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Diabetic Retinopathy Should Not Be a Contraindication to Thrombolytic Therapy for Acute Myocardial Infarction: Review of Ocular Hemorrhage Incidence and Location in the GUSTO-I Trial

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Objectives. **This study sought to evaluate the incidence of ocular hemorrhage in patients with and without diabetes after thrombolytic therapy for acute myocardial infarction.**

Background. **Ocular hemorrhage after thrombolysis has been reported rarely. However, there is concern that the risk is increased in patients with diabetes. In fact, diabetic hemorrhagic retinopathy has been identified as a contraindication to thrombolytic therapy without clear evidence that these patients have an increased risk for ocular hemorrhage.**

Methods. **We identified all suspected ocular hemorrhages from bleeding complications reported in patients enrolled in the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO)-I trial. Additional information was collected on a one-page data form. We compared the incidence and location of ocular hemorrhages in patients with and without diabetes.**

Results. **There were 40,899 patients (99.7%) with information about diabetic history and ocular bleeding. Twelve patients (0.03%) had an ocular hemorrhage. Intraocular hemorrhage was confirmed in only one patient. There were 6,011 patients (15%) with diabetes, of whom only 1 had an ocular hemorrhage (eyelid hematoma after a documented fall). The upper 95% confidence intervals for the incidence of intraocular hemorrhage in patients with and without diabetes were 0.05% and 0.006%, respectively.**

Conclusions. **Ocular hemorrhage and, more important, intraocular hemorrhage after thrombolytic therapy for acute myocardial infarction is extremely uncommon. The calculated upper 95% confidence interval for the incidence of intraocular hemorrhage in patients with diabetes was only 0.05%. We conclude that diabetic retinopathy should not be considered a contraindication to thrombolysis in patients with an acute myocardial infarction.**

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Diabetic hemorrhagic retinopathy has been classified as an absolute contraindication to thrombolytic therapy in patients with acute myocardial infarction because of the risk of retinal hemorrhage (1). It is listed as a relative contraindication to alteplase (Genentech, Inc.) and to streptokinase (KabiVitrum, Inc.) on package inserts. However, there is no clear evidence that patients with diabetic retinopathy are at an increased risk for intraocular hemorrhage after thrombolytic therapy. We have found only two published case reports of patients with intraocular hemorrhage associated with thrombolysis—one of these patients had a history of diabetes, the other did not (2,3).

To better define the incidence and location of ocular hemorrhage in patients with and without diabetes treated with thrombolytic therapy for acute myocardial infarction, we analyzed the patients with ocular hemorrhage in the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO)-I trial (4).

Methods

Study population. The study population was the 41,021 patients enrolled in the GUSTO-I trial (4). Patients were enrolled at 1,081 centers in 15 countries between December 1990 and February 1993. In brief, patients presenting with an acute myocardial infarction within 6 h of symptom onset were randomized to one of four thrombolytic strategies: 1) streptokinase, 1.5 million U, intravenously over 60 min and subcutaneous heparin, 12,500 U, twice daily; 2) streptokinase, 1.5 million U, intravenously over 60 min and intravenous heparin, 5,000 U bolus followed by 1,000 U/h; 3) alteplase in an accelerated regimen (15-mg intravenous bolus followed by

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Abbreviations and Acronyms

ACC/AHA = American College of Cardiology/American Heart Association
GUSTO-I = Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (trial)
TAMI = Thrombolysis and Angioplasty in Myocardial Infarction (trial)

0.75 mg/kg body weight over 30 min, then 0.5 mg/kg over the next 60 min) and intravenous heparin, 5,000 U bolus followed by 1,000 U/h; or 4) both streptokinase, 1 million U, and alteplase, 1.0 mg/kg over 60 min, and intravenous heparin, 5,000 U bolus followed by 1,000 U/h. All patients received aspirin (160 to 325 mg) daily.

Patients were excluded from enrollment if there was active bleeding, a history of previous stroke, previous treatment with streptokinase or alteplase, recent trauma or major operation, previous participation in the trial or recent noncompressible vascular puncture. Patients with severe, uncontrolled hypertension (systolic blood pressure ≥180 mm Hg unresponsive to therapy) were considered to have a relative contraindication to enrollment. Patients with diabetes mellitus or diabetic complications were not excluded by the protocol.

Data collection. Case report forms were completed by study coordinators at each site, reviewed by the principal investigator and submitted to the GUSTO-I Coordinating Center. The case report form collected information about patient baseline clinical and historical characteristics, medications, procedures and clinical events and complications, including bleeding with severity and location. Diabetic history, including the age at diagnosis and whether there was a history of insulin therapy, was also collected. A patient was defined as having diabetes mellitus if a physician had made a diagnosis of diabetes mellitus before or during the hospital period for the acute myocardial infarction that resulted in enrollment in the GUSTO-I trial.

Supplemental ocular hemorrhage form. For all patients identified on the case report form as having an ocular hemorrhage, a supplemental form was sent to the study coordinator at the site where the patient was enrolled. This form requested additional information about the timing of the ocular hemorrhage in relation to the administration of thrombolytic therapy, the location of the ocular hemorrhage, the presence of diabetic complications, including previous diagnosis of diabetic retinopathy, and history of other ocular disease. If the patient was seen by an ophthalmologist, a copy of the consultation note was requested. In addition, information about suspected ocular hemorrhage was collected by direct contact with study coordinators or principal investigators at the site.

Statistical analysis. Clinical and historical data are reported using percentages for categoric variables and 25th, 50th and 75th percentiles for continuous variables. We used odds ratios and 95% confidence intervals to compare the incidence of ocular hemorrhage in patients with and without diabetes.

Table 1. Baseline Characteristics of Patients With and Without Ocular Hemorrhage

	Patients With Ocular Hemorrhage (n = 12)	Patients Without Ocular Hemorrhage (n = 40,877)
Age (yr)	66 (47, 72)	62 (52, 70)
Male	9 (75.0)	30,580 (74.8)
Female	3 (25.0)	10,286 (25.2)
Killip class		
I	11 (91.7)	34,734 (85.4)
II	1 (8.3)	5110 (12.6)
III	0 (0.0)	545 (1.3)
IV	0 (0.0)	308 (0.8)
Infarct location		
Anterior	4 (33.3)	15,911 (39.0)
Inferior	8 (66.7)	23,447 (57.5)
Other	0 (0.0)	1346 (3.3)
None	0 (0.0)	50 (0.1)
Systolic blood pressure (mm Hg)	140 (113, 163)	130 (112, 144)
Heart rate (beats/min)	81 (74, 90)	74 (62, 86)
History of hypertension	2 (16.7)	15,513 (38.1)
Diabetes mellitus	1 (8.3)	5994 (14.7)

Data presented are number (%) of patients or median (25th, 75th percentiles).

The logit estimators for the odds ratio and 95% confidence intervals used a correction of 0.5 in every cell that contained zero. Upper 95% confidence limits for the incidence of intraocular hemorrhage were estimated using the formula of Hanley and Lippman-Hand (5).

Results

There were 41,021 patients enrolled in the GUSTO-I trial. Data on diabetic history and ocular bleeding during the trial were known for 40,899 patients (99.7%). The baseline clinical characteristics for patients with and without ocular hemorrhage are shown in Table 1.

Twelve patients (0.03%) had an ocular hemorrhage in the GUSTO-I trial. These hemorrhages included 11 extraocular hemorrhages and only 1 confirmed intraocular (subretinal) hemorrhage. The rate of intraocular hemorrhage was 0.002% (1 of 40,889). Ocular hemorrhage location in patients with and without diabetes is shown in Table 2. There was no difference in the rate of ocular hemorrhage in patients with diabetes compared with patients without diabetes (odds ratio 0.53, 95% confidence interval 0.07 to 4.09). The incidence and 95% confidence intervals for intraocular hemorrhage in patients with and without diabetes are shown in Table 3. Table 4 shows the age, gender, allocated thrombolytic regimen, location of ocular hemorrhage and diabetic history for the 12 patients with ocular hemorrhage.

There were 6,011 patients (15%) with a history of diabetes, of whom 5,995 had information about ocular bleeding complications. Only one patient with diabetes had an ocular hemorrhage, and this was not an intraocular hemorrhage. Rather, it

Table 2. Location of Ocular Hemorrhages in GUSTO-I Trial (n = 40,889)

Location	Number of Patients		
	Diabetes	No Diabetes	Total
Extraocular			
Periorbital hematoma	1	3	4
Subconjunctival hemorrhage	0	7	7
Intraocular			
Retinal hemorrhage	0	1	1
Vitreal hemorrhage	0	0	0
Total	1	11	12 (0.03%)
OR*			0.53
95% CI*			0.07–4.09

*Odds ratio (OR) and 95% confidence interval (CI) for incidence of ocular hemorrhage in patients with versus without diabetes.

was a soft tissue extraocular (eyelid) hematoma secondary to a documented fall. The duration of the diagnosis of diabetes mellitus and history of insulin therapy at the time of enrollment were known for 4,105 patients (68%) with diabetes enrolled in the GUSTO-I trial (Table 5).

Discussion

The results presented here from the GUSTO-I trial indicate that ocular hemorrhage was a rare complication after thrombolytic therapy for acute myocardial infarction. There were only 12 patients (0.03%) with ocular hemorrhage and, more important, only 1 patient without diabetes had confirmed intraocular hemorrhage. None of 6,011 patients with diabetes had a clinically recognized intraocular hemorrhage. The one diabetic patient with an ocular hemorrhage had an extraocular (eyelid) hematoma after a documented fall. The upper 95% confidence interval for the incidence of intraocular hemorrhage in patients with diabetes was 0.05%. These data suggest that diabetic retinopathy should not be a contraindication to thrombolytic therapy for acute myocardial infarction. Others (6,7) also support this recommendation from their institutional experiences. In addition, the newly published American College of Cardiology/American Heart Association (ACC/AHA) guidelines for management of patients with acute myocardial infarction (8) no longer list diabetic hemorrhagic retinopathy as a contraindication to thrombolysis.

Patients with diabetes are at an increased risk for coronary artery disease and have a worse clinical outcome after acute myocardial infarction than patients without diabetes (9–11). Despite the significant survival benefit associated with thrombolytic therapy for these patients (12,13), they are often excluded from such treatment (14). Although the reason for this exclusion is not entirely clear, it may relate to the increased age of these patients, longer delays in seeking medical attention or a higher incidence of concomitant medical problems, such as diabetic retinopathy.

Table 3. Incidence and Confidence Intervals for Intraocular Hemorrhage in Patients With and Without Diabetes in the GUSTO-I Trial

	Diabetes (n = 5,995)	No Diabetes (n = 34,818)
Incidence	0 (0%)	1 (0.003%)*
95% CI	0.0–0.05	0.0–0.006

*Odds ratio and 95% confidence interval (CI) for intraocular hemorrhage in patients with versus without diabetes (0.52, 0.02 to 12.68).

Diabetic retinopathy. The term diabetic hemorrhagic retinopathy, used by Gunnar et al. (1) in the previous ACC/AHA guidelines for management of patients with acute myocardial infarction, is imprecise. Most ophthalmologists describe diabetic retinopathy as either *nonproliferative* (background) or *proliferative* (15). Nonproliferative retinopathy classically includes retinal microaneurysms and retinal blot hemorrhages in which blood is contained within retinal extracellular spaces. Vitreous hemorrhage is not included in the classification of nonproliferative retinopathy. Eyes with proliferative retinopathy often demonstrate preretinal neovascularization but no preretinal hemorrhage.

Vitreous hemorrhage in patients with diabetic retinopathy is generally thought to result from posterior vitreous detachment, which can cause traction on and damage to adherent blood vessels (16,17). It is unclear how thrombolysis would increase the risk for a detachment unless there was a recent violation of the structural integrity of the microvasculature that had an associated thrombus. Vitreous hemorrhage in a diabetic patient is not an irreversibly blinding event. Hemorrhage often clears in patients with recovery of vision or can be removed with vitreous surgery, allowing recovery of vision.

Previous reports. Fava et al. (18) retrospectively reviewed data from 507 diabetic patients admitted to their institution with an acute myocardial infarction. Fourteen patients had documented nonproliferative retinopathy; no ocular hemorrhages were clinically recognized after treatment with thrombolytic therapy. However, 26 patients with a history of proliferative diabetic retinopathy were not treated with thrombolysis.

A retrospective analysis (11) of clinical outcomes of diabetic patients after acute myocardial infarction studied the 158 patients (14%) with diabetes in the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) trials, which evaluated various thrombolytic regimens and interventional strategies in patients with an acute myocardial infarction. Eleven patients (7%) had a history of diabetic retinopathy, and no clinically evident intraocular hemorrhagic complications were recognized. The GUSTO-I trial had fewer exclusion criteria than the TAMI trials; as a large, simple, multicenter trial, it included a population at higher risk and more representative of the general acute myocardial infarction population. The median patient age was higher in the GUSTO-I population than the TAMI population (62 vs. 56 years). The effect of this increased age in the GUSTO-I trial on ocular hemorrhage is unknown.

Several investigators (19) have studied the association between the development of diabetic retinopathy and the age at diagnosis of diabetes, the duration of diabetes and the need

Table 4. Twelve Patients With Ocular Hemorrhage: Age, Gender, Treatment Assignment, Ocular Hemorrhage Location and Diabetic History (GUSTO-I trial)

Pt No./Gender	Age (yr)	Treatment	Ocular Hemorrhage Location	Diabetic History
1/M	68	t-PA	Right conjunctival	None
2/M	49	t-PA	Bilateral conjunctival	None
3/F	74	Combo	Eyelid (after documented fall)	13-yr history; not taking insulin
4/F	66	Combo	Right choroidal (subretinal)	None
5/F	66	t-PA	Periorbital	None
6/M	72	Combo	Periorbital	None
7/M	56	Combo	Right conjunctival	None
8/M	34	SK+SQ	Bilateral conjunctival	None
9/M	34	SK+IV	Bilateral scleral	None
10/M	72	Combo	Periorbital (after documented fall)	None
11/M	76	Combo	Left conjunctival	None
12/M	44	SK+SQ	Left conjunctival	None

Combo = combination therapy with streptokinase (SK) and tissue-type plasminogen activator (t-PA); F = female; IV = intravenous heparin; M = male; Pt = patient; SQ = subcutaneous heparin.

for insulin therapy. Data on the duration of diabetes and insulin therapy were available for patients in the GUSTO-I trial. By applying these relations to the diabetic population in GUSTO-I, we estimate that ~2,000 patients may have had nonproliferative retinopathy, and ~300 could have had proliferative retinal changes.

Outcome after ocular hemorrhage. Outcome after intraocular hemorrhage associated with thrombolytic therapy is unknown. Data on visual deficits at the time of ocular hemorrhage and follow-up at hospital discharge were known for 9 GUSTO-I patients (75%) with ocular hemorrhage. Only the patient with the choroidal (subretinal) hemorrhage had a documented visual deficit that improved dramatically but was still present at the time of hospital discharge. Others (20,21) have reported that three patients with anterior chamber intraocular hemorrhage after thrombolytic therapy for acute myocardial infarction within 8 days of cataract extraction had no limitation in visual acuity at follow-up. Some argue (22) that in the setting of thrombolytic and antiplatelet therapy, there may be improved resolution of an intraocular hemorrhage. In addition, the use of antiplatelet agents such as aspirin has been questioned in patients with diabetes, but the Early Treatment Diabetic Retinopathy Study (ETDRS) (23) investigators reported no increase in the occurrence or severity of vitreous or preretinal hemorrhages in patients with diabetes.

Table 5. Duration of Diagnosis of Diabetes Mellitus and History of Insulin Therapy in Patients With Diabetes in GUSTO-I

Duration of Diagnosis (yr)	No. of Pts	Insulin Therapy [no. (%) of pts]
<10	2,490	450 (18.1)
10–14	681	260 (38.2)
15–19	390	190 (48.7)
>20	551	296 (53.7)
Unknown	1,899	447 (24.3)
Total	6,011	1,643 (27.3)

Pts = patients.

Diagnosis of retinopathy. The diagnosis of retinopathy is often difficult in the emergency setting of an acute myocardial infarction. Opiates may have been administered; patients may be unable to fully cooperate with a fundal examination; and although many patients with diabetes may have had a previous detailed funduscopic examination, medical records may not be available at the time that decisions have to be made about administration of thrombolytic therapy. In addition, without a complete fundus examination, significant diabetic retinopathy will be missed. In two studies (24,25) comparing examination with and without dilation of the pupil, diabetic retinopathy was correctly identified in only 50% of eyes. Excluding diabetic patients from thrombolysis because of a concern about the possibility of retinopathy could potentially withhold life-saving therapy from an important group of patients.

Limitations of the study. There are several limitations to this study. The small number of ocular hemorrhages limits the ability to determine factors statistically associated with such a complication. However, the absolute numbers confirm that there is indeed a very low risk for intraocular hemorrhage associated with thrombolytic therapy.

There was no systematic assessment of all patients to determine the incidence of diabetic retinopathy; therefore, the precise risk for ocular hemorrhage among patients with diabetic retinopathy treated with thrombolysis cannot be determined. However, it would have provided a better estimate of the risks and benefits associated with thrombolytic therapy. The estimated incidence of diabetic retinopathy in the GUSTO-I population may have been affected by the exclusion of diabetic patients from the trial. However, a reliable estimate of the potential number of patients with diabetic retinopathy in the GUSTO-I trial can be provided from analysis of the 4,112 patients with data about duration of diabetes and insulin therapy requirements.

Many patients with diabetes or with diabetic retinopathy may have been excluded from enrollment in GUSTO-I, although the protocol did not indicate that such patients should not be enrolled. The reason for study exclusion was not documented for all patients considered for enrollment in the GUSTO-I trial.

Finally, the incidence of unrecognized intraocular hemorrhage, and its associated long-term consequences, is not known.

Conclusions. Ocular hemorrhage and, more important, intraocular hemorrhage after thrombolytic therapy for acute myocardial infarction, is extremely uncommon. In the GUSTO-I trial there were 12 ocular hemorrhages (0.03%), only 1 of which was an intraocular hemorrhage. No patient with diabetes had an intraocular hemorrhage despite an estimated 2,000 diabetic patients with nonproliferative retinopathy and 300 with proliferative retinopathy. The calculated upper 95% confidence interval of 0.05% for the incidence of intraocular hemorrhage in patients with diabetes in the GUSTO-I population is small and probably negligible compared with the proven life-saving benefit associated with thrombolysis for acute myocardial infarction in these patients. Excluding patients with diabetes because of a potentially increased risk for intraocular hemorrhage is not supported by our data. We conclude that diabetic retinopathy should not be considered a contraindication to the administration of thrombolytic therapy in patients with acute myocardial infarction.

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