7	94.2	92.4	96.9	98.2
Rosuvastatin	3.2	6.0	22.3	36.9	35.7	1.3	5.8	7.6	3.1	1.8
ACEI	94.9	98.4	99.0	98.9	94.5	29.1	59.7	74.3	25.0	29.2
ARB	4.1	4.2	6.5	4.6	2.4	0.9	2.6	2.8	3.1	1.9
Nitrates	87.8	53.8	49.2	67.7	53.2	0.8	1.0	2.1	3.1	2.2
Diuretics	11.1	15.5	8.3	8.1	9.2	100	99.0	97.9	96.9	94.6
CCB	4.6	6.4	4.2	3.8	5.1	2.1	1.8	1.6	2.4	1.9

Data are presented as percentages within groups. PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker

group received a prescription for dual-antiplatelet therapy at discharge. Amongst those undergoing CABG, only in the last three years, did all patients receive a prescription for aspirin. Clopidogrel was prescribed in >90 per cent of patients in the CABG group throughout the study period. Prescription for BB remained high (at or above 90%) in both groups. Prescription rates for statins remained >95 per cent for both the groups over the duration of analysis. In the first year of the analysis, nearly 20 per cent patients were not prescribed a statin at discharge following CABG. The use of rosuvastatin increased gradually in the PCI group from 2012 onwards, while in the CABG group, it remained low. While the prescription of ACEI was consistently >95 per cent in the PCI group, it remained sub-optimal amongst those undergoing CABG over the entire duration of the study. Prescription for diuretics was low in the PCI group and remained >90 per cent in those undergoing CABG throughout (Table IV).

### Discussion

In this retrospective analysis of patients following CABG and PCI, the two groups were comparable in terms of age, gender, prevalence of hypertension, tobacco use, mean left ventricular (LV) systolic function and lipid profiles, while diabetes was more frequent in those who underwent CABG. All patients discharged following PCI received dual-antiplatelet therapy in compliance with the current guidelines recommendations<sup>3,4</sup>. Although aspirin was prescribed in nearly all patients post-CABG, a high proportion

of these patients also received a prescription for a thienopyridine. However, as per the ACCF/AHA guidelines for patients undergoing CABG, only aspirin has a Class I recommendation at discharge and clopidogrel is a reasonable alternative only in patients who are allergic to or are intolerant to aspirin (Class IIa)<sup>2</sup>. Therefore, prescription of dual-antiplatelet therapy following CABG as observed in our study does not represent a Class I indication as per the guidelines. However, it is to be noted that since a third of the patients undergoing CABG had a history of ACS, they would have any way merited a prescription for dual-antiplatelet therapy.

More patients received a prescription for BB following PCI as compared to CABG. A small proportion of patients were not prescribed BB due to contraindications. The next most frequent reason for non-prescription was related to non-adherence to GDMT despite no apparent contraindication. It was also observed that the PCI group was more often prescribed a higher dose of BB. Although a few studies reported that the efficacy of BB use in CABG patients after hospital discharge was uncertain<sup>16-18</sup>, other observational analyses confirmed the effectiveness of BB, especially in high-risk subgroups (those with perioperative myocardial ischaemia or elderly subjects with heart failure)<sup>19</sup>. Prescription analysis of 3102 patients subsequently reported that those receiving BB at discharge had an improved survival, irrespective of perioperative myocardial ischaemia or heart failure<sup>20</sup>.

In our study, while most patients (post-PCI) received a prescription for an ACEI, less than half of those who underwent CABG were prescribed ACEI at discharge. Guidelines recommend using ACEI as a Class I indication for patients with CAD and ejection fraction (EF) <40 per cent and other risk factors, including heart failure, diabetes and hypertension with chronic kidney disease, and as a Class IIa indication in all patients, irrespective of risk factors (in the absence of contraindications)<sup>5,6,21,22</sup>. The current CABG guidelines also suggest that it is reasonable to initiate ACEI (or ARBs) postoperatively and to continue indefinitely in all CABG patients who were not receiving them preoperatively and are considered to be at low risk<sup>3</sup>. Thus, despite contemporary guidelines recommending routine ACEI use (unless contraindicated), these were under-used in patients being discharged following CABG.

Prescription of statins was also significantly less amongst patients discharged following CABG in our study. Although atorvastatin was the most frequently prescribed statin in both groups, rosuvastatin was prescribed three times more common in those who underwent PCI. The current guidelines recommend that patients with CAD receive high-intensity statin therapy<sup>5,6,21,22</sup>. In our study, this happened more frequently in patients undergoing PCI than in patients undergoing CABG who tended to receive low-dose statin. The current ACC/AHA guidelines for patients undergoing CABG also do not stipulate the dose of statin to be used and only state that all patients undergoing CABG should receive statin therapy unless contraindicated<sup>2</sup>. An adequate dose should be used to reduce low-density lipoprotein (LDL) cholesterol to <100 mg/dl and to achieve at least a 30 per cent lowering of LDL cholesterol<sup>2</sup>. However, CABG patients who presented with recent ACS should have received high-intensity statin according to the current ACC/AHA recommendations. Therefore, despite existent data supporting the use of high-dose statins in patients with CAD (both in the ACS group and in stable CAD), in our study some patients were often not prescribed statins at all.

Routine use of nitrates following PCI is not recommended by the ACC/AHA guidelines, and the use of nitrates in nearly half of the PCI patients in our study was not in conformity with this. Despite comparable mean EF, post-CABG patients were almost without exception prescribed diuretics, which was not in conformity with the currently accepted practice of

using them only temporarily to relieve congestion secondary to pump-related issues.

Despite evidence supporting the use of aspirin, BB, ACEI and lipid-lowering therapies in appropriate patients, adoption of these secondary prevention measures after CABG has been inconsistent<sup>7-9,23</sup>. In an analysis of 200 patients, Fox *et al*<sup>24</sup> reported sub-optimal use of secondary prevention prescription after CABG as compared to PCI. While 100 per cent of PCI patients and 92 per cent CABG patients were prescribed aspirin at discharge, prescription rate for BB was 82 per cent versus 70 per cent ( $P<0.001$ ), for statin (any dose) 96 per cent versus 73 per cent and for ACEI 65 per cent versus 26 per cent ( $P<0.001$ ). The study concluded that both interventional cardiologists and (especially) cardiac surgeons must improve their prescription rates of use of secondary prevention therapy at hospital discharge<sup>24</sup>. The AHA Get With the Guidelines-Coronary Artery Disease (GWTG-CAD) Programme is an AHA initiative which uses a web-based patient management tool to improve hospital discharge prescription of secondary preventive measures in patients with CAD<sup>12</sup>. Hiratzka *et al*<sup>12</sup> used the GWTG-CAD database to determine whether compliance with individual and composite secondary prevention performance measures for CABG patients were different from for non-surgical patients including PCI. Hlatky *et al*<sup>13</sup> analyzed a cohort of the Kaiser Permanente Northern California integrated healthcare delivery system and reported that patients post-CABG were more likely not to be prescribed a statin and an ACEI/ARB as compared to those post-PCI. However, the lack of prescription for BB was similar in both groups. In contrast to our study where most patients received a prescription for clopidogrel following CABG, Hlatky *et al*<sup>13</sup> reported that most CABG patients (88.5%) did not receive a prescription for clopidogrel.

The use of clopidogrel in a high proportion of CABG patients is a significant deviation from recommended guidelines. The increase in the proportion of CABG patients receiving statins in the later part of the study was a positive development. In the analysis by Hlatky *et al*<sup>13</sup>, the percentage of patients who never filled a prescription for an ACEI/ARB, BB, or statin declined progressively and the gap between CABG and PCI narrowed over time for statins and BB but persisted for ACEI/ARBs. In our study also, ACEI continued to be grossly under-prescribed in those discharged following CABG.

An important limitation of our analysis was that prescription at discharge from hospital could not be considered to be the operative prescription through the entire period of the follow up. Often, at follow up, prescriptions were revised by the treating physicians/surgeons leading to addition of drugs which might not have been prescribed at discharge. Although advice regarding smoking cessation, diet and physical exercise was routinely given to all patients, separate data regarding the prescription rates for non-pharmacological advice were not analyzed.

In conclusion, significant differences in prescription of GDMT existed at hospital discharge after PCI or CABG in this tertiary care centre in north India. Although post-PCI patients usually received optimal medical therapy at discharge, those undergoing CABG were often less likely to do so. These results indicate the need to improve the quality of medical therapy in patients discharged from hospital after coronary revascularization.

**Conflicts of Interest:** None.

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