The influence of time from symptom onset and reperfusion strategy on 1-year survival in ST-elevation myocardial infarction: A pooled analysis of an early fibrinolytic strategy versus primary percutaneous coronary intervention from CAPTIM and WEST

Cynthia M. Westerhout, PhD,[a,d] Eric Bonnefoy, MD,[b,d] Robert C. Welsh, MD,[a,d] Philippe Gabriel Steg, MD,[c,d] Florent Boutitie, PhD,[b,d] and Paul W. Armstrong, MD[a,d] ***Edmonton, Canada; and Lyon and Paris, France***

Background The CAPTIM trial suggested a survival benefit of prehospital fibrinolysis (FL) compared to primary percutaneous coronary intervention (PCI) in patients with ST-elevation myocardial infarction (STEMI) with a presentation delay of <2 hours. We examined the relationship between reperfusion strategy and time from symptom onset on 1-year mortality in a combined analysis of 1,168 patients with STEMI.

Methods Individual patient data from CAPTIM (n = 840, 1997-2000) and the more recent WEST trial (n = 328, 2003-2005) were pooled.

Results Median age was 58 years, 81% were men, and 41% had anterior myocardial infarction; 640 patients were randomized to FL versus 528 patients to PCI. Both arms received contemporary adjunctive medical therapy. Presentation delay (ie, symptom onset to randomization) was similar in FL and PCI patients (median 105 [72-158] vs 106 [74-162] minutes, P = .712). Rescue PCI after FL occurred in 26% and 27%, and 30-day PCI, in 70% and 71% in CAPTIM and WEST, respectively. Mortality was not different between FL and PCI (4.6% vs 6.5%, P = .263); however, the interaction between presentation delay and treatment was significant (P = .043). Benefit with FL was observed with time <2 hours (2.8% [FL] vs 6.9% [PCI], P = .021, hazard ratio [HR] 0.43, 95% CI 0.20-0.91), whereas beyond 2 hours, no treatment difference was observed (6.9% [FL] vs 6.0% [PCI], P = .529, HR 1.23, 95% CI 0.61-2.46).

Conclusions A strategy of early FL demonstrated a reduction in 1-year mortality compared to primary PCI in early presenters. Time from symptom onset should be a key consideration when selecting reperfusion therapy for STEMI. (Am Heart J 2011;161:283-90.)

The optimal reperfusion therapy for patients with ST-elevation myocardial infarction (STEMI) has attracted great interest, stimulated vigorous controversy, and led to constructive enhancement of health care systems aimed at abbreviating time from symptom onset to reperfusion. Although contemporary STEMI guidelines recommend primary percutaneous coronary intervention (PCI) as the preferred strategy, provided it can be delivered promptly in an expert facility, this is often not feasible.[1,2] However these guidelines also emphasize the desirability of a total ischemic time of <2 hours and support the use of fibrinolytic therapy if primary PCI cannot be performed within 90 minutes of first medical contact. It follows that patient and situational specific reperfusion strategies, that is, fibrinolysis (FL) or primary PCI, require consideration, and the optimal approach remains an active source of debate in many circumstances. Although some trials and a systematic overview conclude that PCI is the preferred therapy, there are notable caveats arguing against a "one size fits all" strategy favoring a more nuanced approach.[3,4]

An important and well-recognized modulator of prognosis after STEMI is time from symptom onset until reperfusion,[5,6] which is now a required consideration in therapeutic decision making.[1,2] Indeed, recent STEMI guidelines indicate a goal of curtailing total ischemic time

From the [a]University of Alberta, Edmonton, Canada, [b]Universite Lyon, Lyon, France, and [c]Universite Paris, Paris, France.
ClinicalTrials.gov Identifier: NCT00121446 (WEST).
[d]For the CAPTIM/WEST Investigators.
Submitted August 25, 2010; accepted October 15, 2010.
Reprint requests: Paul W. Armstrong, MD, 251 Medical Sciences Building, University of Alberta, Edmonton, Canada T6G 2H7.
E-mail: paul.armstrong@ualberta.ca
0002-8703/$ - see front matter

doi:10.1016/j.ahj.2010.10.033

to <2 hours.[1] Major advancements in the delivery of STEMI care have been aimed at minimizing time to treatment, particularly in prehospital diagnosis, early delivery of reperfusion,[7] and timely triage to an appropriate hospital. The CAPTIM trial was the first large-scale trial to evaluate the efficacy of prehospital FL versus PCI[8] and, importantly, provided evidence of an early window of benefit with prehospital FL when time from symptom onset was within 2 hours and mechanical coronary cointervention was frequently employed.[9] However, the CAPTIM trial was hypothesis-generating in this regard and concluded enrollment (after 840 patients) before its target sample of 1,200 patients.

The current study extends this observation through collaboration between CAPTIM and the WEST trialists, the latter adding over 300 similarly randomized contemporaneous patients with STEMI, thereby approximating the initial CAPTIM enrollment.[10] Our primary goal was to examine the influence of reperfusion choice on 1-year mortality and the extent to which it is modulated by time from symptom onset. In addition, we explored this issue on the prespecified events of recurrent myocardial infarction (MI), cardiogenic shock, and safety.

Methods

The details and primary results of the CAPTIM and WEST trials have been previously published.[8,10] In brief, the CAPTIM trial randomized eligible patients at the site of initial management to prehospital FL or direct transfer for primary PCI. All patients received an intravenous bolus of 5,000 U heparin and 250 to 500 mg aspirin. Patients assigned to prehospital FL received an intravenous bolus of alteplase followed by an infusion over 90 minutes. Coronary angiography and subsequent revascularization were allowed in the FL group at the discretion of the responsible physicians and, when appropriate, rescue angioplasty was done. Patients assigned to primary PCI were transported immediately to the hospital for coronary angiography and angioplasty, if indicated. Angioplasty was done according to local standards with the intention of restoring blood flow in the infarct-related artery as soon as possible. After randomization, heparin was continued for at least 48 hours. Those receiving stents were treated with a thienopyridine for 1 month. In addition to aspirin, the protocol recommended use of atenolol in all patients and lisinopril in those with anterior infarcts.

The WEST trial had a parallel-group design that randomized patients into one of the following 3 treatment arms, at the earliest point of care, including the prehospital setting and participating study hospitals: (1) usual care: optimal pharmacologic therapy (prompt administration of tenecteplase [TNK], aspirin, and enoxaparin); (2) early invasive strategy: identical pharmacologic therapy and early invasive strategy including mandatory rescue PCI; or (3) primary PCI (after aspirin, enoxaparin, and 300 mg clopidogrel). Abciximab was recommended for all PCI procedures unless performed within 3 hours of fibrinolytic therapy, and clopidogrel was used in patients in the pharmacologic therapy groups according to American College of Cardiology/American Heart Association PCI guidelines.

Patients

The CAPTIM trial enrolled patients if they presented within 6 hours of symptom onset (ie, characteristic pain lasted for at least 30 minutes, not responsive to nitrates, with electrocardiographic [ECG] ST-segment elevation of at least 0.2 mV in ≥2 contiguous leads, or left bundle branch block) in mobile emergency care units (Service d'Aide Médicale d'Urgence) with 27 affiliated tertiary hospitals in France. Patients could be excluded if the transfer time to hospital was expected to be >60 minutes.

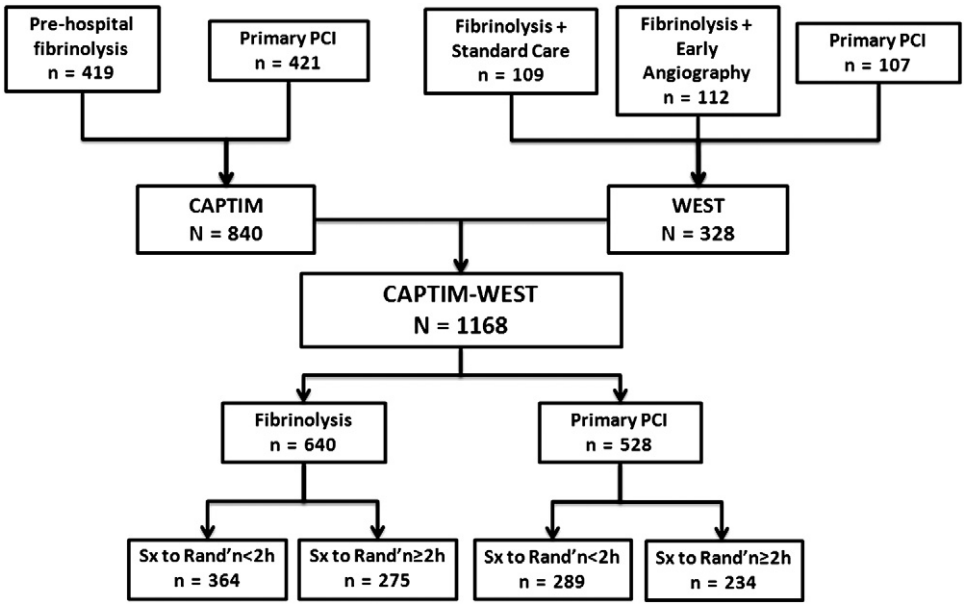
Like CAPTIM, the WEST trial enrolled patients with STEMI within 6 hours of symptom onset. Specifically, patients were sought in whom primary PCI could not be delivered within 60 minutes but for whom primary PCI and/or transfer for rescue PCI was feasible within 3 hours of randomization.[11] Symptoms presumed secondary to STEMI lasting at least 20 minutes were required, accompanied by ECG evidence of high risk, which included ≥2 mm of ST-elevation in ≥2 contiguous precordial leads or limb leads or ≥1-mm ST-elevation in ≥2 limb leads coupled with ≥1-mm ST-depression in ≥2 contiguous precordial leads (total ST-deviation ≥4 mm) or presumed new left bundle branch block. An emphasis on the earliest possible randomization was a cardinal feature of WEST and prehospital ECG; randomization and initiation of therapy (using paramedics vs physicians in CAPTIM) were strongly encouraged for those patients using 911/ambulance access to health care facilities. Forty-four percent of patients were randomized prehospital: 45.7% with FL and 41.1% with primary PCI. The enrollment period was extended beyond the prespecified sample of 304 patients to include an additional 24 patients to expand the prehospital randomization. Fifteen sites within 4 metropolitan areas in Canada (Edmonton, Halifax, Montreal, and Vancouver) were involved in enrollment. The maximum follow-up in WEST was 1 year.

Statistical analysis

Discrete variables are reported as counts and percentages of nonmissing cases; median and 25th and 75th percentiles are reported for continuous variables. Differences between studies and between study treatments were tested by χ^2, Wilcoxon-Mann-Whitney U, and Kruskal-Wallis tests as appropriate. Analyses were conducted according to the intention-to-treat principle, which included all patients who gave informed consent and were randomized to study treatment, irrespective of whether treatment was actually received. In the WEST trial, the 2 FL arms (TNK + usual care and TNK + early angiography) were not statistically different with respect to the primary end point of the trial[10]; thus, these 2 arms were combined with the fibrinolytic arm in CAPTIM.

The primary end point of this study was all-cause mortality within 1 year. Eight patients were lost to follow-up in the WEST study, whereas CAPTIM had a complete 1-year follow-up. Kaplan-Meier survival curves were constructed to illustrate the time to death within 1 year after randomization, with between-group differences evaluated by the log-rank test (and accounting for the between-trial variation by stratification). Via stratified Cox proportional hazards regression, the adjusted HR and corresponding 95% CI for 1-year mortality were estimated for study treatment, time from symptom onset, and the

Figure 1



Derivation of study cohort.

Table I. Selected baseline characteristics

	CAPTIM		WEST		CAPTIM-WEST		
	FL	Primary PCI	FL	Primary PCI	All	FL	Primary PCI
n	419	421	221	107	1168	640	528
Age, y	58 (49-68.5)	58 (50-68)	58 (50-68.5)	60 (49-71)	58 (49-69)	58 (49-68.3)	58.5 (50-69)
Male, %	82.5	81.5	77.4	80.4	81.0	80.7	81.3
Systolic BP, mm Hg	125 (110-140)	128 (111-140)	140 (122.3-160)	143 (124-158.5)	131 (23.5)	130 (115-147)	130 (115-145)
Pulse, beat/min	75 (64-84)	75 (66-88)	72 (62-85)	74 (62-88)	75 (65-86)	74 (63-84)	75 (65-88)
Weight, kg	75 (68-85)	75 (67-84)	83 (73-94)	82 (73-93)	77 (69-86)	78 (70-88)	75 (68-85)
Height, cm	170 (165-175)	170 (165-175)	173 (167-178)	173 (167.5-179)	170 (165-176)	171 (165-176)	170 (165-176)
Killip Class >1, %	8.7	12.2	5.4	6.5	9.1	7.5	11.0
Hypertension, %	34.1	34.8	45.2	34.6	36.5	38.0	34.8
History of diabetes, %	11.1	13.6	11.8	15.0	12.5	11.3	13.9
History of angina, %	13.5	14.6	28.5	18.7	17.2	18.7	15.4
Prior MI, %	8.2	6.7	12.7	13.1	9.0	9.8	8.0
Previous PCI, %	5.3	4.3	8.1	4.7	5.4	6.3	4.4
Current smoker, %	52.7	49.2	49.5	39.3	49.5	51.6	47.1
Anterior MI, %	40.1	42.7	38.9	42.1	41.0	39.7	42.9

Continuous variables as median (25th to 75th percentile).

interaction of these 2 factors, again accounting for between-trial variation. Time from symptom onset was treated as a discrete variable (ie, time from symptom onset to randomization <2 vs ≥2 hours), which was prespecified based on previous analyses of time from symptom onset and is in accord with current STEMI guidelines relating to reperfusion options and total ischemic time.[1,2,5,9] The relationship between time from symptom onset, treatment, and 1-year mortality was also expressed with time in a continuous fashion. The linearity and proportional hazard assumptions were evaluated. Adjustment of the relationship was performed via backward selection using an inclusion criterion of $\alpha = .05$ and exclusion criterion of $\alpha = .10$ (and confirmed with forward selection). Baseline patient characteristics considered in adjustment included age, sex, systolic blood pressure, heart rate, Killip class, hypertension, history of diabetes, history of angina, prior MI, previous PCI, current smoking status, and anterior MI.

Because the DANAMI-2 study reported that the benefit observed for PCI in their study was restricted to patients with

Table II. Timing intervals

	CAPTIM		WEST		CAPTIM-WEST		
	FL	Primary PCI	FL	Primary PCI	All	FL	Primary PCI
n	419	421	221	107	1168	640	528
Symptom onset to randomization, min	107 (75.8-158.3)	108 (76-162)	105 (66-159)	101 (70-163.8)	105.5 (73-161)	105 (72.5-158.5)	106 (74-161.5)
<2 h, %	55.3	55.0	60.2	56.1	56.1	57.0	55.3
≥2 h, %	44.7	45.0	39.8	43.9	43.9	43.0	44.7
Symptom onset to first medical contact, min	78 (48-135)	77 (48-135)	52.5 (29-101.5)*	54 (29.3-108.8)*	72 (42-130)	70 (40-125)	73 (44.8-131)
First medical contact to randomization, min	25 (18-34)	26 (19-35)	38 (28-59)*	39 (26-60)*	29 (20-40)	30 (21-41)	28 (20-38)
Symptom onset to FL, min	130 (95-180)	–	117 (75-179.3)*	–	–	122 (85-180)	–
Symptom onset to primary PCI, min	–	190 (148.5-255)	–	189 (150.5-293)	–	–	189 (148.3-256.8)
Randomization to FL, min	16 (10-23)	–	9 (6-15)*	–	–	13 (8-21)	–
Randomization to primary PCI, min	–	72 (60-88)	–	90 (64.5-97.3)*	–	–	76 (62-94)
Length of stay, d	8 (6-11)	8 (6-10)	3 (2-5)	3 (2-5)	7 (3-10)	7 (3-10)	7 (4-9)

* $P < .05$ for comparison between studies within treatment.

high Thrombolysis In Myocardial Infarction (TIMI) risk, we undertook a secondary analysis to examine this in high- versus low-risk patients as defined by the TIMI risk score (high risk ≥5 points, low risk <5 points).[12,13]

Additional analysis was undertaken on prespecified events, that is, recurrent MI and cardiogenic shock, and the incidence of major systemic bleeding and nonfatal intracranial hemorrhage (ICH) inhospital.

All statistical comparisons were done at the 5% level of significance using a 2-sided alternative hypothesis, unless stated otherwise. Analyses were performed using SAS (version 9.2, SAS Institute, Cary, NC).

No extramural funding was used to support this work.

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

Results

Individual patient data from the CAPTIM, which enrolled 840 patients with STEMI between 1997 and 2000, and WEST trials, which enrolled 328 patients with STEMI between 2003 and 2005, were obtained for the current study (Figure 1). Baseline patient characteristics according to study treatment are presented in Table I for the individual trials as well as the pooled cohort. Overall, the patients enrolled in the CAPTIM and WEST trials were comparable across the trials and between the study treatments: median age of 58 years, 81% men, 9% with prior MI, and median weight of 77 kg.

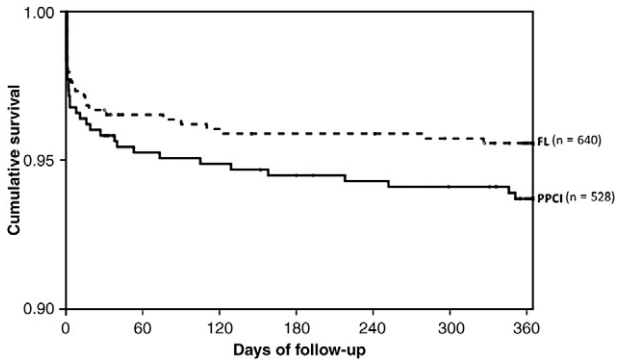
Time from symptom onset

In Table II, the overall median time from symptom onset to randomization was 106 minutes and was similar in both trials with 56% of patients randomized within 2 hours of symptom onset. Although there was a shorter interval from symptom onset to first medical contact in WEST than in CAPTIM (median 53 vs 78 minutes), CAPTIM's time from first medical contact to randomization was shorter at 26 minutes versus 38 minutes in WEST. Overall, time from symptom onset to treatment with FL was shorter in WEST compared to CAPTIM ($P = .006$); however, time to PCI was comparable between the studies (Table II). The median length of stay was 8 days in CAPTIM and 3 days in WEST.

One-year mortality

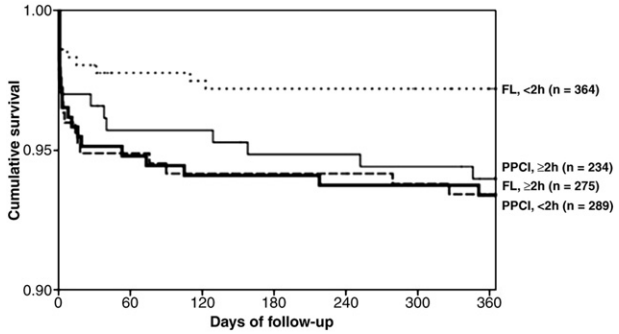
Overall, 63 (5.4%) of 1,160 patients with complete follow-up died within 1 year of randomization. There was no difference in overall 1-year mortality between FL and primary PCI ([29/633] 4.6% vs [34/527] 6.5%, unadjusted HR 0.75 [FL vs PCI], 95% CI 0.46-1.24, $P = .546$) (Figure 2). When 1-year mortality was further examined according to the TIMI risk score (high risk ≥5 points [17.8% of patients], low risk <5 points [82.2%]), mortality was comparable in low-risk patients (FL [12/513] 2.3% vs PCI [9/405] 2.2%, $P = .899$). One-year mortality was nominally higher in PCI than in FL in high-risk patients, but this did not reach statistical significance (FL [13/99] 13.1% vs PCI [18/101] 17.8%, $P = .373$). However, when mortality was examined according to time from symptom onset to randomization (Figures 3 and 4), the interaction was statistically significant ($P = .043$). Patients randomized within 2 hours of symptom onset had improved survival with FL compared to those receiving primary PCI ([10/358] 2.8% vs [20/288] 6.9%, $P = .021$, HR 0.43, 95% CI 0.20-

Figure 2



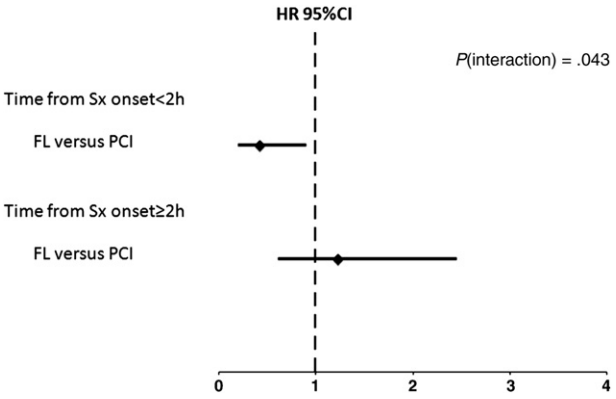
Kaplan-Meier curve of 1-year survival according to study treatment (P = .263) (FL, dashed; PCI, solid line).

Figure 3



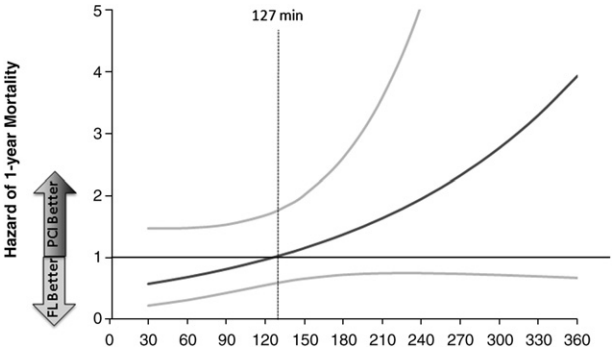
Kaplan-Meier curve of 1-year survival according to study treatment and time from symptom onset (P = .021, FL <2 hours vs PCI <2 hours; P = .529, FL ≥2 hours vs PCI ≥2 hours) (FL <2 hours, dotted; FL ≥2 hours, dashed; PCI <2 hours, thick solid; PCI ≥2 hours, thin solid line).

Figure 4



Association between time from symptom onset and study treatment according to 1-year mortality.

Figure 5



Fibrinolysis versus PCI on 1-year mortality according to increasing time from symptom onset. The hazard of mortality for FL approximated that of PCI at 127 minutes (note that time <127 minutes, 59.1% of all patients; time <240 minutes, 91.6% of all patients). Hazard ratio indicated by thick solid line and 95% CI in thick gray lines.

0.91). Beyond 2 hours, however, no treatment difference in 1-year mortality was observed (FL [19/274] 6.9% vs PCI [14/234] 6.0%, P = .529, HR 1.23, 95% CI 0.61-2.46). After adjustment for age, systolic blood pressure, heart rate, diabetes, and Killip class, a significant interaction between time from symptom onset and study treatment remained (P = .037) such that FL patients had a (relative) 42% lower hazard of 1-year mortality than PCI patients with symptom onset within 2 hours (ie, in time <2 hours, FL vs PCI, adjusted HR 0.58, 95% CI 0.26-1.29). In patients randomized beyond 2 hours, there appeared to be an excess hazard associated with FL versus PCI (ie, FL vs PCI, adjusted HR 1.81, 95% CI 0.87-3.77). When examining time from symptom onset in a continuous fashion (Figure 5), the point estimates for FL versus PCI suggest a survival benefit for FL until approximately 127 minutes from when symptom onset had elapsed; thereafter, a reversal occurred with improved survival with PCI.

Inhospital and 30-day events and interventions

Table III provides the 30-day occurrence of cardiogenic shock and re-MI and inhospital safety events. Although 30-day cardiogenic shock appeared to be higher in primary PCI patients than in FL patients, this did not achieve statistical significance (5.3% vs 3.8%, P = .203); re-MI, however, was over 2-fold higher in FL patients (2.0% vs 5.3%, P = .004). Intracranial hemorrhage was rare in this patient population. Although major systemic bleeds were nominally higher in primary PCI than in FL patients, this did not reach statistical significance. In FL

Table III. Cardiogenic shock, re-MI, ICH, and major systemic bleeding

	CAPTIM		WEST		CAPTIM-WEST		
	FL	Primary PCI	FL	Primary PCI	All	FL	Primary PCI
n	419	421	221	107	1168	640	528
30-day cardiogenic shock, n (%)	12 (2.9)	19 (4.5)	12 (5.4)	9 (8.4)	52 (4.5)	24 (3.8)	28 (5.3)
Onset to randomization <2 h, n (%)	5 (2.2)	11 (4.8)	9 (6.8)	6 (10.0)	31 (4.7)	14 (3.8)	17 (5.9)
Onset to randomization ≥2 h, n (%)	7 (3.7)	8 (4.3)	3 (3.4)	3 (6.4)	21 (4.1)	10 (3.6)	11 (4.7)
30-day re-MI, n (%)	15 (3.7)	7 (1.7)	18 (8.1)	3 (2.8)	43 (3.8)	33 (5.3)	10 (2.0)*
Onset to randomization <2 h, n (%)	9 (4.0)	3 (1.4)	11 (8.3)	3 (5.0)	26 (4.1)	20 (5.6)	6 (2.2)*
Onset to randomization ≥2 h, n (%)	6 (3.4)	4 (2.2)	7 (8.0)	0 (0.0)	17 (3.5)	13 (4.9)	4 (1.8)
Inhospital ICH, n (%)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	2 (0.3)	0 (0.0)
Inhospital major systemic bleeding, n (%)	2 (0.5)	8 (1.9)	3 (1.4)	1 (0.9)	14 (1.2)	5 (0.8)	9 (1.7)

* $P < .05$.

patients, rescue PCI occurred in 26% of patients and PCI within 30 days in 70% of patients.

Discussion

Our novel findings not only support the critical relationship between time from symptom onset and 1-year survival after reperfusion, but also provide new evidence about the impact of this relationship on the relative efficacy of the 2 standard modes of therapy. A survival advantage existed for patients treated with FL within 2 hours of symptom onset relative to those treated with primary PCI (P interaction [unadjusted] = .043). When time from symptom onset was explored in a continuous fashion, a progressive attenuation of the benefit of FL was observed until approximately 127 minutes had elapsed; thereafter, the survival advantage of PCI appeared and increased with time (Figure 5).

What might account for the difference in our findings and those previously reported in a systematic overview and meta-analysis?[3,5] A key distinguishing characteristic of the current versus prior trials comparing pharmacologic and mechanical reperfusion was the short time between symptom onset and randomization (including prehospital randomization) such that more than one half of the patients achieved this within 2 hours. The influence of time to treatment in myocardial salvage in patients treated with primary PCI versus FL has been examined by Schomig et al.[14] Using myocardial scintigraphy to quantify the salvage index in 264 patients from 2 randomized trials, this group demonstrated that, although a similar salvage index occurred within the first tertile of time from symptom onset (approximately 165 minutes), there was a progressive decrease in salvage with FL versus PCI. Noteworthy and perhaps accounting for these findings was that median door-to-needle time was 35 minutes, that is, beyond current recommendations, whereas the door-to-balloon time was a remarkably short 65 minutes, thus resulting in an unusually brief half-hour difference between reperfusion strategies. Important additional distinguishing features of patients in the CAPTIM-WEST analysis include systematic use of fibrin-specific pharmacologic therapy, rescue PCI in 26% of patients, and frequent cointervention with PCI in 70% of the fibrinolytic-treated patients by 30 days. The earlier time-to-treatment and more frequent cointervention likely account for the better outcome of fibrinolytic-treated patients in the current study versus the DANAMI-2 trial; thereafter, mechanical rescue and cointervention were discouraged and infrequent in the fibrinolytic-treated patients. Although prior data and guidelines suggest an advantage for PCI in high-risk patients, they represented a minority of the overall STEMI population and our combined cohort (17.8% of patients), whereas they represented 26% of the DANAMI-2 trial.[12,13] Importantly, both the CAPTIM and WEST trials also used contemporary adjunctive antithrombotic and antiplatelet therapy in patients assigned to the primary PCI arms to ensure optimal overall results in both treatment arms. Our findings are in accordance with those of the GRACIA-2 investigators who demonstrated that routine stent/angioplasty within 3 to 12 hours of FL proved both safe and equivalent to primary stenting in preserving myocardial function.[15] Although these investigators found better myocardial perfusion in the fibrinolytic-treated patients, their study of 212 patients was underpowered to address whether there was associated clinical improvement and called for "a larger clinical outcome study for confirmation."

We observed an increase in the occurrence of inhospital re-MI among fibrinolytic-treated patients. This finding could relate not only to surveillance bias and the challenge of defining and detecting periprocedural MI after PCI for STEMI, but also to the possibility that early fibrinolytic-treated patients had more salvaged but subsequently jeopardized myocardium.

Fibrinolytic therapy was well tolerated by this patient population with low ICH rates and minimal major bleeding that was numerically greater in the PCI group as has been observed previously.[3] The low rate of ICH in the current report likely relates the relatively young age of our patients and the careful exclusion of prior

stroke, a feature that has not been uniformly applied in other studies.

Our data are also consistent with recent observational reports from the French registry of acute ST-elevation myocardial infarction and respond to the recent call for confirmation of those findings in a randomized design.[16,17] They are also aligned with the 3-state regional approach from the Mayo Clinic and the Vienna STEMI registry, which both attest to the excellent results after fibrinolytic administration in the early post–symptom-onset period.[18,19] The primacy of time from symptom onset as a modulator of outcome is underscored by the recent data of Francone et al,[20] which showed marked attenuation of the potential for myocardial salvage in patients undergoing primary PCI >90 minutes after symptom onset. Hence, the relatively flat relationship between survival and time from symptom onset that we observed in primary PCI-treated patients is perhaps not surprising, given that, even under the optimal circumstances existing for timely access to expert PCI in both CAPTIM and WEST, the median time to achieve it was 189 minutes; hence, only one quarter of our patients underwent PCI within 148 minutes of symptom onset.

Limitations and strengths

Some limitations of our analysis should be noted. Although combining these 2 trials was not prespecified, we believe it to be warranted given the demonstrated similar baseline characteristics and times to randomization and reperfusion. The populations studied were part of clinical trials; hence, caution regarding the generalizability of our results to a broader clinical population would be prudent. However, they are in accordance with substantial data acquired in registries.[21]

Although the interaction between treatment and delay was evaluated on 5-year mortality in the CAPTIM trial, this relationship did not achieve statistical significance.[22] By merging the WEST and CAPTIM trials, we increased the size of the study population and events resulting in a statistically significant interaction for 1-year mortality, indicating that we had sufficient power to test this association.

Conclusion

Given persisting evidence of failure to meet guideline-suggested times to PCI, especially among patients presenting to non-PCI hospitals, our data provide additional evidence to support the efficacy of an alternative reperfusion strategy, that is, fibrinolytic therapy (in patients without contraindications, coupled with contemporary adjunctive therapy, timely rescue PCI, and subsequent revascularization), especially in those presenting early after symptom onset either in the prehospital setting or in the non-PCI hospital setting. Such an approach is also likely to be welcome in countries and regions where there is a relative paucity of PCI centers and where climate and geography may complicate immediate transfer for primary PCI.

Acknowledgements

The authors would like to acknowledge the expert editorial assistance of Jo-An Padberg.

Disclosures

The original WEST study was supported by an unrestricted grant from Hoffmann-LaRoche Limited; Aventis Pharma, a member of the Sanofi-Aventis group; as well as Eli-Lilly Canada. The original CAPTIM study was supported by a grant from the French Ministry of Health (Projet Hospitalier de Recherche Clinique, 96/045), by the Hospices Civils de Lyon, and by an unrestricted research grant from AstraZeneca France. Biotronic GmbH provided balloons and guidewires free of charge.

Drs Armstrong and Welsh received Clinical Trial funding from Boehringer-Ingelheim.

References

1. Antman EM, Hand M, Armstrong PW, et al. 2007 focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association task force on practice guidelines: developed in collaboration with the Canadian Cardiovascular Society endorsed by the American Academy of Family Physicians. Circulation 2008;117:296-329.
2. The Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation. Eur Heart J 2008;29:2909-45.
3. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomized trials. Lancet 2003;361:13-20.
4. Willerson JT. Editor's commentary: one size does not fit all. Circulation 2003;107:2543-4.
5. Boersma E and the Primary Coronary Angioplasty versus Thrombolysis (PCAT)-2 trialists' collaborative group. Does time matter? A pooled analysis of randomized clinical trials comparing primary percutaneous coronary intervention and in-hospital fibrinolysis in acute myocardial infarction patients. Eur Heart J 2006;27:779-88.
6. Armstrong PW, Westerhout CM, Welsh RC. Duration of symptoms is the key modulator of the choice of reperfusion for ST-elevation myocardial infarction. Circulation 2009;119:1293-303.
7. Solis P, Amsterdam EA, Bufalino V, et al. Development of systems of care for ST-elevation myocardial infarction patients. Policy recommendations. Circulation 2007;116:e73-6.
8. Bonnefoy E, Lapostolle F, Leizorovicz A, et al, on behalf of the Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction (CAPTIM) study group. Primary angioplasty versus prehospital fibrinolysis in acute myocardial infarction: a randomized study. Lancet 2002;360:825-9.
9. Steg PG, Bonnefoy E, Chabaud S, et al, for the Comparison of Angioplasty and Prehospital Thrombolysis in acute Myocardial infarction (CAPTIM) Investigators. Impact of time to treatment on

mortality after prehospital fibrinolysis or primary angioplasty. Data from the CAPTIM randomized clinical trial. Circulation 2003;108:2851-6.
10. Armstrong PW, and the WEST steering committee. A comparison of pharmacologic therapy with/without timely coronary intervention vs primary percutaneous intervention early after ST-elevation myocardial infarction: the WEST (which early ST-elevation myocardial infarction therapy) study. Eur Heart J 2006;27:1530-8.
11. Buller CE, Welsh RC, Westerhout CM, et al. Guideline adjudicated fibrinolytic failure: incidence, findings, and management in a contemporary clinical trial. Am Heart J 2008;155:121-7.
12. Thune JJ, Hoefsten DE, Lindholm MG, et al, for the Danish Multicenter Randomized Study on Fibrinolytic Therapy Versus Acute Coronary Angioplast in Acute Myocardial Infarction (DANAMI)-2 Investigators. Simple risk stratification at admission to identify patients with reduced mortality from primary angioplasty. Circulation 2005;112:2017-21.
13. Morrow DA, Antman EM, Parsons L, et al. Application of the TIMI risk score for ST-elevation MI in the National Registry of Myocardial Infarction 3. JAMA 2001;286:1356-9.
14. Schomig A, Ndrepepa G, Mehilli J, et al. Therapy-dependent influence of time-to-treatment interval on myocardial salvage in patients with acute myocardial infarction treated with coronary artery stenting or thrombolysis. Circulation 2003;108:1084-8.
15. Fernandez-Aviles F, Alonso JJ, Pena G, et al, for the GRACIA-2 Investigators. Primary angioplasty vs early routine post-fibrinolysis angioplasty for acute myocardial infarction with ST-segment elevation: the Gracia 2 non-inferiority, randomized, controlled trial. Eur Heart J 2007;28:949-60.
16. Danchin N, Coste P, Ferrieres J, et al, for the FAST-MI Investigators. Comparison of thrombolysis followed by broad use of percutaneous coronary intervention with primary percutaneous coronary intervention for ST-segment elevation acute myocardial infarction: data from the French registry in acute ST-elevation myocardial infarction (FAST-MI). Circulation 2008;118:268-76.
17. Nielsen PH, Maeng M, Busk M, et al, for the DANAMI-2 Investigators. Primary angioplasty versus fibrinolysis in acute myocardial infarction: long-term follow-up in the Danish acute myocardial infarction 2 trial. Circulation 2010;121:1484-91.
18. Ting HH, Rihal CS, Gersh BJ, et al. Regional systems of care to optimize timeliness of reperfusion therapy for ST-elevation myocardial infarction: the Mayo Clinic STEMI protocol. Circulation 2007; 116:729-36.
19. Kalla K, Christ G, Karnik R, et al, for the Vienna STEMI Registry Group. Implementation of guidelines improves the standard of care: the Viennese Registry on reperfusion strategies in ST-elevation myocardial infarction (Vienna STEMI Registry). Circulation 2006; 113:2398-405.
20. Francone M, Bucciarelli-Ducci C, Carbone I, et al. Impact of primary coronary angioplasty delay on myocardial salvage, infarct size, and microvascular damage in patients with ST-segment elevation myocardial infarction: insight from cardiovascular magnetic resonance. J Am Coll Cardiol 2009;54:2145-53.
21. Goldberg RJ, Spencer FA, Fox KAA, et al. Prehospital delay in patients with acute coronary syndromes (from the Global Registry of Acute Coronary Events [GRACE]). Am J Cardiol 2009;103: 598-603.
22. Bonnefoy E, Steg PG, Boutitie F, et al, for the CAPTIM investigators. Comparison of primary angioplasty and pre-hospital fibrinolysis in acute myocardial infarction (CAPTIM) trial: a 5-year follow-up. Eur Heart J 2009;30:1598-606.