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Focus On: Anticoagulation in AF and ACS

Anticoagulant and Antiplatelet Agents: Update From AHA 2009

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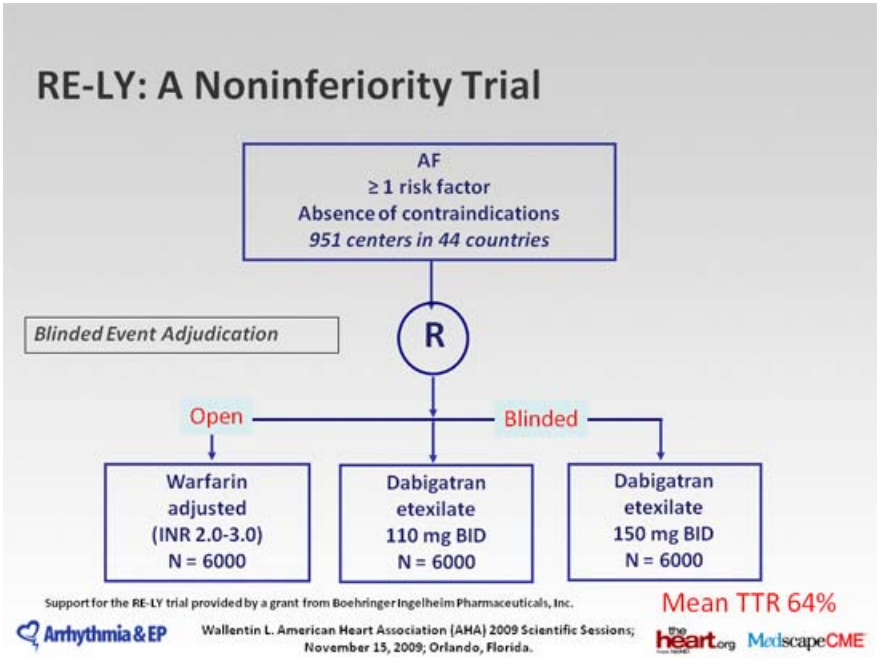
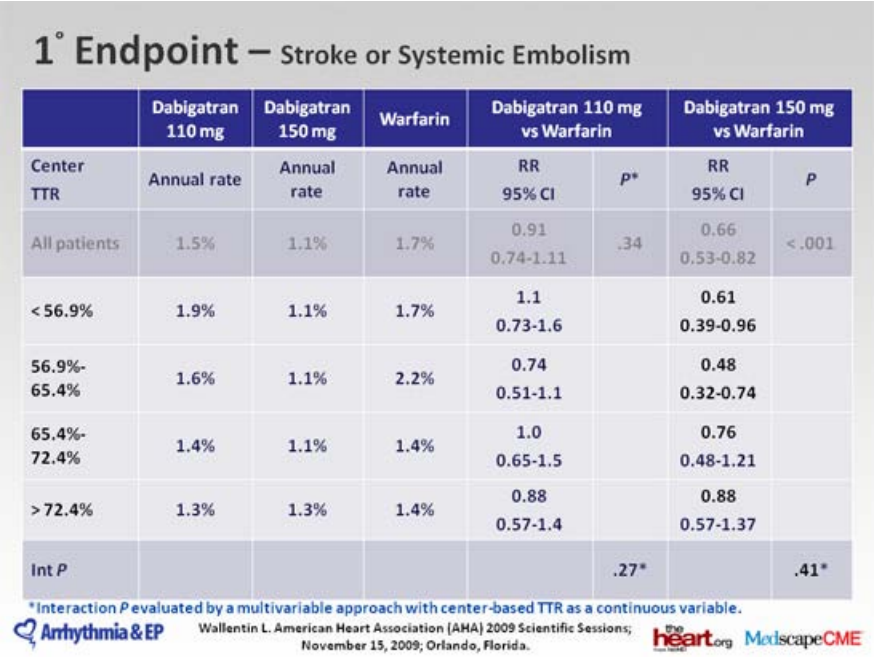
The American Heart Association (AHA) Scientific Sessions 2009 in Orlando, Florida was highlighted by several exciting clinical trials featuring promising drugs in development. Here, we discuss 2 large clinical trials of the oral anticoagulant dabigatran: RE-LY (Randomized Evaluation of Long-term anticoagulant therapY) and RE-DEEM (Dose Finding Study for Dabigatran Etexilate in Patients With Acute Coronary Syndrome); and review the results of 2 high-profile antiplatelet trials: the ticagrelor vs clopidogrel trial, PLATO-STEMI (PLATelet inhibition and patient Outcomes - ST-Segment Elevation Myocardial Infarction), and the cangrelor vs clopidogrel trial, CHAMPION-PCI (Cangrelor vs Standard Therapy to Achieve Optimal Management of Platelet Inhibition).

RE-LY (Atrial Fibrillation)

Dr. Lars Wallentin, Director of the Uppsala Clinical Research Center at Uppsala University Hospital in Sweden presented the results of the RE-LY trial, a phase 3 randomized, controlled noninferiority trial of 2 blinded doses of dabigatran etexilate (110 mg and 150 mg twice daily) vs open-label adjusted-dose warfarin for the prevention of stroke or systemic embolism in atrial fibrillation.[1]



RE-LY enrolled 18,113 patients (from 44 countries, 951 clinical centers) with ECG-proven atrial fibrillation (AF) in the preceding 6 months and at least 1 additional risk factor for stroke. The mean $CHADS_2$ score of the cohort was 2.1. The median duration of follow-up was 2 years. The study endpoints were adjudicated by at least 2 members of an international coalition who were blinded to the treatment assignment. Patients in the dabigatran arm were blinded to the study drug and dose, and the therapeutic level was not monitored. Patients randomized to warfarin received the drug open-label, and underwent at least monthly follow-up to achieve an international normalized ratio (INR) of 2.0 -3.0. For warfarin, there was considerable heterogeneity in the time in treatment range (TTR) by study center, ranging from 41%-77% of the time in range (mean TTR 64%).



1° Endpoint – Stroke or Systemic Embolism

	Dabigatran 110 mg	Dabigatran 150 mg	Warfarin	Dabigatran 110 mg vs Warfarin		Dabigatran 150 mg vs Warfarin	
Center TTR	Annual rate	Annual rate	Annual rate	RR 95% CI	*P**	RR 95% CI	*P*
All patients	1.5%	1.1%	1.7%	0.91 0.74-1.11	.34	0.66 0.53-0.82	< .001
< 56.9%	1.9%	1.1%	1.7%	1.1 0.73-1.6		0.61 0.39-0.96	
56.9%-65.4%	1.6%	1.1%	2.2%	0.74 0.51-1.1		0.48 0.32-0.74	
65.4%-72.4%	1.4%	1.1%	1.4%	1.0 0.65-1.5		0.76 0.48-1.21	
> 72.4%	1.3%	1.3%	1.4%	0.88 0.57-1.4		0.88 0.57-1.37	
Int *P*					.27*		.41*

*Interaction *P* evaluated by a multivariable approach with center-based TTR as a continuous variable.

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Wallentin L. American Heart Association (AHA) 2009 Scientific Sessions; November 15, 2009; Orlando, Florida.

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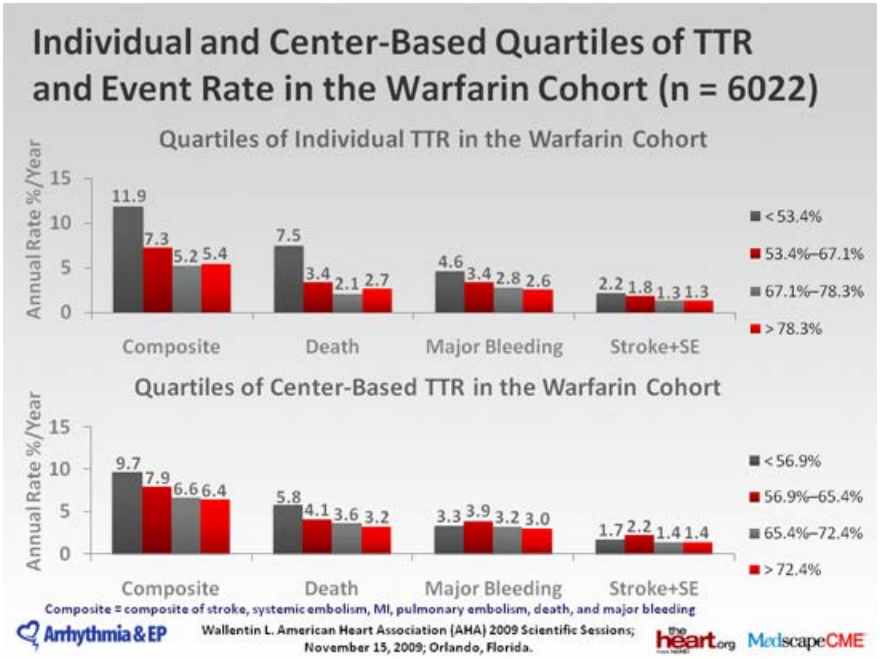
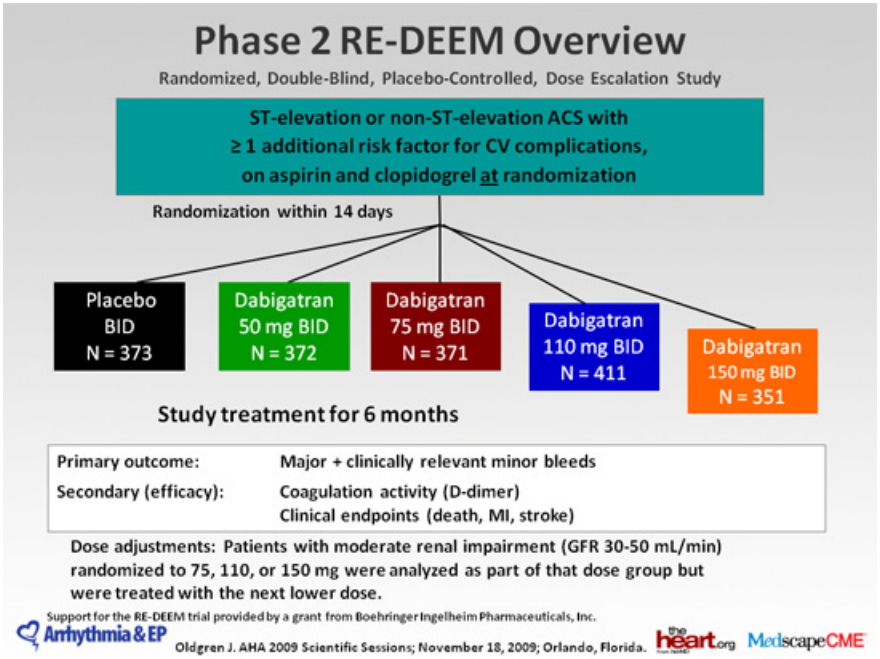
The main results of the RE-LY study suggest that low-dose dabigatran (110 mg BID) is noninferior to warfarin therapy for the prevention of stroke and systemic embolism, with a decrease incidence of major bleeding. High-dose dabigatran (150 mg BID) results in a significant reduction in the primary endpoint, with similar major bleeding and a reduction in life-threatening bleeding as compared with warfarin. Patient discontinuation of therapy is higher with dabigatran than warfarin however, driven by dyspepsia.



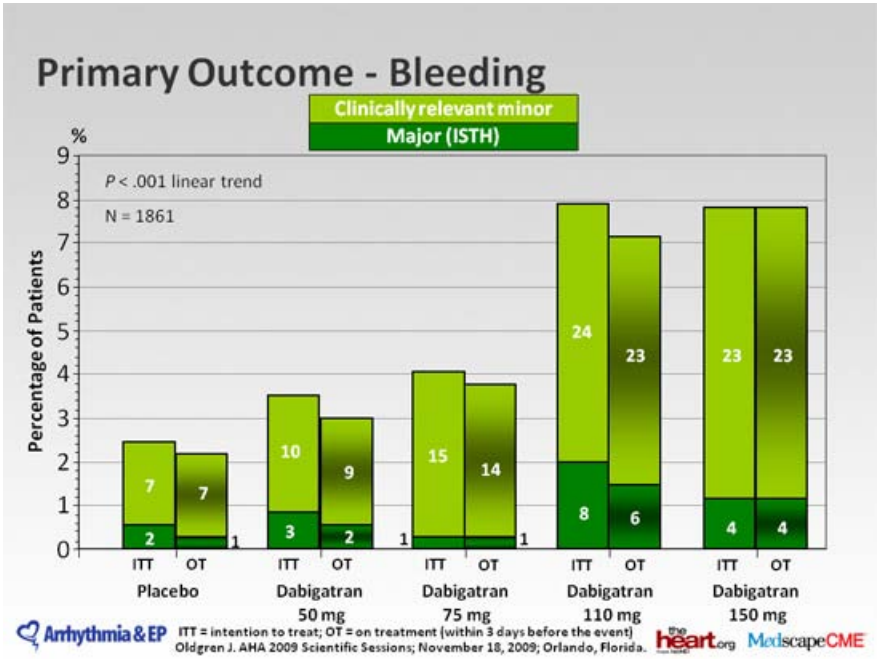
A critical question is whether the mean TTR of the study center (as a measure of the effectiveness of warfarin therapy on a local clinical center level) played an important part in the study outcome. Stated differently, is dabigatran a useful drug only when the local experience with warfarin therapy is poor? As presented at the AHA this year, there was no heterogeneity in the primary results of the trial in a secondary analysis stratified by TTR quartile. Dabigatran appears to be similarly effective at all levels of INR control. For secondary outcomes such as total vascular events and mortality, the advantages of dabigatran therapy may be greater at sites with poorer INR control, suggesting a potential immediate application of this drug in poorly compliant patients should dabigatran be approved for use.

RE-DEEM (Acute Coronary Syndrome)

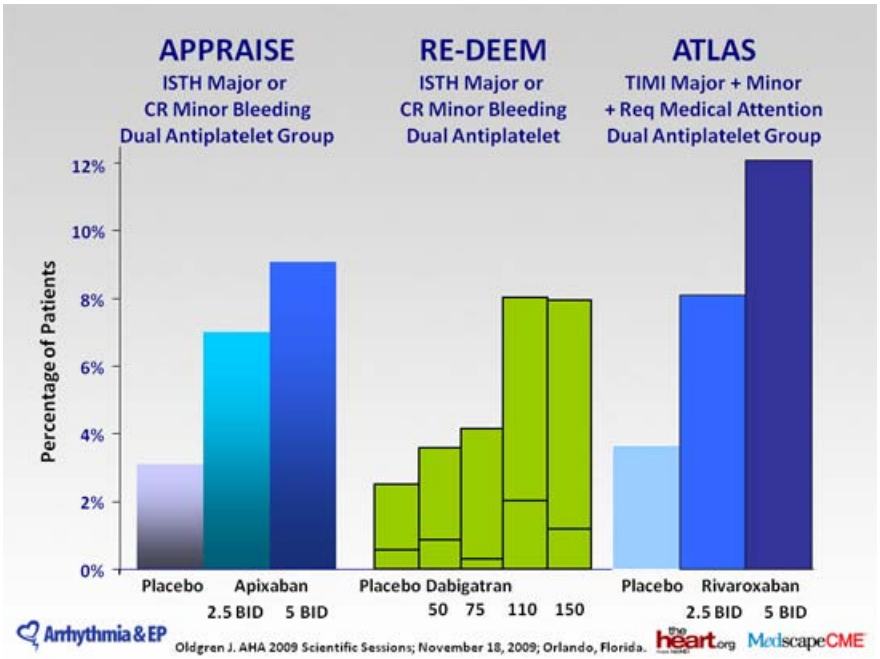
Dr. Jonas Oldgren, Head of the Coronary Care Unit at Uppsala University Hospital in Sweden presented the results of the RE-DEEM trial, a phase 2 double-blind, placebo-controlled, randomized-dose escalation clinical trial of dabigatran therapy in patients after acute coronary syndrome.



RE-DEEM randomized 1878 patients within 14 days of a ST-elevation or non-ST-elevation acute coronary syndrome. All patients were on aspirin and clopidogrel at the time of randomization. Patients were randomized to placebo or 4 dabigatran-dosing regimens (50 mg BID, 75 mg BID, 110 mg BID, and 150 mg BID). Patients were treated for 6 months. RE-DEEM was primarily a safety study. The primary outcome was major and clinically relevant minor bleeds, and the secondary outcome was both anticoagulant activity and a composite clinical endpoint of death, myocardial infarction, and stroke.



There was a dose-dependent increase in the primary endpoint with increasing doses of dabigatran. However, absolute rates of bleeding were modest. There was less than 1% absolute increase in major bleeding with the doses of dabigatran used in RE-LY (110 mg, and 150 mg BID).



Absolute rates of bleeding at these doses were similar to the absolute rates observed with low- dose apixaban and rivaroxaban in the APPRAISE (Apixaban for Prevention of Acute Ischemic and Safety Events) and ATLAS ACS – TIMI 51 (Anti-Xa Therapy to Lower cardiovascular events in addition to Aspirin with or without thienopyridine therapy in Subjects with Acute Coronary Syndrome—Thrombolysis in Myocardial Infarction) clinical trials.

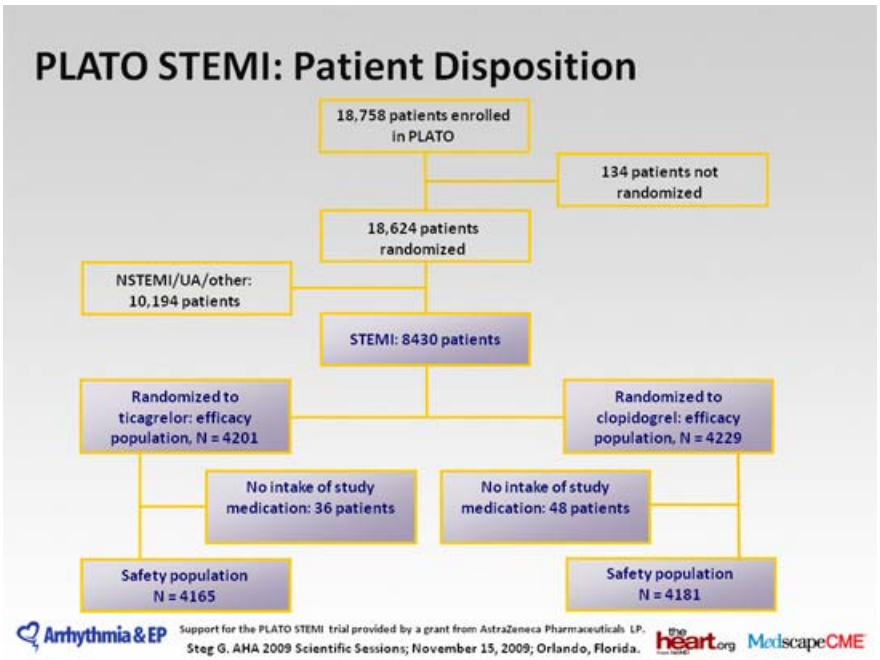
At all dosing levels of dabigatran, there was a marked anticoagulant effect with little difference between the doses. After cessation of treatment at 26 weeks there was an increase in D-dimer levels to levels similar to the placebo group 2 weeks later on.

There were no important differences observed in the clinical endpoints of death, nonfatal myocardial infarction, and stroke between placebo and dabigatran doses. However, there were very few clinical endpoints in this safety trial.

RE-DEEM shows that dabigatran, added to aspirin and clopidogrel after acute coronary syndrome, is associated with dose-dependent increase in bleeding, as seen in all trials of added anticoagulant therapy. The absolute increase in bleeding was modest, suggesting safety and opening the door for larger, more definitive trials of dabigatran in the prevention of recurrent events after acute coronary syndrome.

PLATO-STEMI (Acute Coronary Syndrome)

Dr. Gabriel Steg, from the Hôpital Bichat-Claude Bernard in France, presented the results of the PLATO-STEMI subgroup analysis.



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Patients presenting with ST-segment elevation myocardial infarction treated with primary (STEMI) PCI are a particularly high-risk group that requires urgent and effective platelet inhibition. A total of 8430 patients within PLATO presented with STEMI. Patients treated with fibrinolytic therapy and patients with a contraindication to clopidogrel were excluded from this study.

Study Medication and Procedures

	Ticagrelor (n = 4201)	Clopidogrel (n = 4229)
Start of randomized treatment Median time after start of chest pain, hours	5.6	5.8
Premature discontinuation of study drug, %	19.5	18.9
Invasive procedures at index hospitalization, % Coronary angiography PCI during index hospitalization CABG during index hospitalization	92.6 80.6 2.2	92.8 80.0 2.9
Received at least 1 stent, % Bare metal stent only Drug-eluting stent (at least 1)	74.3 57.9 16.1	74.2 57.6 16.3
Open-label clopidogrel prerandomization, % None 75 mg 300 mg 600 mg	56.5 4.8 18.1 20.7	55.5 5.1 18.6 20.8
Total clopidogrel (OL + IP)* prerandomization to 24 hours, % 300 mg 600 mg	65.2 34.8	65.4 34.6

*Includes placebo in the ticagrelor arm

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Comedication

Medication	Ticagrelor (n = 4201)	Clopidogrel (n = 4229)
Antithrombotic treatment in hospital, % Aspirin prior to index event Aspirin from index event to discharge Unfractionated heparin Low-molecular-weight heparin Fondaparinux Bivalirudin GP IIb/IIIa inhibitor from index event to randomization	21.4 99.0 66.3 45.8 1.8 1.3 34.7	20.7 98.8 65.8 46.1 1.7 1.4 35.2
Other medication in hospital or at discharge, % Beta-blockade ACE inhibition and/or angiotensin II receptor blocker Cholesterol lowering (statin) Calcium-channel blocker Diuretic Proton pump inhibitor	85.8 86.0 94.8 17.1 36.2 49.1	86.2 85.9 95.1 17.1 35.4 49.1

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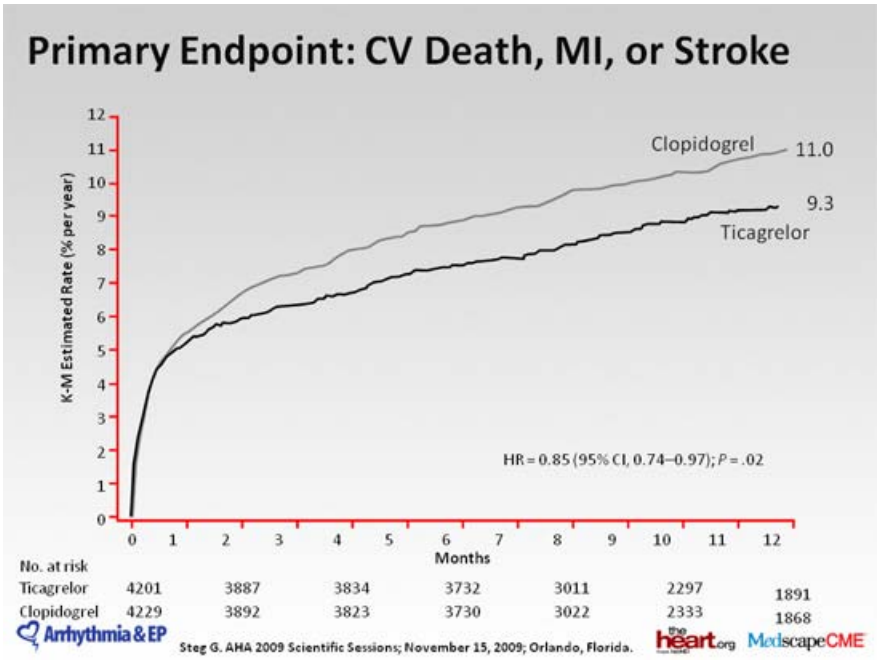
Approximately 45% of patients were taking clopidogrel prior to randomization. In general prerandomization medical therapy was aggressive, with 86% of patients on beta-blockers and angiotensin-converting enzyme (ACE)-inhibitors, and 95% of statin therapy.



Ticagrelor reduced the primary endpoint by 15% (11.0% vs 9.3% absolute event rate, number needed to treat 59). This benefit was, in general, consistent across all important prespecified subgroups, including the varying defintions of STEMI, intended clopidogrel dose (300 vs 600 mg) within 24 hours of the initial bolus, and time from index event to time of therapy (< 12 hours vs ≥ 12 hours).

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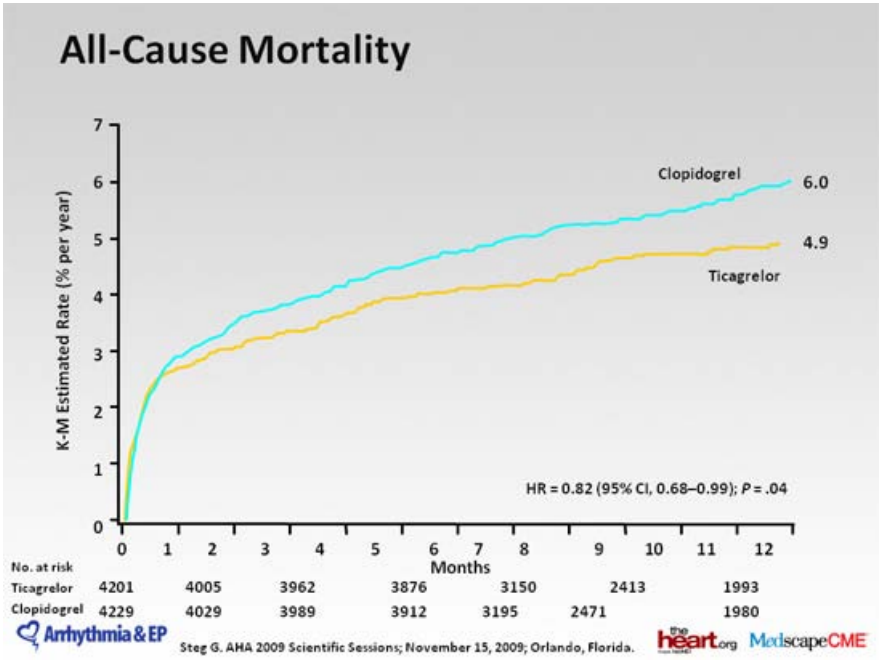
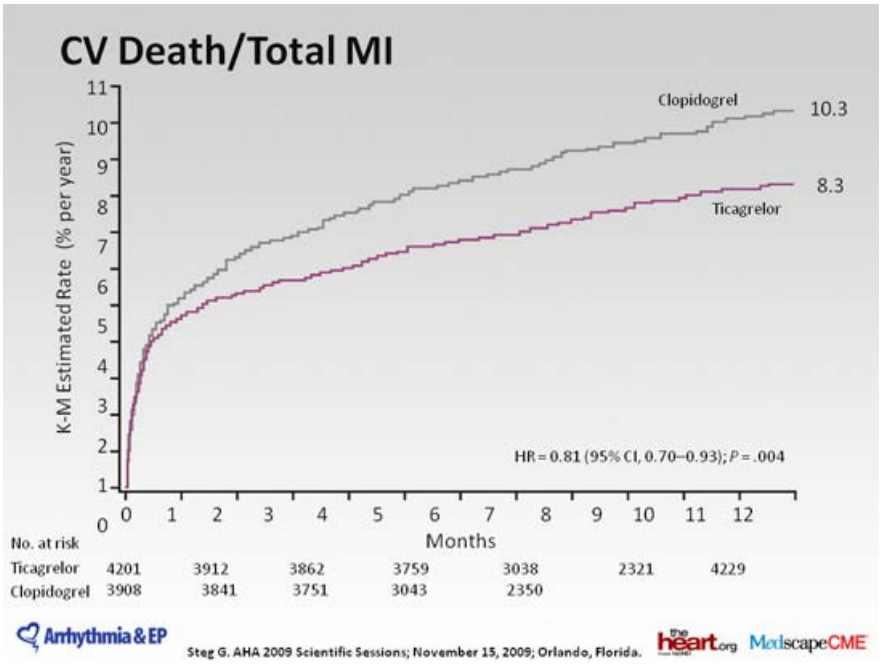
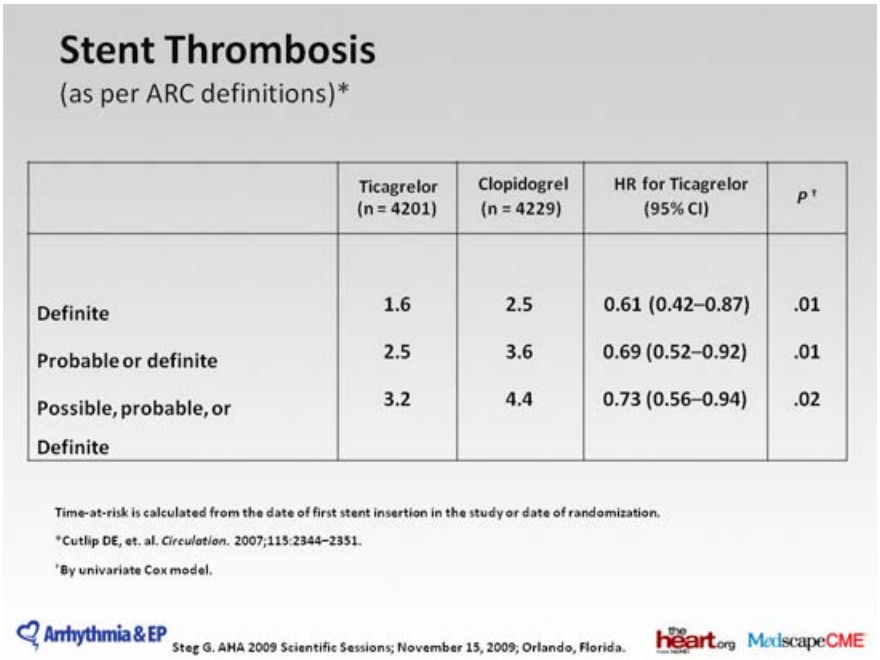
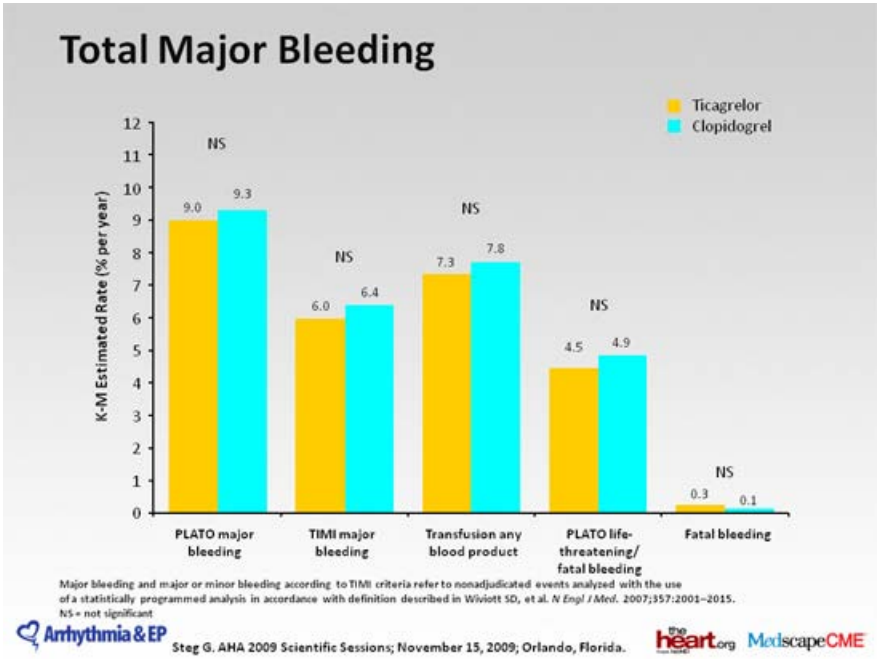




All-cause mortality, a prespecified secondary endpoint, was reduced by 18%. Total cardiovascular death and myocardial infarction was reduced by 19%.



Definite stent thrombosis, which of course is a critically important complication that must be minimized, was reduced by 39% with ticagrelor. Interestingly however, patients who received ticagrelor reported more dyspnea (12.9% vs 8.3%).



Importantly, there was no difference in total major bleeding episodes between the 2 groups (9.3% with ticagrelol vs 9.0% with clopidogrel). Other definitions of major bleeding were also tested. There was no difference in TIMI (thrombolysis in myocardial infarction) major bleeding, need for blood product transfusion, PLATO life-threatening bleeding, or fatal bleeding.

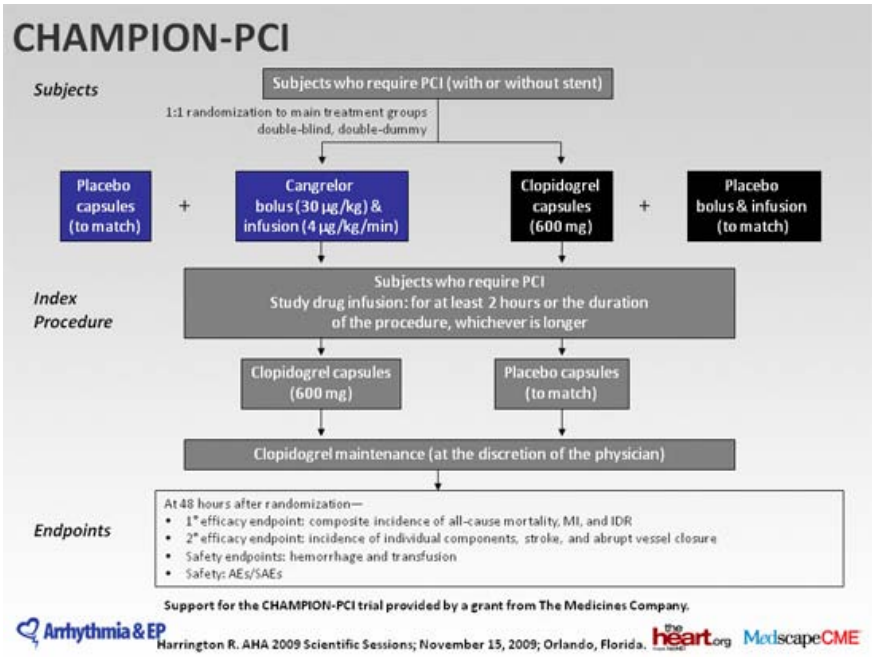
There are a few limitations to the PLATO study. Some observers have commented that the trial should have mandated that the study drug be given for at least 1 year, which is growing to be standard of care. Also, some have noted that 600-mg clopidogrel has become standard dosing prior to PCI, thus perhaps all study patients should have received this dose.

In conclusion, ticagrelor is a very attractive potent $P2Y_{12}$ receptor blocker that results in effective platelet inhibition and a reduction in major adverse cardiovascular events in both all comers with acute coronary syndrome, as well as the subset of patients with STEMI receiving PCI. Despite this increased efficacy, there is no increase in major bleeding. In the future, ticagrelor may become the preferred agent in higher-risk compliant patients who have unknown coronary anatomy (and thus may have 3-vessel disease), based on its potency and more rapid reversibility. Based on the results from PLATO, ticagrelor may play an important role in the treatment of acute coronary syndromes if it is approved by the United States Food and Drug Administration.

CHAMPION-PCI (Acute Coronary Syndrome)

Dr. Robert Harrington of the Duke Clinical Research Institute in Durham, North Carolina presented the CHAMPION-PCI trial, a double-blind, comparative effectiveness, randomized, placebo-controlled trial of

IV cangrelor plus 600-mg clopidogrel vs 600-mg clopidogrel alone, in patients with acute coronary syndromes undergoing PCI.



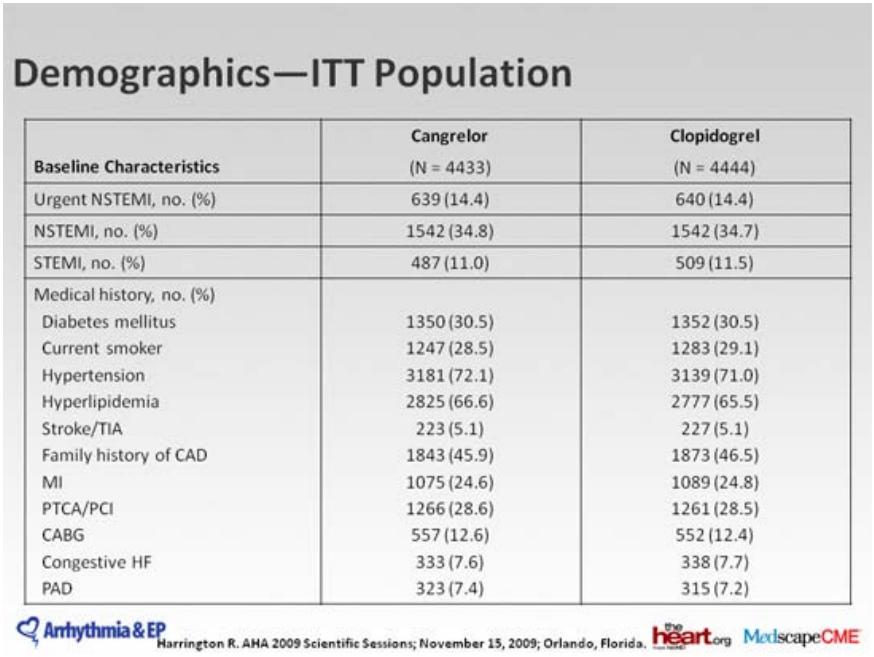
In general, patients did not receive adenosine diphosphate (ADP)-receptor blockade up front upon presentation. Rather, participants were randomized and treated with ADP-receptor blockage only after coronary angiography revealed the need and feasibility of coronary intervention. A total of 8716 patients underwent PCI and were randomized to the 2 groups.

Cangrelor was dosed as an initial weight-based IV bolus, and then a weight-based continuous infusion for at least 2 hours. Patients then received 600-mg clopidogrel after the cangrelor infusion was complete. Participants in the clopidogrel arm received 600-mg clopidogrel at the time of randomization. All patients then were prescribed a maintenance dose of clopidogrel for a duration that was at the discretion of the treating physician.

The primary endpoint of the study was a composite endpoint of death, myocardial infarction, and ischemia-driven revascularization at 48 hours. Important secondary outcomes included stent thrombosis and a composite of all-cause mortality, Q-wave myocardial infarction, and ischemia-driven revascularization. The primary safety endpoint was major bleeding using 3 separate definitions – the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy), GUSTO (Global Utilization of Strategies to Open Occluded Arteries), and TIMI criteria definitions.

The primary hypothesis of this study was the cangrelor would reduce the primary endpoint as compared with clopidogrel alone. The study enrolled sufficient patients to have 82% power to

demonstrate a 22% difference between the 2 groups. Two interim analyses were planned after 50% and 70% of the planned enrollment. The study continued until the CHAMPION PLATFORM (Cangrelor Versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition) study also achieved 70% of its planned enrollment, at which time (May 2009) enrollment into both trials was stopped due to low anticipated power to show a difference between the 2 groups. In the final analysis, CHAMPION enrolled 98.6% of the planned sample size.



Demographics—ITT Population

Baseline Characteristics	Cangrelor (N = 4433)	Clopidogrel (N = 4444)
Age, years	62.0 (54.0, 70.0)	62.0 (54.0, 71.0)
Sex, no. (%)		
Male	3275 (73.9)	3209 (72.2)
Female	1158 (26.1)	1235 (27.8)
Race, no. (%)		
White	3658 (82.6)	3626 (81.7)
Asian	311 (7.0)	313 (7.1)
Black	215 (4.9)	239 (5.4)
Weight, kg	84.0 (73.0, 97.0)	84.0 (73.0, 97.0)
Height, cm	172.0 (165.0, 178.0)	172.0 (165.0, 178.0)
Stable angina, no. (%)	668 (15.1)	665 (15.0)
Unstable angina, no. (%)	1097 (24.7)	1088 (24.5)

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Approximately 11% of patients in CHAMPION had STEMI, 35% had NSTEMI, 25% had unstable angina, and 15% had stable angina. The mean age of the population was 62 years, and approximately 73% of the enrollment was male patients.

Procedural Details

	ITT		ITT Without STEMI		ITT With STEMI	
Baseline Characteristics	Cangrelor (N = 4433)	Clopidogrel (N = 4444)	Cangrelor (N = 3946)	Clopidogrel (N = 3935)	Cangrelor (N = 487)	Clopidogrel (N = 509)
Number of target vessels, no. (%)						
1	3836 (88.0)	3796 (87.4)	3406 (87.3)	3360 (86.5)	430 (94.1)	436 (95.2)
2	484 (11.1)	509 (11.7)	457 (11.7)	488 (12.6)	27 (5.9)	21 (4.6)
3	38 (0.9)	36 (0.8)	38 (1.0)	35 (0.9)	0 (0.0)	1 (0.2)
Drug-eluting stent, no. (%)	2581 (59.2)	2560 (59.0)	2422 (62.1)	2383 (61.4)	159 (34.8)	177 (38.6)
Nondrug-eluting stent, no. (%)	1640 (37.6)	1635 (37.7)	1367 (35.0)	1380 (35.5)	273 (59.7)	255 (55.7)

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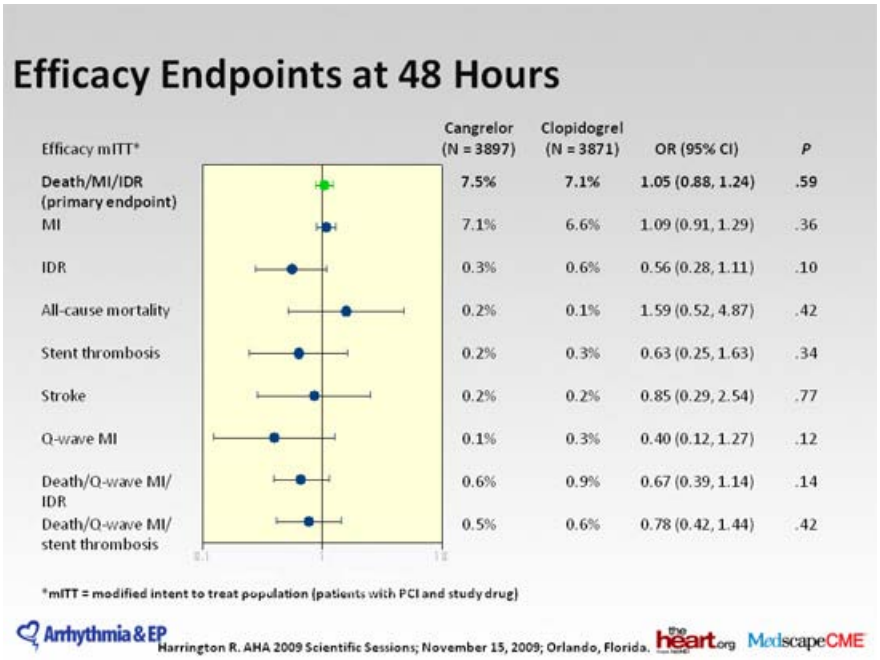
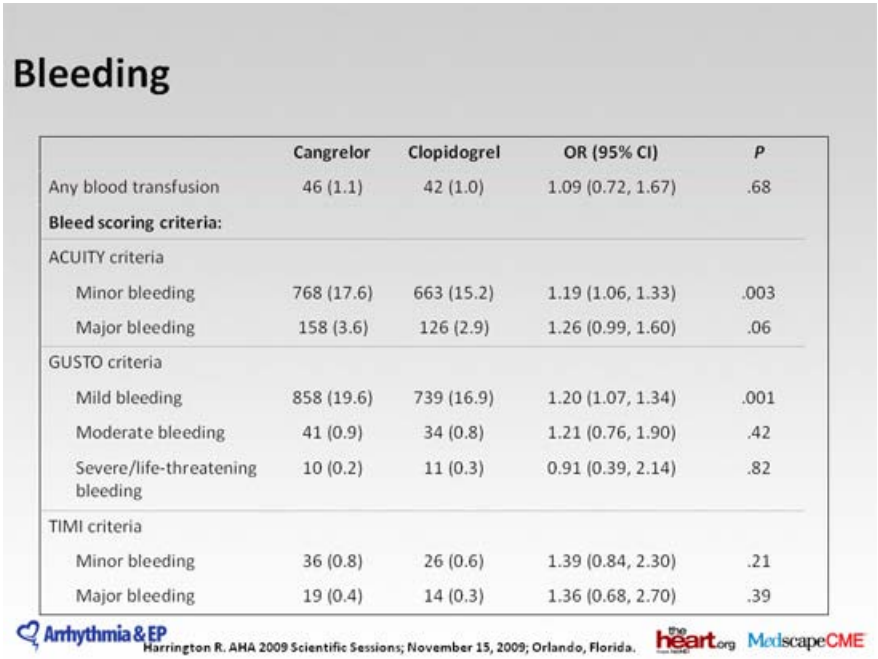
PCI was largely confirmed to a single culprit vessel. Approximately 59% of patients received a drug-eluting stent, and 38% received a bare metal stent.



The incidence of the primary endpoint did not differ between the groups (7.5% for cangrelor vs 7.1% for clopidogrel alone, *P* = .59). None of the prespecified secondary endpoints differed between the groups. In particular, instances of all-cause mortality (0.2% vs 0.1%) and stent thrombosis (0.2% vs 0.3%) were low and not different with the 2 treatment strategies. Equipoise remained when considering NSTEMI and STEMI patients separately.



	Cangrelor	Clopidogrel	OR (95% CI)	*P*
Any blood transfusion	46 (1.1)	42 (1.0)	1.09 (0.72, 1.67)	.68
Bleed scoring criteria:				
ACUITY criteria				
Minor bleeding	768 (17.6)	663 (15.2)	1.19 (1.06, 1.33)	.003
Major bleeding	158 (3.6)	126 (2.9)	1.26 (0.99, 1.60)	.06
GUSTO criteria				
Mild bleeding	858 (19.6)	739 (16.9)	1.20 (1.07, 1.34)	.001
Moderate bleeding	41 (0.9)	34 (0.8)	1.21 (0.76, 1.90)	.42
Severe/life-threatening bleeding	10 (0.2)	11 (0.3)	0.91 (0.39, 2.14)	.82
TIMI criteria				
Minor bleeding	36 (0.8)	26 (0.6)	1.39 (0.84, 2.30)	.21
Major bleeding	19 (0.4)	14 (0.3)	1.36 (0.68, 2.70)	.39

Major bleeding was not statistically different between the 2 groups, although there was an increase in ACUITY-criteria major bleeding in the cangrelor group that approached statistical significance (3.6% vs 2.9%, *P* = .06). Minor bleeding was more common with cangrelor when using ACUITY and GUSTO criteria (*P* = .003 and *P* = .001, respectively).

In summary, CHAMPION enrollment was stopped early for futility in regard to the primary endpoint. From this trial, we can conclude that cangrelor is not superior to 600-mg clopidogrel at the time of PCI for the prevention of total adverse cardiovascular events. While achieving a greater degree of platelet inhibition, cangrelor also led to a trend towards more major bleeding and likely produced more minor bleeding.

Why did this trial of cangrelor fall short? Several theories abound. First of all, the optimal length of IV infusion time of cangrelor is not known. Do patients need to receive much longer infusions to receive therapeutic benefit? In addition, patients may need to be followed for longer than 48 hours to observe benefit, as the benefit of ADP-receptor blockade may be observed 1 month or more after coronary intervention.

The fact that patients did not receive any ADP-receptor blockers until the time of coronary intervention is unusual. Based on the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Even) trial and other studies, standard of care in most instances included treating with ADP-receptor blocker upon presentation. Cangrelor may still reduce overall bleeding in the real-world setting, as earlier use of this

reversible drug may be safer for patients with 3-vessel disease who may need coronary artery bypass surgery. Clearly, despite disappointing results, the idea of an IV ADP-receptor blocker still holds considerable promise.

References:

1. Ezekowitz MD, Connolly SJ, Parekh A, et al. Rationale and design of RE-LY: randomized evaluation of long-term anticoagulant therapy, warfarin, compared with dabigatran. Am Heart J. 2009;157:805-810.