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Clinical research

Combining warfarin and antiplatelet therapy after coronary stenting in the Global Registry of Acute Coronary Events: is it safe and effective to use just one antiplatelet agent?†

Michael C. Nguyen[1]*, Yean L. Lim[1], Antony Walton[1], Jeffrey Lefkovits[2], Giancarlo Agnelli[3], Shaun G. Goodman[4], Andrzej Budaj[5], Dietrich C. Gulba[6], Jeanna Allegrone[7], and David Brieger[8] for the GRACE Investigators

[1]*Centre for Cardiovascular Therapeutics, Western Hospital, Melbourne, Australia;* [2]*Department of Cardiology, Royal Melbourne Hospital, Melbourne, Australia;* [3]*Department of Internal and Cardiovascular Medicine, University of Perugia, Perugia, Italy;* [4]*Canadian Heart Research Centre and Terrence Donnelly Heart Centre, St Michael's Hospital, University of Toronto, Toronto, Ontario, Canada;* [5]*Postgraduate Medical School, Grochowski Hospital, Warsaw, Poland;* [6]*Department of Cardiology, Krankenhaus Düren, Düren, NRW, Germany;* [7]*Center for Outcomes Research, University of Massachusetts Medical School, Worcester, MA, USA; and* [8]*Department of Cardiology, Concord Hospital, Sydney, Australia*

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KEYWORDS
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Aims To identify factors associated with the use of single or dual antiplatelet therapy in patients prescribed warfarin following coronary stenting and to investigate whether single (aspirin or thienopyridine) vs. dual antiplatelet therapy plus warfarin leads to an excess of adverse outcomes.
Methods and results We analysed data from 800 patients with an acute coronary syndrome who underwent coronary stenting (130 patients received a drug-eluting stent) and were discharged on warfarin and either dual ($n = 580$) or single ($n = 220$) antiplatelet therapy. The use of single antiplatelet therapy was more common in Europe than in the USA (34 vs. 17%, $P < 0.001$). There was no difference in major bleeding in hospital or in 6-month mortality or myocardial infarction. In the single antiplatelet group, the use of either aspirin or thienopyridine (clopidogrel or ticlopidine) in combination with warfarin resulted in similar outcomes.
Conclusion Use of single vs. dual antiplatelet therapy and warfarin following stenting is common. In this observational study, there was no difference in mortality or myocardial infarction at 6 months; however, larger trials are needed to assert any firm recommendations.

Introduction

Dual antiplatelet therapy with aspirin and a thienopyridine following coronary stenting is superior to aspirin alone in reducing cardiovascular events in both the acute coronary syndrome (ACS) and the elective setting;[1,2] however, dual antiplatelet therapy is associated with an increased risk of bleeding.[3] Dual antiplatelet therapy tends to be prescribed long term, and the duration of treatment now often extends to 12 months or longer.[2] Dual antiplatelet therapy has also been proven to be superior in terms of safety and efficacy when compared with anticoagulation with warfarin following coronary stenting.[4–6]

Identifying the optimal regimen for antiplatelet therapy in patients requiring warfarin following coronary stenting is an area that has been understudied. Small, single-centre studies[7–9] and larger observational studies[10] and meta-analyses[11] have examined the safety of antiplatelet therapy in combination with warfarin. These studies primarily analysed safety rather than efficacy outcomes and do not address the comparison of single vs. dual antiplatelet in combination with warfarin following coronary stenting in patients with a strong indication for warfarin.

Clinical trials in patients with ACS have supported an early invasive approach in those at high risk of a subsequent coronary event.[12–14] These patients are triaged to coronary angiography, often leading to percutaneous coronary revascularization. They tend to comprise an elderly population with often substantial vascular, valvular, and conduction

* Corresponding author: Department of Cardiology, Beth Israel Deaconess Medical Center, 185 Pilgrim Road, Baker 4, Boston, MA 02215, USA. Tel: +1 617 632 7718; fax: +1 617 632 7460.
E-mail address: mcnguyen@bidmc.harvard.edu

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system disease. Therefore, a significant proportion of these patients also requires warfarin for various co-morbid conditions (e.g. atrial fibrillation, mechanical valve replacement, deep-vein thrombosis/pulmonary embolus, or large anterior myocardial infarcts).

In patients requiring warfarin, standard practice is to combine both antiplatelet and antithrombotic drugs; however, the use of single or dual antiplatelet in combination with warfarin for this population needs further investigation. The choice of single antiplatelet (aspirin vs. thienopyridine) also needs to be examined. In this study, we attempted to identify factors associated with the use of single or dual antiplatelet therapy in patients who required warfarin following coronary stenting in an unselected population presenting with an ACS. We compared the clinical outcomes of each regimen, including those in patients prescribed either aspirin or a thienopyridine (either clopidogrel or ticlopidine) in combination with warfarin.

Methods

Full details of the GRACE methods have been published.[15–17] GRACE is designed to reflect an unbiased population of patients with ACS, irrespective of geographical region. A total of 113 hospitals located in 14 countries in North and South America, Europe, Australia, and New Zealand have contributed data to this observational study.

Patients entered in the registry had to be at least 18 years old and alive at the time of hospital presentation, be admitted for ACS as a presumptive diagnosis (i.e. have symptoms consistent with acute ischaemia), and should have at least one of the following: electrocardiographic changes consistent with ACS, serial increases in serum biochemical markers of cardiac necrosis, and/or documentation of coronary artery disease. The qualifying ACS must not have been precipitated by significant non-cardiovascular co-morbidity (e.g. trauma or surgery). Approximately 6 months after hospital discharge, patients were followed-up to ascertain the occurrence of selected long-term study outcomes. Where required, study investigators received approval from their local hospital ethics or institutional review board.

The study aimed to enrol an unbiased population and sites were encouraged to recruit the first 10 to 20 consecutive eligible patients each month. Data were collected by trained coordinators using standardized case report forms. Demographic characteristics, medical history, presenting symptoms, duration of pre-hospital delay, biochemical and electrocardiographic findings, treatment practices, and a variety of hospital outcome data were collected. Standardized definitions of all patient-related variables, clinical diagnoses, and hospital complications and outcomes were used.[15]

We analysed data from 800 patients (entered between April 1999 and September 2006) who underwent coronary stenting following presentation with an ACS and who were subsequently discharged on warfarin and dual antiplatelet therapy or warfarin and single antiplatelet therapy. Baseline demographics, geographical differences, hospital interventions, hospital events, and 6-month outcomes were analysed.

Statistical analysis

Data are expressed as percentages, or as medians and interquartile ranges, as appropriate. Differences between warfarin/single and warfarin/dual antiplatelet groups were evaluated by χ^2 or Fisher's exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables. Two-sided univariate analyses were performed.

Results

Of the patients in this cohort, 580 (73%) received warfarin and dual antiplatelet therapy and 220 (28%) warfarin and single antiplatelet therapy. The use of single antiplatelet therapy was more frequent outside the USA (35 vs. 17%, $P < 0.001$; *Figure 1*). Within the single antiplatelet group, 107 patients received aspirin and 113 a thienopyridine. The use of a thienopyridine (clopidogrel or ticlopidine) in combination with warfarin was most common in Australia/New Zealand when compared with the rest of the world (97 vs. 43%, $P < 0.001$).

The baseline characteristics of patients receiving warfarin/dual antiplatelet therapy and warfarin/single antiplatelet therapy are shown in *Table 1*. Patients receiving single antiplatelet therapy were older and more likely to have a history of prior angina.

A total of 226 (28%) patients were taking warfarin before presentation; 182 had a history of atrial fibrillation. The specific indications for warfarin therapy during admission were not collected on the GRACE case report form. However, of the 574 (72%) patients not on warfarin therapy before hospitalization, the assumed indications for in-hospital initiation of long-term anticoagulation are indicated in *Table 2* and included new onset atrial fibrillation, anterior myocardial infarcts, valve surgery, and venous thrombo-embolism. In total, 299 (37%) of the

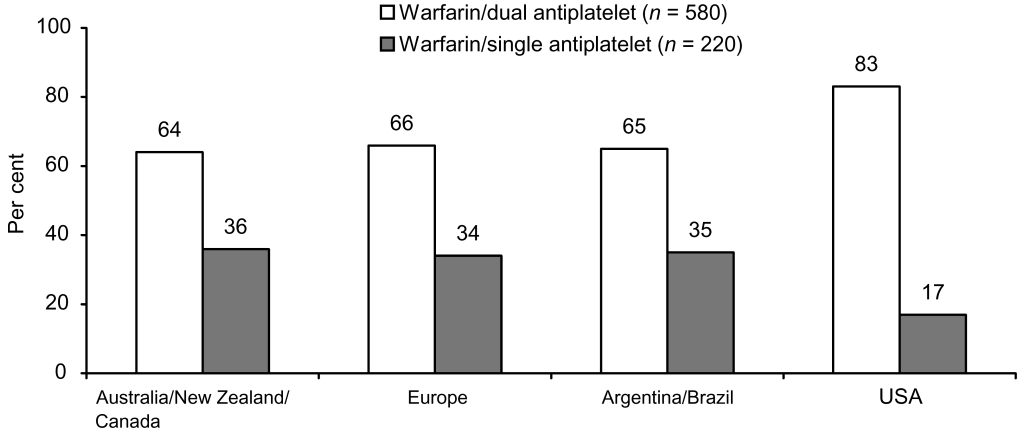

Figure 1 Geographical variation in combination regimen at discharge. Four-way *P*-value less than 0.001.

Table 1 Patients' demographic and baseline characteristics and clinical presentation according to antiplatelet therapy at discharge

	Combination discharge therapy		
	Warfarin/dual antiplatelet ($n = 580$)	Warfarin/single antiplatelet ($n = 220$)	*P*-value
Demographics *n* (%)			
Median age, years (IQR)	55–75 (64)	58–77 (66)	0.02
Men	432 (74)	129 (70)	0.23
Prior angina	227 (39)	105 (48)	0.02
Prior myocardial infarction	59 (27)	58 (26)	0.78
Prior heart failure	60 (10)	29 (13)	0.26
Prior coronary intervention	108 (19)	34 (16)	0.32
Prior CABG surgery	86 (15)	27 (12)	0.36
Prosthetic valve	20/356 (5.6)	5/124 (4.0)	0.49
Smoker (current or former)	336 (58)	116 (53)	0.16
Diabetes	130 (23)	49 (23)	0.99
Hypertension	331 (57)	129 (59)	0.73
Hyperlipidaemia	301 (52)	100 (47)	0.16
Atrial fibrillation	130 (22)	52 (24)	0.67
Major surgery/trauma	26 (4.5)	13 (5.9)	0.41
Clinical presentation *n* (%)			
Cardiac arrest	15 (2.6)	8 (3.7)	0.41
Killip class I	452 (80)	180 (84)	0.34
Killip class II–IV	114 (19)	35 (16)	
STEMI	355 (61)	134 (61)	0.97
Non-STEMI	134 (23)	50 (23)	
Unstable angina	91 (16)	36 (16)	

CABG, coronary artery bypass grafting; IQR, interquartile range; STEMI, ST-segment elevation myocardial infarction.

Table 2 Assumed indications for warfarin therapy

Indication *n* (%)	Prior warfarin ($n = 226$)	New warfarin therapy ($n = 574$)
Atrial fibrillation or flutter	182 (80)	137 (24)
STEMI	0	343 (60)
Prosthetic valve surgery	20 (9)	0
Venous thrombo-embolism	20 (9)	12 (2)
Unidentified	4 (2)	82 (14)

STEMI, ST-segment elevation myocardial infarction.

cohort had either a history of atrial fibrillation or developed atrial fibrillation during admission.

Patients discharged on warfarin/single antiplatelet therapy were less likely than those given warfarin/dual therapy to receive unfractionated heparin, glycoprotein IIb/IIIa antagonists, beta-blockers, or statins while in hospital; the use of low-molecular-weight heparin did not differ between groups. They were also less likely to have received a drug-eluting stent, although 28 (22%) of the patients who received a drug-eluting stent were discharged on single antiplatelet therapy (*Table 3*).

Patients discharged on warfarin/single antiplatelet therapy were more likely to have experienced atrial fibrillation or congestive heart failure during their admission, but there were no differences in the incidences of myocardial infarction, recurrent ischaemia, cardiogenic shock, or major bleeding (*Table 4*).

The use of antiplatelet therapy at 6 months differed significantly between the two groups with those discharged on single antiplatelet being more likely to be on no antiplatelet at 6 months (*Table 5*).

There was no difference in rates of 6-month mortality or myocardial infarction between the groups. The frequency of 6-month stroke was lower in the warfarin/dual antiplatelet group (0.7 vs. 3.4%, $P = 0.02$), although the number of events was small (*Table 6*).

Among patients with atrial fibrillation, there were no significant differences in 6-month outcomes between the single and dual antiplatelet groups (*Table 6*). Of the patients discharged on warfarin/single antiplatelet therapy, 107 (49%) received aspirin and 113 (51%) a thienopyridine. The aspirin/warfarin combination was associated with similar 6-month outcomes to that of thienopyridine/warfarin (*Table 6*).

Of the 130 patients discharged on warfarin following placement of a drug-eluting stent, antiplatelet therapy was more likely to be continued for 6 months. There were no differences in outcomes between patients discharged on single vs. dual antiplatelet therapy (*Table 7*).

Discussion

The aim of this study is to review an area of clinical practice that is commonly encountered but grossly understudied. Our real-world data suggest that, in patients with an ACS who are discharged on antiplatelet therapy and warfarin following coronary stenting, the use of single vs. dual antiplatelet therapy leads to similar 6-month efficacy outcomes. A dual antiplatelet regimen of aspirin and a thienopyridine is the

Table 3 Prior medications, and hospital treatment and interventions, according to combination regimen

	Combination discharge therapy		
	Warfarin/ dual antiplatelet ($n = 580$)	Warfarin/ single antiplatelet ($n = 220$)	*P*-value
Prior medications *n* (%)			
Aspirin	179 (31)	61 (28)	0.39
Warfarin	167 (29)	59 (27)	0.57
Thienopyridines	31 (5)	15 (7)	0.44
Hospital treatment and interventions *n* (%)			
Aspirin	574 (99)	198 (90)	<0.001
Thienopyridines	408 (95)	108 (68)	<0.001
Unfractionated heparin	433 (75)	136 (62)	<0.001
LMWH	307 (53)	118 (54)	0.87
GP IIb/IIIa inhibitors	356 (61)	108 (49)	0.003
Beta-blockers	532 (92)	187 (85)	0.008
ACE-inhibitors	479 (83)	174 (79)	0.22
Fibrinolytic drug	102 (18)	33 (15)	0.37
Pulmonary artery catheter	34 (6)	22 (10)	0.04
Drug-eluting stent	102/358 (28)	28/124 (22)[a]	

ACE, angiotensin-converting enzyme; GP, glycoprotein; LMWH, low-molecular-weight heparin.

[a]Data on the type of stent (drug-eluting vs. bare-metal stent) were collected from 482 patients.

Table 4 Hospital events according to combination regimen

Event *n* (%)	Combination discharge therapy		
	Warfarin/dual antiplatelet ($n = 580$)	Warfarin/single antiplatelet ($n = 220$)	*P*-value
Cardiogenic shock	33 (5.7)	17 (7.7)	0.27
Myocardial infarction >24 h/ re-infarction	48 (8.3)	26 (12)	0.12
Recurrent ischaemic symptoms	164 (28)	57 (26)	0.49
Atrial fibrillation/ flutter	127 (22)	66 (30)	0.01
Stroke	6 (1.0)	7 (3.2)	0.05
Congestive heart failure	128 (22)	65 (30)	0.02
Major bleeding	34 (5.9)	10 (4.6)	0.46

optimal treatment strategy following coronary stenting based on superior safety and efficacy when compared with aspirin alone or aspirin in combination with warfarin.[5,6] In the Stent Anticoagulation Restenosis Study (STARS),[5] three antiplatelet/antithrombotic regimens (aspirin alone, aspirin/ticlopidine, and aspirin/warfarin) were compared

Table 5 Antiplatelet use at 6-month follow-up (671 of 800 patients had completed medication at 6-month follow-up)

Antiplatelet use *n* (%)	Combination discharge therapy		
	Warfarin/dual antiplatelet ($n = 479$)	Warfarin/single antiplatelet ($n = 192$)	*P*-value
Dual antiplatelet at follow-up	116 (24)	24 (12)	
Single antiplatelet at follow-up	235 (49)	94 (49)	<0.001
None at follow-up	128 (27)	74 (39)	

in an elective coronary stenting cohort. The Full Anticoagulation vs. Aspirin and Ticlopidine (FANTASTIC) trial[6] compared a regimen of dual antiplatelet therapy vs. aspirin/warfarin in both elective and unplanned (to salvage failed angioplasty or optimize the results of balloon angioplasty) cohorts. Both randomized trials demonstrated a significant benefit in terms of safety and efficacy in favour of dual antiplatelet therapy alone. The STARS trial[5] indicated that most of the benefits were from reductions in subacute stent thrombosis in the dual antiplatelet group. Both trials occurred during the early bare-metal stent era and involved a cohort of patients primarily undergoing elective procedures.

No large trial has addressed the population of patients with a strong indication for warfarin or presenting with an ACS. Our registry analysis, with the largest sample size in the current literature, reflects real-world practice in a real-world population, investigating a common clinical problem that clinicians face on a daily basis. The fine balance between safety and efficacy in this cohort needs careful consideration. Arab *et al.*[18] performed a systematic review of the literature on the optimal antiplatelet/antithrombotic regimen in those requiring long-term anticoagulation who undergo coronary stenting and found no significant studies or randomized trials addressing this issue.

Our results demonstrate varying practices with significant differences between the USA and other parts of the world such as Europe, Australasia, and Argentina/Brazil. The type of single antiplatelet chosen in combination with warfarin also varied significantly, with Australasia almost exclusively using a thienopyridine in combination with warfarin. The regional variations may reflect differences in healthcare systems as well as economic and social influences.

Our results suggest that, in combination with warfarin, the use of single antiplatelet therapy may be a safe treatment option in selected patients, with similar 6-month efficacy outcomes when compared with dual antiplatelet therapy. There was no difference in major bleeding in-hospital between the groups; however, 6-month bleeding outcomes were not captured. There was a trend towards an increase in events in patients receiving single antiplatelet therapy at 6 months; however, the only significant difference in favour of dual antiplatelet therapy involved stroke at 6 months (0.7 vs. 3.4%, $P = 0.02$). This result should be interpreted with caution as the event rates were extremely small (3 vs. 6). The type of stroke (ischaemic vs. haemorrhagic) was not identified in this registry.

Table 6 Six-month outcomes in the overall cohort, in patients with atrial fibrillation, and according to use of aspirin or thienopyridine

	Warfarin/dual antiplatelet	Warfarin/single antiplatelet	*P*-value
Overall cohort *n* (%)			
Death	23/453 (5.1)	12/184 (6.5)	0.47
Stroke	3/426 (0.7)	6/179 (3.4)	0.02[a]
Unscheduled PCI	45/424 (10.6)	22/176 (12.5)	0.50
Myocardial infarction	13/391 (3.3)	7/154 (4.5)	0.49
Cohort with atrial fibrillation *n* (%)			
Death	9/156 (5.8)	7/75 (9.3)	0.32
Stroke	0/148 (0)	1/71 (1.4)	0.32
Unscheduled PCI	13/148 (8.8)	7/68 (10.3)	0.72
Myocardial infarction	3/138 (2.2)	2/61 (3.3)	0.64
Aspirin vs. thienopyridine *n* (%)	Warfarin/aspirin ($n = 107$)	Warfarin/thienopyridine ($n = 113$)	
Death	7/91 (7.7)	5/93 (5.4)	0.52
Stroke	4/88 (4.5)	2/91 (2.2)	0.44
Myocardial infarction	3/75 (4.0)	4/79 (5.1)	1.00
Unscheduled PCI	15/87 (17.2)	7/89 (7.9)	0.06

PCI, percutaneous coronary intervention.
[a]Fisher's exact test.

Table 7 Antiplatelet use at 6-months, and 6-month outcomes, among the cohort who received a drug-eluting stent

	Combination discharge therapy		
	Warfarin/dual antiplatelet ($n = 75$)	Warfarin/ single antiplatelet ($n = 25$)	*P*-value
Antiplatelet use at follow-up *n* (%)[a]			
Dual antiplatelet	44 (59)	8 (32)	0.02
Single antiplatelet	14 (19)	11 (44)	
No antiplatelet	17 (22)	6 (24)	
Six-month outcomes *n* (%)	($n = 102$)	($n = 28$)	
Death	5/67 (7.5)	3/25 (12)	0.67
Stroke	0/62 (0)	0/21 (0)	
Unscheduled PCI	14/62 (23)	3/22 (14)	0.54
Myocardial infarction	2/63 (3.2)	0/23 (0)	1.0

PCI, percutaneous coronary intervention.
[a]Information on antiplatelet therapy at 6-month follow-up was available in only 100 of the 130 patients.

The use of either aspirin or a thienopyridine as the single antiplatelet in combination with warfarin also proved to be equivalent in terms of efficacy. Thienopyridine use was significantly reduced in patients with a history of major surgery or trauma (1.8 vs. 10.3%, $P < 0.01$). The incidence of subacute and late stent thrombosis was not collected, but it is a rare event that would be captured in the 6-month myocardial infarction and mortality outcome data. Most patients had ceased dual antiplatelet therapy at 6 months (reflecting a cohort receiving mainly bare-metal stents). There was a significant difference between the two groups, with those discharged on single antiplatelet therapy more likely to be on no antiplatelet at 6 months (39 vs. 27%, $P < 0.001$) (*Table 6*). Despite this, there was no excess in events. In the single antiplatelet group, there were only seven myocardial infarcts at 6 months when compared with 13 in the dual antiplatelet group (4.5 vs. 3.3%, $P = 0.49$) and 12 deaths compared with 23 (6.5 vs. 5.1%, $P = 0.47$).

The perceived increased risk of late stent thrombosis in those receiving drug-eluting stents has resulted in a recommendation of prolonged dual antiplatelet therapy in these patients.[19,20] An alternative strategy of bare-metal stenting in those requiring warfarin may avoid the need for long-term dual antiplatelet therapy. In this registry, which has been accruing data since 1999, only a minority of patients received drug-eluting stents. Among the warfarin/dual antiplatelet group, 102 of 358 (28%) patients received drug-eluting stents when compared with 28 of 124 (22%) in the warfarin/single antiplatelet. Analysis of this small cohort of patients revealed no difference in 6-month outcomes between the two groups (*Table 7*). However, as this registry is ongoing, we will have the opportunity to describe practice and associated outcomes among these patients in the future.

The optimal antiplatelet strategy for stented patients requiring warfarin is an unresolved clinical question. Practice at present is guided by the clinician's discretion, with no significant evidence to date to validate any one regimen. Although ours is an observational study with a limited number of events, the data suggest the use of single antiplatelet therapy combined with warfarin in patients with an indication for long-term anticoagulation to be an acceptable management option. There remains a pressing need for further investigation into this important area.

Strengths and limitations

GRACE is a large, ongoing, multinational registry. The strength of this study stems from its assessment of a real-world population. It highlights the varying practices from region to region, reflecting both economical and social differences but also the fact that there is no clear evidence or guidelines in this cohort of patients. The GRACE registry is the largest multinational registry to include the spectrum of ACS patients and follows

standardized criteria for defining ACS and hospital outcomes allowing an accurate and reliable data set. The limitations of our registry are similar to those of any observational study. The lack of substantial numbers (even though the study is significantly larger than any previous study in this area) also makes it difficult to draw firm conclusions. The study does not capture data on long-term bleeding outcomes, which is important to evaluate the ongoing safety of each regimen.

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