

Note that, compared to the imbalances in baseline characteristics of patients enrolled in study ARG-911, (where argatroban-treated patients were uniformly more compromised than historical control patients), study populations were much more similar in study ARG-915, with historical control patients often more compromised in several disease, surgical, and medical history categories. Thus, the numerical trend of greater deaths in argatroban-treated patients in study ARG-911 would be expected to be less evident (if not non-existent) in study ARG-915, IF these excess deaths were due primarily to greater underlying disease in argatroban-treated patients. Thus, analyses of the incidences and causes of death in studies ARG-911 and ARG-915, do not support the contention that the observed trends toward increased mortality in argatroban-treated patients were due solely to imbalances in baseline characteristics.

Validity of the NEW THROMBOSIS Endpoint

Whether a relative lack of vigilance to new thrombotic events in argatroban-treated patients (due to greater underlying comorbidity), could have accounted for the significantly lower incidence of this endpoint compared to historical control patients, was considered. However, pre- and post-therapy Doppler Ultrasound examinations and VQ scans, as well as daily assessments of clinical signs and symptoms of ischemia (while hospitalized), were performed on argatroban-treated patients. Thus, significant attention to new thrombotic events was paid during study ARG-911, particularly during the period when approximately 80% of the overall composite endpoint events occurred in historical control patients (compared to 48% of overall composite endpoints in argatroban-treated patients).

Whether new thrombotic events were relatively over-called in historical control patients was also considered. This could result from the fact one of the sponsor's suggestions for the initial identification of historical control patients was to start with patients who had experienced a DVT or PE. The actual extent of this practice in study ARG-911 could not be assessed from the information provided. Note however, that any enrichment of historical control patients with new thrombotic events was not reflected in higher death or amputation rates, when compared to argatroban-treated patients.

Whether the greater incidence of HIT antibody positivity of historical control patients, compared to argatroban-treated patients, could have accounted for the greater incidence of new

thrombotic events in historical control patients, was considered. Specifically, 68% of argatroban-treated HIT patients were positive for a HIPA, SRA, or H-PF4 ELISA for the HIT antibody (13% were negative, and 19% were not tested); 67% of argatroban-treated HITTS patients were positive for a HIPA, SRA, or H-PF4 ELISA for the HIT antibody (5% were negative, and 28% were not tested). Similarly, 78% of historical control HIT patients were positive for a HIPA or SRA for the HIT antibody (22% were negative); 96% of historical control HITTS patients were positive for a HIPA or SRA for the HIT antibody (4% were negative). However, as shown below, the effectiveness of argatroban in HIT antibody positive patients is supported by the efficacy outcome results in the SRA Positive HIT population, and in the population of patients with a history of a positive laboratory test for HIT. Note that the incidences of the overall composite endpoint were similar for argatroban-treated and historical control, SRA Positive HITTS patients, due to numerical trends of greater amputation and all-cause death in argatroban-treated patients.

Efficacy Outcomes for the SRA Positive Population in Study ARG-911

Efficacy Outcomes	HIT			HITTS		
	Hist Ctrl 35	Argatro 70	P-value*	Hist Ctrl 72	Argatro 86	P-value*
New Thromboses	21 (60%)	3 (4%)	<0.0001	30 (42%)	19 (22%)	0.010
Amputation	0 (0%)	4 (6%)	0.299	5 (7%)	11 (13%)	0.293
All-cause Death	5 (14%)	7 (10%)	0.529	7 (10%)	15 (17%)	0.178
Overall Composite	24 (69%)	14 (20%)	<0.0001	34 (47%)	38 (44%)	0.750

* two-sided Fisher's Exact Test

Adapted from Tables 26 and 27, vol. 105, pp. 154-5

Efficacy Outcomes of the Subgroup of HIT patients with a HISTORY of a Positive Laboratory Test for HIT

Efficacy Outcomes	HIT		
	Hist Ctrl 108	Argatro 31	P-value*
New Thromboses	25 (23%)	2 (6%)	0.041
Amputation	4 (4%)	1 (3%)	N.S.
All-cause Death	12 (11%)	0 (0%)	0.068
Overall Composite	36 (33%)	3 (10%)	0.012

* two-sided Fisher's Exact Test

From information from Volume 4.1, pg. 335

Overall Safety Experience with Argatroban**Study ARG-911**

The primary causes of death in both argatroban-treated and historical control patients were thrombosis and organ system failure (cardiac, respiratory, and renal). Note that 14% and 27% of deaths in argatroban-treated HIT and HITTS patients, respectively, occurred during the argatroban infusion period, while 67% and 75% of deaths for HIT and HITTS patients, respectively, occurred during the equivalent period in historical control patients. Specific causes of death in argatroban-treated and historical control HIT and HITTS patients have been discussed.

A total of 11(7%) of HIT patients and 11(8%) HITTS patients receiving argatroban withdrew from the study. Among the HIT patients, 1 patient was withdrawn due to death, and 2 patients withdrew due to hemorrhage. Among HITTS patients, 8 patients withdrew secondary to hemorrhage or anemia, and 3 patients withdrew due to a thrombotic event. Most serious adverse events in argatroban-treated HIT/HITTS patients were related to thrombosis or bleeding. Serious adverse events were not specifically identified in historical control patients.

For HIT patients, a total of 101(63%) argatroban-treated patients and 49(45%) historical control patients experienced adverse or emergent (defined as first 7 days of observation) adverse events, respectively, **during the period of argatroban infusion**. For HITTS patients, a total of 105(73%) argatroban-treated and 72(66%) historical control patients experienced adverse and emergent events, respectively, for the same time period.

No individual treatment-emergent adverse event occurred more often in argatroban-treated HIT patients, by a difference of $\geq 5\%$.

Individual treatment-emergent adverse events that occurred more often in argatroban-treated HITTS patients, by a difference of $\geq 5\%$, were constipation (7% of argatroban-treated patients compared 0% of historical control patients), and urinary tract infection (8% of argatroban-treated patients compared to 2% in historical control patients).

Major bleeding was defined as bleeding which was overt AND 1) was associated with a decrease in hemoglobin of ≥ 2 g/dL, 2) led to a transfusion of ≥ 2 units PRBCs, OR 3) was intracranial, retroperitoneal, or occurred into a major prosthetic joint. Bleeding was considered **minor** if it was reported but did not require more than 2 units of PRBCs. Note that significantly **more** argatroban-treated HIT patients received concomitant antithrombotic therapy (other than heparin): 134(84%) patients in the argatroban group compared to 76(70%) patients in the historical control group. Significantly **fewer** argatroban-treated HITTS patients received concomitant antithrombotic therapy (other than heparin): 122(85%) patients in the argatroban group compared to 105(96%) patients in the historical control group.

No statistically significant difference in the rates of major bleeding were seen between argatroban and historical control groups for HIT or HITTS patients. The incidence of major bleeding in argatroban-treated patients was 3.1% in HIT patients, and 10.4% in HITTS patients. Most major bleeding sites in argatroban-treated patients were gastrointestinal, genitourinary, or related to a procedure or surgery, and there was no intracranial or retroperitoneal bleeding.

Total transfusions in the HIT population were significantly greater in the historical control patients: 59(37%) argatroban-treated patients compared to 58(54%) historical control patients. Total transfusions were not significantly different between argatroban-treated and historical control patients in the HITTS population.

The incidence of minor bleeding was significantly greater in argatroban-treated patients (40% and 42% of argatroban HIT and HITTS patients, respectively; compared to 12% and 17% of historical control HIT and HITTS patients, respectively). However the sponsor stated that "minor bleeds were heavily biased against test drug because there was no way of retrospectively identifying minor bleeds in the historical control group".

The highest rate of transfusion-requiring minor bleeding for argatroban-treated HIT patients was a 2% incidence of GU-, Thoracic-, Abdominal-, and CABG-related bleeding. The highest rate of transfusion-requiring minor bleeding for argatroban-treated HITTS patients was a 3% incidence of GI bleeding.

The highest rates of non-transfusion-requiring minor bleeding for argatroban-treated HIT patients were: GI (6%), GU (9%), Limb sites (5%), and Hemopytosis (7%). The highest rates of

non-transfusion-requiring minor bleeding for argatroban-treated HITTS patients were: GI (8%), GU (6%), and Limb sites (6%).

No clinically significant changes in laboratory parameters except for expected increases in the PT, APTT, and platelet count, were seen.

Note that the evaluation of the safety profile for argatroban in study ARG-911 is complicated by: 1) the imbalances in patient characteristics, with argatroban-treated patients having been sicker at baseline, and 2) the lack of the specific identification of serious adverse events AND minor bleeding events in historical control patients.

Study ARG-915

All deaths were reconstructed and reclassified from case report form data, and have been discussed.

A total of 5(6%) HIT patients, and 7(8%) HITTS argatroban-treated patients withdrew from ARG-915 for an adverse event. Similar rates were seen in study ARG-911.

Treatment-emergent and serious adverse events for patients in study ARG-915 were not provided.

Those adverse events that occurred more often in argatroban-treated HIT patients, by a difference of $\geq 5\%$, were nausea (0% of historical control, compared to 9% of argatroban-treated patients), and ventricular tachycardia (2% of historical control, compared to 11% of argatroban-treated patients).

A total of 72(66%) historical control, and 70(79%) argatroban-treated HITTS patients experienced an adverse event. Those adverse events that occurred more often in argatroban-treated HITTS patients, by a difference of $\geq 5\%$, were: ventricular tachycardia (1% of historical control, compared to 8% of argatroban-treated patients), acute renal failure (1% of historical control, compared to 6% of argatroban-treated patients), fever (2% of historical control, compared to 11% of argatroban-treated patients), and dyspnea (6% of historical control, compared to 11% of argatroban-treated patients).

The incidences of major bleeding were 8.2% and 12.3% in argatroban-treated HIT and HITTS patients, respectively. These rates are higher than the major bleeding rates seen in

argatroban-treated patients in study ARG-911 (3.1% and 10.4% in HIT and HITTS patients, respectively), and not significantly different than those reported for historical control patients.

Blood product transfusion requirements were similar for argatroban-treated patients in studies ARG-911 and ARG 915.

The incidences of minor bleeding in argatroban-treated patients in study ARG-915 were 25% in HIT, and 26% in HITTS patients. In study ARG-911, the incidences of minor bleeding were 40% and 42% for HIT and HITTS patients, respectively.

As seen for study ARG-911, the evaluation of the safety profile of argatroban in study ARG-915, was complicated by baseline imbalances in patient characteristics.

Integrated Summary of Safety

A summary of the 1340 patients included in the Integrated Summary of Safety (ISS) who received argatroban is shown below. Note that study ARG-915 was NOT included in the ISS.

Clinical Studies Included in the ISS

Phase	Study Type	Number of Argatroban-treated Patients
I	Healthy Volunteers (ARG-100, 101, 102, 105, 108, 109, 112)	128
	Special Populations	41
	ARG-103 Renal Disease (creat clearance <80 ml/min/1.73 m2)	24
	ARG-106 Hepatic Disease (Child's score > 6)	17
II/III	Randomized Studies	731
	ARG-210 PTCA	5
	ARG-230 Acute MI (Adjunctive therapy to argatroban vs. placebo)	725
	ARG-912 HIT/HITTS	1
	Open-Label Studies	327
	ARG-216 PTCA	21
	ARG-240 HIT/HITTS	2
	ARG-911 HIT/HITTS (Pivotal Study)	304
	Ongoing Studies	112
	ARG-231 Acute MI (Adjunctive therapy to r-TPA)	85
	ARG-310 HIT/HITTS in Setting of PTCA	27

A total of 63% of patients received 1 to 7 days of argatroban therapy; 23% received 12 hours or less, and 1% received > 14 days of therapy. The majority (70%) of patients who received < 1 day of argatroban, received argatroban for a PTCA procedure. All 9 patients who received argatroban for > 14 days were being treated for HIT/HITTS.

A summary of ON-THERAPY DEATHS reported in the ISS is shown below:

ON-THERAPY DEATHS

Studies	Hist Ctl	Active Ctl	Placebo	Argatro	Comments
Normal Volunteers	--	0(0%)	--	0(0%)	--
Special Populations	--	--	--	0(0%)	--
Randomized Studies	--	--	11(3%)	32(4%)	Causes of death were similar in both treatment groups, and were cardiovascular in origin (cardiac arrest, circulatory failure, MI, and ventricular fibrillation).
Open-Label Studies	18(8%)	--	--	11(3%)	Causes of death that occurred more often in argatroban-treated patients were <u>single</u> events of acidosis, DIC, ECG abnormal, and encephalopathy.
Ongoing Studies	--	0(0%)	--	2(2%)	Causes of death in argatroban-treated patients were cardiovascular in origin.

A summary of TREATMENT-EMERGENT ADVERSE EVENTS THAT LED TO PREMATURE STUDY WITHDRAWAL reported in the ISS is shown below:

TREATMENT-EMERGENT ADVERSE EVENTS THAT LED TO PREMATURE STUDY WITHDRAWAL

Studies	Hist Ctl	Active Ctl	Placebo	Argatro	Comments
Normal Volunteers	--	0(0%)	--	1(1%)	Rash
Special Populations	--	--	--	0(0%)	--
Randomized Studies	--	--	33(9%)	90(12%)	No individual adverse event occurred more often in argatroban-treated patients, by a difference of $\geq 1.0\%$.
Open-Label Studies	1(0.5%)	--	--	24(7%)	No individual adverse event occurred more often in argatroban-treated patients, by a difference of $\geq 1.0\%$.
Ongoing Studies	--	4(10%)	--	8(7%)	The adverse event that occurred more often in argatroban-treated patients, with a difference of $\geq 1.0\%$, was "vascular disorder" (1.8% vs 0.0%).

A summary of SERIOUS ADVERSE EVENTS reported in the ISS is shown below:

SERIOUS ADVERSE EVENTS

Studies	Hist Ctl	Active Ctl	Placebo	Argatro	Comments
Normal Volunteers	--	0(0%)	--	0(0%)	--
Special Populations	--	--	--	0(0%)	--
Randomized Studies	--	--	87(24%)	214(29%)	Adverse events that occurred more often in argatroban-treated patients, by a difference of $\geq 1.0\%$, were cardiac failure (1.8% vs 0.5%), circulatory failure (3.7% vs 2.5%), and MI (5.1% vs 3.3%).
Open-Label Studies	--	--	--	142(43%)	Serious adverse events were not specifically identified in historical control patients.
Ongoing Studies	--	9(23%)	--	13(12%)	The serious adverse that occurred more often in argatroban-treated patients, with a difference of $\geq 1.0\%$, was cardiac arrest (1.8% vs 0.0%).

Note that the increased incidences of cardiovascular adverse events in argatroban-treated patients in randomized and ongoing studies, may have resulted from a lack of efficacy of argatroban, as an anticoagulant in patients with acute MI or undergoing PTCA.

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A summary of TREATMENT-EMERGENT ADVERSE EVENTS reported in the ISS is shown below:

TREATMENT-EMERGENT ADVERSE EVENTS

Studies	Hist Ctl	Active Ctl	Placebo	Argatro	Comments
Normal Volunteers	--	14 (39%)	--	49 (38%)	The adverse event that occurred more frequently in argatroban-treated subjects, with a difference of $\geq 5\%$, was dizziness (11% vs 6%). (Active control medications were heparin, warfarin, or no therapy).
Randomized Studies	--	--	330 (90%)	671 (92%)	The adverse events that occurred more often in argatroban-treated patients, by a difference of $\geq 3.0\%$, was abdominal pain (8.9% vs 5.5%).
Open-Label Studies	121 (56%)	--	--	261 (80%)	Adverse events that occurred more frequently in argatroban-treated patients, by a difference of $\geq 3.0\%$, were: rash (5.2% vs 1.4%), constipation (5.8% vs 0.5%), diarrhea (7.0% vs 3.2%), hypotension (8.3% vs 3.7%), cardiac arrest (5.8% vs 2.8%), purpura (3.7% vs 0.5%), fever (6.1% vs 1.8%), infection (4.3% vs 0.9%), and sepsis (5.8% vs 2.3%).
Ongoing Studies	--	30 (75%)	--	73 (65%)	Adverse events that occurred more frequently in argatroban-treated patients, by a difference of $\geq 3.0\%$, were: hypotension (9.8% vs 5.0%), diarrhea (3.6% vs 0.0%), and back pain (12.0% vs 5.0%).

Note that although an increased incidence of hypotension was seen in open-label and ongoing studies, such a trend was not noted among serious adverse events, and no clinically significant changes in vital signs (including blood pressure), were reported with the use of argatroban.

Aside from expected increases in the PT and APTT, no other clinically significant changes in clinical laboratory parameters were reported.

Argatroban has been approved in Japan for 1) chronic arterial disease, at a dose of 10 mg iv bid (approved in 1990), 2) acute cerebral thrombosis, at a dose of 60 mg iv for 2 days, then 10 mg iv bid for the next 5 days (approved in 1996), and 3) hemodialysis in patients with ATIII deficiency, at an initial dose of 10 mg, followed by 5-40 mg/hour during dialysis (approved in 1996)

The results of a required 6-year post-marketing survey in Japan, supports the overall safety of argatroban, at doses that are approximately 100x and 10x the average daily, and cumulative 7-day doses, respectively, of those used in studies ARG-911 and ARG-915.

In summary, the primary safety consideration with the use of argatroban is bleeding. Interestingly, the rate of major bleeding was not significantly different in argatroban-treated and historical control patients in studies ARG-911 and ARG-915. This suggests that argatroban may not substantially contribute to bleeding in excess of that due to heparin, and/or the concomitant use of warfarin and aspirin. The greater incidence of major bleeding (and lower incidence of minor bleeding) in patients in study ARG-915 compared to that found in study ARG-911, is unexplained.

OVERALL CONCLUSIONS

Study ARG-911 was a multicenter, open-label, historically-controlled, prospective study of 304 patients with HIT/HITTS treated with argatroban. Primary efficacy outcomes were death, amputation, or development of a new thrombosis for HIT patients, and death or amputation for HITTS patients. Study ARG-915 was a compassionate-use, continuation study of ARG-911, designed to collect additional safety information. Study ARG-915 enrolled 271 HIT/HITTS patients, and employed the same historical control as study ARG-911.

Highly significant reductions in the incidence of new thrombotic events were observed for both HIT and HITTS patients in studies ARG-911 and ARG-915. Further support for the efficacy of argatroban included the significantly reduced overall composite endpoint (of death, amputation, or new thrombosis) for 1) SRA Positive HIT patients, 2) Patients with a history of a positive HIT antibody test on study entry, 3) the primary analysis of HITTS patients in study ARG-915, and 4) the secondary analysis of HITTS patients in study ARG-911 following adjustment for those baseline patient characteristics that were predictors of all-cause mortality.

However, numerical trends of greater all-cause mortality were also seen in study ARG-911. These trends were attributed to greater underlying disease in argatroban-treated patients, which was supported by the more compromised health status of these

patients at baseline. An even greater incidence of all-cause mortality in argatroban-treated HIT and HITTS patients in study ARG-915 however, argued against this explanation, as patient baseline characteristics between treatment groups were much more similar in this study (with historical control patients being more compromised in several body system/disease categories).

All deaths that occurred in studies ARG-911 and ARG-915 were reconstructed and reclassified from case report form data. The results of this analysis found that the incidences of thrombotic deaths were essentially the same for historical control and argatroban-treated HIT and HITTS patients. Ongoing thrombosis was not identified in the remainder of deaths, and many were not likely related to a thrombotic complication of HIT/HITTS. However, the overall increased mortality in argatroban-treated patients in studies ARG-911 and ARG-915, compounded by the 27% mortality rate reported so far for the remaining 97 argatroban-treated patients who have completed study ARG-915, raise significant concerns with regard to the efficacy of argatroban in patients with HIT/HITTS. Thus, approval of argatroban for the proposed indication of "anticoagulant therapy in patients with heparin-induced thrombocytopenia", cannot be recommended at this time.

ISI 1-1-98
Kurt Sizer, M.D.

cc:

NDA 20-803

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HFD-180/JChoudary

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Appendix 1: Analysis of Deaths that Occurred in Study ARG-911

A summary of deaths that occurred in historical control HIT patients which were attributed to thrombosis is shown below (Section 14.3.4, vol. 106, pp. 106-149; Table 55, vol. 105, pp. 245-260; Appendix 16.4.15, vol. 4.1, pp. 193-321; and individual Case Report Forms, vols. 201-283).

Deaths in Historical Control HIT Patients Attributed to Thrombosis

PATIENT	ADMIT DIAGNOSIS and HISTORY	HEPARIN ADMIN.	CLINICAL COURSE
037-H01 60 F	9/16 dizziness, ringing in ears, leukocytosis and thrombocytopenia s/p recent discharge for Rx for respiratory failure, sepsis, and renal failure (dialysis-dependent) H/O Connective Tissue Disease	unknown recent exposure prior to admission	Platelet count 34K/mm ³ on 9/16, 30K/mm ³ on 9/19, and 78K/mm ³ on 9/23; H-PF4 Positive 9/22: Bilateral subclavian vein thromboses following central line placement 9/26: Clinical impression of thrombotic CVA; Patient made DNR and died.
200-H14 67 F	6/26 angina H/O angina, uterine cancer	6/23-7/6	6/29: CABG Platelet count 339K/mm ³ on 6/23, 231K/mm ³ on 6/29, 117K/mm ³ on 7/1, 51K/mm ³ on 7/7, and 131K/mm ³ on 7/11; SRA Positive 7/7: Complaint of dyspnea; LE IPGs Negative 7/12: Discharged to Home 7/14: Death at Home Autopsy: Massive PE and Bilateral LE DVTs
201-H04 69 M	11/11 respiratory failure H/O CHF, COPD	11/12-11/24	11/11-11/21: Intubation/ventilation Platelet count 259K/mm ³ on 11/12, 166K/mm ³ on 11/17, 70K/mm ³ on 11/18, 30K/mm ³ on 11/20, 10K/mm ³ on 11/26, and 21K/mm ³ on 12/2; SRA Positive 12/2: Complaint of R Foot pain (not investigated) 12/3: Patient found dead in room. No autopsy performed. As per Dr. Warkentin, "This death can be classified as (caused by thrombosis), although it is uncertain whether it represented fatal pulmonary embolism or cardiac death."
202-H01 73 F	1/23 R Total Knee Replacement	1/23-1/30	Platelet count 181K/mm ³ on 1/23, 92K/mm ³ on 2/2, 64K/mm ³ on 2/4, and 258K/mm ³ on 2/11; SRA Positive 1/24: R Total Knee Replacement 1/30: Necrotic skin reaction at heparin injection site 1/31: Lethargy, nausea, vomiting, pleuritic chest pain; LE Dopplers Negative and VQ scan Low Probability 2/5: R Finger blue 2/6: R Foot numb/cold. Danaparoid initiated. 2/7: CVA with progressive neurologic deterioration. 2/12: Death due to "CVA"

A summary of deaths that occurred in historical control HIT patients which were attributed to underlying disease is shown below (Section 14.3.4, vol. 106, pp. 106-149; Table 55, vol. 105, pp. 245-260; Appendix 16.4.15, vol. 4.1, pp. 193-321; and individual Case Report Forms, vols. 201-283).

**Deaths in Historical Control HIT Patients Attributed
to Underlying Disease**

PATIENT	ADMIT DIAGNOSIS and HISTORY	HEPARIN ADMIN.	CLINICAL COURSE
016-H04 55 F	4/27 H/O Aortobifemoral bypass for PVD 5 mos PTA, CML, RA	4/27- 4/29	4/27: Urokinase and heparin administered for L Leg graft/arterial occlusions Platelet count 123K/mm ³ on 4/27, 51K/mm ³ on 4/28, 16K/mm ³ on 4/30, and 29K on 5/5; HIPA and SRA Negative 4/28: Baseline Doppler and VQ scan Not Done 5/1: Bilateral AKAs 5/4: Dopplers Not Done; VQ scan Low Probability 5/11: Elective intubation followed by endotracheal tube mucous plug obstruction, cardiac arrest, and death
016-H06	12/7 Hospitalized since 11/16 for CHF. Transferred 12/7 for mitral valvuloplasty H/O CAD, Mitral Valve disease, CHF, CVAs, a-fib	Unk - 11/29	Platelet count 51K/mm ³ on 12/7, 110K/mm ³ on 12/9, 236K/mm ³ on 12/11; HIPA and SRA Negative 12/12: Mitral Valvuloplasty 12/15: Duplex Dopplers Indeterminate or Not Done; VQ scan Not Done Platelet count 175K/mm ³ on 12/13, 91K/mm ³ on 12/16, 24K/mm ³ on 12/18, and 55K/mm ³ on 12/22 Post-procedure hospital course: hemodynamic instability, unable to wean from ventilator, infection 1/3: Patient DNR 1/6: Death secondary to "multi-system failure"
018-H01 69 M	3/17 L Hip fracture H/O Metastatic Prostate Cancer, Multiple Sclerosis	3/13- 3/24	3/13-3/24: Heparin given for DVT prophylaxis Platelet count 490K/mm ³ on 3/13, 263K/mm ³ on 3/15, 142K/mm ³ on 3/23, and 8K/mm ³ on 3/24; HIPA Negative, SRA Not Done 3/17: Gram negative bacteremia 3/20: Aspiration pneumonia and post-thoracentesis pneumothorax Platelet count 55K/mm ³ on 3/25 and 92K/mm ³ on 3/26 3/27: Death due to overwhelming sepsis
020-H18 77 F	8/11 Heart Block and Worsening Right Heart Failure H/O CABG one month prior to admission, CRF	8/12- 8/17	Hospital course: Admitted to CCU, treated for digitalis toxicity, GI bleeding, UTI, and Pneumonia. Received a permanent pacemaker. 8/26: Transferred out of CCU Platelets 288 K/mm ³ on 8/11, 176K/mm ³ on 8/16, 88K/mm ³ on 8/17, 44K/mm ³ on 8/23, 20K/mm ³ on 8/26, 55K/mm ³ on 9/2, and 13K/mm ³ on 9/7; HIPA Positive Dopplers and VQ scans Not Done 9/10: Death secondary to hepatic and renal failure

022-H02 49 M	6/24 Chest pain and R hand ischemia H/O HIT four years prior to admission, L Ventricular Aneurysm and Thrombus (on Warfarin), CAD, CVAs, MIs, Seizures	6/25-6/27	6/25: Seizure on heparin and Coumadin: initial Head CT negative; repeat Head CT 6/27 with intracerebral bleed and midline shift. Ventricular drain placed. Platelet count 156K/mm3 on 6/25, 98K/mm3 on 6/28, 156K/mm3 on 7/1, 288K/mm3 on 7/5; HIPA Negative, SRA Not Done Dopplers and VQ scans Not Done Hospital course: Unable to be extubated 7/18: Death secondary to intracerebral bleed and pneumonia. Autopsy: Generalized atherosclerosis, infarctions of fingers of R hand and brain
081-H01 84 M	2/5 Acute MI and cardiogenic shock	2/5-2/6	2/5: Emergent cardiac catheterization, PTCA, and IABP insertion 2/6: GI bleed Platelet count 168K/mm3 on 2/6, 109K/mm3 on 2/9, and 98K/mm3 on 2/13; Hep Ab Tests Not Done 2/6: LE Dopplers Positive for DVTs; VQ scan Moderate Probability Hospital Course: Patient remained intubated and was hemodynamically unstable throughout hospital course 2/13: Death secondary to "MI with cardiogenic shock"
201-H14 58 F	3/14 w/u of cervical carcinoma H/O cervical carcinoma	3/16-3/29	3/16: Cystoscopy confirmed recurrence of cervical ca 3/17: Respiratory failure requiring intubation/ventilation and resulting in hypoxic encephalopathy 3/16-3/25: Heparin administered for DVT prophylaxis Platelet count 413K/mm3 on 3/17, 157K/mm3 on 3/20, 124K/mm3 on 3/24, 78K/mm3 on 3/25; SRA Positive 3/25: Heparin discontinued 3/27-3/29: Heparin readministered Platelet count 164K/mm3 on 3/27, and 215K/mm3 on 3/29 Dopplers and VQ scans Not Done 3/28: Pneumonia and hypotension secondary to pneumothorax 3/29: Death Autopsy Results: No thrombosis or embolism, L Broad Ligament Hemorrhage extending into abdominal wall, and extensive pneumonitis (secondary to Herpes)
201-H16 78 M	10/16 Abdominal pain and fever s/p Head trauma 10 days prior to admission and subsequently bedridden H/O Dementia, CVAs, colonic polyps/bowel resection, heel decubitus ulcers	10/17-10/23 and 10/27-11/2	10/17-10/23: Heparin administered for DVT prophylaxis Platelet count 185K/mm3 on 10/16 and 182K/mm3 on 10/20 10/23: Discharged to nursing home care 10/26: Readmitted with new buttock decubitus ulcer and general deterioration 10/27-11/2: Heparin administered for DVT prophylaxis Platelet count 167K/mm3 on 10/26, 86K/mm3 on 10/30, and 57K/mm3 on 11/2; SRA Positive 11/2: Heparin discontinued Platelet count 70K/mm3 on 11/4 and 109K/mm3 on 11/6 Dopplers and VQ scans Not Done 11/19: Death secondary to "sepsis"

A summary of the death that occurred in argatroban-treated HIT patients which was labeled as "treatment emergent" is shown below (Section 14.3.4, vol. 105, pp. 440 through vol. 106, pp. 1-149; Table 55, vol. 105, pp. 245-260; Appendix 16.4.15, vol. 4.1, pp. 193-290; and individual Case Report Forms, vols. 201-283).

Treatment-Emergent Death in an Argatroban-Treated HIT Patient

PATIENT	ADMIT DIAGNOSIS and HISTORY	HEPARIN ADMIN.	CLINICAL COURSE
077-001 67 F	3/12 CABG and MVR H/O HTN, PUD	3/6- 3/12	3/6: Admission for w/u of unstable angina 3/8: Cardiac catheterization 3/9: Discharged 3/12: Readmitted for CABG and MVR Platelet count 205K/mm ³ on 3/5, 150K/mm ³ on 3/12, 51K/mm ³ on 3/15, and 82K/mm ³ on 3/18; H-PF4 Positive 3/14: L Hemiparesis; L Foot mottled and pulseless 3/16: Bronchospasm and tachycardia 3/18: Argatroban administered for 6 hours. Discontinued due to GI bleeding, hypotension, and ischemic hepatitis and/or ischemic enteritis 3/18: Death secondary to "HIT with possible thrombosis of the mesenteric and hepatic vessels with ischemic damage leading to hepatic and possible intestinal necrosis, coagulopathy, and ultimate death."

A summary of deaths that occurred in argatroban-treated HIT patients which were attributed to underlying disease is shown below (Section 14.3.4, vol. 105, pp. 440 through vol. 106, pp. 1-149; Table 55, vol. 105, pp. 245-260; Appendix 16.4.15, vol. 4.1, pp. 193-290; and individual Case Report Forms, vols. 201-283).

**Deaths in Argatroban-Treated HIT Patients Attributed
to Underlying Disease**

PATIENT	ADMIT DIAGNOSIS and HISTORY	HEPARIN ADMIN.	ARGAT. ADMIN.	CLINICAL COURSE
002-003 60 M	2/23 Pneumonectomy for Lung Ca H/O Lung ca, COPD, IHSS	2/23- 2/27	2/28- 2/29	2/26: Mitral Valve Replacement requiring ECMO postoperatively Platelet count 105K/mm ³ on 2/23, 55K/mm ³ on 2/25, 47K/mm ³ on 2/27, and 75K on 3/4; H-PF4 Positive 2/28 - 2/29: Argatroban administered; discontinued due to planned procedure 3/3: Developed chest infiltrates and gram-negative bacteremia 3/5: Post Rx Doppler positive for L Arm venous thrombus; VQ scan indeterminate 3/9: Died secondary to hypoxemia, acidosis and "multiorgan failure"
012-003 66 F	9/11 Heart Failure, Anasarca H/O Valvular Heart Disease (on Warfarin), Chronic CHF, Endometrial Ca	9/14- 9/16	9/16- 9/30	9/13: Platelet count 168K/mm ³ , 66K/mm ³ on 9/15; HIPA Test Negative 9/16: UE and LE Dopplers Negative for DVT Platelet count 156K/mm ³ on 9/22, 170K/mm ³ on 9/27, then 70K/mm ³ on 9/30 and 52K/mm ³ on 10/1 9/26-9/30: Warfarin administration (for Valve) Fluid overload included inotropic and dialysis therapy. 9/30: No Post Rx Doppler or VQ scan done 10/14: Patient died with diagnoses of right heart failure, renal failure, and hepatic encephalopathy
016-005 70 M	6/26 Elective AAA repair	6/27- 7/2	7/2-7/2 (5 hrs)	6/27: Platelet count 48K/mm ³ , 32K/mm ³ on 6/29, 26K/mm ³ on 6/30, 23K/mm ³ on 7/1, and 16K/mm ³ on 7/2; H-PF4 Positive 7/2: Argatroban administered for 5 hours; discontinued due to APTT>100 sec Returned to OR x 2 for poor wound closure 7/3: Post Rx Dopplers negative; VQ scan not done 7/7: Death associated with bleeding, hemodynamic instability, possible sepsis, liver and renal dysfunction
017-004 73 F	11/4 MI H/O COPD	11/5- 11/7 and 11/12- 11/14	11/18- 11/21	11/11: PTCA then CABG, MVR, and IABP Placement Platelet count 135K/mm ³ on 11/12, 18K/mm ³ on 11/14, 63K/mm ³ on 11/18, and 117K/mm ³ on 11/20; Hep Ab Tests Not Done 11/12: Reexploration for bleeding 11/20: GI Bleeding 11/22: Intubated 11/22: Post Rx Doppler not done; VQ scan low probability 12/20: Death due to "acute respiratory distress"

017-007 72 F	9/7 Unstable angina H/O CVA, MI, Chronic Renal Insufficiency	9/10- 9/23	9/24- 10/4	9/12: Cardiac cath showed L main and LAD disease; IABP placed. Required intubation due to respiratory failure. Platelet count 168K/mm3 on 9/10, 82K/mm3 on 9/15, 55K/mm3 on 9/20, 38K/mm3 (and SRA Positive) 9/24: Dopplers (UE and LE) and VQ scan Negative Argatroban administered 9/24 - 10/4 Platelet count 131K/mm3 on 9/27 and 168K/mm3 on 10/4 9/27: non QwMI and progressive neurologic deterioration 10/4: Post Rx Dopplers negative; VQ scan not done 10/9: Patient made DNR and died 10/10
020-022 49 M	1/8/96 Re-do CABG H/O CABG, AVR, PVR, and HITTS in 6/95	12/27- 1/8	1/9- 1/18	Platelet count 153K/mm3 on 1/10, and 150K/mm3 on 1/18; HIPA and H-PF4 Negative 1/9: Pre Rx Dopplers and VQ scans Negative 1/18: Re-do CABG with complications of severe bleeding and cardiac tamponade 1/18: Post Rx Dopplers not done; VQ scan normal 1/22: Death associated with "post-CABG cardiac arrest"
020-034 83 F	10/20 CHF, hypotension	10/20	10/27- 10/29 and 11/1	10/20: Mitral Valve repair and IABP insertion, cardiogenic shock, AMI Platelet count 269K/mm3 on 10/20, 30K/mm3 on 10/24; SRA Negative 10/25: Renal failure and hemodialysis Platelet count 8K/mm3 on 10/28, 99K/mm3 on 10/29, and 108K/mm3 on 11/2 After 10/25: "embolization to both feet" 11/5: Death due to "multisystem failure"
026-001 54 M	8/5 H/O PTCA with stent placement on 7/31 Also with H/O MI, CABG, CHF, Renal dysfunction	7/31- 8/5	8/5- 8/11	Post PTCA of SVG x 4, patient experienced renal failure, CHF, A-fib/flutter Rx with Amiodarone Platelet count 95K/mm3 on 8/2, 56K/mm3 on 8/5 and 229K/mm3 on 8/12; HIPA and H-PF4 Positive 8/5: Pre Rx Dopplers and VQ scan Negative 8/11: Post Rx Dopplers and VQ scan Negative 8/11: Discharged to home 8/22: Admitted for Rx of "CHF". "Approximately 5 hours after admission (to the ICU) the patient developed moderate bradycardia with progressive ineffective ventilation and had no pulses and no palpable blood pressure. The patient had been relatively comfortable just prior to that." The patient died the same day.
036-003 29 F	6/27 Colonic obstruction from colon ca	7/5- 7/16	7/17- 7/18	6/27: Colonic obstruction due to metastatic colon ca 6/28: Colon resection 7/4: Bilateral LE DVTs on Dopplers and High Probability VQ scan Platelet count 156K/mm3 on 7/4, 45K/mm3 on 7/17, and 32K on 7/20; SRA Positive 7/18: Dopplers with progression of DVT 7/22: Death associated with worsening hepatic and renal function

039-002 86 F	11/22 Transferred for ERCP H/O COPD	11/22- 11/27	11/27- 12/1	Pre-11/22: DVT 11/22: Transferred for ERCP and admitted to ICU for severe COPD 11/24: CBD stone removed Platelet count 144K/mm3 on 11/22, 42K/mm3 on 11/27; SRA Positive 11/27-12/1: Argatroban administered, followed by warfarin Platelet count 143K/mm3 on 12/2 11/29: UE Dopplers and VQ scan Negative 12/21: Death associated with COPD
040-002 78 M	10/6 CABG and AVR H/O MI	10/6- 10/8	10/12- 10/16	10/6-10/8: Heparin administered for DVT Platelet count 251K/mm3 on 10/6, 114K/mm3 on 10/8, and 52K/mm3 on 10/11; Hep Ab Tests Not Done 10/11: ARDS 10/13: Renal Failure 10/12: Pre Rx Dopplers and VQ scan Negative 10/12-10/16: Argatroban administration Post Rx Dopplers and VQ scan Not Done 10/16: Death associated with ARDS
040-006 61 F	7/2 AVR H/O CHF	7/2, 7/5, and 7/8- 7/10	7/10- 7/27	7/2: AVR 7/5: Septal myomectomy 7/8: Vent Tach, a-fib, renal failure Platelet count 365K/mm3 on 7/1, 161K/mm3 on 7/6 and 113K/mm3 on 7/9; SRA Positive 7/11: Pre Rx UE Doppler and VQ scan Negative; LE Doppler Not Done 7/10-7/27: Argatroban administration Platelet count 151K/mm3 on 7/28 7/31: Post Rx Dopplers Negative; VQ scan Not Done 8/27: Death associated with respiratory arrest
048-001 76 F	1/9 PEs and R Atrial Thrombus H/O CVA, CHF, PVD	1/10- 1/12	1/12- 1/12	1/10-1/12: Heparin administration for multiple PE s and R Atrial Thrombus extending into R Ventricle. EF 20% Platelet count 253K/mm3 on 1/9, and 74K/mm3 on 1/12; H-PF4 Positive 1/12: Death secondary to "pulmonary emboli and poor cardiac function"
059-007 60 M	1/18 Angina and Dyspnea H/O CABG, Lung ca	1/23, 1/24, 1/27, and 1/28	1/28- 2/12	1/24: CABG, MVR, AVR with mediastinal bleeding and hemodynamic instability postoperatively Platelet count 47K/mm3 on 1/28 from 154K/mm3 at baseline; SRA Negative 1/28-2/12: Argatroban administration 2/13: Dopplers Negative; VQ scan Indeterminate 3/13: Gangrenous cholecystitis 5/3: Death due to "multisystem compromise"
059-013 70 F	8/22 s/p Motor Vehicle Accident H/O CAD, PVD	8/22- 8/24 and 8/26- 8/27	8/28- 8/29	8/22: s/p MVA with multiple fractures and bilat pulmonary contusions 8/24: Diagnostic Peritoneal Lavage Negative Platelet count 211K/mm3 on 8/22, and 62K/mm3 on 8/27; H-PF4 Positive 8/28-8/29: Argatroban administration Platelet count 148K/mm3 on 8/30 8/29: ARDS; Pulmonary Angiogram Negative 8/29: IVC filter placed 8/30: Excessive trach site bleeding 9/1: Tracheostomy replaced with Endotracheal tube due to clc: 9/1: Death following hypotension and cardiac arrest

063-001 43 F	8/28 weakness and shortness of breath H/O cervical ca metastatic to liver	8/29- 9/1	9/1-9/3	8/29: PE on VQ scan; Dopplers Negative Platelet count 124K/mm ³ on 8/28, and 53K/mm ³ on 9/1; HIPA Positive 9/1-9/3: Argatroban administered 9/5: Death associated with "end-stage metastatic disease and respiratory failure"
063-002 69 M	11/27 Abdominal and Iliac Artery Aneurysm Resection and Aorto-Iliac Bypass Grafting H/O CAD, CHF, COPD	11/27- 12/13	12/13- 12/14	11/27: Post op course complicated by COPD and hemodynamic instability 12/6: Resuscitated cardiopulmonary arrest 12/7: Resuscitated cardiopulmonary arrest 12/9: Renal failure and Hemodialysis Platelet count 172K/mm ³ on 11/27, and 38K/mm ³ on 12/13; SRA Negative 12/13-12/14: Argatroban administration; discontinued for anticipated abdominal surgery Pre and Post Rx Dopplers and VQ scans Not Done 12/14: Exploratory laparotomy and cholecystectomy with postoperative bleeding complication 12/15: Death following cardiopulmonary arrest
063-003 79 F	10/25 Shortness of Breath H/O COPD, CRI, CHF, PE, Obesity	3/5- 3/15	3/15- 3/17	Hospital course complicated by renal failure requiring hemodialysis, septicemia with probable DIC, ventilator dependency, and hemodynamic instability with resuscitated cardiac arrests on 3/17 and 3/19 3/6: L Leg DVT on Doppler; Indeterminate VQ scan Platelet count 127K/mm ³ on 3/5, and 96K/mm ³ on 3/15; Hep Ab Tests Not Done 3/15-3/17: Argatroban administration Platelet count 115K/mm ³ on 3/16 and 77K/mm ³ on 3/17 Post Rx Dopplers Negative; VQ scan Not Done 3/21: Death associated with sepsis and multisystem failure
074-001 53 F	11/25 s/p Motor Vehicle Accident	11/26- 12/3	12/4- 12/6	11/26: Orthopedic surgeries, rhabdomyolysis, splenectomy, and chest tube insertion Platelet count 81K/mm ³ on 11/26, and 31K/mm ³ on 12/3; H-PF4 Positive 12/4: Pre Rx Dopplers with R UE DVT; VQ scan not done 12/4-12/6: Argatroban administration Platelet count 141K/mm ³ on 12/7 12/7: Post Rx Dopplers unchanged; VQ scan not done 12/15: R parietal CVA 12/22: Death associated with "multiorgan failure"

<p>079-008 68 M</p>	<p>8/23 Bacterial Joint Infection and Pericardial Effusion H/O Gout, Lung ca metastatic to bone</p>	<p>9/1-9/3</p>	<p>9/3-9/9</p>	<p>9/1: Pre Rx Doppler with bilat UE Venous thromboses; VQ scan Moderate Probability; Heparin initiated Platelet count 156K/mm3 on 9/1, and 51K/mm3 on 9/3; SRA Positive 9/3-9/9: Argatroban administration followed by warfarin Platelet count 169K/mm3 on 9/9, and 332K/mm3 on 9/10 9/9: Post Rx Dopplers and VQ scan Not Done 9/11: Patient Discharged on <u>SO Heparin for 3 days</u> Platelet count 119K 10/3: Patient brought to ER by ambulance with altered mental status felt secondary to self-overmedication (? with Methadone; no details given) and discharged to home via ambulance. 10/4: Patient reported dead</p>
<p>081-006 45 M</p>	<p>3/25 PE H/O AIDS, PCP Dxed on 3/13</p>	<p>3/24- 4/3</p>	<p>4/3-4/5 and 4/8-4/9</p>	<p>3/25: PE on VQ scan; Rxed with Heparin Platelet count 151K/mm3 on 3/24, 69K/mm3 on 3/30, and 52K/mm3 on 4/2; Hep Ab Tests Not Done 4/3-4/5, and 4/8-4/9: Argatroban administration; Warfarin given on 4/2 Platelet count 55K/mm3 on 4/5 and 58K/mm3 on 4/10 4/3: Resolving PE on VQ scan 4/4: UE and LE Venous Dopplers Negative 4/10: Death associated with "PCP pneumonia"</p>
<p>091-001 60 F</p>	<p>4/16 Pulmonary HTN, and Acute Renal Failure H/O TIA, COPD, morbid obesity, obstructive sleep apnea</p>	<p>4/18- 4/22</p>	<p>5/3- 5/17</p>	<p>4/18: L LE DVT Rxed with Heparin Platelet count 159K/mm3 on 4/18, 66K/mm3 on 4/20, and 87K/mm3 on 4/22; Hep Ab Tests Not Done 4/22: IVC Filter placed 5/1, 5/3: Pre Rx Doppler Positive for R UE and L LE Venous Thrombi; VQ scan Low Probability 5/3-5/17: Argatroban administration; Respiratory decompensation requiring intubation Platelet count 211K/mm3 on 5/4, 199K/mm3 on 5/11, and 282K/mm3 on 5/17 5/21: Discharged on oxygen and CPAP which patient refused to comply with; no warfarin given 5/22: Death due to "respiratory failure"</p>
<p>096-001 48 F</p>	<p>3/29 Yeast Peritonitis H/O ESRD on peritoneal dialysis</p>	<p>4/1-4/5</p>	<p>4/5-4/9</p>	<p>(Patient believed to have received heparin for a femoral line 2 days prior to this admission) Platelet count 48K/mm3 on 4/1, and 46K/mm3 on 4/5; H-PF4 Positive 4/5: Pre Rx Dopplers Positive for a R LE DVT; VQ High Probability 4/5-4/9: Argatroban administered Platelet count 68K/mm3 on 4/8 Post Rx Dopplers and VQ scan not done 4/9: Death. On-site investigator: "This thromboembolic process (DVT and PE associated with HIT) may have contributed to her death; however, the principal diagnosis was Candida peritonitis."</p>

100-004 67 F	7/10 PTCA H/O HTN, DM, PVD, CVA 1989	7/10- 7/15	7/20- 7/22	7/12: Cardiopulmonary arrest followed by CABG, complicated by postop bleeding Platelet count 277K/mm3 on 7/12, 78K/mm3 on 7/14, and 62K/mm3 on 7/15; SRA Negative 7/19, 7/20: Pre Rx Arterial and UE Venous Dopplers not done; LE Venous Dopplers Negative; VQ scan Low Probability 7/20-7/22: Argatroban administration Platelet count 91K/mm3 on 7/21 7/22: Post Rx Dopplers and VQ scan not done 7/22: Death associated with "anoxic encephalopathy"
103-001 74 M	Unknown admission Date Shortness of Breath H/O HTN, DM, ESRD on Peritoneal dialysis beginning 3/23	3/23- 4/3	4/4- 4/11	Platelet count 133K/mm3 on 3/23, and 43K/mm3 on 4/3; SRA Positive 4/3, 4/4: Pre Rx Dopplers with "significant LE arterial occlusive disease bilaterally"; Venous Dopplers Negative; VQ scan normal 4/4-4/11: Argatroban administration Platelet count 112K/mm3 on 4/12 4/12: Post Rx Dopplers and VQ scan unchanged from Pre Rx examinations 4/17: Patient discharged to home 4/23: Admission for hypoglycemia; Platelet count 256K/mm3 5/4: Death at home due to "renal failure"
121-002 58 M	8/29 PE H/O CLL	8/30- 9/1	9/1- 9/15	8/30: VQ scan High Probability Platelet count 109K/mm3 on 8/30, and 15K/mm3 on 9/1; Heparin Ab Test Not Done 9/2: Pre Rx Dopplers Positive for L LE DVT 9/1-9/15: Argatroban administration; followed by warfarin Platelet count 72K/mm3 on 9/14 9/16: Dopplers with interval improvement of L LE DVT 9/17: VQ scan with interval improvement Renal insufficiency requiring hemodialysis developed. 9/17: Patient Discharged 10/14: Admission for fever, neutropenia and sepsis requiring mechanical ventilation and inotropic support 10/21: Death associated with sepsis
126-001 76 M	7/5 CHF H/O CABG, AVR, and MV Annuloplasty one month prior to admission	7/7- 7/11	7/12- 7/17	Platelet count 214K/mm3 on 7/5, and 73K/mm3 on 7/11; SRA Negative 7/12: Pre Rx Dopplers not done; VQ scan Low Probability 7/12-7/17: Argatroban administration followed by warfarin Platelet count 139K/mm3 on 7/16, and 156K/mm3 on 7/19 7/18: Post Rx Dopplers Indeterminate for Arterial Thrombi and Negative for Venous Thrombi; VQ scan Low Probability 7/27: Discharged to home 7/28: Admitted to another hospital with CHF with "no evidence of bleeding or thrombosis" as per an interview with the admitting MD. 8/1: Death associated with CHF

A summary of deaths that occurred in historical control HITTS patients which were attributed to thrombosis is shown below (Section 14.3.4, vol. 106, pp. 106-149; Table 55, vol. 105, pp. 245-260; Appendix 16.4.15, vol. 4.1, pp. 193-321; and individual Case Report Forms, vols. 201-283).

**Deaths in Historical Control HITTS Patients Attributed
to Thrombosis**

PATIENT	ADMIT DIAGNOSIS and HISTORY	HEPARIN ADMIN.	CLINICAL COURSE
059-H01 74 F	6/20 s/p cardiac arrest H/O HTN, DJD	6/20- 6/23 and 6/29- 7/1	6/19: Cardiac Arrest secondary to MI 6/22: PTCA Platelet count 261K/mm ³ on 6/20, 212K/mm ³ on 6/29, 101K/mm ³ on 6/30, 29K/mm ³ on 7/1, 9K/mm ³ on 7/2; Hep Ab Tests Not Done 7/1: L LE DVT on Doppler; VQ scan Low Probability 7/1: IVC Filter placed Hospital course: Hypoxemia requiring intubation and renal failure requiring dialysis; "Cyanosis of fingers and feet" 7/4: Death associated with arrhythmia and "progression of peripheral manifestations of thrombosis."
060-H10 66 M	9/15 CHF H/O Polymyalgia rheumatica and myelofibrosis	9/16	9/16: CABG Platelet count 96K/mm ³ on 9/18 and 84K/mm ³ on 9/20; HIPA Positive 9/22: Discharged to Home 9/24: Readmitted with R LE edema, platelet count of 42K/mm ³ , and CVA; Carotid angiogram showed a "fresh clot" and stenosis of L internal carotid artery. Dopplers were Positive for LE DVT; VQ scan was Indeterminate. 10/1: IVC Filter placed. "The patient's respiratory status continued to deteriorate, presumably because of PE, and he required intubation." 10/2: Death due to cardiac arrest
125-H01 67 F	7/5 Unstable angina	7/5- 7/10	7/6: Cardiac catheterization 7/8: R Carotid endarterectomy 7/10: CABG Platelet count 221K/mm ³ on 7/6, 172K/mm ³ on 7/10, 12K/mm ³ on 7/13; HIPA Positive 7/12: Both feet cool and waxy in appearance; Dopplers Positive for Bilateral LE Arterial Thromboses Platelet count 10K/mm ³ on 7/16, and 42K/mm ³ on 7/19 7/17: Dopplers Positive for Bilateral Arterial and Venous Thromboses; VQ scan Not Done 7/17: Dextran initiated, followed by warfarin 7/24: IVC filter placed; Bilateral BKAs performed 7/25: Postoperative hypotension, metabolic acidosis and death Autopsy Results: Atherosclerotic CAD, LE Arterial and Venous Thromboses, and Acute Pulmonary Embolus

128-H03 48 F	12/24 Heart and Double Lung Transplantation H/O Idiopathic Pulmonary Fibrosis	12/24-1/11	12/25: Heart and Double Lung Transplantation Platelet count 94K/mm ³ on 12/25, and 27K/mm ³ on 1/6; HIPA Positive 1/1: Edematous L UE for which heparin was administered. Vascular studies revealed thromboses of L jugular and subclavian veins. 1/10: Head CT showed bilateral cerebral infarcts Hospital course: Neurologic function continued to deteriorate. 1/24: Patient experienced cardiopulmonary arrest and died Autopsy Results: Basal artery and infarcts of pons, L occipital pole, and R parietal lobe; Bilateral renal cortical infarcts; Posterior papillary muscle infarct; splenic and liver infarcts
140-H02 70 M	5/13 MI H/O COPD, AAA repair, PVD	5/14-5/22	Platelet count 486K/mm ³ on 5/13, 181K/mm ³ on 5/21, 27K/mm ³ on 5/22, and 39K/mm ³ on 5/23; HIPA Positive 5/20: Cardiac catheterization followed by instrumentation-site bleeding and femoral artery thrombosis requiring embolectomy 5/21: Thrombectomy of Aortic graft and R Fem-pop revascularization procedure 5/22: Emergent Aortic graft thrombectomy and L Fem-pop revascularization procedure 5/23: R AKA and repeat thrombectomy of aortic graft 5/24: Death
200-H42 69 M	4/28 R LE ischemia s/p L femoral thrombectomy on 4/24 for acute L LE ischemia	4/24	4/24: Thrombectomy for acute L LE ischemia. Platelet count 17K/mm ³ at this time. Diagnosis of DIC was given and patient was treated with IVIG. 4/28: R LE ischemia developed and patient was transferred. Platelet count was 23K/mm ³ ; SRA Positive 4/29-5/3: Ancrod administered 4/30-5/2: Warfarin administered Platelet count on 5/2 was 38K/mm ³ 4/30-5/1: LE arterial ischemia leading to thrombectomies 5/2: Bilateral AKAs 5/3: Death due to cardiac arrest Autopsy Results: Coronary thrombosis of LAD, AAA with mural thrombus, Thrombosis of L external and internal iliac arteries and L femoral artery, Pulmonary Embolus, and Liver venous thrombi.
201-H13 72 M	1/19 L LE DVT H/O squamous cell cancer metastatic to L groin lymph nodes	1/19-1/28 and 2/4-2/5	1/19: Heparin initiated for L LE DVT (by Doppler). XRT to L groin continued. Platelet count 241K/mm ³ on 1/19, 48K/mm ³ on 1/29, 60K/mm ³ on 2/2, and 70K/mm ³ on 2/5; SRA Positive 1/28: Infection of L groin 1/28: Heparin discontinued due to guaiac positive emesis 1/29-1/30: Complaint of abdominal pain, then hypotension and tachycardia 2/4: L LE noted edematous, red, warm, swollen, and painful. Then "sudden desaturation" felt secondary to a PE, and hypotension resulting in transfer to ICU. Heparin was re-instituted. 2/4: Patient died shortly after transfer to the ICU. The death certificate listed "? pulmonary embolism" as the immediate cause of death. No autopsy was performed.

068-H01 61 M	Transferred 7/3 for mgmt. of respiratory failure H/O IDDM, renal transplant 1 year earlier, CAD	7/4- 7/15	7/4-7/10: Intubated for respiratory failure Platelet count 263K/mm3 on 7/4, 326K/mm3 on 7/12, and 88K/mm3 on 7/15;SRA Positive 7/11: Subclavian catheter-associated DVT; VQ scan Low Probability 7/15: L LE arterial thrombosis followed by an acute MI and death Autopsy Results: "White clot syndrome in multiple tissue beds including lungs and heart."
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A summary of deaths that occurred in historical control HITTS patients which were attributed to underlying disease is shown below (Section 14.3.4, vol. 106, pp. 106-149; Table 55, vol. 105, pp. 245-260; Appendix 16.4.15, vol. 4.1, pp. 193-321; and individual Case Report Forms, vols. 201-283).

**Deaths in Historical Control HITTS Patients Attributed
to Underlying Disease**

PATIENT	ADMIT DIAGNOSIS and HISTORY	HEPARIN ADMIN.	CLINICAL COURSE
016-H03 69 M	6/12 unstable angina	6/12- 6/30	Platelet count 184K/mm ³ on 6/12, 96K/mm ³ on 6/13, 65K/mm ³ on 6/15, 52K/mm ³ on 6/20, 28K/mm ³ on 6/23, 16K/mm ³ on 6/25, 120K/mm ³ on 6/28, and 375K/mm ³ on 7/2; SRA Positive 6/12: CABG, IABP placed, and chest reopened to perform thrombectomies of all venous grafts. 6/18: Bilateral LE fasciotomies for compartment syndromes 6/20: R LE Arterial Thrombi requiring surgical thrombectomy 6/21: Secondary closure of sternotomy wound 6/26: LE Dopplers Positive; VQ scan Not Done 6/27: Renal failure requiring dialysis 7/2: Death secondary to "multiorgan failure"
050-H01 66 M	1/13 PTCA	1/13- 1/17 and 1/22- 1/23	1/13: PTCA 1/14: Emergent IABP due to acute closure of LAD 1/17: CABG Platelet count 127K/mm ³ on 1/13, 81K on 1/17, 128K/mm ³ on 1/21, 83K/mm ³ on 1/22, 33K/mm ³ on 1/23, and 90K/mm ³ on 1/29; HIPA Positive 1/21: LE Dopplers Positive; VQ scan Not Done 1/23: Pulmonary Angiogram performed for acute respiratory distress (Results Not Provided) 2/8: Death due to "hemodynamic instability"
113-H21 75 M	8/4 R Hip fracture H/O CVA two years earlier, HTN, DM	8/4-8/9	8/8: Cardiac catheterization Platelet count 218K/mm ³ on 8/4, 83K/mm ³ on 8/9, 36K/mm ³ on 8/11, 96K/mm ³ on 8/13, and 135K/mm ³ on 8/16; HIPA Positive 8/15: Bilateral LE DVT on Doppler; VQ scan Not Done 8/16: IVC Filter placed for PE prophylaxis 8/18: Aortic Valve Replacement 8/19: Tenckoff catheter placement for renal insufficiency 8/21: Death secondary to an "acute MI"
115-H01 67 M	2/8 DVT and heme positive stool H/O morbid obesity, and prior DVT/PEs	2/8- 2/17	2/8: Dopplers Positive for bilateral LE arterial, and L Leg DVT; VQ scan Not Done 2/9: Adenomatous GI polyp found on colonoscopy 2/14: Hemicolectomy and placement of IVC filter Platelet count 180K/mm ³ on 2/8, 84K/mm ³ on 2/16, 69K/mm ³ on 2/18, 146K/mm ³ on 2/21, 244K/mm ³ on 2/24, and 204K/mm ³ on 2/28; Hep Ab Tests Not Done 2/18: Dopplers Positive for Bilateral LE Arterial and Venous Thromboses 2/19: Warfarin begun Postoperative Hospital Course: Renal failure requiring dialysis, Staph epi bacteremia, and intubation/ventilation. "Patient developed progressive thrombosis of iliofemoral, popliteal, and (bilateral) fingers." 3/8: Death due to "sepsis/multiorgan failure"

128-H02 70 F	4/19 sepsis s/p hospitalization for MI and thrombolysis on 4/12	4/21- 4/23	4/21: L arm DVT on Doppler and heparin started Platelet count 326K/mm ³ on 4/20, 197K/mm ³ on 4/21, 30K/mm ³ on 4/23, 41K/mm ³ on 4/26, and 81K/mm ³ on 4/27; HIPA Positive 4/25: CVA 4/25: Acute MI 4/25: Warfarin and Dextran given 4/27: Death secondary to "sepsis"
200-H19 73 M	11/16 gastrocolic fistula secondary to bowel adenocarcinoma H/O COPD, CAD	11/25- 12/7	11/25-12/7: Heparin administered for DVT prophylaxis Platelet count 365K/mm ³ on 11/16, 111K/mm ³ on 11/28, 59K/mm ³ on 12/7, 114K/mm ³ on 12/12, 192K/mm ³ on 12/13, and 172K/mm ³ on 12/14; SRA Positive 12/6: Tumor resection and GI anastomosis surgery 12/8: Bilateral LE DVTs on Dopplers 12/8-12/13: administered 12/10: Progression of R LE DVT on Doppler 12/13: Sudden onset of dyspnea and hypoxemia requiring intubation; PE was suspected but a lung scan was not performed "because of the critically ill status of the patient." 12/13-12/15: Danaparoid administered with the complication of major bleeding 12/15: Death "with HIT playing a major role" (as per Dr. Warkentin)
200-H26 63 F	12/30 s/p MVA with multiple fractures	12/30- 1/19	Platelet count 116K/mm ³ on 1/1, 234K/mm ³ on 1/8, 256K/mm ³ on 1/11, 122K/mm ³ on 1/17, 102K/mm ³ on 1/22, 189K/mm ³ on 1/30, and 240K/mm ³ on 2/3; SRA Positive 1/1: ORIF of ankles and patella bilaterally 1/4: Pseudomonas pneumonia 1/12: R LE DVT on Doppler 1/17: OR and fusion of cervical spine; IVC Filter placed 1/19: Candidemia Rxed with Amphotericin 1/25: R UE DVT on Doppler 1/25-2/4: Ancrod administered 2/4: Pulmonary hemorrhage 2/10: As per Dr. Warkentin, "The death certificate indicates that pulmonary hemorrhage contributed to her death (respiratory failure secondary to septicemia and bleeding). Thus, this patient developed serious thrombotic and hemorrhagic complications during the treatment of her HITT."
200-H29 44 M	8/31 symptomatic bradycardia	8/31- 9/15	8/31: Bradycardia followed by status epilepticus and coma Platelet count 334K/mm ³ on 8/31, 210K/mm ³ on 9/5, 194K/mm ³ on 9/14, and 89K/mm ³ on 9/15; SPA Positive 9/14: Bilateral LE DVT 9/15-9/22: administration followed by warfarin Platelet count 102K/mm ³ on 9/16, 191K/mm ³ on 9/19, and 346K/mm ³ on 9/23 10/1: Pneumonia 10/3: Death Autopsy Results: No unexpected thrombotic events, significant CAD but no MI seen, and brain injury consistent with status epilepticus

No deaths that occurred in argatroban-treated HIT patients were attributed to thrombosis. A summary of death that occurred in an argatroban-treated HITTS patient which was attributed to thrombosis is shown below (Section 14.3.4, vol. 106, pp. 106-149; Table 55, vol. 105, pp. 245-260; Appendix 16.4.15, vol. 4.1, pp. 193-321; and individual Case Report Forms, vols. 201-283).

Death in an Argatroban-treated HITTS Patient Attributed to Thrombosis

PATIENT	ADMIT DIAGNOSIS and HISTORY	HEPARIN ADMIN.	CLINICAL COURSE
020-008 63 F	6/16 Tranferred for Rx of HITTS	6/2- 6/10	6/4-6/15: Admission for Rx of CHF. Cardiac catheterization showed 3-vessel CAD. Patient developed SRA Positive HITTS with a R Common Iliac Artery Thrombosis Rxed with Plasmapheresis 6/12-6/15 6/17: Urokinase administration for R Common Iliac Artery Thrombosis; Complete obstruction of the R Superficial Femoral Artery observed at this time. Patient intubated due to acute respiratory distress. 6/17-6/24: Argatroban administration 6/19: Patient self-extubated and reintubated on 7/1 6/22: New R Iliac Arterial Thrombi 6/22: "Severe episode of respiratory failure" and reintubation 6/24: Two episodes of cardiac arrest 6/25: Death due to "acute MI"

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A summary of deaths that occurred in argatroban-treated HITTS patients which were labeled as "treatment emergent" is shown below (Section 14.3.4, vol. 105, pp. 440 through vol. 106, pp. 1-149; Table 55, vol. 105, pp. 245-260; Appendix 16.4.15, vol. 4.1, pp. 193-290; and individual Case Report Forms, vols. 201-283).

Treatment-Emergent Deaths in an Argatroban-Treated HITTS Patients

PATIENT	ADMIT DIAGNOSIS and HISTORY	HEPARIN ADMIN.	CLINICAL COURSE
020-009 61 F	6/15 MI H/O CAD	6/15- 6/27	6/21: Cardiac catheterization 6/23: CABG 6/29: High Probability VQ scan; L LE DVT on Doppler Platelet count 271K/mm ³ on 6/15, and 4K/mm ³ on 6/29; SRA Positive 6/30-7/4: Argatroban and plasmapheresis administration 7/3-7/4: Streptokinase administration for L LE DVT Platelet count 47K/mm ³ on 7/4 7/4: Bleeding, pericardial and pleural effusion, hemothorax, hemoptysis, epistaxis, DIC, renal and liver failure, respiratory arrest, and hypotension 7/5: Death due to "consumptive coagulopathy secondary to acute hepatic failure, streptokinase administration and thrombin inhibition with argatroban, acute renal failure, auto- anticoagulation with fibrin split products and plasmapheresis therapy" (as per Investigator B. Lewis).
066-003 54 M	8/13 cardiac evaluation H/O CAD, myotonic dystrophy	8/15- 8/16, 8/19- 8/23, and 8/30	8/14: CABG Platelet count 103K/mm ³ on 8/17, and 26K/mm ³ on 8/24; SRA Positive 8/25: Discharged to home 8/30: Readmitted for shortness of breath; VQ scan Low Probability; R LE DVT on Doppler; RV Thrombus on ECHO 8/30: Heparin initially given, then discontinued 8/31-9/1: Argatroban administered; discontinued for hematuria Platelet count 106K/mm ³ on 9/1, 150K/mm ³ on 9/6, and 398K/mm ³ on 9/12 9/3: Reocclusion of 2 coronary bypass grafts; Pulmonary angiogram with RUL thrombi in corresponding pulmonary arteries 9/3-9/6: Patient intubated for respiratory failure; also with azotemia and GI bleeding 9/6: Patient extubated 9/23: Acute renal failure requiring dialysis beginning 9/25 9/25: Head CT with possible cavernous sinus thrombosis 9/30: Sepsis and DIC with generalized bleeding 10/1: Death Autopsy Results: Pulmonary arterial thromboemboli, CAD, CHF, Acute renal tubular injury, and Acute hemorrhagic gastritis

A summary of deaths that occurred in argatroban-treated HITTS patients which were attributed to underlying disease is shown below (Section 14.3.4, vol. 105, pp. 440 through vol. 106, pp. 1-149; Table 55, vol. 105, pp. 245-260; Appendix 16.4.15, vol. 4.1, pp. 193-290; and individual Case Report Forms, vols. 201-283).

Deaths in Argatroban-Treated HITTS Patients Attributed to Underlying Disease

PATIENT	ADMIT DIAGNOSIS and HISTORY	HEPARIN ADMIN.	ARGAT. ADMIN.	CLINICAL COURSE
002-006 76 F	7/10 Bilateral LE DVTs H/O metastatic colon ca	7/9- 7/12	7/12- 7/16	7/10: IVC filter placed; Platelet count 130K/mm ³ 7/11: VQ scan High Probability Platelet count 73K/mm ³ on 7/12 and 55K/mm ³ on 7/13; SRA Positive 7/12-7/16: Argatroban administration; discontinued due to bilat adrenal hemorrhages 7/17: Repeat Dopplers and VQ scan with no interval changes 7/21: Death associated with becoming "increasingly short of breath at rest."
002-007 46 F	8/1 Weakness, Shortness of Breath H/O Non-Hodgkin's Lymphoma	8/1- 8/10 and 8/23- 8/26	8/18- 8/19	8/4: Intubated due to respiratory failure 8/10: Platelet count 132K/mm ³ on 8/3, 70K/mm ³ on 8/6, 9K/mm ³ on 8/8, and 48K on 8/10; SRA Positive 8/13: IVC filter placed due to iliofemoral and internal jugular thromboses 8/16: Right upper extremity ischemia 8/18-8/19: Argatroban administered; discontinued due to bleeding Platelet count 72K/mm ³ on 8/18 and 125K/mm ³ on 8/20 8/20: Dopplers Positive for Bilateral UE Arterial thromboses and R External Jugular DVT 8/27: Death due to "respiratory failure secondary to lung fibrosis"
007-001 70 M	2/23 Angina and LV dysfunction H/O PVD, MI, arrhythmia	2/23- 2/24 and 2/28- 2/29	2/29- 3/1	2/23: Emergent cardiac cath and CABG x 4 Required LV Assist Device, ionotropes and ventilator assistance postoperatively. 2/27: Platelet count 63 K/mm ³ with development of "ischemic lower extremities" 2/29: Platelet count 42 K/mm ³ ; HIPA and H-PF4 Positive 2/29-3/1: Argatroban administered; discontinued due to bleeding and "negative SRA" Subsequently developed respiratory failure, renal failure, fever, GI bleed, and DIC 3/6: Death due to "cardiopulmonary collapse"

012-002 71 F	9/8 s/p MI and CABG	8/28- 9/4	9/9- 9/12	8/29: CABG 8/28: Platelet count 204K/mm ³ , 53K/mm ³ on 9/1, and 26K/mm ³ on 9/4; Hep Ab Tests Not Done 9/8: R UE DVT and Bilateral Arterial and Venous LE Thromboses 9/9-9/12: Argatroban and Urokinase administration 9/10: VQ scan High Probability Hospital course: acute renal failure, hypoxia and hypotension 9/12: Platelet count 29K/mm ³ . "Patient expired following a brief episode of respiratory distress."
016-004 54 M	2/10 Emergent CABG	2/10- 2/21	2/22- 2/26	2/10: Emergent CABG Platelet count 206K/mm ³ on 2/10, 78K/mm ³ on 2/11, 40K/mm ³ on 2/21; SRA Positive 2/16: Two Right Hemispheric CVAs 2/20: R LE DVT; Moderate Probability PE on VQ scan 2/21: Bilat Ischemic Feet with Demarcation and L Leg DVT Platelet count 160K/mm ³ on 2/24, 336K/mm ³ on 2/26 2/22-2/26: Argatroban administration 2/26: Death "with nonprogressing arterial lesions in the lower extremities with demarcation, with an open chest wound and sepsis"
017-006 58 F	2/1 R/O Bowel Obstruction	2/23- ? and 3/4-3/8	3/9- 3/10	2/1: Metabolic acidosis, Guaiac Positive Stool, R/O Bowel Obstruction 2/23: Bilateral DVTs on Doppler 3/1: Sepsis, Acidosis and Intubation Platelet count 104K/mm ³ on 3/4, 40K/mm ³ on 3/6, and 49K/mm ³ on 3/8; Hep Ab Tests Not Done 3/9-3/10: Argatroban administered; discontinued due to GI bleeding 3/10: Warfarin started. No Post Rx Dopplers or VQ scans performed 3/13: Patient extubated and died on a MSO4 drip
020-006 77 F	5/24 Acute MI, renal failure, liver failure H/O Ischemic cardiomyopathy and EF 10%, CABG	5/24- 5/29	5/29- 6/2	5/24: Admitted with AMI, renal and liver failure. Intubated for respiratory compromise. 5/25: Hypotension, cardiogenic shock Platelet count 165K/mm ³ on 5/24, 62K/mm ³ on 5/29; SRA Negative 5/30: R Femoral Vein Thrombosis on Doppler 6/5: Post Rx Dopplers and VQ scan Negative 6/5: Pneumonia, respiratory failure and arrhythmia 6/7: Death

<p>020-017 74 M</p>	<p>10/25 CABG H/O CVA</p>	<p>10/25- 10/26</p>	<p>10/31- 11/6</p>	<p>10/25: CABG Platelet count 128K/mm3 on 10/25, 107K/mm3 on 10/26 10/26: R Femoral Artery Thrombus requiring thrombectomy Platelet count 76K/mm3 on 10/28; HIPA and H-PF4 Positive 10/28: new CVA; ARF due to contrast dye, ventricular arrhythmia due to procainamide toxicity 10/28-10/31: Plasmapheresis 10/29: VQ scan Indeterminate 10/31-11/6: Argatroban administered Platelet count 145K/mm3 on 11/1, 254K/mm3 on 11/3, and 329K/mm3 on 11/6 11/7: Post Rx Dopplers Negative; VQ scan low probability 11/8: Patient died following CPR for EMD</p>
<p>029-003 60 M</p>	<p>7/3 IVC Thrombus s/p CABG on 6/7; discharged then returned with massive IVC thrombosis secondary to HITS on 7/1</p>	<p>6/4- 6/26 and 7/1-7/3</p>	<p>7/4-7/9</p>	<p>Platelet count 255K/mm3 on 6/3, 34K/mm3 on 6/25, 57K/mm3 on 7/2; H-PF4 Positive 7/1-7/3: Patient received heparin for IVC thrombosis 7/4-7/9: Argatroban administration Platelet count 123K/mm3 on 7/9 7/11-7/13: Urokinase infusion for IVC thrombosis 7/13: Intracranial bleed 7/14: Death</p>
<p>036-004 70 M</p>	<p>9/15 Resection of AAA</p>	<p>9/15- 9/22</p>	<p>9/23- 9/27</p>	<p>Platelet count 168K/mm3 on 9/15, 53K/mm3 on 9/16, 52K/mm3 on 9/18, 29K/mm3 on 9/19, and 15K/mm3 on 9/22; SRA Positive 9/16: Emergent AAA resection and repair; LVAD placed 9/17: Reoperated for bleeding 9/21: Embolectomy of Common femoral a., posterior tibial a., and dorsalis pedis a. thromboses 9/22: gram negative bacteremia 9/23: VQ scan Low Probability 9/23-9/27: Argatroban administration 9/27: Patient "experienced cardiorespiratory arrest considered possibly associated with sepsis, and died."</p>
<p>036-005 76 M</p>	<p>9/5 CHF H/O Pulmonary Fibrosis</p>	<p>9/5- 9/20</p>	<p>9/24- 9/27</p>	<p>9/11: AVR Platelet count 228K/mm3 on 9/5, 68K/mm3 on 9/19, and 11K/mm3 on 9/24; SRA Positive 9/24: R Proximal LE DVT on Doppler 9/24-9/27: Argatroban administration 9/26: Dopplers Positive for Bilateral UE DVTs 9/26: Platelet count 17K/mm3 9/27: Reintubation due to tracheostomy complications "at which point (the patient) became asystolic (and did not respond to CPR)"</p>

037-007 65 F	7/23 CABG following failed PTCA	7/22- 7/25	7/26- 7/27	7/23: CABG following failed PTCA Platelet count 245K/mm3 on 7/22, 89K/mm3 on 7/24 and 62K/mm3 on 7/25; SRA Negative 7/25: Bilateral LE arterial thromboses on Doppler; Rxed with thrombectomy and urokinase 7/26-7/27: Argatroban administered; discontinued due to bleeding 7/30: Complete heart block and hypotension 7/31: As per Investigator: "The final cause of death was multiorgan system failure secondary to HITTS."
052-003 75 F	5/29 Transferred following R Leg Revascularization complicated by renal failure, stroke, and thrombocytopenia H/O AAA Repair, COPD	5/29- 6/1	6/4-6/4 (2 hrs)	5/22: R Fem-Pop Bypass Graft Revision and Thrombectomy 5/27: R CVA Platelet count 96K/mm3 on 5/29, 19K/mm3 on 6/1; SRA Positive Pre and Post Rx Dopplers and VQ scans not done 6/4-6/4: Argatroban administered for 2 hours, then consent withdrawn 6/11: renal failure, arrhythmia, and GI bleeding 6/14: Cardiac arrest 6/16: Cardiac arrest and death
075-001 75 M	1/17 Cardiac Cath H/O CAD, CHF	1/19- 1/30	1/30- 2/7	1/19: CABG complicated by severe bleeding and pneumothorax Platelet count 247 K/mm3 on 1/19 and 56K/mm3 on 1/28; HIPA and H-PF4 Positive 1/19 and 1/26: Intubation due to respiratory failure 1/26: CVA 2/1: Dopplers with L LE arterial thrombi; VQ scan not done 1/30-2/7: Argatroban administration, followed by warfarin until 2/7 Platelet count 324K/mm3 on 2/6 2/13: Post Rx Dopplers not done for arterial thrombi, and negative for venous thrombi; VQ scan not done 2/15-2/18: "On 2/15, the patient's respiratory rate increased and he was unresponsive. Later he developed ventricular tachycardia with a marked drop in blood pressure. Over the next two days the patient remained unresponsive, his blood pressure continued to drop, and his heart rate slowed. He eventually converted to asystole and died on 2/18."
080-002 70 F	3/4 Unstable Angina	3/4- 3/17	3/22- 3/26	3/6: AMI, emergent CABG and IABP placement Platelet count 261K/mm3 on 3/4, and 81K/mm3 on 3/10; Hep Ab Tests Not Done 3/17: Gangrene of both feet 3/22: Pre Rx Dopplers Positive for bilat LE DVT; VQ scan Intermediate to High Probability 3/22: Bilateral BKA 3/22-3/26: Argatroban administration Platelet count 260K/mm3 on 3/25, and 428K/mm3 on 3/30 Post Rx Dopplers and VQ scan Not Done 4/12: "The patient remained intubated and expired secondary to CHF." Autopsy Results: CAD, aortic and renal arteriosclerosis, possible aspiration pneumonia, and mild COPD

081-001 73 F	Unknown Admission Date H/O AAA surgery 11/20 with subsequent renal failure, spinal artery occlusion, and anasarca	11/20 and 12/7 - 12/22	12/23 - 12/29	12/21: R DVT on Venogram Platelet count 120K/mm ³ on 11/20, 147K/mm ³ on 12/22, and 303K/mm ³ on 12/30; H-PF4 Positive 12/23-12/29: Argatroban administration 12/30: VQ scan Intermediate Probability; LE Dopplers with No Interval Change 12/31: Transferred to Rehabilitation hospital 3/5: "Respiratory failure occurred and the patient expired."
082-002 65 M	Unknown Admission Date Chronic Renal Failure H/O CRI, CAD, PVD	Dates Unknown - Heparin Given During Hemodialysis	2/17-2/28	During hospitalization, patient experienced "severe leg ischemia that demanded bilateral amputations". Cardiac arrests during dialysis occurred on 2/13, 2/14, and 2/17; This was subsequently prevented with the prophylactic administration of atropine and lidocaine prior to each dialysis. Platelet count 32K/mm ³ on 2/16; HIPA and H-PF4 Positive 2/17: Pre Rx Dopplers Positive for bilat LE (Femoral and Iliac) Venous thromboses; VQ scan Low Probability 2/17-2/28: Argatroban administration followed by Warfarin Platelet count 69K/mm ³ on 2/27 2/29: VQ scan High Probability; Investigator writes that, "There is no clinical improvement and worsening of thrombus throughout the study." 3/1: Cardiac arrest during dialysis, and death
082-003 70 F	4/13 Diabetic Ketoacidosis	4/20-5/1	5/3-5/11	4/21: L CVA 4/22: PE Platelet count 236K/mm ³ on 4/20, 113K/mm ³ on 4/27, and 17K/mm ³ on 5/1; SRA Positive 5/1: IVC filter placed 5/3: Pre Rx Dopplers Positive for R external iliac and popliteal vein thromboses, and L superficial femoral and popliteal vein thromboses 5/3-5/11: Argatroban administration followed by warfarin Platelet count 157K/mm ³ on 5/7 and 288K/mm ³ on 5/11 5/10: Doppler Positive for <u>new</u> R UE thromboses; VQ scan with <u>new</u> thromboemboli 5/12: Positive Anti-cardiolipin Ab Test 5/13: Gangrenous R Foot noted 5/19: fever, sepsis, and respiratory failure 5/25: Death following cardiac arrest

114-003 76 M	9/1 Unstable Angina and MI	9/2- 9/16	9/16- 9/19	9/4: CABG complicated by multiple postoperative reintubations and renal failure requiring peritoneal dialysis 9/5: L CVA Platelet count 227K/mm3 on 9/3, 96K/mm3 on 9/6, 66K/mm3 on 9/15, and 26K/mm3 on 9/16; SRA Positive 9/17, 9/18: Pre Rx Doppler Positive for a R IJ DVT; VQ scan Negative 9/16-9/19: Argatroban administration Platelet count 101K/mm3 on 9/23 9/26: Post Rx Dopplers unchanged from Pre Rx examination; VQ scan not done 9/29: Patient noted tachypneic and desaturating on ventilator; 4 hours later patient experiences EMD and died following unsuccessful CPR
115-003 68 F	10/12 Thrombosed AAA H/O metastatic colon ca	10/12- 10/20	10/21- 10/22	10/12: Arterial Bypass Graft Surgery for limb preservation; complicated by graft clotting on two separate occasions (10/13 and 10/20) requiring reexploration and thrombectomy (10/20) Platelet count 215K/mm3 on 10/11, 145K/mm3 on 10/13, and 59K/mm3 on 10/20; SRA Positive 10/21: Pre Rx Doppler Positive for L IJV thrombosis; VQ scan not done 10/21-10/22: Argatroban administration Platelet count 72K/mm3 on 10/22 10/22: Patient aspirated food, developed respiratory distress, hypotension, bradycardia, and death
118-001 52 M	5/24 Cardiac arrest during coronary angiography	5/24- 5/30	5/30- 5/31	5/25: CABG and IABP 5/26: Evacuation of mediastinal hematoma Platelet count 270K/mm3 on 5/24 to 39K/mm3 10 hours later, and 12K/mm3 on 5/29; HIPA Weakly Positive 5/29: Unsuccessful L foot arterial revascularization and thrombectomy 5/30: Pre Rx Dopplers Positive for L LE Arterial Thrombus; VQ scan not done 5/30-5/31: Argatroban administration; discontinued due to GI bleeding (1 dose of warfarin given on 5/29) Platelet count 40K/mm3 on 5/31 Post Rx Dopplers and VQ scan not done 6/1: Death. As per Investigator, "Support was terminated due to multiple complications of HITTS-related thrombosis."
137-001 61 M	Unknown admission date H/O recent hospitalization for Staph bacteremia. On warfarin for prosthetic Aortic Valve	8/30- 9/3	9/4-9/6	Platelet count 193K/mm3 on 8/30, 59K/mm3 on 9/1, and 31K/mm3 on 9/3; HIPA Positive 9/3: CVA 9/3: Pre Rx Dopplers not done; VQ scan Low Probability 9/4-9/6: Argatroban administration Platelet count 76K/mm3 on 9/6 Post Rx Dopplers and VQ scan not done 9/6: worsening renal failure requiring hemodialysis, and Staph bacteremia 9/15: Death associated with "sepsis and multi-organ failure"

138-001 61 M	8/29 elective CABG (cardiac cath 8/16) H/O CABG	8/29 and 9/2-9/4	9/5-9/9	8/29: MI, CABG, and IABP; required inotropic support postoperatively 8/31: Pneumonia Platelet count 186K/mm3 on 8/28, 55K/mm3 on 9/1, and 51K/mm3 on 9/4; SRA Negative 9/2: Bilateral LE thromboses; R BKA on 9/11 9/5: Plasmapheresis 9/5-9/9: Argatroban administration Platelet count 117K/mm3 on 9/8, and 122K/mm3 on 9/12 9/22: Death due to acute MI Autopsy Results: Acute MI (<24 hours old), MI (3 weeks old), Severs CAD, s/p multiple coronary artery bypasses, acute bilateral bronchopneumonia, and ARDS
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Appendix 2: Analysis of Deaths that Occurred in Study ARG-915

All deaths that occurred in study ARG-915 were reconstructed from case report forms, and are tabulated below. Particular attention was paid to patient medical history, timing of heparin and argatroban administration, platelet count profile, HIT antibody status (not required to be collected in the study), clinical and objective evidence of thrombosis, on-site investigator assessment of clinical course and cause of death, and autopsy results whenever available. (Vol. 4.7, pp. 472 ff., and vol. 12.2 - 12.7)

Deaths in HIT Patients

PATIENT	ADMIT DIAGNOSIS and HISTORY	HEPARIN ADMIN.	ARGAT. ADMIN.	CLINICAL COURSE
014-002 71 F	6/10 Peripheral Vascular Bypass Surgery H/O COPD, Cor Pulmonale	6/11- 6/12	6/12- 6/18	6/10: Aortobifemoral bypass surgery 6/11: Embolectomy of graft clot. 6/11-6/12: Received heparin for thromboprophylaxis Platelet count 247K/mm ³ on 6/9, 141K/mm ³ on 6/11, 62K/mm ³ on 6/12 6/12-6/18: Argatroban administration; followed by warfarin 6/22: MI, hypotension, and oliguria 6/25: Death secondary to "MI" (Classified as a death due to thrombosis)
017-001 60 M	10/18 CHF secondary to a large AAMI at home H/O PVD	10/18- 10/31	11/1- 11/3	10/18-10/31: Heparin administration for LV thrombus on ECHO 10/25: Cardiac catheterization with severe CAD; IABP placed for 5 days Platelet count 297K/mm ³ on 10/18, 201K/mm ³ on 10/25, 150K/mm ³ on 10/27, and 31K/mm ³ on 10/30; H-PF4 Positive 11/1-11/3: Argatroban administration Platelet count 107K/mm ³ on 11/3 Bilateral LE ischemia requiring (unsuccessful) embolectomy and a R AKA 11/3: Patient "suddenly became hypotensive and could not be resuscitated. The immediate cause of death could not reliably be determined." (Classified as death due to cardiac arrest)

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017-003 49 M	12/2 Repair of dissecting Thoracoabdominal aneurysm H/O Renal Insufficiency, HTN	12/3- 12/13	12/13- 12/18	12/4: Resection of Thoracoabdominal Aneurysm; postoperative wound infection, DIC and sepsis ensued 12/11: Return to OR for wound debridement Platelet count 153K/mm3 on 12/3, 70K/mm3 on 12/5, 68K/mm3 on 12/10, and 39K/mm3 on 12/13 12/13-12/18: Argatroban administration Platelet count 61K/mm3 on 12/18, and 80K/mm3 on 12/20 First 3 weeks following surgery: renal failure requiring hemodialysis; progressive liver failure; sepsis and DIC continued Four weeks after surgery: Renal function improved; liver function continued to worsen; DIC and generalized bleeding 1/1: Candidemia, progressive liver failure, renal failure, and hemodynamic instability 1/8: Patient died following withdrawal of life support (Classified as death due to liver failure)
017-004 56 M	11/9 abdominal pain and bacteremia H/O MI x 2, TIAs, Peripheral Bypass graft surgeries	11/23- 12/6	12/7- 12/8	11/9-11/17: Hospitalization for treatment of fever, abdominal pain, and bacteremia; Discharged to home 11/18: Admission for MI with hemodynamic compromise; IABP placed, followed by an ischemic R LE Platelet count 288K/mm3 on 11/24, 163K/mm3 on 11/28, 80K/mm3 on 12/2, and 66K/mm3 on 12/5; HIT Ab Positive 12/5: 3-vessel CABG 12/6: Bilateral LE ischemic changes prompting bypass grafting and embolectomy 12/7-12/8: Argatroban administration 12/7-12/8: Patient continued to be hemodynamically unstable, his renal function deteriorated, and "he became increasingly coagulopathic." Life support was withdrawn and the patient died on 12/8 (Classified as death due to myocardial infarction)
036-006 70 M	6/14 PE H/O CABG on 5/19	6/14- 6/17	6/17- 6/18	5/19: CABG; postoperative course complicated by an ischemic stroke 6/14: VQ scan with Bilateral PE "occupying more than half of the lung parenchyma"; Rxd with thrombolysis with tPA and heparinized Platelet count 166K/mm3 on 6/14, 51K/mm3 on 6/15, and 40K/mm3 on 6/17; HIPA Positive Hospital course complicated by acute renal failure, shock liver, and sepsis 6/17-6/18: Argatroban administration; discontinued due to liver failure 6/23: Death due to sepsis (Classified as death due to sepsis)

036-007 74 M	6/18 AAA Repair H/O HTN, DM	6/18- 6/24	6/27- 6/30	6/18: AAA Repair Platelet count 141K/mm3 on 6/17, 95K/mm3 on 6/19, 66K/mm3 on 6/20, 14K/mm3 on 6/24; Heparin Ab Test Positive 6/24: Sepsis, pneumonia, and clot in arterial line noted. Coumadin started 6/24-6/27: Patient developed ARDS, and "it was suggested that there was intravascular thrombosis in the pulmonary tree." 6/27-6/30: Argatroban administration Platelet count 2K/mm3 on 6/27, and 8K/mm3 on 6/30 6/30: Death due to sepsis/ARDS
039-002 74 M	1/11 Ruptured AAA Repair H/O atrial fibrillation, COPD, BPH	1/23- 1/26	1/30- 2/5	1/11: Ruptured AAA Repair Platelet count 94K/mm3 on 1/23 and 34K/mm3 on 1/26; Heparin Ab Positive 1/30: Pulseless R hand noted; R UE arterial clot diagnosed, and Urokinase administered 1/30-2/5: Argatroban administered Platelet count 115K/mm3 on 2/1, 147K/mm3 on 2/2, and 143K/mm3 on 2/5 1/30: "The patient was already in renal failure and respiratory failure." 2/3-2/6: Warfarin administered 2/5: Bilateral pneumothoraces 2/5: "The patient's condition continued to worsen and it was felt he had undergone irreversible damage to multi-organ systems." 2/6: Patient was made DNR and died (Classified as death due to DIC)
039-003 56 M	1/29 R LE DVT H/O Stage IIIB lung ca	1/29- 2/1	2/1- 2/10	1/29: Heparinized for DVT; VQ scan Negative Platelet count 172K/mm3 on 1/29, 86K/mm3 on 1/30, and 53K/mm3 on 2/1 2/1-2/10: Argatroban administration Platelet count 69K/mm3 on 2/3, 117K/mm3 on 2/5, and 228K/mm3 on 2/10 Lung ca w/u with suspected mets to kidneys, adrenals, and abdominal LNs 2/10: Discharged on warfarin 2/22: Acute onset of seizures and ventricular tachycardia. Head CT: L frontal mass with edema - felt to be lung ca met. Patient intubated; neurologic status continued to decline 2/25: Life support withdrawn and patient died (Classified as death due to lung ca with metastasis to brain)

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<p>052-004 45 F</p>	<p>2/10 Tricuspid Valve Replacement H/O Tetralogy of Fallot (repaired age 10 y/o) s/p Pulmonic and Tricuspid Valve Replacement 2 years prior</p>	<p>2/10- 2/13</p>	<p>3/8- 3/16</p>	<p>2/10: Replacement of thrombosed tricuspid valve 2/13: "Developed HIT" (no details provided); heparin discontinued and warfarin continued 2/19: Pacemaker insertion 2/28: UE DVT x 2 on Doppler 3/8: Argatroban given perioperatively during surgery to close sternal wound (Platelet count 332K/mm3) 3/8-3/16: Argatroban administration; followed by warfarin 3/18: Pacemaker site infection noted; pacemaker failing to capture 3/22: Death following cardiac arrest (Classified as death due to cardiac arrest) Autopsy Results: "Probable Cause of Death: Tricuspid Valve Thrombosis."</p>
<p>052-005 77 M</p>	<p>4/10 MVR and CABG</p>	<p>4/2- 4/15</p>	<p>4/15- 4/17</p>	<p>4/9: AV Node ablation Platelet count 138K/mm3 on 4/2, 66K/mm3 on 4/8, and 69K/mm3 on 4/11 4/11: 3-vessel CABG and MVR 4/13: IABP placement for worsening biventricular failure Platelet count 43K/mm3 on 4/13, 19K/mm3 on 4/15, and 20K/mm3 on 4/18 4/13-4/15: renal failure and worsening liver function 4/15-4/17: Argatroban administration for mechanical valve 4/18: Death in the setting of renal failure, anasarca, worsening heart failure, and sepsis (Classified as death due to diffuse alveolar damage) Autopsy Results: Ischemic cardiomyopathy, diffuse alveolar damage, subacute L Parietal Lobe Infarct, and systemic atherosclerosis. "Probable Cause of Death: Respiratory Failure"</p>
<p>116-002 57 F</p>	<p>5/28 Workup of adenocarcinoma of unknown primary; metastatic to bone</p>	<p>6/3-6/8</p>	<p>6/25- 7/9</p>	<p>Platelet count 247K/mm3 on 6/1, and 5K/mm3 on 6/8; SRA Positive 6/3-6/8: Patient treated with heparin, and platelet and cryoprecipitate transfusions for presumed diagnosis of DIC (SRA Results were pending during this time) 6/25-7/9: Argatroban administration with improvement of coagulopathy 7/4: Discharge to inpatient rehabilitation unit 7/24: L LE DVT on Doppler 8/18: Discharged to Home where patient died on an unspecified date (Classified as death due to adenocarcinoma)</p>
<p>126-004 72 M</p>	<p>5/19 Anterior MI and cardiogenic shock</p>	<p>5/19- 5/22</p>	<p>5/23</p>	<p>5/19: Anterior MI and cardiogenic shock. Patient Rxed with pressors and an IABP Platelet count 193K/mm3 on 5/19, 100K/mm3 on 5/21, and 64K/mm3 on 5/22 5/23: Argatroban administration; discontinued as Hep Ab Test Negative 5/26: CABG and AoVR on heparin ("with stable platelet count"); postoperatively with nosocomial pneumonia, hypotension, and gram negative sepsis 6/7: Death (Classified as death due to sepsis)</p>

145-001 85 F	12/24 Surgery for Hip Fracture H/O HIT	12/31- 1/2	1/2-1/5	12/24: Hip fracture surgery s/p fall 12/26: Antero-lateral MI 12/30: R Iliac artery thrombosis on angiogram; thrombolysis administered 12/31-1/2: Heparin administration Pre-argatroban platelet counts not provided 1/2-1/5: Argatroban administration 1/3: L Common Iliac Artery thrombosis; thrombolysis administered 1/5: R groin hematoma requiring 2 u PRBC 1/5: Rhabdomyolysis and acute renal failure 1/5: Death due to pulmonary edema, acute renal failure, and myocardial infarction (as per death certificate)
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Deaths in HITTS Patients

PATIENT	ADMIT DIAGNOSIS and HISTORY	HEPARIN ADMIN.	ARGAT. ADMIN.	CLINICAL COURSE
007-001 34 F	4/4 pancreatitis	4/15 ff. and 4/21- 4/22	4/23- 5/10 and 5/20- 5/22	4/15: ERCP: pancreatitis and 3 pseudocysts 4/16: Discharged with subclavian catheter 4/19: Admission for pancreatitis; Noted with R LE and L subclavian catheter DVT 4/21-4/22: Heparin administered Platelet count 388K/mm3 on 4/19, 62K/mm3 on 4/22, and 39K/mm3 on 4/23 4/23: Bilat LE diagnosed 4/24: Pulmonary angiogram performed, followed by Greenfield filter placement for "PE"; patient intubated 4/23-4/48: Argatroban administration; complicated by major vaginal bleeding Platelet count 87K/mm3 on 4/24, 120K/mm3 on 4/25, 63K/mm3 on 4/28, 160K/mm3 on 5/1, 196K/mm3 on 5/4, and 261K/mm3 on 5/8 4/29: Patient extubated 5/6-5/18: Coumadin administration 5/20: Argatroban restarted; ERCP planned for 5/23 5/22: "During the 12 hours prior to her death, she experienced prolonged tachycardia and tachypnea." (Classified as death due to aspiration)
012-001 38 F	11/14 Mitral Valve Replacement H/O Rheumatic Fever, Pulm HTN, MS, MR, and previous MVR 2 years prior	11/14- 11/22	11/22- 11/26	11/14: Mitral Valve Replacement; required biventricular device placement for poor cardiac function postoperatively Platelet count 105K/mm3 on 11/14, 79K/mm3 on 11/21, 66K/mm3 on 11/23, 90K/mm3 on 11/25 11/20: Unable to wean from cardiopulmonary bypass due to ventricular tachycardia. Clots noted in Ventricular Assist Device requiring changing of pump 11/21: L LE noted pulseless; L Femoral artery embolectomy performed 11/23: Bilateral chest tubes placed 11/25: Head CT showed a "probable Left Middle Cerebral Artery large embolic stroke." 11/26: Patient made DNR, biventricular support was withdrawn, and patient died. (Classified as death due to withdrawal of life support)
020-002 84 F	12/1 Acute AWMI	12/1	12/5- 12/6	12/1: Acute AWMI. Cardiac cath showed 99% L main occlusion; EF was 30%; Emergent CABG was performed Platelet count 204K/mm3 on 12/1, 34K/mm3 on 12/2, 40K/mm3 on 12/5, and 47K/mm3 on 12/6 12/4: Mesenteric Ischemia: "Possible SMA thrombus" 12/5: Bilateral LE DVTs on Doppler 12/5: Intubation for respiratory failure 12/5-12/6: Argatroban administration 12/6: Patient died following cardiac arrest during placement of a new Swan-Ganz catheter (Classified as death due to cardiac arrest)

020-009 52 F	2/12	2/13- 2/18	2/20- 2/21	<p>2/12: Elective Thymoma resection Platelet count 285K/mm³ on 2/13, 353K/mm³ on 2/16, and 50K/mm³ on 2/20; HIPA Positive</p> <p>2/15: High Probability VQ scan</p> <p>2/18: Dopplers Negative for LE DVT</p> <p>2/20: Left hemiparesis and slurred speech noted; R CVA diagnosed</p> <p>2/20-2/21: Argatroban administered</p> <p>2/21: Head CT showed a large R CVA with cerebral edema and herniation. Life support was withdrawn and the patient died (Classified as death due to brain herniation)</p>
020-018 70 M	5/20 CABG Transferred following an acute AWMI at another hospital H/O DM, PVD, CRI, BKA	5/20- 5/22	6/1-6/2	<p>5/19: IABP placed and L LE ischemia noted</p> <p>5/20-5/22: Heparin administered</p> <p>5/22: 3-vessel CABG Performed; complicated by postoperative sternal wound infection</p> <p>5/31: pulmonary edema requiring intubation</p> <p>Platelet count 443K/mm³ on 6/1 and 308K/mm³ on 6/3 (No other values provided)</p> <p>6/1-6/2: Argatroban administered for suspected PE</p> <p>6/2: Low Probability VQ Scan; argatroban discontinued</p> <p>6/4: TEE showed severe cardiac dysfunction, MR, and a pericardial clot. Patient developed wet gangrene of L heel and decreased urine output</p> <p>6/18: Hemodialysis begun</p> <p>6/23: Patient self-extubated. Patient made DNR, pressor support withdrawn, and the patient died on 6/26 of "cardiac arrest". (Classified as death due to "acute MI")</p>
024-002 84 M	5/2 Transferred for Rx of HITTS	4/22- 4/23 and 4/29- 5/2	5/2-5/4	<p>4/22: CABG</p> <p>Platelet count 151K/mm³ on 4/25, 32K/mm³ on 4/30, and 17K/mm³ on 5/1; HIPA Positive</p> <p>Prior to transfer on 5/2: Bilateral UE and LE ischemic necrosis and non-QwMI</p> <p>5/2-5/4: Argatroban administration</p> <p>5/4: Patient made DNR and died on 5/5 (Classified as death due to multiorgan failure)</p>
025-001 68 M	5/6 CABG and MVR	5/6- 5/11	5/13- 5/26	<p>5/6: CABG and MVR</p> <p>Platelet count 185K/mm³ on 5/6, 107K/mm³ on 5/8, 74K/mm³ on 5/9 and 57K/mm³ on 5/11</p> <p>5/10: Patient intubated</p> <p>5/11: Bilateral LE ischemia</p> <p>5/11-5/13: Dextran 70 administered</p> <p>5/13-5/26: Argatroban administration</p> <p>Platelet count 79K/mm³ on 5/13, 117K/mm³ on 5/15, 230K/mm³ on 5/18, and 522K/mm³ on 5/26</p> <p>5/16: R hip hematoma (major bleed).</p> <p>5/22: Coumadin started</p> <p>5/27: LE gangrenous changes "stabilized" with demarcation noted</p> <p>5/28: Gastric distention noted</p> <p>5/29: Respiratory distress noted. Coumadin discontinued (due to inadequate absorption) and LMWH started. "The patient was believed to have an acute abdomen." Life support was withdrawn and the patient died. (Classified as death due to thrombosis)</p>

<p>036-002 86 F</p>	<p>12/3 AVR</p>	<p>12/3- 12/12</p>	<p>12/31</p>	<p>12/3: AVR Platelet count 203K/mm3 on 12/3, 75K/mm3 on 12/5, and 52K/mm3 on 12/12; HIPA Positive 12/5: Respiratory distress requiring intubation and subsequent tracheostomy 12/11 as unable to wean 12/12: R LE swelling; superficial venous thrombosis on Doppler. Heparin discontinued and Coumadin started Platelet count 47K/mm3 on 12/16, 84K/mm3 on 12/22, 129K/mm3 on 12/26, and 143K/mm3 on 1/1 12/30: Worsening R LE swelling; R DVT on Doppler 12/31-12/31: Argatroban administered; discontinued as therapeutic on Coumadin 1/11: Acute abdomen, hypotension, ventricular fibrillation arrest and death. Autopsy Results: Perforated Duodenal Ulcer, R LE DVT, and RUL PE (felt to be an incidental finding) (Classified as death due to duodenal perforation)</p>
<p>037-002 80 F</p>	<p>12/13 Cardiac catheterization H/O AS, AI, CHF, PE, breast ca</p>	<p>12/17- 12/23</p>	<p>12/24- 12/27</p>	<p>12/16: Cardiac cath with MR, severe AS, good LV function 12/17: AVR with subsequent mediastinal reexploration for bleeding Platelet count 200K/mm3 on 12/13, 120K/mm3 on 12/17, 85K/mm3 on 12/21, and 88K/mm3 on 12/23 12/19: acute renal failure 12/19: R hand noted cool and pulseless; R brachial embolectomy performed 12/20: atrial fibrillation 12/21: Coumadin started 12/24-12/27: Argatroban administration; discontinued due to high INR 12/25: CHF requiring intubation; renal dialysis started Platelet count 118K/mm3 on 12/26, 99K/mm3 on 12/27, 108K/mm3 on 1/2, and 64K/mm3 on 1/4 12/25-1/6: Progressive multiorgan failure. Patient died on 1/6 (Classified as death due to cardiogenic shock/sepsis)</p>

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<p>039-106 60 F</p>	<p>1/29 Evaluation of Aortic Aneurysm</p>	<p>1/30 - unk</p>	<p>3/14- 3/20</p>	<p>1/30: cardiac catheterization 1/31: aortography 2/3: AVR and aneurysm repair Platelet counts not available Postoperative course complicated with mediastinal bleeding, DIC, renal failure, and "after several days her platelet count went down and HIT was diagnosed and argatroban was started on 2/20." 3/14: L hemicolectomy for ischemic bowel Over the next 2 weeks: multiple laparotomies for "progressive ischemic bowel. These appeared (by arteriogram) to be embolic in nature." 3/14-3/20: Argatroban administration Post 3/20: "Despite continued anticoagulation, these (mesenteric) emboli continued to progress." 4/15: Last laparotomy for ischemic bowel performed - little viable bowel remained at this time. Patient subsequently treated for comfort measures only, and died on 4/19. (Classified as death due to ischemic bowel)</p>
<p>043-001 72 M</p>	<p>11/21 CABG</p>	<p>11/21- 12/4</p>	<p>12/4- 12/5</p>	<p>11/22: CABG Platelet count 223K/mm3 on 11/22, 131K/mm3 on 11/24, and 14K/mm3 on 12/4 12/3: Bilateral iliofemoral thromboses on Doppler 12/4-12/5: Argatroban administration 12/5: L Femoral thrombectomy for worsening LE ischemia; patient with hypotension, renal failure, and DIC postoperatively 12/9: Patient died after withdrawal of life support Autopsy results: "The immediate cause of death was respiratory failure due to bilateral pulmonary emboli and infarcts." (Classified as death due to cardiopulmonary arrest)</p>
<p>079-001 63 M</p>	<p>1/28 L UE DVT Recent H/O CABG on 1/20</p>	<p>Around 1/20 and 1/28- 1/29</p>	<p>1/31- 2/1</p>	<p>Platelet count 165K/mm3 on 1/20, 294K/mm3 on 1/26, and 55K/mm3 on 1/28 1/28: Admission for L UE DVT 1/28-1/29: New L-sided weakness and disorientation; CVA diagnosed and iv heparin administered 1/29-1/30: Enoxaparin administered Platelet count 13K/mm3 on 1/30, and 10K/mm3 on 2/1 1/31-2/1: Argatroban administration; discontinued due to APTT prolongation and "clinical deterioration" "The final events since 1/30 included fever, more disorientation, hypotension, renal deterioration, and respiratory failure. In summary, it was multi-organ failure, probably secondary to multiple factors (possible infection/sepsis, heart disease, and multiple thrombotic events)." (Classified as death due to multi-organ failure)</p>

<p>081-003 77 M</p>	<p>6/1 MI</p>	<p>6/10- 6/12</p>	<p>6/17- 6/23</p>	<p>6/1: Admission for MI 6/5: CABG Platelet count 55K/mm3 on 6/10, 14K/mm3 on 6/12, and 61K/mm3 on 6/15 6/9: Low Probability VQ scan 6/15: R LE DVT on Doppler 6/17-6/23: Argatroban administration Platelet count 29K/mm3 on 6/17, 39K/mm3 on 6/19, and 53K/mm3 on 6/23 Post-argatroban: R LE ischemia and distal necrosis 6/27: Discharged to Continuing Care Center; platelet count was 60-70K/mm3 6/28: Patient intubated following cardiac arrest 7/1: Death following cardiac arrest (Classified as death due to MI/cardiac arrest) Autopsy Results: Myocardial Infarction involving anterior and posterior L Ventricle, and posterior intraventricular septum</p>
<p>088-001 72 M</p>	<p>3/24 CABG post MI</p>	<p>3/21- 4/1</p>	<p>4/3-4/7</p>	<p>3/24: CABG post MI; poor LV function noted Platelet count 226K/mm3 on 3/23, 121K/mm3 on 3/28, 109K/mm3 on 3/29, and 86K/mm3 on 4/1 3/28-4/1: Warfarin administration 4/1: worsening renal function 4/1: R foot ischemia and gangrenous distal UE and LE changes noted 4/1-4/17: Urokinase administration for thromboembolic episodes 4/3-4/7: Argatroban administration Platelet count 98K/mm3 on 4/4, 127K/mm3 on 4/5, 249K/mm3 on 4/8, and 233K/mm3 on 4/10 4/7: Head CT obtained for increasing confusion demonstrated a small L corona radiata infarct, age indeterminate 4/8: R BKA 4/13: Patient "became lethargic" 4/16: Dialysis initiated for renal failure 4/18: Death following cardiorespiratory arrest (Classified as death due to cardiac arrest)</p>

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089-001 64 F	7/20 Acute infero-posterior MI H/O CABG (6 years earlier), CVA (6 years earlier), pulmonary fibrosis	7/20- 7/25	7/31- 8/6	7/20: Acute infero-posterior MI due to occlusion of a SVG from previous CABG surgery; Patient underwent emergent cardiac catheterization with subsequent cardiogenic shock, pulmonary edema, and IABP placement following PTCA attempt 7/23, 7/24, and 7/30: PRBC transfusions for unexplained drops in hematocrit Platelet count 99K/mm3 on 7/24, 66K/mm3 on 7/25 and 41K/mm3 on 7/27; Hep Ab Test Positive 7/25: ATIII administered for low ATIII level 7/25: Extensive L LE DVT on Doppler 7/26: Greenfield filter placed 7/28: Bronchoscopy 7/29: Open lung biopsy 7/31-8/6: Argatroban administration Platelet count 107K/mm3 on 7/31, 184K/mm3 on 8/3, and 217K/mm3 on 8/6 8/7: Transfusion of 4 U PRBC for Hb drop. Melena was noted; Upper Endoscopy was negative for a source of GI bleeding 8/12: Death due to bleeding, ARDS, hypoxemia, and MI (These causes of death were reported at various locations in the CRF; the sponsor classified this death as due to "bleeding/cardiogenic shock")
114-007 69 M		2/10, 2/12, 2/13- 2/15, and 2/18	2/19- 2/27	2/12: CABG; 2 grafts clotted post surgery 2/17: Bilateral DVTs; heparin restarted and IVC filter placed Platelet count 24K/mm3 on 2/20 2/19-2/27: Argatroban administration Platelet count 32K/mm3 on 2/23, 48K/mm3 on 2/24, 103K/mm3 on 2/25, and 242K/mm3 on 2/27 2/22: Urokinase administered 2/24: R AKA 2/25: GI Bleed requiring 2 U PRBCs 2/26: L BKA 3/4: Discharged 3/24: Hospitalized off-site for urosepsis; patient intubated 4/13: Death due to sepsis (Classified as death due to sepsis)
115-003 72 F	1/19 Acute MI	1/19- 1/24 and 1/30- 2/1	2/10- 2/17	1/19: Acute MI complicated by CHF and MR 1/24: CABG and MVR; complicated by prolonged intubation and reintubation Platelets 30K/mm3 on 1/31 2/3: R LE ischemia 2/6: UE DVT 2/3-2/10: Warfarin administration 2/10-2/17: Argatroban administration Post 2/17: "She had respiratory failure, CHF, pneumonia, azotemia, deterioration of her neurological status with the inability to definitely rule out multifocal embolic strokes vs. brainstem infarction" 2/17: "multiorgan failure secondary to sepsis along with coma." 2/21: Death following withdrawal of life support (Classified as death due to sepsis)

121-204 54 M	1/7 Pre-heart transplant workup (Dilated cardiomyopathy with EF < 15%)	1/7- 1/24	2/24- 3/25	Platelet count 272K/mm3 on 1/7 and 69K/mm3 on 1/24; HIPA Positive 1/27: Thrombectomy for L LE ischemia 1/27: ECHO with large LV thrombus 1/27: Thrombectomy for Aortic thrombus 1/27-3/25: Argatroban administration 2/12: R Pulmonary artery clot; treated with tPA 2/17-2/22: warfarin administration Post 2/22: Patient continued to deteriorate and required pressors and IABP placement 3/25: Cardio-respiratory arrest followed by death (Classified as death due to endstage cardiomyopathy)
122-001 75 F	3/28 Iliofemoral thrombectomy and fem-pop graft placement	3/28- 4/4	4/4	3/28: Iliofemoral thrombectomy and fem-pop graft placement Platelet count 361K/mm3 on 3/28, 167K/mm3 on 4/1, 49K/mm3 on 4/3, and 47K/mm3 on 4/4 4/2: R graft thrombectomy; L foot cyanotic but maintained a pulse 4/4: Doppler Negative for LE DVT 4/4: Argatroban administration 4/4: ARDS, sepsis, and acute abdomen, "with probable mesenteric infarction." 4/5: Death (Classified as death due to ARDS)
133-001 70 M	2/21 CABG and AoVR	2/21- 2/25	2/26- 3/3	2/21: CABG and AoVR 2/25: IABP removal and femoral artery repair Platelet count 77K/mm3 on 2/24, and 54K/mm3 on 2/25 2/26: UE and LE ischemia noted 2/26-3/3: Argatroban administration Platelet count 48K/mm3 on 2/26, 75K/mm3 on 2/28, 126K/mm3 on 3/1, and 286K/mm3 on 3/3 2/28: Coumadin started 3/3: Clinical improvement of ischemia noted; patient extubated 3/4: Massive hemoptysis, intubation, and electromechanical dissociation (No objective evidence of a PE was sought) 3/17: Patient died (Classified as death due to anoxic encephalopathy)
143-001 78 F	6/18 Sudden onset of ischemic L Hand H/O colon ca, DVT (patient on warfarin), HTN, DM, CRI	6/18- 6/19	6/20- 6/27	6/18: Brachial arterial thrombectomy 6/19: Rethrombosis of brachial artery; repeat thrombectomy and brachial artery bypass performed 6/13-6/18: Warfarin administration 6/19: Urokinase administration 6/20: HIPA Positive serology 6/20-6/27: Argatroban administration 6/27: L Hand amputation 7/19: Death following worsening renal dysfunction, generalized edema, and refusal to undergo dialysis (Classified as death due to worsening renal failure)

<p>146-001 49 F</p>	<p>7/30 unstable angina</p>	<p>7/30- 7/31</p>	<p>8/4-8/5</p>	<p>6/26: IWMI and PTCA 7/31: Emergent CABG; IABP placed 8/1: Reexploration and pericardial clot removed Platelet count 195K/mm3 on 7/10, 118K/mm3 on 7/30, 147K/mm3 on 8/1, 40K/mm3 on 8/2, and 43K/mm3 on 8/4 8/3: Bluish discoloration and mottling of hands and feet 8/4-8/5: Argatroban administration Post 8/4: Acute renal and hepatic failure; "Her extremities continued to deteriorate as more and more small vasculature was occluded with the platelet clots." 8/5: Death (Classified as death due to multisystem failure)</p>
<p>149-001 58 M</p>	<p>2/19 redo-CABG H/O HIT with first CABG 10 years earlier</p>	<p>2/19- 2/22</p>	<p>2/22- 2/24</p>	<p>2/19: redo-CABG 2/21: LIMA graft closure 2/22-2/24: Argatroban administration; discontinued due to a GI bleed 2/24: Death following a ventricular fibrillation arrest Autopsy Results: "Severe coronary atherosclerosis with recent thrombosis of left internal mammary artery bypass graft and acute massive apical myocardial infarct."</p>

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