Clinical outcomes associated with type II myocardial infarction caused by bleeding

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Background Type II myocardial infarction (T2MI) is caused by a mismatch between myocardial oxygen supply and demand. One subset of individuals is T2MI caused by acute hemorrhage. Traditional MI treatments including antiplatelets, anticoagulants, and revascularization can worsen bleeding. We aim to report outcomes of T2MI patients due to bleeding, stratified by treatment approach.

Methods The MGB Research Patient Data Registry followed by manual physician adjudication was used to identify individuals with T2MI caused by bleeding between 2009 and 2022. We defined 3 treatment groups: (1) invasively managed, (2) pharmacologic, and (3) conservatively managed Clinical parameters and outcomes for 30-day, mortality, rebleeding, and readmission were abstracted compared between the treatment groups.

Results We identified 5,712 individuals coded with acute bleeding, of which 1,017 were coded with T2MI during their admission. After manual physician adjudication, 73 individuals met the criteria for T2MI caused by bleeding. 18 patients were managed invasively, 39 received pharmacologic therapy alone, and 16 were managed conservatively. The invasively managed group experienced lower mortality ($P = .021$) yet higher readmission ($P = .045$) than the conservatively managed group. The pharmacologic group also experienced lower mortality ($P = .017$) yet higher readmission ($P = .005$) than the conservatively managed group.

Conclusion Individuals with T2MI associated with acute hemorrhage are a high-risk population. Patients treated with standard procedures experienced higher readmission but lower mortality than conservatively managed patients. These results raise the possibility of testing ischemia-reduction approaches for such high-risk populations. Future clinical trials are required to validate treatment strategies for T2MI caused by bleeding. (Am Heart J 2023;263:85–92.)

Background

Type II myocardial infarction (T2MI) is defined as a myocardial infarction caused by a mismatch between myocardial oxygen supply and demand.[1,2] T2MI is a heterogeneous syndrome that is caused by a variety of other pathophysiological processes such as coronary artery spasm, embolism, anemia both from bleeding and other causes, hypertension or hypotension, and arrhythmias.[3]

The optimal treatment approach to T2MI remains a significant challenge, and treatment guidelines are not well established.[4–6] In the setting of uncertain best care pathways, the approach to treatment usually ranges from pharmacologic treatment with antiplatelets and anticoagulants to more invasive measures, such as coronary angiography, percutaneous coronary intervention (PCI) or percutaneous transluminal coronary angioplasty (PTCA), and/or coronary artery bypass surgery (CABG).[7]

A particularly challenging subset of T2MI arises in patients with acute blood loss causing a supply-demand mismatch. Traditional treatments for traditional type 1 acute myocardial infarction (T1MI) include anticoagulant and antiplatelet therapy as well as revascularization strategies.[8] For example, CABG requires high-dose anticoagulation for cardiopulmonary bypass[9] and percutaneous coronary intervention requires anticoagulation and then also creates a need for antiplatelet therapy.[10] Trials that have evaluated the effectiveness of these strategies for myocardial infarction, in general, have either (1) not clearly included or excluded T2MI patients or (2) probably excluded T2MI patients, for example by excluding patients with concurrent acute con-

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Abbreviations: T1MI, Type 1 myocardial infarction; T2MI, Type II myocardial infarction; PCI, Percutaneous coronary intervention; PTCA, Percutaneous transluminal coronary angioplasty; CABG, Coronary artery bypass surgery; MGB, Mass General Brigham; IRB, Institutional review board; RPDR, Research patient data registry; ICD, International Classification of Diseases; PCS, Procedure coding system; ECG, Electrocardiogram; TIA, Transient ischemic attack.

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ditions.[11–14] Although clinicians extrapolate results from these trials to treat T2MI, the extent to which this is an effective strategy is unclear. There is a plausible mechanism of harm since antiplatelet and anticoagulant therapy could worsen bleeding and does not address the underlying biology of nonthrombotic fixed coronary artery disease.[15] As such, although little is understood about clinical outcomes when bleeding-related T2MI is treated with traditional myocardial infarction therapies, there is reason to suspect these treatments could be potentially harmful.

Ultimately, a better understanding of outcomes of T2MI caused by bleeding when traditional strategies are used cannot establish treatment pathways, because of the difficulty distinguishing between the effects of therapies and the characteristics of patients who receive them (treatment effects versus confounding bias, sometimes called "treatment selection bias").[16] However, these raw associations are still important because they may ultimately could generate important hypotheses and estimates for event rates that could inform the development of clinical trials that eventually could validate therapies for T2MI caused by bleeding. In the setting of this evidence gap, we aim to describe the clinical outcomes of patients with T2MI due to bleeding stratified by treatment approach.

Materials and methods

Study design

The Institutional Review Board (IRB) at Mass General Brigham approved this study and waived the patient consent requirement for this retrospective study of previously collected data. Using the Mass General Brigham Research Patient Data Registry (RPDR), we first identified unique subjects with hospitalization due to acute bleeding between 2009 and 2022 at all Massachusetts General Brigham (MGB) hospitals. Using the International Classification of Diseases (ICD-10-CM) codes and Procedure Coding System (PCS) for bleeding, we identified subjects admitted with gastrointestinal bleeding, intracranial hemorrhage, and other hemorrhage causes. (See Supplementary Table S1.) Among those patients, we then queried for acute myocardial infarction (ICD-9/ICD-9-CM: 410; and ICD-10-CA: I21, I22) before October 2017 and queried for T2MI (I21.A1) after. We took this approach because the ICD-10 code specific for T2MI was not available until October 2017, after the introduction of ICD-10.

Clinical adjudication and review

Mindful that the specificity of administrative data for T2MI is low,[17] we then performed a physician chart review to adjudicate clinical definitions. Using the 4th Universal Definition of Myocardial Infarction,[18] an MI was defined as a rising or falling elevation in cardiac troponin more than the 99th percentile with at least one of the following: (1) symptoms of ischemia, (2) new electrocardiographic evidence of ischemia, (3) new pathological Q waves, (4) new regional wall motions on imaging in an ischemic territory, or (5) coronary thrombus on angiography. T2MI was defined as an MI with an identifiable preceding imbalance between myocardial oxygen supply and demand not associated with coronary thrombus. Strict clinical adjudication was then applied to confirm the diagnosis yielding n=73 T2MI patients with bleeding being the primary cause of their diagnosis. Data on baseline characteristics, diagnostic testing such as electrocardiograms (ECGs), cardiac stress test results, and angiography results, as well as treatment regimens such as antiplatelets, anticoagulation, and invasive procedures, were collected from clinical physician review. For primary outcomes, we included in-hospital and postdischarge 30-day mortality, bleeding reoccurrence, and readmission rates within 30 days. These clinical outcomes were adjudicated by physician chart review (J.A.). Standardized definitions for bleeding events using ICD-10-CM and diagnostic codes to identify bleeding events in EPIC were used, as well as the Bleeding Academic Research Consortium (BARC) classification for severity of events. The physician also determined the type of bleeding event causing the T2MI. After reviewing the cases, we defined 3 treatment groups based on the concept that some treatments could worsen bleeding more than others. The 3 categories were defined as follows:(1) the invasively managed group received coronary angiography and potential revascularization including any percutaneous coronary intervention (PCI), percutaneous transluminal coronary angioplasty (PTCA), and/or coronary artery bypass graft surgery (CABG), (2) the pharmacologic group received antiplatelet and anticoagulant therapy but no procedures, and (3) the conservatively managed group received no procedures or revascularization and no anticoagulant or antiplatelet therapy. In the invasively managed group and the pharmacologic group, the physician reviewer also extracted information about the decision to pursue those therapies in the setting of potential risk for rebleeding. In the conservatively managed group, the physician reviewer extracted reasons for avoiding aggressive strategies.

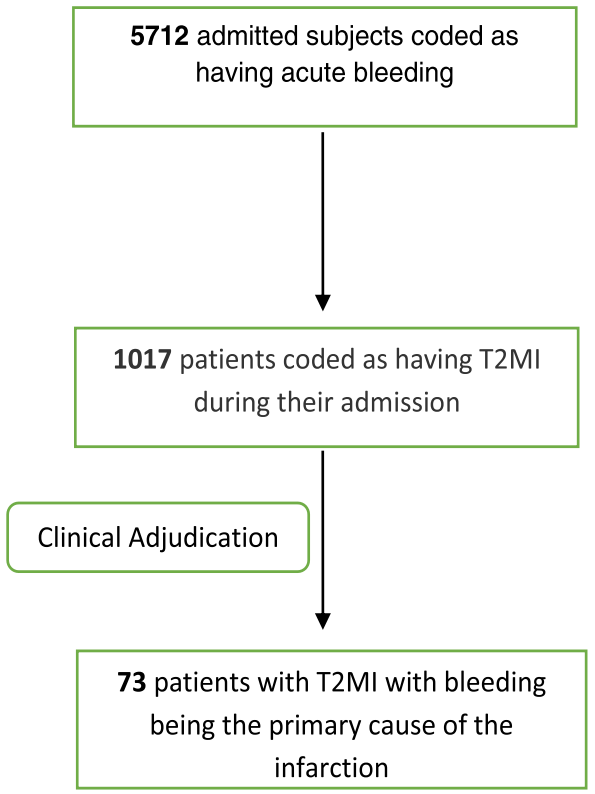
Finally, we compared the 3 outcomes in the 3 treatment groups using chi-squared tests. We did not use risk-adjustment given the relatively low statistical power for this relatively rare condition. Statistical calculations were performed using GraphPad Prism 9 software (La Jolla, CA).

Results

Patients

Over the study period, we initially identified 5712 patients who were coded as having acute bleeding. Of those, 1017 patients (17.8%) were coded as potentially

Figure 1



Study outline.

having T2MI during their admission. After clinical adjudication, n = 73 subjects (7.2%) met the criteria for T2MI primarily caused by bleeding. These 73 patients formed the primary analytic cohort for analysis (Figure 1).

Descriptive characteristics appear in Table I. 48 patients (65.1%) were male. The median age was 79 (interquartile range, 67.5-84.5). Out of 73, 60 patients were white (82.2%), 4 patients were Black (5.5%), and 9 patients were recorded as Other (12.3%). In total, 41.1% of the patients had known diabetes mellitus, and 45.2% had a history of known coronary artery disease. A total of 16 patients (22%) had known chronic lung disease, 17 patients (23.3%) had active malignancy, and 16 patients (22%) had prior bleeding. A total of 17 patients (23.3%) had a previous stroke or transient ischemic attack (TIA), 26 patients (35.6%) had a previous myocardial infarction, 19 patients (26%) had a previous PCI/PTCA procedure done, and 14 patients (19.2%) had a prior CABG surgery performed (See Table I). 57 patients (78%) presented with gastrointestinal bleeding,8 patients (11%) with bleeding intra and/or postoperatively, 5 patients (6.8%) presented with retroperitoneal bleeding, and 3 patients presented with hematuria, epistaxis, and epidural hematoma, respectively. Additionally, the standardized Bleeding Academic Research Consortium (BARC) classification for severity of bleeding was used to classify the events in the different groups[19] (See Table S2). In the pharmacologic group, 27 patients (69%) had a type 2 BARC bleeding classification, 10 patients (25.6%) had a type 3a BARC bleeding classification, and 2 patients (5.1%) had a type 3b BARC bleeding classification. In the invasively managed group, all patients had a type 2 BARC bleeding classification. In the conservatively managed group, 8 patients (50%), 5 patients (31.3%) and 3 patients (18.8%) had a type 2, type 3a, and type 3b BARC bleeding classification, respectively.

Treatment groups

After the application of the definitions described in the methods section, there were 18 patients (24.7%) in the invasively managed group, 39 patients (53.4%) in the pharmacologic group, and 16 patients (21.9%) in the conservatively managed group.

Of the 18 patients in the invasively managed group, 7 patients (38.9%) had PCI/PTCA, and 1 patient (5.6%) had a CABG. Consistent with the definition of T2MI, all 18 patients undergoing coronary angiography had biologically fixed ischemic disease with the absence of plaque erosion and/or rupture. As such, any PCI or CABG was performed for biologically fixed coronary disease even in the setting of this acute syndrome.

Of the 39 patients in the pharmacologic group, a total of 7 patients (17.9%) were administered an anticoagulant.In the invasively managed group, the decision to revascularize the patients mainly depended on the severity of bleeding. All 18 patients who were managed invasively were thought to have a bleeding source that had been thought to be fully controlled,

Similarly in the pharmacologic group, a similar risk-benefit assessment guided the treatment decision of the patients. All patients had their active bleeding controlled prior to administration of antiplatelets and/or anticoagulation. However, a clinical impression not suggestive of ongoing ischemic symptoms guided the medical team to manage these patients medically and to avoid invasive measures that would increase the risk of bleeding.

In the conservatively managed group, 8 subjects (50%) had uncontrolled bleeding, 3 patients (18.8%) were on comfort measures only due to patient preference or terminal conditions, and 5 patients (31.3%) had noninvasive stress tests that established no significant CAD.

Comparison of adverse outcomes between the 3 treatment groups

When comparing the 3 different groups, the invasively managed group experienced lower mortality rates (5.6% vs 37.5%, $P = .021$) yet higher readmission rates (22.2% vs 0%, $P = .045$) than the conservatively managed group.

Table I. Patient demographics and characteristics.

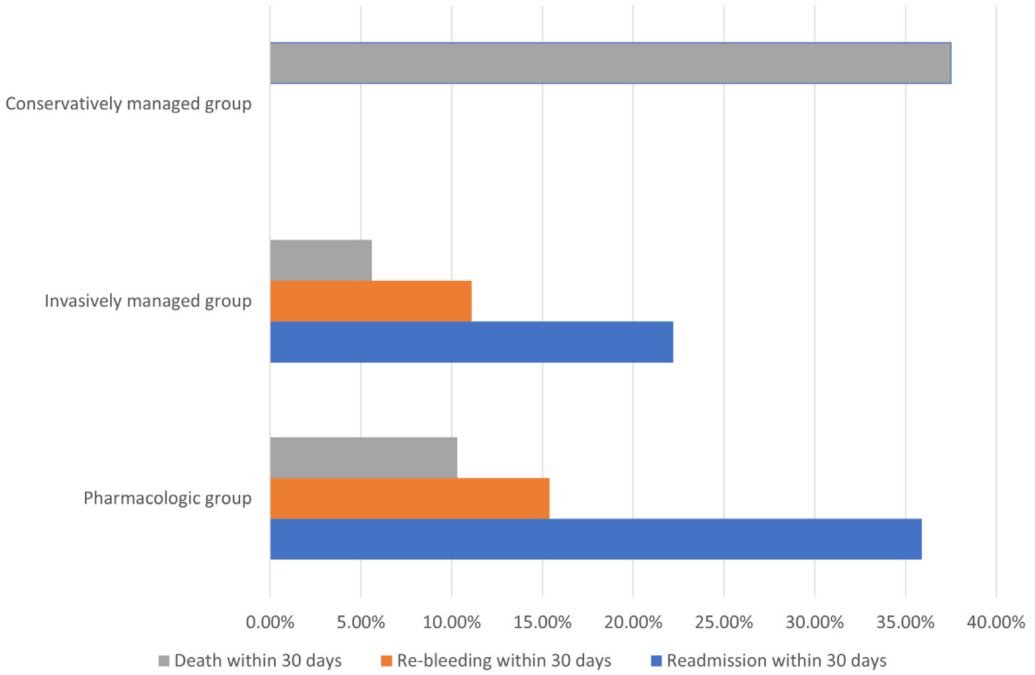
Characteristic	Pharmacologic group (n=39)	Invasively managed group (n=18)	Conservatively managed group (n= 16)	Total (n=73)
Demographics				
Age, Mean	74.5	79.05	76.1	76.1
Age, Median (IQR)	77.5 (67-83)	82 (69-86)	78 (66.5-86)	79 (67.5-84.5)
Men	23 (59%)	13 (72.2%)	12 (75%)	48 (65.8%)
Race				
White	33 (84.6%)	15 (83.3%)	12 (75%)	60 (82.2%)
Black	2 (5.1%)	1 (5.6%)	1 (6.3%)	4 (5.5%)
Other	4 (10.3%)	2 (11.2%)	3 (18.8%)	9 (12.3%)
Cause of bleeding				
Gastrointestinal bleed	32 (82%)	14 (77.8%)	11 (68.8%)	57 (78%)
Retroperitoneal bleed	3 (7.7%)	1 (5.6%)	1 (6.3%)	5 (6.8%)
Intraoperative bleed	3 (7.7%)	2 (11.2%)	3 (18.8%)	8 (11%)
Hematuria	1 (2.5%)	0 (0%)	0 (0%)	1 (1.4%)
Epidural Hematoma	0 (0%)	0 (0%)	1 (6.3%)	1 (1.4%)
Epistaxis	0 (0%)	1 (5.6%)	0 (0%)	1 (1.4%)
BARC classification				
Type 2	27 (69%)	18 (100%)	8 (50%)	53 (72.6%)
Type 3a.	10 (25.6%)	0 (0%)	5 (31.3%)	15 (20.5%)
Type 3b.	2 (5.1%)	0 (0%)	3 (18.8%)	5 (6.8%)
Medical history				
Diabetes	16 (41%)	7 (38.9%)	7 (43.8%)	30 (41.1%)
Current smoker	19 (48.7%)	11 (61.1%)	8 (50%)	38 (52.1%)
COPD	6 (15.4%)	4 (22.2%)	6 (37.5%)	16 (22%)
Hypertension	38 (97.4%)	16 (88.9%)	13 (81.3%)	67 (91.8%)
Hyperlipidemia	32 (82%)	16 (88.9%)	10 (62.5%)	58 (79.5%)
Coronary artery disease	18 (46.2%)	9 (50%)	6 (37.5%)	33 (45.2%)
Atrial fibrillation	20 (51.2%)	7 (38.9%)	7 (43.8%)	34 (46.6%)
Heart Failure	10 (25.6%)	3 (16.7%)	9 (56.3%)	22 (30.1%)
Malignancy	11 (28.2%)	3 (16.7%)	3 (18.8%)	17 (23.3%)
History of malignancy	8 (20.5%)	7 (38.9%)	0 (0%)	15 (20.5%)
CKD	21 (53.8%)	9 (50%)	5 (31.3%)	35 (47.8%)
CKD undergoing dialysis	4 (100%)	0 (0%)	0 (0%)	4 (5.5%)
Cirrhosis	0 (0%)	0 (0%)	2 (12.5%)	2 (2.7%)
Prior bleeding	8 (20.5%)	7 (38.9%)	1 (6.3%)	16 (22%)
Substance use disorder	1 (2.6%)	1 (5.6%)	1 (6.3%)	3 (4.1%)
Prior				
Stroke/TIA	8 (20.5%)	5 (27.8%)	4 (25%)	17 (23.3%)
MI	16 (41%)	6 (33.3%)	4 (25%)	26 (35.6%)
PTCA or PCI	9 (23%)	5 (27.8%)	5 (31.3%)	19 (26%)
CABG	8 (20.5%)	5 (27.8%)	1 (6.3%)	14 (19.2%)

Similarly, the pharmacologic group experienced lower mortality rates (10.3% vs 37.5%, $P = .017$) yet higher readmission rates (35.9% vs 0%, $P = .005$) than the conservatively managed group (See Figure 2). When comparing the pharmacologic vs invasively managed group, no significant difference was noted in terms of mortality ($P = .56$) or readmission ($P = .30$). Finally, there were no statistical differences demonstrated in terms of rebleeding episodes between the 3 different groups (See Table II). Of the 18 invasively managed patients, 3 patients had an escalation of anticoagulation and antiplatelet therapy postinvasive procedures, and 2 out of those 3 patients experienced readmission and reoccurrence of bleeding. All patients in the invasively managed and pharmacologic groups received DAPT for at least 30 days.

Discussion

Here, in a clinically adjudicated sample including both academic and community hospitals in an integrated system, we demonstrate that about three-quarters of patients with T2MI caused by bleeding received antiplatelet and anticoagulant therapy with or without revascularization procedures. We also demonstrate the overall poor prognosis of T2MI caused by bleeding, regardless of treatment strategy. Particularly, all main treatment groups had 30-day mortality equal to or higher than 10%. Among the patients who do not receive any antiplatelets therapy, anticoagulants, or procedures (the conservatively managed group), mortality is very high, with more than one-third dying within 1 month. Comparatively, mortality is lower among patients managed more aggressively with both anticoagulants/antiplatelets and invasive strategies.

Figure 2



Bar chart representing the 3 outcomes among the pharmacologic, invasively managed, and conservatively managed groups.

Table II. Adverse outcomes rate for patients in the pharmacologic group, invasively managed group, and conservatively managed group.

	Pharmacologic group n=39 (53.4%)	Invasively managed group n=18 (24.7%)	Conservatively managed group n=16 (21.9%)
Readmission within 30 days	14 (35.9%)	4 (22.2%)	0 (0%)
Rebleeding episode within 30 days	6 (15.4%)	2 (11.1%)	0 (0%)
Death within 30 days	4 (10.3%)	1 (5.6%)	6 (37.5%)

The high mortality rate among patients who were managed conservatively likely reflects confounding bias (ie, "treatment selection bias"). For example, clinicians may withhold these therapies in patients who have severe or unreversed bleeding, or a poor clinical prognosis for other reasons such as age. We have in fact shown here that two-thirds of conservatively managed patients had either uncontrolled bleeding or comfort measures only code status. These results underscore that whether or not antiplatelet therapy and anticoagulants, potentially with invasive angiography with the intent to revascularize, might be an effective treatment strategy for T2MI caused by bleeding despite the conceptual and mechanistic risks needs to be tested in a prospective trial. On one hand, perhaps revascularization therapies directed towards increasing the threshold of ischemia occurrence could reduce the rates of recurrent T2MI and thus decrease postdischarge mortality. On the other hand, these strategies could be risky in patients with recent bleeding events and no recent biological plaque erosion or thrombosis. The high prevalence of CAD among patients with T2MI raises the possibility that coronary angiography with intravascular imaging to exclude other causes of MI could be valuable to such patients.[20] All of these types of concepts could be prospectively validated in randomized trials. Our preliminary data here could help generate estimates for event rates needed to plan such trials.

Our results are concordant with other recent work demonstrating high mortality for T2MI due to acute bleeding. Prior studies using the 2018 Nationwide Readmission Database show high in-hospital mortality among a large sample of T2MI patients hospitalized with gastrointestinal bleeding.[21] To confirm and extend these prior results, our strictly adjudicated data using physician chart review include additional outcomes such as postdischarge death. Additionally, prior studies have demon-

strated that a substantial percentage (up to 50%) of patients coded as having T2MI actually had a myocardial injury.[17] The lower rate of included subjects in our study sample (≈ 7% of the queried patients coded to have T2MI) is attributed to including only patients with confirmed T2MI caused by acute hemorrhage and excluding patients with other causes for T2MI. Our results showed that about one-tenth of patients with T2MI due to bleeding receive PCI, similar to prior results. Specifically, another study demonstrated that 13.7% of T2MI had a PCI after coronary angiography including patients who were all T2MI, not only those due to bleeding.[22] Moreover, in a recent trial MANAGE (Management of Myocardial Injury After Noncardiac Surgery), the use of oral anticoagulants such as dabigatran was correlated with lower adverse cardiovascular event rates as well as comparable bleeding complications to those who received a placebo.[23] In a recent meta-regression analysis study, higher rates of PCI in T2MI patients were associated with lower mortality rates both in-hospital and at 1 year. However, whether these results could be extrapolated to T2MI due to acute bleeding remains unclear.[24] Our work is novel and important because it reports clinical outcomes, stratified by treatment strategy, specifically for T2MI caused by bleeding – which is where the conceptual risks of antiplatelets, anticoagulants, and revascularization are highest.

Even before trials establish a validated treatment strategy for those with T2MI of varying causes, other approaches could provide more insight into treatment strategies and outcomes for T2MI. For instance, although the introduction of the ICD-10 code, I21.A1, in 2017 allowed the distinction between T2MI in claims data,[25,26] failure to indicate the underlying cause of T2MI in claims data remains a problem. T2MI is a heterogeneous syndrome, and thus, establishing more specific coding systems would better allow the measurement of outcomes. Furthermore, there is a need for more precise epidemiological studies to better understand the prevalence of T2MI due to acute bleeding.[27,28] Another vital area for investigation is the establishment of novel diagnostic platforms as an adjunct to traditional cardiac assays. One particularly rapidly evolving field is the recent expansion of metabolomics studies. The identification of specific biomarkers that differentiate the different types of MI show promise in the early diagnosis of disease for optimal patient management.[29]

Limitations

Our study should be interpreted in the setting of key limitations. Although we included several community and academic hospitals, all the hospitals were in the same health system. As such, the extent to which we can extrapolate these results to other settings is unclear. Second, although we compared clinical outcomes associated with different treatment approaches, we cannot distinguish between treatment effects and the characteristics of patients who receive specific treatments. Third, since this is a relatively rare subtype of a specific type of MI, we do not have sufficient statistical power to exclude smaller differences in some outcomes such as bleeding endpoints. To determine the best strategy for patient management with T2MI caused by bleeding, ultimately prospective trials will be needed and the work here could lead to those trials by providing estimates of event rates that could inform power calculations and trial planning. Finally, the limited statistical power and retrospective analysis does not allow us to prospectively determine definitions for different bleeding endpoints such as major and minor bleeding. Finally, as a study of clinical outcomes after T2MI stratified by short-term management study, our work here does not provide information about later clinical events over time for patients who have different management of antiplatelet and anticoagulants after T2MI caused by bleeding.

Conclusions

Among patients with T2MI caused by bleeding, mortality is high. Patients who were discharged without antiplatelet or anticoagulant therapy have low rebleeding and readmission rates but very high mortality. On the other hand, those treated with antiplatelets, anticoagulants, and/or invasive procedures have higher rebleeding rates but lower mortality. Trials will be needed to establish treatment strategies for this high-risk population.

Authors' Contributions

Jason H. Wasfy: Conceptualization, Methodology, Data Curation, Formal analysis, Investigation, Original Draft Preparation, Writing – Original Draft Preparation, Writing – Review & Editing, Supervision, Funding Acquisition; Johnny Atallah: Conceptualization, Methodology, Data Curation, Formal analysis, Investigation, Original Draft Preparation, Writing – Original Draft Preparation, Writing – Review & Editing; Tania Chiha: Methodology, Formal Analysis, Writing – Original Draft Preparation, Writing – Review & Editing; Chen Chen: Methodology, Formal Analysis; Cian P. McCarthy: Investigation, Writing-Original Draft Preparation, Writing-Review & Editing; James L. Januzzi: Investigation, Writing-Original Draft Preparation, Writing-Review & Editing; Jolanta M. Siller-Matula: Investigation, Writing-Original Draft Preparation, Writing-Review & Editing. All authors have read and agreed to the published version of the manuscript.

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Data Availability Statement

The data underlying this article are available in the article and in its online supplementary material.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2023.05.008.

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