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Heart Online First, published on April 21, 2005 as 10.1136/hrt.2005.064501

Extra-Cardiac vascular disease and effectiveness of sustained clopidogrel therapy

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Keywords: Peripheral arterial disease, Clopidogrel, Vascular disease, Antiplatelet therapy

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Abstract

Objective: To assess the effectiveness of long-term clopidogrel therapy in patients with extra-cardiac vascular disease [ECVD] (i.e., history of either peripheral arterial disease or cerebrovascular disease).

Design: Subgroup analysis of a prospective randomized clinical trial.

Setting: The Clopidogrel for the Reduction of Events During Observation (CREDO) trial was a randomized, double-blind, placebo-controlled trial conducted at 99 centres in North America from June 1999 through April 2001.

Patients: 2116 patients who were to undergo elective coronary intervention or were deemed at high likelihood of undergoing PCI were enrolled in the CREDO trial. The current study sample consisted of 272 patients with ECVD.

Main outcome measure: One-year incidence of the composite of death, myocardial infarction (MI), or stroke in the intent-to-treat population.

Results: Patients with ECVD had a > 2-fold greater relative risk reduction with clopidogrel for the primary endpoint compared with patients without ECVD (47.9%, 95% CI -4.2% to 73.9%, and 18.2 %, 95% CI -10.5 % to 39.5 %, respectively).

Conclusions: Longer term clopidogrel therapy provides added protection against thrombotic events throughout the arterial vasculature, not limited to the coronary arteries and may be especially effective for patients with more diffuse atherosclerosis such as ECVD.

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Extra cardiac vascular disease [ECVD] is associated with an increased risk of in-hospital mortality and other complications following coronary interventions, independently from other comobidities and baseline characteristics[1-3]. Therapies that may potentially improve clinical outcomes in this high risk cohort warrant further investigation. We analyzed the effectiveness of long-term clopidogrel therapy in patients in the Clopidogrel for the Reduction of Events During Observation [CREDO] trial with ECVD (i.e., history of either peripheral arterial disease or cerebrovascular disease). The study shows that patients with ECVD derive particular benefit from long-term clopidogrel therapy.

Methods

We hypothesized that patients with ECVD being at high risk for cardiovascular events would derive particular benefit from extended clopidogrel regimens. The design and methods of the CREDO trial have been previously described[4]. Briefly, 2,116 patients with symptomatic coronary artery disease and objective evidence of ischemia who underwent elective percutaneous coronary intervention [PCI] or had a strong likelihood of undergoing PCI were enrolled from June 1999 to April 2001 from 99 centres in North America. Patients were randomized to a loading dose of clopidogrel (300 mg) or placebo 3 to 24 hours before PCI. All patients were given clopidogrel 75 mg/day for 28 days after PCI. After this, the clopidogrel group (which were treated with the 300-mg loading dose) continued receiving clopidogrel 75 mg/day from day 29 through 12 months, whereas the control group (which received the placebo loading dose) received placebo for the same duration. All patients also were given aspirin daily. The primary end point of CREDO was a composite of 1-year death, myocardial infarction, and stroke [4]. In this subgroup analysis, patients were categorized as having ECVD if they had either a history of peripheral arterial disease or cerebrovascular disease.

Statistical analysis

Baseline characteristics were compared using chi-square and Fisher's exact tests for discrete variables and Wilcoxon rank-sum tests for continuous variables. Kaplan-Meier estimates and log-rank tests were used to compare 1-year events among ECVD patients treated with and without long-term clopidogrel tharapy. Hazard ratios and 95% confidence intervals are generated from Cox proportional hazards models. Relative risk reductions with corresponding 95% confidence intervals were calculated for patients with and without ECVD treated with long-term clopidogrel therapy. Finally, risk-adjusted hazard ratios were calculated for the composite events of death, myocardial infarction, stroke and urgent revascularization. A p-value of <0.05 was considered statistically significant. All analyses were performed using SAS 8.2 [SAS Institute, Cary, NC].

Results

The study sample consisted of 272 patients with ECVD, 132 of whom received clopidogrel. Baseline demographics were similar among the ECVD patients treated with and without clopidogrel (Table 1), except that the clopidogrel group tended to be older.

The main CREDO trial observed an overall relative risk reduction of 26.9% (95% CI 3.9% to 44.4%) in the 1-year primary composite end point (death, myocardial infarction and stroke) with clopidogrel compared with placebo (8.6% vs 11.8%, $p = 0.02$). Patients with ECVD had a > 2-fold greater relative risk reduction with clopidogrel for the primary endpoint compared with patients without ECVD (47.9%, 95% CI -4.2% to 73.9%, and 18.2 %, 95% CI -10.5 % to

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39.5 %, respectively), as shown in Figure 1. Overall event rates were significantly lower with long-term clopidogrel therapy in patients with ECVD considering all possible composite ischemic outcomes (Table 2) (Figure 2).

A Cox proportional hazards analysis adjusting for age, diabetes and history of prior myocardial infarction showed that clopidogrel therapy was associated with a substantially lower risk of death + myocardial infarction +stroke + urgent target vessel revascularization [odds ratio 0.49, 95% CI 0.25 – 0.99, p =0.04] (Table 3).

Discussion

Clopidogrel pretreatment and long-term therapy after PCI has been shown to reduce short- (30-day) and long-term (8 months to 1 year) adverse cardiovascular outcomes [4,5]. Clopidogrel therapy also improves clinical outcomes among patients undergoing peripheral vascular interventions [6]. Our post hoc analysis of the CREDO trial suggests that long-term clopidogrel therapy particularly benefits patients with ECVD. Peripheral arterial disease is a marker of systemic atherosclerosis and it is conceivable that presence of ECVD may be an indicator of more advanced, active, or aggressive vascular disease[7 6]. It appears that longer term therapy provides added protection against thrombotic events throughout the arterial vasculature, not limited to the coronary arteries and may be especially effective for patients with ECVD.

Our study has inherent limitations given the post hoc analyses, thus precluding definitive conclusions. Because the ECVD group was nonrandomized, potential selection bias may exist. However, clopidogrel treatment was randomized and blinded, so any bias should be balanced between the clopidogrel and control groups. Moreover, we used a risk-adjusted Cox proportional hazards model to account for differences in baseline demographics comorbidities, and long-term clopidogrel remained a significant independent predictor of lower 1-year death + myocardial infarction+ stroke + urgent target vessel revascularization.

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Acknowledgements:

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Figure Legends

Figure 1. Bar graph showing relative risk reductions with clopidogrel therapy in patients with and without extracardiac vascular disease [ECVD]. Patients with extracardiac vascular disease had higher relative risk reduction with sustained clopidogrel therapy.

Figure 2. Kaplan-Meier curves showing significantly lower incidence of the composite of death, myocardial infarction, stroke and urgent revascularization in patients with extracardiac vascular disease [ECVD] treated with clopidogrel.

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Table 1. Baseline characteristics of the patients with history of extra-cardiac vascular disease in the CREDO trial stratified by clopidogrel use.

	Clopidogrel		P value
	-- (n = 140)	+ (n = 132)	
Age (Mean ± SD) (years)	65.4 ± 10.3	67.9 ± 9.4	0.032
Women	33.5%	34.1%	0.928
Weight, mean (SD), kg	86.1 ± 19.6	83.7 ± 19.1	0.212
Body mass index > 30, (%)	41.7%	37.2%	0.438
Risk factors, No, (%)			
Prior myocardial infarction	37.5%	35.1%	0.692
Diabetes	32.3%	32.5%	0.972
Hypertension	75.7%	76.3%	0.905
Smoking (within past year)	32.8%	27.3%	0.330
Family history of heart disease	47.1%	48.6%	0.804
Hyperlipidemia	71.8%	76.5%	0.383
Baseline medications			
Aspirin	28.6%	34.1%	0.326
Beta-blocker	65%	63.6%	0.814
Statin	58.5%	61.3%	0.639
ACE inhibitor	34.3%	40.9%	0.259
Calcium channel blocker	46.4%	37.1%	0.120
Treatment after initial angiogram			
PCI	84.8%	91.65	0.088
Medical therapy	5%	0%	0.015
Bypass surgery	3.57%	3.79%	1.000
Indications for PCI			
Recent myocardial infarction	5.1%	8.5%	0.124
Unstable angina	62.7%	50.8%	0.124
Stable angina	32.15	40.7%	0.124

ACE = Angiotensin converting enzyme inhibitor; PCI = percutaneous coronary intervention

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Table 2. Clinical outcomes of patients with extra-cardiac vascular disease at 1-year using Kaplan-Meier method

1-year outcomes	Clopidogrel		P value
	-- (n=140)	+ (n=132)	
Death	2.96%	1.57%	0.454
Myocardial infarction [MI]	14.57%	8.42%	0.133
Target vessel revascularization [TVR]	18.58%	11.09%	0.069
Stroke	0.75%	1.62%	0.535
Death/MI	16.71%	9.22%	0.080
Death/MI/TVR	29.89%	19.41%	0.046
Death/MI/urgent TVR	18.89%	9.22%	0.029
Death/MI/Stroke	17.45%	9.22%	0.058
Death/MI/stroke/urgent TVR	19.63%	9.22%	0.020

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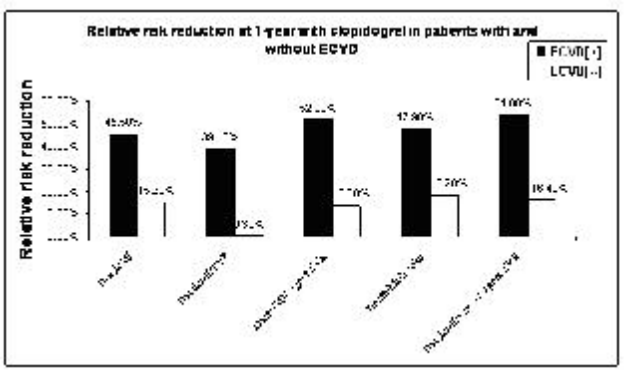
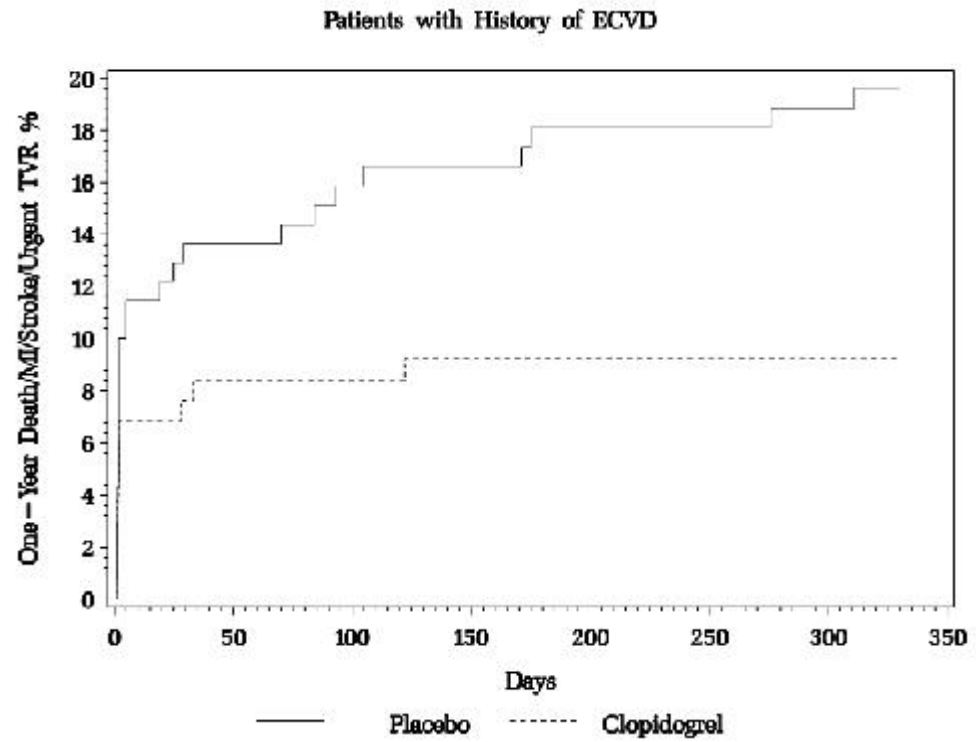
Table 3. Multivariate risk adjusted* odds ratios or hazard ratios of adverse clinical outcomes in patients with extra-cardiac vascular disease treated with clopidogrel

1-year outcomes	Crude hazard ratio and 95% CI	Adjusted hazard ratios and 95% CI
Death/MI/TVR	0.61 [0.37 – 1.01]	0.61[0.36 – 1.02]
Death/MI/urgent TVR	0.48 [0.24 – 0.95]	0.51 [0.26 – 1.04]
Death/MI/stroke/urgent TVR	0.46 [0.23 – 0.91]	0.49 [0.25 – 0.99]

*Adjusted for age, prior myocardial infarction, and diabetes.


Relative risk reduction at 1 year with clopidogrel in patients with and without ECVD
Relative risk reduction


Patients with History of ECVD
One – Year Death/MI/Stroke/Urgent TVR %
0
2
4
6
8
10
12
14
16
18
20
0
50
100
150
200
250
300
350
Days
Placebo
Clopidogrel

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Heart published online April 21, 2005

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