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Original Article

Trends in use of anti-thrombotic agents and outcomes in patients with non-ST-segment elevation myocardial infarction (NSTEMI) managed with an invasive strategy

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ABSTRACT

Objective: To analyze trends in utilization of anti-thrombotic agents (ATA) and in-hospital clinical outcomes in non-ST-elevation myocardial infarction (NSTEMI) patients managed with an invasive strategy from 2007 to 2010.

Methods & results: Using ACTION Registry®-GWTG™ data, we analyzed trends in use of ATA and in-hospital clinical outcomes among 64,199 NSTEMI patients managed invasively between 2007 and 2010. ATA included unfractionated heparin (UFH), low molecular weight heparin (LMWH), glycoprotein IIb/IIIa inhibitors (GPI) and bivalirudin. Although the proportion of NSTEMI patients treated with PCI within 48 h of hospital arrival was similar in 2007 and 2010, percentage use of bivalirudin (13.4–27.3%; $p < 0.01$) and UFH increased (60.0–67.5%, $p < 0.01$), and that of GPI (62.3–41.0%; $p < 0.01$) and LMWH (41.5–36.8%; $p < 0.01$) declined. Excess dosing of UFH (75.9–59.3%, $p < 0.01$), LMWH (9.6–5.2%; $p < 0.01$) and GPI (8.9–5.9%, $p < 0.01$) was also significantly lower in 2010 compared with 2007. Though in-hospital mortality rates were similar in 2007 and 2010 (2.3–1.9%, $p = 0.08$), the rates of in-hospital major bleeding (8.7–6.6%, $p < 0.01$) and non-CABG related RBC transfusion (6.3–4.6%, $p < 0.01$) were significantly lower in 2010 compared with 2007.

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Abbreviations: NSTEMI, non-ST-elevation myocardial infarction; ATA, anti-thrombotic agents; GPI, glycoprotein IIb/IIIa inhibitor; ACS, acute coronary syndrome; MI, myocardial infarction; NCDR, National Cardiovascular Database Registry; STEMI, ST-elevation myocardial infarction; DCF, data collection form; UFH, unfractionated heparin; LMWH, low molecular weight heparin; CABG, coronary artery bypass surgery; CHF, congestive heart failure; PCI, percutaneous coronary intervention; PAD, peripheral arterial disease.

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Conclusion: Compared with 2007, patients with NSTEMI, who were managed invasively in 2010 received GPI and LMWH less often and bivalirudin and UFH more frequently. There were sizeable reductions in the rates of excess dosing of UFH (though still occurred in 67% of patients), GPI and LMWH. In-hospital major bleeding complications and post-procedural RBC transfusion were lower in 2010 compared with 2007.

1. Introduction

Anti-thrombotic agents (ATA) are the cornerstone for treatment of non-ST-segment elevation myocardial infarction (NSTEMI).[1,2] Parenteral anticoagulants and concomitant GP IIb/IIIa inhibitors (GPI) prevent recurrent ischemic events and peri-procedural myocardial infarction (MI) among patients with NSTEMI.[3,4] However, due to the inherent nature of an invasive procedure coupled with use of anticoagulants, this ischemic benefit is accompanied by increased bleeding risk. Numerous studies have shown worse clinical outcomes, including mortality, among patients with major in-hospital bleeding complications.[5–7] Hence, bleeding avoidance strategies have received considerable attention as increased focus has been placed on patient safety. These include alternative approaches for vascular access and access site hemostasis, appropriate dosing of antithrombotic medications and selection of antithrombotic strategies with lower bleeding risk profiles. In the last few years, landmark trials such as REPLACE-2 (The Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events), ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy), ISAR-REACT 3 (Intracoronary Stenting and Antithrombotic Regimen—Rapid Early Action for Coronary Treatment 3) and EARLY-ACS (Early Glycoprotein IIb/IIIa Inhibition in non-ST-segment elevation acute coronary syndrome) have provided a better understanding of the risks and benefits of antithrombotic therapy for acute coronary syndrome (ACS) patients undergoing PCI.[8–12] Although these clinical trials have offered insights into selection of antithrombotic agents for NSTEMI patients, patterns of use of these agents (type of agent and frequency of excess dosing) and outcomes among NSTEMI patients following the publication of these key trials have not yet been analyzed. Hence, our study used data from the National Cardiovascular Data Registry's (NCDR) ACTION Registry®-GWTG™ (ACTION Registry® – Get with the Guidelines™) from 2007 to 2010 to analyze the use of intravenous antithrombotic agents among NSTEMI patients managed with an invasive strategy and to further examine in-hospital ischemic and bleeding outcomes during this period.

2. Methods

2.1. Registry

The NDCR ACTION Registry®-GWTG™ is a national quality improvement registry of ST-segment elevation myocardial infarction (STEMI) and NSTEMI patients who began enrolling on January 1, 2007.[13] Patients are eligible for inclusion in ACTION, if they present within 24 h from onset of ischemic symptoms and receive a primary diagnosis of NSTEMI or STEMI.

De-identified data are extracted from existing medical records onto a web-based case form by trained data collectors at each center. Study participation at each center was approved by local institutional review boards. The NCDR has a data quality program in place to ensure consistent and reliable data. Quality assurance measures, such as data quality reports and random site audits by trained nurse abstractors, are used to maximize the completeness and accuracy of all records submitted.

2.2. Study population

Starting from 158,540 NSTEMI patients enrolled in 569 US hospitals of ACTION Registry®-GWTG™ from January 1, 2007 to December 31, 2010, the following patients were excluded sequentially: Patients in centers using limited data collection form (DCF) ($n = 10, 346$), patients managed medically ($n = 35, 705$), transfer-out patients ($n = 3, 475$), patients in hospitals without PCI capability ($n = 3, 021$ in 49 centers), dialysis patients ($n = 2884$), patients from hospitals that did not enroll patients consecutively annually ($n = 32,627$), and patients from hospitals entering fewer than 25 patients annually ($n = 6283$ in 37 centers). Thus, the final analysis population consisted of 64,199 patients from 100 ACTION Registry®-GWTG™ centers.

2.3. Definitions of antithrombotic agents and excess dosing

Use of unfractionated heparin (UFH) or low molecular weight heparin (LMWH) was defined as use on the day of or the day immediately following admission without the use of other anticoagulants during that period or having the agent initiated after arrival in the cardiac catheterization laboratory. We examined only the use of small molecule GPI (eptifibatide or tirofiban) and defined use as initiation on the day of or the day immediately following hospital arrival.

Standardized dosing regimens recommended in the ACC/AHA guidelines for unstable angina/NSTEMI[14] were used to define appropriate and excess dosing of each antithrombotic agent (except bivalirudin). Excess dosing for intravenous UFH was defined as: a bolus dose >60 units/kg (max 4000 units) or infusion >12 units/kg/h (max 1000 units/h). The recommended daily dose of enoxaparin sodium was (1 mg/kg bid) for patients with a creatinine clearance of ≥30 mL/min and

1 mg/kg for patients with a creatinine clearance <30 mL/min. The patient's recorded body weight was used for this calculation. If the administered daily dose exceeded the recommended daily dose by more than 10 mg, the patient was categorized as having received an "excess" dose of enoxaparin.[15] For glycoprotein IIb/IIIa inhibitor, failure to appropriately reduce doses for creatinine clearance. For eptifibatide, full dose infusion was defined as 2 μg/kg/min, with reduced dose of 1 μg/kg/min for patients with creatinine clearance <50 mL/min. For tirofiban, full dose infusion was defined as 0.1 μg/kg/min, with reduced dose of 0.05 μg/kg/min for patients with creatinine clearance <30 mL/min. Creatinine clearance was estimated using the Cockcroft-Gault equation from age, gender, creatinine and weight. "Pre-procedure/Planned/Upstream" use of GPI was defined as any use from clinical presentation up to an hour before the PCI. "Peri-procedural/Provisional/Downstream" use of GPI was defined as 1-hour pre-procedure use to any time during or after procedure. Other study definitions are available at the NCDR website http://www.ncdr.com/WebNCDR/ACTION/Elements.aspx. Patients with missing dosing information were excluded.

2.4. *Definitions of in-hospital clinical outcomes*

The ACTION major bleeding definition has been validated previously,[16] and includes an absolute hemoglobin (Hb) drop of ≥4 g/dL (initial value to nadir during hospitalization), intracranial hemorrhage, documented or suspected retroperitoneal bleed, any RBC transfusion with baseline Hb ≥9 g/dL, or any RBC transfusion with Hb <9 g/dL and a suspected bleeding event. Given that a majority of patients undergoing coronary bypass graft surgery (CABG) receive blood transfusions related to the surgery, bleeding events for these patients were considered only if they occurred prior to CABG. A suspected bleeding event was defined as any of the following: (a) Hb drop of ≥3 g/dL, (b) transfusion of whole blood or packed RBCs, (c) procedural intervention/surgery at the bleeding site to reverse, stop or correct the bleeding (such as surgical closures/exploration of the arteriotomy site, balloon angioplasty to seal an arterial tear, endoscopy with cautery of a GI bleed). Blood transfusion was defined as any non-autologous transfusion of whole or packed RBCs. Other outcome definitions are available at the NCDR website http://www.ncdr.com/WebNCDR/ACTION/Elements.aspx.

2.5. *Statistical analysis*

Patient baseline characteristics, clinical factors, treatment patterns, and in-hospital outcomes were stratified by year of patient hospital arrival. Continuous variables were described as means (standard deviation), and categorical variables were expressed as frequencies with percentages. The Kruskal–Wallis test was used to determine whether there were any differences between continuous or ordinal variables between years, and the Pearson chi-square test was used to determine if there were any differences in categorical variables between years.

Furthermore, trends in use of antithrombotic agents, excess dosing of these agents, in-hospital all-cause mortality and major bleeding were explored. The p-values testing for linear trends of use of antithrombotic agents, excess dosing and in-hospital outcomes were obtained by modeling year of patient hospital arrival as an ordinal independent variable using the logistic generalized estimating equations method with an exchangeable working correlation matrix to account for within-hospital clustering because patients at the same hospital are more likely to have similar outcomes relative to patients at other hospitals (i.e., within-center correlation for outcomes).[17] This method produces estimates similar to those from logistic regression, but their variances are adjusted for the correlation of outcomes within a hospital. A p-value <0.05 was considered statistically significant for all tests. All analyses were performed using SAS software (version 9.3, SAS Institute, Cary, North Carolina, U.S.).

3. Results

Patient demographic characteristics according to year of patient enrollment appear in Table 1. Mean age and sex distribution remained comparable from 2007 to 2010. Medical history and clinical characteristics at presentation by year of patient admission are presented in Table 2. The proportion of patients with hypertension, dyslipidemia, diabetes, and prior history of MI, congestive heart failure (CHF), percutaneous coronary intervention (PCI) and peripheral arterial disease (PAD) increased (statistically significant but most differences were small) each year from 2007 until 2010. The time to symptom onset to arrival time decreased over the span of four years (from 7 to 5.2 h, $p < 0.01$). Medication use within 24 h of presentation is presented in Table 3.

3.1. *Trends in use of antithrombotic agents*

Trends in antithrombotic agent use are depicted in Fig. 1. Although the proportion of NSTEMI patients treated with PCI within 48 h of hospital arrival was similar in 2007 and 2010 (51.1–51.8%, $p = 0.19$), there was a significant increase in the use of bivalirudin (13.4–27.3%, $p < 0.01$). A similar trend was also seen with UFH (60.0–67.5%, $p < 0.01$). Conversely, the use of LMWH (41.5–36.8%, $p = 0.03$) and GPI (62.3–41.0%, $p < 0.01$) declined during the same time period. Among patients treated with GPI there was also a modest decline in proportion of "pre-procedural/planned/upstream" use (49.2–44.4%, $p < 0.01$) from 2007 to 2010. Among patients receiving GPI, a significant decline in the mean duration of therapy was observed during the same time period (23 h and 32 min to 20 h and 47 min, $p < 0.01$).

3.2. *Trends of excess dosing of antithrombotic agents*

Trends of excess dosing of antithrombotic agents are shown in Fig. 2 and Table 4. There was a significant decline in the rates of excess dosing of GPI (8.9–5.9%, $p < 0.01$). Rates of excess dosing of UFH declined from 75.9% in 2007 to 59.3% in 2010 (Table 4). Though there was no decline in excess dosing of the initial bolus (27.0% in 2007 to 22.0% in 2010, $p = 0.21$) a significant increase in excess dosing of the infusion (10.4% in 2007 to

Table 1 – Demographic characteristics by year of patient enrollment.

Variable	Overall (n = 64,199)	2007 (n = 14,498)	2008 (n = 16,317)	2009 (n = 16,759)	2010 (n = 16,625)	p-Value
Age (years)	63.6 ± 13.1	63.7 ± 13.1	63.4 ± 13.2	63.7 ± 13.0	63.7 ± 13.1	0.45
Males (%)	65.6	65.5	65.5	65.9	65.6	0.70
Weight (kg)	88.1 ± 21.6	87.7 ± 21.4	88.0 ± 21.5	88.3 ± 21.5	88.4 ± 22.1	<0.01
Body mass index (kg/m^2)	29.9 ± 6.7	29.8 ± 6.7	29.8 ± 6.7	29.9 ± 6.7	30.0 ± 6.8	<0.01
Race (%)						
Caucasian	85.4	86.6	85.1	85.2	85.0	<0.01
Black	9.0	8.2	8.8	9.3	9.7	
Asian	1.0	1.0	0.9	1.0	1.2	
Hispanic	2.7	2.2	2.8	2.8	2.8	
Other	1.2	1.7	1.6	0.9	0.7	
Insurance status (%)						
HMO[a]/private	58.0	56.5	57.6	57.9	60.0	<0.01
Medicare	26.6	28.9	27.9	26.2	23.8	
Military/VA[b]	1.6	1.6	1.7	1.7	1.5	
Medicaid	3.5	3.3	3.3	3.8	3.7	
Self/none	9.5	9.2	8.9	9.7	10.2	
Other	0.5	0.0	0.3	0.8	0.8	

Data are expressed as means ± standard deviations or percentages.
[a] HMO – health maintenance organizations.
[b] VA – veterans affairs.

16.6% in 2010, $p < 0.01$) was observed during the same time period. The proportion of patients who received an excess dose of both the bolus and infusion declined during the same time period (38.5% in 2007 to 20.7% in 2010, $p < 0.01$). Changes in mean dosing are depicted in detail in Table 4.

Excess dosing of LMWH also showed declined during the period studied, from 9.6% in 2007 to 5.2% in 2010 ($p < 0.01$).

3.3. *In-hospital clinical outcomes*

In-hospital clinical outcomes for each year of patient hospital arrival are presented in Fig. 3. Rates of major bleeding (8.7–6.6%, $p < 0.01$), requirement of RBC transfusion among non-CABG patients (6.3–4.6%, $p < 0.01$), and any suspected bleeding event (4.6–3.2%, $p < 0.01$) declined significantly. There was also

Table 2 – Clinical characteristics by year of patient enrollment.

Variable	Overall (n = 64,199)	2007 (n = 14,498)	2008 (n = 16,317)	2009 (n = 16,759)	2010 (n = 16,625)	p-Value
Smoking (<1 year) (%)	35.0	34.4	35.4	35.3	35.0	0.38
Hypertension (%)	73.2	70.9	72.9	74.1	74.8	<0.01
Dyslipidemia (%)	62.8	60.0	61.8	64.6	64.5	<0.01
Chronic lung disease (%)	14.1	N/A	14.4	14.2	13.8	0.16
Diabetes mellitus (%)	31.6	30.9	31.0	32.1	32.2	<0.01
Prior myocardial infarction (%)	26.1	25.3	26.3	26.5	26.3	0.04
Prior CHF[a] (%)	10.3	9.7	10.2	10.5	10.7	<0.01
Prior PCI[b] (%)	25.9	24.2	26.0	26.6	26.6	<0.01
Prior CABG[c] (%)	17.2	17.2	17.6	16.9	17.3	0.88
Prior revascularization (%)	34.9	33.3	35.0	35.4	35.6	<0.01
Atrial fib/flutter (<2 weeks) (%)	6.0	N/A	6.2	6.0	5.8	0.25
Cerebrovascular disease (%)	11.4	N/A	11.3	11.5	11.4	0.86
Prior stroke (overall) (%)	7.1	6.9	7.2	7.4	6.7	0.70
Peripheral arterial disease (%)	10.0	9.2	10.0	10.1	10.4	<0.01
ECG[d] findings (%)						
ST depression/transient ST elevation	29.5	32.6	30.7	28.0	27.2	<0.01
T-wave inversion	15.7	12.9	15.1	17.4	17.0	
None	54.8	54.5	54.3	54.6	55.9	
Symptom onset to arrival (h)	5.7 ± 11.8	7.0 ± 20.0	6.0 ± 13.9	4.9 ± 5.6	5.2 ± 7.1	<0.01
Signs of CHF (%)	14.1	14.6	14.1	13.7	14.0	0.12
Cardiogenic shock (%)	1.3	1.0	1.2	1.5	1.4	<0.01

[a] CHF – congestive heart failure.
[b] PCI – percutaneous coronary intervention.
[c] CABG – coronary artery bypass surgery.
[d] ECG – Electrocardiogram.

Table 3 – Medication use within 24 h of hospital arrival by year of patient enrollment.

Variable	Overall (*n* = 64,199)	2007 (*n* = 14,498)	2008 (*n* = 16,317)	2009 (*n* = 16,759)	2010 (*n* = 16,625)
Aspirin (%)	98.1	97.8	97.8	98.3	98.4
Clopidogrel (%)	64.6	66.5	66.9	65.0	60.6
Any oral antiplatelet (%)	98.2	98.2	98.0	98.1	98.4
Ticlopidine (%)	0.2	N/A	0.2	0.2	0.1
Prasugrel (%)	2.7	N/A	0.0	0.6	6.1
Beta blocker (%)	92.2	94.5	93.6	91.3	89.6
ACE[a] inhibitor (%)	44.5	47.7	45.6	43.1	42.0
ARB[b] (%)	8.8	9.3	9.0	8.8	8.1
ACE inhibitor or ARB (%)	50.0	52.6	51.0	49.2	47.7
Aldosterone blocking agent (%)	1.8	2.2	1.8	1.7	1.7
Statin	63.7	61.9	63.5	64.1	65.1
Other lipid-lowering agent	8.9	10.2	8.8	8.4	8.2
Any lipid-lowering agent	64.5	63.1	64.3	64.8	65.5

All comparisons were $p < 0.01$ except for any oral antiplatelet, and ticlopidine.
[a] ACE – angiotensin converting enzyme.
[b] ARB – angiotensin receptor blocker.

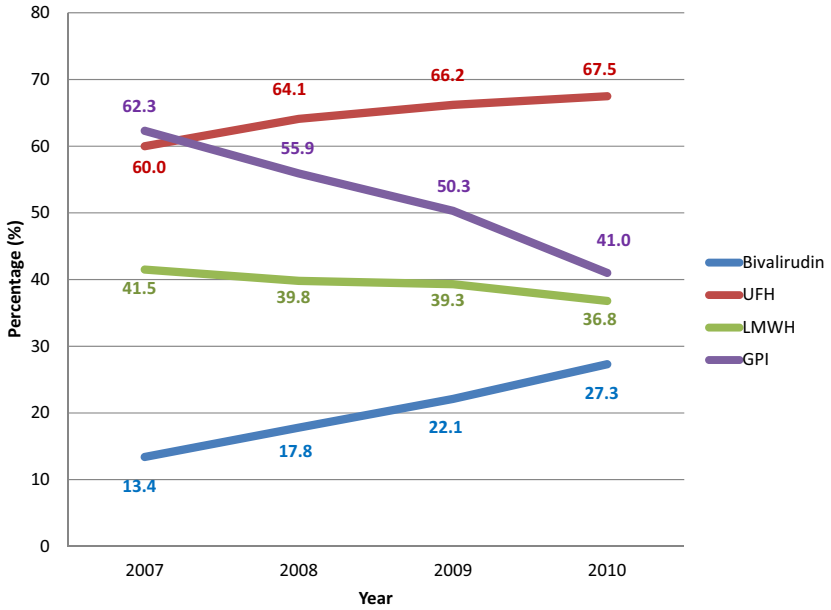
a non-significant trend toward declining all-cause mortality (2.3–1.9%, $p = 0.08$).

4. Discussion

Derived from a large, multicenter national registry, use of antithrombotic agents from 2007 to 2010 revealed a decline in the use of GPI and LMWH among patients with NSTEMI managed with an invasive strategy. However, there was an increase in use of UFH and bivalirudin during the same time period. We also observed a significant reduction in excess dosing of UFH and GPIs during the same time period. Furthermore, there was a significant decline in major bleeding complications during index hospitalization. Our study confirms the changing trends in use of antithrombotic agents, reductions in excess dosing, and bleeding events in recent years among NSTEMI patients.[18]

4.1. *Impact of landmark trials – choice of anticoagulation*

Our data reflects 4 recent years of ATA usage in the management of NSTEMI patients treated invasively, and represents important changing trends in cardiology practice. Contemporary trials have confirmed the safety and efficacy of heparin and bivalirudin used alone.[9,11,12,19,20] and demonstrated lower



- All comparison were $p_{(trend)} < 0.01$
- UFH – Unfractionated Heparin; LMWH – Low molecular weight heparin; GPI – Glycoprotein IIb/IIa inhibito

Fig. 1 – Trends in use of antithrombotic agents by year of patient enrollment. All comparisons were $p_{(trend)} < 0.01$. UFH – unfractionated heparin; LMWH – low molecular weight heparin; GPI – glycoprotein IIb/IIa inhibitors.

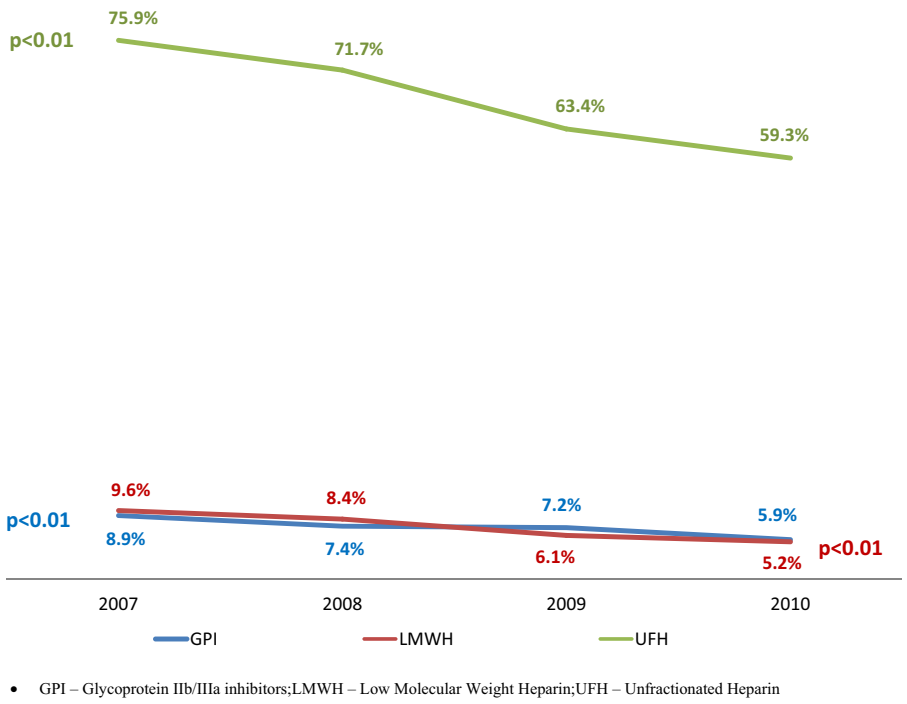


Fig. 2 – Trends in "excess use" of antithrombotic agents by year of patient enrollment. GPI – glycoprotein IIb/IIIa inhibitors; LMWH – low molecular weight heparin; UFH – unfractionated heparin.

bleeding than the combination of heparin and GPI.[9,11,12,20,21]. The early impact of these studies on contemporary practice can be gauged from the trends depicted in a recent publication[22] and more explicitly in our study. Lopes et al. showed that NSTEMI patients undergoing PCI were more likely to receive bivalirudin or heparin alone when presenting with a high baseline bleeding risk.[22] Our study confirms both an increasing trend of UFH and bivalirudin and a distinct declining trend of GPI and LMWH use from 2007 to 2010. These findings may reflect the impact of prior landmark trials on our current practices to minimize bleeding events. It is also of interest that increasing use of bivalirudin appears to be occurring at the expense of LMWH rather than UFH, as overall UFH usage has increased.

Table 4 – Trends in excess dosing of antithrombotic agents by year of patient enrollment.

Variable	Overall (n = 64,199)	2007 (n = 14,498)	2008 (n = 16,317)	2009 (n = 16,759)	2010 (n = 16,625)
(A) Excess dosing of GPI[a]					
Excess GPI (%)	7.4	8.9	7.4	7.2	5.9
Length of GPI therapy for all patients (min)	1357 ± 1085	1412 ± 1067	1411 ± 1102	1345 ± 1091	1247 ± 1067
(B) Excess dosing of LMWH[b]					
Excess LMWH (%)	7.2	9.6	8.4	6.1	5.2
(C) Excess dosing of UFH[c] trends					
Excess UFH (%)	66.9	75.9	71.7	63.4	59.3
Bolus UFH dose only (%)	24.3	27.0	26.3	22.5	22.0
Infusion UFH dose only (%)	13.3	10.4	11.8	13.6	16.6
Bolus & Infusion UFH dose (%)	29.3	38.5	33.5	27.3	20.7
(D) UFH mean dose					
Bolus dose only (U)	5095 ± 818	5108 ± 752	5256 ± 1113	5037 ± 656	4970 ± 594
Infusion dose only (U/h)	1103 ± 273	1161 ± 341	1084 ± 239	1091 ± 259	1096 ± 264
Bolus dose among both excess (U)	5517 ± 1391	5577 ± 1290	5692 ± 1529	5395 ± 1274	5337 ± 1428
Infusion dose among both excess (U/h)	1187 ± 297	1208 ± 299	1202 ± 294	1173 ± 284	1153 ± 314

All comparisons were $p < 0.01$ except for bolus UFH dose only.
[a] GPI – glycoprotein IIb/IIIa inhibitors.
[b] LMWH – low molecular weight heparin.
[c] UFH – unfractionated heparin.

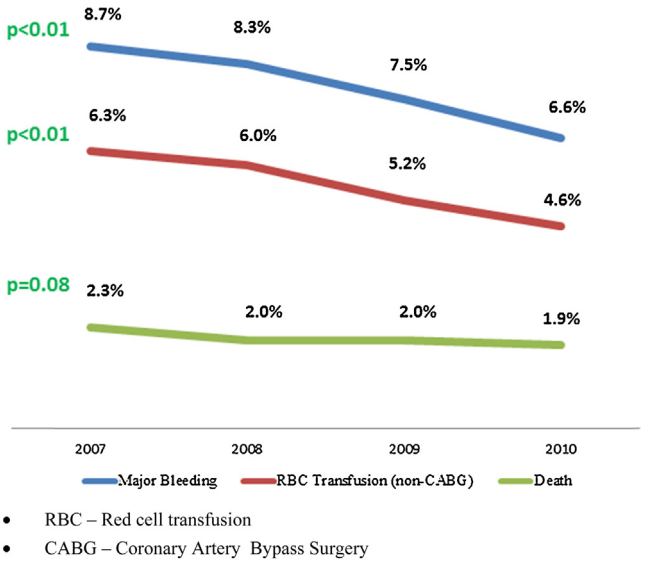


Fig. 3 – Trends in in-hospital clinical outcomes by year of patient enrollment. RBC – red cell transfusion. CABG – coronary artery bypass surgery.

4.2. *Excess dosing of antithrombotic agents*

Despite observing favorable changes in clinical practice with respect to excess doing of antithrombotic agents, particularly for UFH (the most frequently used antithrombotic agent), about two third of patients still received a mean initial dose of UFH substantially greater than the maximum recommended 4000 U and a mean infusion substantially higher than the maximum recommended 1000 U/h. Therefore, there remains a clear opportunity to improve adherence to UFH dosing guidelines. The remarkably high rate of excess UFH dosing may reflect either a knowledge gap or uncertainty regarding currently recommended UFH dosing in U.S. Guidelines. Although the U.S. dosing guidelines for UFH in UA/NSTEMI changed in 2007[1] to the currently recommended dose regimen, it is notable that no are provided in this guideline to support the change to this lower-dose regimen of UFH. Thus, the large discrepancy between clinical practice and the current guideline recommendation may also reflect uncertainty among practitioners regarding the 4000 U maximum bolus in UA/NSTEMI, particularly for obese individuals. Additional data are needed to determine optimal initial UFH dosing in UA/NSTEMI.

Our study also showed approximately 40% relative reductions in the rates of excess dosing of GPI (38%) and LMWH (46%) from 2007 to 2010. Patients with excess dosing of UFH, LMWH, and GPI have higher risks for major bleeding and hemorrhagic complications that increase relative to the degree of excess dose and number of agents dosed excessively.[23] Despite increasing prevalence of clinical characteristics associated with excess dosing of antithrombotic agents and bleeding (from 2007 to 2010) within our study sample, rates of excess dosing and bleeding both declined during the period we studied. These observations support the hypothesis that implementation of guidelines into clinical practice has the potential to significantly impact care practices and clinical outcomes.

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4.3. *Timing of GPI*

Our study revealed a marked decline in overall GPI use, but with only a modest reduction in the proportion of patients receiving GPI as "upstream" therapy (49.2–44.4%, $p < 0.01$), despite the results from the EARLY ACS and ACUITY trials that revealed no incremental benefit on ischemic events and higher bleeding rates with upstream use.[8,10]

4.4. *Decline in bleeding events*

Bleeding is an independent predictor of adverse outcomes that can be modified.[6,7,24] The changes in use of antithrombotic strategies in our study may reflect attempts to employ strategies to mitigate bleeding risks. In addition to an increased preference to use of bivalirudin, there was a decline in GPI use from 2007 to 2010, associated with slightly less upstream use, and lower rates of excess dosing of UFH, LMWH and GPI, all of which again may have contributed to the declining bleeding rates observed in our study. However, our study also highlights that considerable improvement may still be possible, particularly with respect to excess dosing of UFH. Though ACTION Registry®-GWTG™ does not collect data on proportion of radial access, it is possible that an increase in adoption of radial access or other process factors over the last 4 years also may have contributed favorably to improvement in bleeding outcomes that we observed.

5. Study limitations

Our study has several limitations. The hospitals participate in the ACTION Registry®-GWTG™ initiative voluntarily; and hence this database may not be a representation of national practices. The outcomes reported in this observational study reflect in-hospital outcomes; therefore, caution should be taken when considering the long-term implications of these results. Further, although there are standardization and uniformity in ACTION Registry®-GWTG™ data collection, quality control and participant feedback, any large national database effort is inherently imperfect. This study was not designed to analyze results by race and ethnicity, and hence variations in utilization of ATAs and outcomes by race as seen in several cardiovascular studies cannot be interpreted from the results of this study. The ACTION Registry®-GWTG™ does not have data pertaining to bivalirudin dosing; thus, analysis of excess dosing of bivalirudin could not be ascertained. Finally, the exact timing of or switching between antithrombotic agents was not considered.

6. Conclusion

Compared with 2007, patients with NSTEMI, who were managed invasively in 2010 less often received GPI and LMWH

and more frequently received bivalirudin and UFH. There were sizeable reductions in the rates of excess dosing of UFH, GPI and LMWH. Although excess dosing of UFH declined substantially, it still occurred about 67% of patients. In-hospital major bleeding complications and post-procedural RBC transfusion were lower in 2010 compared with 2007.

Sources of funding

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Conflicts of interest

S.A. Wayangankar, A.Y. Chen, R.S. Gupta, K.P. Alexander, T.A. Sanborn, J.F. Saucedo have none to declare. M.T. Roe: research funding: Eli Lilly, Revalesio, Sanofi-Aventis, American College of Cardiology, American Heart Association; consulting or honoraria: Astra Zeneca, Sanofi-Aventis, Janssen Pharmaceuticals, Merck, Regeneron, and Daiichi-Sankyo. All conflicts of interest are listed at www.dcri.org. Conflicts listed inclusive from June, 2012 to April, 2013. R.P. Giugliano is a member of the TIMI Study Group, which has received research grant support from Astra-Zeneca, Bristol Myers Squibb, Daiichi-Sankyo, Lilly, Merck, Sanofi-aventis for clinical trials with antithrombotic therapy. Dr. Giugliano has received honoraria for consulting and/or CME l in use of antithrombotic agectures from Daiichi-Sankyo and Merck for topics related to antithrombotic therapies. K.L. Newby – All of Dr Newby's relationships with industry are available publically at https://www.dcri.org/about-us/conflict-of-interest. J.A. de Lemos – Consulting Janssen Lecture honoraria, Astra Zeneca.

Disclaimer

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Significance of our study

Our study confirms the changing trends in use of antithrombotic agents, with a decline in agents known to predispose patients to bleeding (GPI) and an increased utilization of agents that afford a favorable bleeding profile (bivalirudin). These findings may reflect the impact of prior landmark trials on our current practices to minimize bleeding events. Also, our study has shown a heartening trend of reductions in excess dosing, and bleeding events in recent years among NSTEMI patients. These observations support the hypothesis that implementation of guidelines into clinical practice has the potential to significantly impact care practices and clinical outcomes.

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