Renal insufficiency, bleeding and prescription of discharge medication in patients undergoing percutaneous coronary intervention in the National Heart, Lung, and Blood Institute (NHLBI) Dynamic Registry ☆

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ABSTRACT

Aims: To establish the relationship between renal insufficiency, bleeding and prescription of cardiovascular medication.

Methods and results: This was a prospective, multi-center, cohort study of consecutive patients undergoing PCI during three NHLBI Dynamic Registry recruitment waves. Major and minor bleeding, access site bleeding and rates of prescription of cardiovascular medication at discharge were determined based on estimated glomerular filtration rate (eGFR).

Renal insufficiency was an independent predictor of major adverse cardiovascular events (MACE). Bleeding events and access site bleeding requiring transfusion were significantly associated with degrees of renal insufficiency (p < 0.001). There was an incremental decline in prescription of cardiovascular medication at discharge proportionate to the degree of renal impairment (aspirin, thienopyridine, statin, coumadin (overall p < 0.001), beta blocker (overall p = 0.003), ACE inhibitor (overall p = 0.02). Bleeders were less likely to be discharged on a thienopyridine (95.4% versus 89.9% for bleeding, p < 0.001 and 95.3% versus 87.9% for access site bleeding, p = 0.005), but not aspirin (96.3% versus 96.2%, p = 0.97 and 96.3% versus 93.6%, p = 0.29 respectively). Failure to prescribe anti-platelet therapy at discharge was strongly associated with increased MACE at one year.

Conclusions: Renal insufficiency is associated with bleeding in patients undergoing PCI. Patients with renal insufficiency are less likely to receive recommended discharge pharmacotherapy.

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1. Introduction

Nineteen million patients in the U.S suffer from CKD (GFR <90 ml/min) and cardiovascular disease is the major cause of mortality in this population [1,2]. As the general population ages the burden of patients who present with co-existent cardiovascular disease and CKD will grow [2]. It is estimated that each 10 ml/min decline in creatinine clearance has an impact on death rates that is comparable to a ten-year increase in age [3]. Furthermore, renal insufficiency predicts adverse cardiovascular events in an incremental fashion after PCI [4,5]. Factors that contribute to worse outcome may include the nephrotoxicity of contrast dye, presence of more severe CAD, concomitant PAD, microvascular disease, intrinsic platelet dysfunction, higher periprocedural complication rates and higher risk of bleeding [5,6].

Patients who undergo PCI and suffer bleeding complications are less likely to be discharged on dual anti-platelet therapy. Failure to reintroduce dual anti-platelet therapy following bleeding strongly predicts future cardiovascular events [5–7]. As a result, patients with CKD are less likely to be revascularized and to receive appropriate antiplatelet therapy as renal function declines [8].

Many cardiovascular medications carry precautions with regard to use in patients with renal impairment and thus dose adjustment is required. Furthermore, patients with renal impairment are frequently

prescribed multiple medications. In this study we aimed to demonstrate that patients undergoing PCI with even mild degrees of renal impairment experienced increased bleeding. We also hypothesized that renally impaired patients would be less likely to receive evidence based cardiovascular pharmacotherapy at the time of discharge and not only antiplatelet therapy and that this would influence outcome.

2. Methods

The NHLBI sponsored Dynamic Registry has been previously described and comprises patients who underwent PCI at 27 medical centers in the US, Canada, and Czech Republic [9,10]. The Dynamic Registry enrolled and followed approximately 2000 patients in 'waves.' To date, five 'waves' of patients have been enrolled and followed (wave 1: 1997 to 1998, 2524 patients; wave 2: 1999, 2105 patients; wave 3: 2001 to 2002, 2047 patients; wave 4: 2004, 2112 patients; and wave 5: 2006, 2176 patients). Data on baseline demographic, clinical, angiographic and procedural characteristics during the index PCI, as well as the occurrence of death, MI, and the need for CABG during hospitalization were collected by trained research coordinators and have been previously published [11]. Written informed consent was obtained from participants to be contacted annually after discharge for health status information. Follow-up status, which included vital status, hospitalizations for cardiovascular events and procedures as well as current cardiac medication use, was ascertained at 1 month, 6 months, and 1 year after enrollment. If patients underwent repeat PCI, vessel-specific and lesion-specific data were collected whenever possible to determine target-vessel revascularization. Each clinical center received approval from its institutional review board. The data were compiled and analyzed at the University of Pittsburgh.

2.1. Study sample

For this analysis, only patients from the final three recruitment waves were included because creatinine values were not collected in the first two waves. Each patient's eGFR rate was calculated using the Modification of Diet in Renal Disease (MDRD) equation (using serum creatinine, age, race, and gender). Groups comprised those with normal or minimal renal impairment (eGFR >75 ml/min/1.73 m^2), mild impairment (eGFR 60–74 ml/min/1.73 m^2), moderate impairment (eGFR 45–59 ml/min/1.73 m^2) and severe impairment (<45 ml/min/1.73 m^2). Patients missing information on any of the components that make up eGFR were excluded (n = 267).

2.2. Outcomes

Myocardial infarction was defined as ≥2 of the following: typical chest pain ≥20 min not relieved with nitroglycerin; serial electrocardiograms showing characteristic ST-T changes and/or Q waves in ≥2 contiguous leads; serum enzyme elevation of creatine kinase-MB ≥0.5% of total creatine kinase. Death is defined as all-cause mortality. Repeat PCI was defined as any non-staged repeat PCI in the follow-up period. Lesion specific data, peri-procedural anticoagulation and antiplatelet usage and access site complications have previously been published [11,12]. Repeat revascularization was defined as the combined end point of repeat PCI or CABG during the follow-up period. MACE consisted of death, myocardial infarction, and need for repeat revascularization.

2.3. Definitions

Major or minor bleeding was defined as intracranial hemorrhage, observed blood loss with hemoglobin drop >3 g/dL, and unobserved blood loss with a hemoglobin drop >4 g/dL, requiring greater than 1 unit packed RBC transfusion. Hematoma related transfusion was defined as any patient who required transfusion specifically in response to access site related hematoma as previously defined [11].

2.4. Statistical analysis

Patients were stratified into four groups by their eGFR and descriptive statistics were summarized as means for continuous variables and percentages for categorical variables. Differences between proportions were assessed by chi-square or Fisher's exact test, and continuous variables were compared by the Kruskal–Wallis test. Stepwise logistic regression was used to estimate the independent effect of degrees of renal insufficiency on bleeding and need for transfusion due to access site bleeds. Coefficients were transformed to odds ratios to show comparisons between patients within the highest eGFR category (≥75) against patients who fell into the other three eGFR categories. Using logistic regression at one year, demographic and clinical variables were initially screened for univariate association with bleeding and transfusion outcomes of interest at p < 0.25. The individual variables identified were then assessed in a forward stepwise manner using a p-value criterion of <0.05. In instances when eGFR category variables did not "step" into a model, they were included in the model after entry of all other significant variables. Goodness-of-fit was assessed using the Hosmer–Lemeshow method and all models were considered to be adequate (p > 0.05).

The prevalence of discharge medications (statin, aspirin, thienopyridine, beta blocker, ACE inhibitor, and Coumadin) and both bleeding and transfusion status in patients surviving to hospital discharge were evaluated using chi-square or Fisher's exact test. The incidence of selected one-year outcomes by eGFR categories and discharge medication use were calculated using the Kaplan–Meier approach and compared using the log rank test. Patients who did not experience the outcome of interest were censored at the last known date of contact or at one year if contact extended beyond one year. Trends in bleeding and discharge medications were assessed across GFR groups using the Cochran–Mantel–Haenszel test. All statistical analyses were performed with the use of SAS software, version 9.2, and a two-sided p-value of 0.05 or less was considered to indicate statistical significance.

3. Results

Patients (n = 6050) were stratified based on eGFR into four categories as previously outlined. Of those patients, 661 (10.9%) had severe renal impairment (eGFR <45 ml/min/1.73 m^2). Of this severe renal impairment subgroup, 19.5% were on established renal replacement therapy with hemodialysis.

3.1. Population demographics and in-hospital major adverse cardiovascular events

Baseline patient demographics and disease history are presented in Table 1. Patients with advanced renal impairment were older (p < 0.001) and more commonly female (p < 0.001). As a marker of generalized vasculopathy, patients with lower GFR levels had a higher prevalence of prior MI, diabetes, cerebrovascular disease, PAD, and prior CABG (all p < 0.001). In-hospital death/MI/CABG rates increased incrementally as eGFR declined (2.5% for eGFR >75 ml/min/1.73 m^2 versus 6.8% for eGFR < 45 ml/min/1.73 m^2, p < 0.001).

3.2. Procedural data and peri-procedural medication

Procedural data and peri-procedural medication usage stratified by degree of renal impairment are displayed in Table 2. Patients with higher degrees of renal impairment were less likely to undergo urgent or emergency revascularization (p < 0.001) and less likely to receive peri- and post-procedural anti-thrombotic and antiplatelet agents (p < 0.001).