Key Findings From the 2006 World Congress of Cardiology

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The World Congress of Cardiology (WCC) 2006 meeting was jointly sponsored by the European Society of Cardiology and the World Heart Federation. A total of 3917 peer-reviewed abstracts were presented at the sessions on a comprehensive variety of cardiovascular topics.[1] This article summarizes the key findings of some of the major clinical studies.

Antithrombotic Agents in Acute Coronary Syndromes

Studies on antithrombotic agents provided data on fondaparinux in ST-elevation myocardial infarction (STEMI) and non–ST-elevation myocardial infarction (NSTEMI), patients with STEMI who were undergoing fibrinolysis and received enoxaparin or unfractionated heparin (UFH), and long-term outcomes of immediate thrombolysis or transport for primary percutaneous coronary intervention (PCI).

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Efficacy and Safety of Fondaparinux in STEMI and NSTEMI: A Combined Analysis of OASIS-5 and OASIS-6

Fondaparinux is a factor Xa inhibitor that was shown to have similar efficacy, lower rates of bleeding, and improved clinical outcomes as compared with enoxaparin in patients with NSTEMI enrolled in the Organization for the Assessment of Strategies for Ischemic Syndromes (OASIS) 5 trial.[2] In the OASIS-6 trial, fondaparinux significantly reduced the composite of death or myocardial infarction (MI) at 9, 30, and 180 days in patients with acute STEMI, except in patients undergoing primary PCI. A trend towards a lower rate of bleeding for fondaparinux was also observed in this study.[3]

An analysis of the combined OASIS-5 and OASIS-6 data sets was presented at the WCC 2006. This combined analysis revealed that fondaparinux was superior to UFH or enoxaparin in the prevention of a composite endpoint of death, MI, or stroke in patients with NSTEMI and STEMI.[4] Fondaparinux was also associated with a significantly lower rate of bleeding in this combined analysis. The effect on the primary composite endpoint was

Table 1
Efficacy and Bleeding Outcomes at 30 Days in the OASIS-5 and OASIS-6 Trials Combined Analysis

	UFH + Enoxaparin n = 13242 (%)	Fondaparinux n = 13270 (%)	Hazard Ratio (95% CI)	*P* Value
Death/MI/stroke	8	7.2	0.91 (0.83-0.99)	.03
Death	4.3	3.8	0.89 (0.79-1)	.052
MI	3.8	3.5	0.92 (0.81-1.04)	.196
Stroke	1	0.8	0.82 (0.64-1.07)	.143
Major bleeding	4.4	3	0.67 (0.59-0.76)	< .00001

OASIS, Organization for the Assessment of Strategies for Ischemic Syndromes; UFH, unfractionated heparin; CI, confidence interval; MI, myocardial infarction. Adapted with permission from Mehta S.[4]

primarily driven by a reduction in death (Table 1).

The risk of catheter thrombosis in patients undergoing PCI is one concern with fondaparinux that originated from the OASIS-6 data. Among patients receiving PCI for unstable angina or NSTEMI and patients receiving rescue, facilitated, and routine PCI after STEMI, the incidence of the combined endpoint was identical between groups (7.9% vs 7.9%). Catheter thrombosis was higher in all PCI patients (hazard ratio [HR] 3.58, 95% confidence interval [CI], 1.64-7.83), but the rate of catheter thrombosis was essentially eliminated when standard doses of UFH were administered prior to PCI. No patients randomized to UFH/enoxaparin experienced catheter thrombosis, whereas 1 patient randomized to fondaparinux who received a very low dose (5 IU/kg) of UFH prior to PCI had catheter thrombosis. The risk of major bleeding in all PCI patients was lower for patients randomized to fondaparinux as compared with UFH/enoxaparin (HR 0.54, 95% CI, 0.42-0.69), but no significant differences in major bleeding were detected between groups in patients who received UFH prior to PCI. The investigators observed a reduction in the primary endpoint for patients treated with clopidogrel or ticlopidine and in patients receiving a glycoprotein IIb/IIIa inhibitor. The bleeding risk with fondaparinux in these subgroups was lower than that observed with the use of enoxaparin/UFH (Table 2). Based on this analysis, the investigators concluded that fondaparinux may be preferred over enoxaparin and UFH as a medical treatment in patients with acute coronary syndrome.[4] The use of fondaparinux in the catheterization laboratory will be limited due to the association with catheter thrombosis, although this risk seems to be modified by the concurrent use of unfractionated heparin.

Enoxaparin or UFH in STEMI Patients Undergoing PCI

The Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment–Thrombolysis in Myocardial Infarction 25 (ExTRACT-TIMI 25) study randomized 20,506 patients with STEMI who were undergoing fibrinolysis to receive enoxaparin or UFH.[5] Enoxaparin was associated with a 17% reduction in the relative risk of death or nonfatal recurrent MI at 30 days. A prespecified subanalysis of this trial (PCI ExTRACT-TIMI 25) in patients undergoing PCI was reported at the WCC 2006.[6] The primary objective

Table 2
Efficacy and Bleeding Outcomes in the OASIS-5 and 6 Trials Combined Analysis According to Clopidogrel and GP IIb/IIIa Use

	Patients (n)	Enoxaparin/ UFH (%)	Fondaparinux (%)
Death/MI/Stroke at 30 days			
Clopidogrel/ticlopidine	18,141	7.3	6.6
No clopidogrel/ticlopidine	8371	9.4	8.5
GP IIb/IIIa inhibitor	5408	9.5	8.6
No GP IIb/IIIa inhibitor	21,104	7.6	6.9
Major Bleeding at 9 Days			
Clopidogrel/ticlopidine	18,141	3.8	2.2
No clopidogrel/ticlopidine	8371	3.4	2.1
GP IIb/IIIa inhibitor	5408	5.6	3.6
No GP IIb/IIIa inhibitor	21,104	3.2	1.8

OASIS, Organization for the Assessment of Strategies for Ischemic Syndromes; GP, glycoprotein; UFH, unfractionated heparin; MI, myocardial infarction. Adapted with permission from Mehta S.[4]

of this analysis was to determine whether enoxaparin is superior to UFH as adjunctive therapy for STEMI patients initially treated with fibrinolytic therapy undergoing PCI.

In PCI ExTRACT-TIMI 25, a total of 4676 patients underwent PCI; 2272 were assigned to enoxaparin and 2404 were assigned to UFH. The mean time to PCI was 122 and 109 hours in the enoxaparin and UFH groups, respectively. The rate of death or recurrent MI at 30 days was 10.7% in the enoxaparin group compared with 13.8% in the UFH group (relative risk [RR] 0.77; $P = .001$). This effect was primarily driven by a reduction in recurrent MI. The benefit associated with enoxaparin was present in patients whose study drug was not discontinued (RR 0.75; $P = .018$) and in patients whose study drug was discontinued but restarted prior to PCI (RR 0.41; $P = .004$). No significant differences between enoxaparin and UFH were detected in the rates of major or minor bleeding, or intracranial hemorrhage. Enoxaparin treatment was associated with a lower relative risk of any stroke as compared with UFH (0.3% vs 0.9%, RR 0.30, 95% CI, 0.12-0.75; $P = .006$). The investigators concluded that enoxaparin could be administered as the sole antithrombin therapy before and during PCI and that periprocedural enoxaparin was preferred over UFH in STEMI patients treated with fibrinolysis who are undergoing PCI.[6]

Long-Term Outcomes of Immediate Thrombolysis or Transport for Primary PCI

Multiple studies have demonstrated the short-term benefit (30 days) of PCI as compared with pharmacologic reperfusion in terms of reducing the risk of death, recurrent MI, or stroke.[7,8] However, the long-term outcomes of these strategies have not been thoroughly evaluated. The PRimary Angioplasty in patients transferred from General community hospitals to specialized PTCA Units with or without Emergency thrombolysis (PRAGUE) 2 trial studied the effect of immediate thrombolysis or transportation for PCI in 850 patients presenting with acute MI to community hospitals without PCI capabilities.[9] The study was terminated early because of a 2.5-fold higher 30-day mortality in the thrombolytic subjects who were treated more than 3 hours from symptom onset.[9] The 5-year follow-up results were presented at the WCC 2006 Hot Line and Clinical Trial Update Session. The complete results have recently been published.[10] The 30-day findings persisted throughout the 5-year follow-up (Table 3). The primary outcome of all-cause mortality, recurrent MI, stroke, or revascularization was significantly higher for the immediate thrombolysis group as compared with patients transferred for primary PCI.[10] The composite endpoint was driven primarily by a reduction in recurrent infarction and revascularization, and, to a lesser extent, all-cause death (Table 3). These benefits were observed largely within the first 30 days after the event and sustained over the 5-year follow-up. The investigators concluded that hospital transfer for PCI in patients with acute MI improves outcomes as compared with immediate thrombolysis, and implementation strategies are needed to ensure that PCI is available to patients with acute MI.

Stents

New data were presented regarding an everolimus-eluting coronary stent and elective stenting in patients with viable myocardium.

Table 3
Cumulative Proportion of Patients With Endpoints at 5 Years in the PRAGUE-2 Follow-Up Trial

	Thrombolytic Group n = 416	PCI Group n = 428	Hazard Ratio (95% CI)	*P* Value
All-cause death/ recurrent MI/stroke/ revascularization (95% CI)	0.53 (0.47-0.59)	0.4 (0.34-0.46)	1.8 (1.38-2.33)	< .001
All-cause death/ recurrent MI/ stroke (95% CI)	0.54 (0.48-0.6)	0.47 (0.41-0.53)	1.35 (1.02-1.7)	.04
All-cause death (95% CI)	0.23 (0.19-0.27)	0.19 (0.15-0.23)	1.34 (0.99-1.82)	.06
Recurrent MI (95% CI)	0.19 (0.15-0.23)	0.12 (0.08-0.16)	1.72 (1.15-2.58)	.009
Stroke (95% CI)	0.08 (0.04-0.12)	0.08 (0.04-0.12)	1.65 (0.84-2.23)	.18
(Re-) PCI (95% CI)	0.38 (0.32-0.44)	0.22 (0.16-0.28)	2.12 (1.51-2.99)	< .001
CABG (95% CI)	0.13 (0.07-0.19)	0.12 (0.06-0.18)	1.13 (0.75-1.71)	.56

PRAGUE, PRimary Angioplasty in patients transferred from General community hospitals to specialized PTCA Units with or without Emergency thrombolysis; PCI, percutaneous coronary intervention; CI, confidence interval; MI, myocardial infarction; CABG, coronary artery bypass grafting.
Reprinted with permission from Widimsky P et al.[10]

Everolimus-Eluting Coronary Stent

The SPIRIT II study was a clinical evaluation of the XIENCE™ V everolimus-eluting coronary stent system (Abbott Laboratories, Abbott Park, IL) in the treatment of patients with de novo, native coronary artery lesions. The study was a prospective, randomized (3:1), single-blind study evaluating the noninferiority of the everolimus-eluting (XIENCE™ V) stent to the paclitaxel-eluting stent (TAXUS®; Boston Scientific, Natick, MA). A total of 300 patients were enrolled from 31 sites in the European Union, India, and New Zealand. The primary endpoint was in-stent late loss. At 6 months, patients randomized to the everolimus-eluting stent had an in-stent late loss in the analysis lesion of 0.11 ± 0.27 mm as compared with 0.36 ± 0.39 mm for patients randomized to the paclitaxel-eluting stent ($P < .0001$ on both noninferiority and superiority analyses). Diameter stenosis at follow-up was 16% in the everolimus group and 21% in the paclitaxel group ($P < .001$). No statistically significant differences were noted in the occurrence of in-stent or in-segment binary restenosis. The in-stent intravascular ultrasound results demonstrated a 73% reduction in neointimal volume ($P < .0001$) and a 66% reduction in volume obstruction ($P < .0001$) for patients randomized to the everolimus stent as compared with the paclitaxel stent. Fewer patients randomized to the everolimus stent experienced major adverse cardiovascular events (2.7% vs 6.5%), but the difference did not reach statistical significance.[11] The authors concluded that the clinical, angiographic, and in-stent intravascular ultrasound results of SPIRIT II confirm the findings of the first in-man SPIRIT FIRST study.[12]

Elective Stenting in Patients With Viable Myocardium

After MI, patients with residual viability in the infarcted area are at high risk of recurrent ischemia or reinfarction, but specific treatment approaches in these patients have not been well studied. The Viability Guided Angioplasty After Acute Myocardial Infarction (VIAMI) trial was conducted in 293 post-MI patients who were treated with thrombolysis or no reperfusion therapy because of late presentation. Viability was assessed by dobutamine echocardiography in stable patients 2 to 3 days after the acute event.[13] Viability was defined as an improvement in 2 or more myocardial segments. Patients with viability in the infarct-related artery (n = 216) were randomized to an invasive strategy (n = 106) of stenting the infarct-related artery with concomitant use of abciximab as soon as possible, or to a conservative approach (n = 110), in which angioplasty was performed only in the presence of recurrent signs or symptoms of ischemia. Patients with nonviable myocardium in the infarct-related artery (n = 75) were followed in an observational registry for outcomes. The primary endpoint was the composite of death, recurrent MI, and unstable angina at 6 months. Fewer patients in the invasive group reached the primary endpoint (6.6% vs 15.5%, HR 0.41; $P = .04$) (Table 4). The reduction in events appeared to be driven by a decrease in unstable angina. These data suggest that patients with viable myocardium after MI who undergo stenting of the infarct-related artery have a lower rate of clinical events, particularly unstable angina, within 6 months after the MI. Assessing viability post-MI may be a useful tool in the management of post-MI patients.[13]

Heart Failure

Researchers discussed beta-blockers and sudden cardiac death, and perindopril in elderly people with chronic heart failure.

Beta-Blockers and Sudden Cardiac Death: An Analysis From CIBIS-III

The Cardiac Insufficiency Bisoprolol (CIBIS) III trial was a randomized trial of patients with mild to moderate heart failure and a left ventricular ejection fraction at or less than 35%. A total of 1010 patients were randomized to monotherapy with bisoprolol or enalapril for 6 months, followed by the combination for up

Table 4
Six-Month Clinical Outcomes in the VIAMI Trial

	Invasive Group n = 106	Conservative Group n = 110	*P* Value
Primary endpoint (%)	6.6	15.5	.04
Death (%)	1.9	0.9	NS
Recurrent MI (%)	1.9	2.7	NS
Unstable angina (%)	2.8	11.8	.012
Elective revascularization (%)	0	17.3	< .0001
All revascularizations (%)	4.7	27.3	< .0001

VIAMI, Viability Guided Angioplasty After Acute Myocardial Infarction; NS, not significant; MI, myocardial infarction. Reprinted with permission from Veen G.[13]

to 24 months. The primary endpoint was all-cause mortality or hospitalization. The intention-to-treat analysis demonstrated noninferiority for the bisoprolol-first regimen as compared with the enalapril-first regimen.[14] A secondary analysis of this trial evaluated the effect of these regimens on the occurrence of sudden cardiac death.[15] During the initial 6 months of monotherapy, the bisoprolol-first group appeared to have a lower rate of sudden cardiac death as compared with the enalapril-first group (8 patients vs 16 patients), but the difference did not achieve statistical significance (Table 5). The rate of sudden cardiac death was lower during the first year of the study for patients randomized to bisoprolol-first as compared with enalapril-first. The absolute number of sudden deaths was lower for the bisoprolol-first group as compared with the enalapril-first group by the end of the entire follow-up period, but the difference was not statistically significant (Table 5). No significant differences were detected in the rate of hospitalizations between treatment groups, although a slightly higher rate of hospitalizations for worsening heart failure was observed for the bisoprolol-first group (monotherapy phase 7.7% vs 5%; 12 months 9.7% vs 7.9%; end of study 10.5% vs 8.7%; all not significant [NS]).[15] These data suggest that early initiation of beta-blockers may result in a lower rate of sudden cardiac death, particularly within the first 12 months after initiation. However, none of the patients enrolled in CIBIS III had an implantable cardioverter defibrillator. Thus, the relevance of these findings in patients with implantable cardioverter defibrillators cannot be determined from these data. Despite this limitation, these data from CIBIS III provide additional evidence regarding the benefits of beta-blockers in the prevention of sudden arrhythmic death. Heart failure patients should be initiated on beta-blocker therapy as soon as possible, and they should be appropriately monitored for worsening heart failure symptoms.

Table 5
Sudden Death and All-Cause Mortality in CIBIS-3

	Bisoprolol First n = 505	Enalapril First n = 505	Hazard Ratio (95% CI)	*P* Value
Sudden Death				
Monotherapy	8	16	0.5 (0.21-1.16)	.107
First 12 months	16	29	0.54 (0.29-1.0)	.049
Entire study	29	34	0.84 (0.51-1.38)	.487
All-Cause Mortality				
Monotherapy	23	32	0.72 (0.42-1.24)	.24
First 12 months	42	60	0.69 (0.46-1.02)	.06
Entire study	65	73	0.88 (0.63-1.22)	.44

CIBIS, Cardiac Insufficiency Bisoprolol; CI, confidence interval. Data from Willenheimer R et al.[14]

Perindopril in Elderly People With Chronic Heart Failure

The Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) study was a double-blind, multicenter, international, randomized trial of the angiotensin-converting enzyme (ACE) inhibitor perindopril versus placebo in patients 70 years or younger with clinical heart failure and echocardiographic evidence of diastolic dysfunction. The primary endpoint of the study was all-cause mortality or unplanned heart failure hospitalization. The results were presented at the WCC 2006 and subsequently published.[16] Perindopril was associated with a trend towards fewer events in the first year of follow-up as compared with placebo (10.8% vs 15.3%, HR 0.69, 95% CI, 0.47-1.01; $P = .055$). When the individual components of the composite at 1 year were evaluated, heart failure hospitalization was reduced by perindopril, but all-cause mortality was not (Table 6). Perindopril-treated patients were more likely to have improved New York Heart Association (NYHA) class and a greater 6-minute walk distance at 1 year as compared with placebo. However, no difference between treatment groups in the primary endpoint was evident for the entire duration of follow-up (mean 26.2 months) (HR 0.92, 95% CI 0.7-1.21; $P = .545$). A major limitation of the trial was the high rate of patients who discontinued perindopril at 18 months (62%), the majority of whom went on open-label ACE inhibitors (~90%). Additionally, the event rate in the trial was lower than expected, further reducing the power of the trial.

Despite the lack of significant findings, the data indicate that ACE inhibitors may be beneficial in patients with clinical heart failure and preserved systolic function from the standpoint of symptomatic improvement, improved exercise tolerance, and potentially a reduction in hospitalizations for heart failure. The PEP-CHF trial was underpowered to determine whether such an effect was

Table 6
1-Year Outcomes in PEP-CHF

	1 Year				Entire Follow-Up			
	Placebo	Perindopril	Hazard Ratio (95% CI)	*P* Value	Placebo	Perindopril	Hazard Ratio (95% CI)	*P* Value
Death or heart failure hospitalization	65	46	0.69 (0.47-1.01)	.055	107	100	0.92 (0.7-1.21)	.545
Death	19	17	0.9 (0.47-1.73)	.747	53	56	1.09 (0.75-1.58)	.665
Cardiovascular death	17	10	0.59 (0.27-1.29)	.181	40	38	0.98 (0.63-1.53)	.928
Hospitalization for heart failure	53	34	0.63 (0.41-0.97)	.033	73	64	0.86 (0.61-1.2)	.375
Worsening heart failure events	71	59	0.81 (0.58-1.15)	.239	106	97	0.89 (0.68-1.18)	.413

PEP-CHF, Perindopril in Elderly People with Chronic Heart Failure; CI, confidence interval. Reprinted with permission from Cleland JG et al.[16]

present or absent. The results of similar, ongoing studies are needed to fully determine the role of renin-angiotensin-aldosterone system inhibition on outcomes in this population.

Anticoagulation and Antiplatelet Therapy

Data were presented regarding elderly patients with atrial fibrillation, and peripheral arterial disease.

Elderly Patients With Atrial Fibrillation

An analysis of the National Study for Prevention of Embolism in Atrial Fibrillation (NASPEAF) was performed to evaluate appropriate antithrombotic therapy in the elderly with atrial fibrillation, and the findings were reported during WCC 2006. The NASPEAF study compared standard anticoagulation (target international normalized ratio [INR] 2.5) with combined anticoagulation (target INR 2.1) and antiplatelet therapy using the cyclooxygenase inhibitor triflusal. The randomization was stratified by age and prior embolic events. The primary results of NASPEAF revealed a lower rate of vascular death and nonfatal stroke or systemic embolism over 3 years for patients treated with combination therapy as compared with anticoagulation alone.[17] Perez-Gomez[18] reported the clinical and bleeding outcomes between patients 75 years and older and those younger than 75 years. The older patients had a higher rate of clinical events (4.6% vs 2%; $P = .003$) as compared with the younger patients. No significant difference in major bleeding was observed. The composite of clinical events or major bleeding was also significantly higher in the elderly (6% vs 2.8%; $P = .001$). The analysis was also performed based on the presence of a prior embolic event. In patients with a history of an embolic event treated with anticoagulation alone, the rate of events was almost 2.5 times higher for older patients as compared with younger patients (11.1% vs 4.6%; $P = .04$). In contrast, older and younger patients randomized to combination therapy had similar rates of clinical events (5% vs 3.4%; P = NS). Similarly, older patients without previous embolic events randomized to anticoagulation therapy alone had a higher rate of clinical events as compared with younger patients (5% vs 1.8%; $P = .046$), whereas no differences in outcomes were observed by age among patients receiving combination therapy (1.1% vs 0.8%; P = NS).[18] In the older subgroup, combination therapy was associated with a 67% reduction in the rate of vascular death, nonfatal stroke, or systemic embolism (HR 0.33, 95% CI, 0.13-0.84; $P = .12$). In contrast, there were no significant differences in outcomes between treatment groups in those younger than 75 years (HR 0.59, 95% CI, 0.29-1.17; $P = .124$). Within the anticoagulation group, bleeding events were higher in subjects 75 years or older as compared with subjects younger than 75 years, but no differences in bleeding risk were observed by age in subjects receiving combination therapy. These data suggest that the addition of the antiplatelet agent trifusal may improve the risk-benefit ratio of dose-adjusted moderate oral anticoagulation in high-risk patients with atrial fibrillation, and particularly in the elderly. This approach requires additional investigation.

Peripheral Arterial Disease

As compared with aspirin alone, combination anticoagulation and antiplatelet therapy is an effective treatment strategy that reduces cardiovascular death, reinfarction, and stroke after MI.[19] However, the utility of this approach for patients with peripheral arterial disease was not known. The Warfarin Antiplatelet Vascular Evaluation (WAVE) study was designed to evaluate the effect of oral anticoagulation therapy with warfarin (target INR 2 to 3) plus antiplatelet therapy as compared with antiplatelet therapy alone on the incidence of cardiovascular death, MI, or stroke over 3 years.[20] Following a 2-week to 4-week run-in phase in which all patients were treated with an oral anticoagulant (OAC) plus antiplatelet therapy, patients were randomized in an open-label manner to OAC with warfarin in addition to antiplatelet therapy (n = 1080) or antiplatelet therapy alone (n = 1081). In the OAC group, target INR was 2.4 to 3.0. Antiplatelet agents included aspirin (81 mg to 325 mg), ticlopidine, or clopidogrel.

A total of 2100 patients were enrolled. The qualifying conditions were peripheral arterial disease limbs (82% of patients) and other peripheral arterial disease (18% of patients). Baseline mean ankle-brachial index was 0.83. Prior coronary artery disease was present in 47% of patients, and a history of stroke was present in 15%. The OAC therapy was discontinued in 319 patients (29.5%) in the OAC group; antiplatelet therapy was discontinued in only 21 patients. No benefit for combined therapy was observed in the primary endpoint. Life-threatening bleeding rates were higher in the OAC group (4.0% vs 1.2%, RR 3.41; $P < .001$), as was moderate bleeding (2.9% vs 1.0%; $P = .0018$) and the composite of either type of bleeding (6.9% vs 2.2%; $P = .0001$). Fatal bleeds trended higher in the OAC group (0.9% vs 0.3%; $P = .0513$). However, patients receiving OAC had a major increase in severe or moderate bleeding, despite an INR of 2.2 (Table 7). One proposed hypothesis for these findings is that the patients were lower risk as compared with patients enrolled in post-MI studies. These results indicate that warfarin should not be added to aspirin for the treatment of peripheral artery disease. Further research is needed to identify effective and safe therapies to improve outcomes in this population.[20]

Table 7
Clinical Outcomes in the WAVE Trial

	Combination n = 1080 (%)	Aspirin Alone n = 1081 (%)	Hazard Ratio	*P* Value
CV death, MI, stroke	12.2	13.3	0.92	.49
CV death, MI, stroke, severe coronary or peripheral ischemia	15.9	17.4	0.91	.38
Life-threatening bleeding	4	1.2	3.41	< .001
Moderate bleeding	2.9	1	2.82	.0018

WAVE, Warfarin Antiplatelet Vascular Evaluation; CV, cardiovascular; MI, myocardial infarction. Data from Anand S.[20]

Renin Inhibitors in Hypertension

Aliskiren is an oral renin inhibitor approved for the treatment of hypertension. Weir and colleagues[21] reported safety and efficacy data from a pooled analysis of 8570 patients with mild to moderate hypertension. In this analysis, aliskiren effectively lowered mean sitting diastolic blood pressure (MSDBP) and mean sitting systolic blood pressure (MSSBP). The tolerability of aliskiren was comparable with placebo. Treatment-emergent adverse events were reported by 40.2% of placebo patients and 39.8% of aliskiren patients; discontinuation due to adverse events was similar among patients receiving placebo (3.5%) and aliskiren (1.9%). A higher rate of diarrhea was observed with the 600 mg dose, but not the 150 mg and 300 mg doses. The authors concluded that aliskiren effectively lowered systolic and diastolic blood pressure and was well tolerated.[21]

Aliskiren was evaluated for its effectiveness as add-on therapy with amlodipine in a separate trial also reported at WCC.[22] In this study, patients with MSDBP at or under 90 mm Hg after 4 weeks of amlodipine 5 mg/d were randomized to continued amlodipine 5 mg/d monotherapy (n = 180), amlodipine 10 mg/d (n = 178), or aliskiren 150 mg/d plus amlodipine 5 mg/d (n = 187). Patients were treated for 6 weeks. The primary outcome of the study was the change from baseline in MSDBP and MSSBP, the proportion of patients achieving an MSDBP of less than 90 mm Hg and/or at least a 10 mm Hg reduction from baseline, and patients achieving blood pressure levels of less than 140/90 mm Hg. Combination therapy lowered MSDBP and MSSBP as compared with amlodipine 5 mg alone. The overall incidence of adverse events was similar among

Table 8
Blood Pressure Reductions and Adverse Events in Patients Treated With Aliskiren and Amlodipine

	Amlodipine 5 mg (n = 180)	Amlodipine 10 mg (n = 178)	Aliskiren 150 mg/ Amlodipine 5 mg (n = 187)
MSDBP (mean change, mm Hg)	−4.84	−8.04*	−8.46*
MSSBP (mean change, mm Hg)	−4.96	−9.63*	−10.98*
Responder rate (%)	45.2	59.9*	64.2*
Control rate (%)	22.6	37.9*	42.8*
Overall AEs (%)	28.5	30.9	31.6
Edema (%)	3.4	11.2†	2.1

*$P < .005$ vs amlodipine 5 mg.
†$P < .001$ vs combination.
MSDBP, mean sitting diastolic blood pressure; MSSBP, mean sitting systolic blood pressure; AE, adverse events. Reprinted with permission from Munger MA et al.[22]

groups; however, the rate of edema was significantly higher for the amlodipine 10 mg/d group as compared with the combination aliskiren and amlodipine group (Table 8). Thus, add-on therapy with aliskiren effectively lowered systolic and diastolic blood pressure without the adverse effects associated with increasing amlodipine doses.[22]

Diabetes Mellitus

Topics in diabetes included stroke prevention and predictors of new onset diabetes among hypertensive patients.

Stroke Prevention in Patients With Type 2 Diabetes Mellitus

The PROactive study was a prospective, randomized trial of pioglitazone versus placebo in patients with type 2 diabetes mellitus and evidence of macrovascular disease.[23] The study enrolled 5238 patients, and the primary endpoint was a composite of all-cause mortality, non-fatal MI, stroke, acute coronary syndrome, endovascular or surgical intervention of the coronary or leg arteries, and above-the-ankle amputation. A nonsignificant trend toward reduction of the primary endpoint was observed in patients randomized to pioglitazone. A prespecified analysis of PROactive was designed to evaluate the effect of pioglitazone on the risk of stroke and other cardiovascular outcomes in patients with or without a prior stroke history.[24] A total of 984 patients (19%) had a prior history of stroke, and 4254 did not. Pioglitazone significantly reduced the incidence of fatal or non-fatal stroke among patients with a previous stroke. No significant differences between treatment groups were observed among patients without a prior stroke. Within the prior stroke subgroup, hemoglobin A_{1c}, triglycerides, and the ratio of low-density lipoprotein (LDL) cholesterol to high-density lipoprotein (HDL) cholesterol were significantly lower, and HDL cholesterol was significantly higher, for patients randomized to pioglitazone as compared with placebo. No difference in adverse events was observed by treatment regardless of stroke history. In this prespecified analysis, pioglitazone was associated with a significant reduction in the

Table 9
Predictors of New Onset Diabetes in the ASCOT-BPLA Study

	Hazard Ratio	95% CI	*P* Value
Age > 55 (per 5 year)	0.94	0.9-0.98	.006
Fasting blood sugar (per mmol/L above 5 mmol/L)	5.8	5.24-6.43	< .001
Male sex	0.98	0.84-1.14	.75
BMI (per 5 units increase)	1.49	1.39-1.62	< .001
SBP (per 10 mm Hg)	1.07	1.04-1.1	< .001
Amlodipine ± perindopril	0.66	0.59-0.74	< .001
HDL cholesterol (per mmol/L)	0.72	0.58-0.89	.002
Triglyceride (per mmol/L)	1.12	1.07-1.17	< .001
Total cholesterol (per mmol/L)	0.89	0.84-0.94	< .001
Use of non-CAD medication (Yes/No)	1.25	1.11-1.4	< .001
Alcohol intake (units/week)	0.99	0.99-1.0	.017

ASCOT-BPLA, Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm; CI, confidence interval; BMI, body mass index; SBP, systolic blood pressure; HDL, high-density lipoprotein; CAD, coronary artery disease. Reprinted with permission from Gupta AK.[25]

risk of recurrent stroke among patients with type 2 diabetes.[24]

Predictors of New Onset Diabetes Among Hypertensive Patients

Hypertension is a known risk factor for the development of diabetes, but the influence of antihypertensive drugs and other factors on this risk has not been fully described. The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) database was used to evaluate predictors of developing new onset diabetes and to establish a risk score to identify high-risk patients.[25] A total of 19,257 evaluable patients were enrolled in the ASCOT trial. Of these, 5137 had diabetes at baseline, leaving 14,120 patients at risk of developing new-onset diabetes. New-onset diabetes developed in 799 (11.4%) of 7046 patients in an atenolol-based treatment group and 567 (8%) of 7074 patients in an amlodipine-based treatment group. The multivariable Cox proportional hazard model demonstrated that fasting blood sugar, body mass index, serum triglycerides, and systolic blood pressure were important predictors of developing new-onset diabetes. In contrast, age younger than 55 years, amlodipine with or without perindopril, HDL cholesterol, total cholesterol, and alcohol intake were found to have a protective effect (Table 9). A risk score was developed based on the findings of the multivariate model. The risk of new-onset diabetes increased with increasing risk quartiles. The HR for the development of new onset diabetes in quartile 4 as compared to quartile 1 was 19 (Figure 1). The model demonstrated close agreement between observed and predicted events, indicating excellent internal validity and discriminative ability. These data provide important, practical information that physicians can easily implement to determine the risk of new-onset diabetes among their hypertensive patients. The predictive factors identified by the multivariate model are commonly assessed in routine clinical practice. Physicians should be aware of these factors in their hypertensive patients and use them as appropriate when developing management plans.

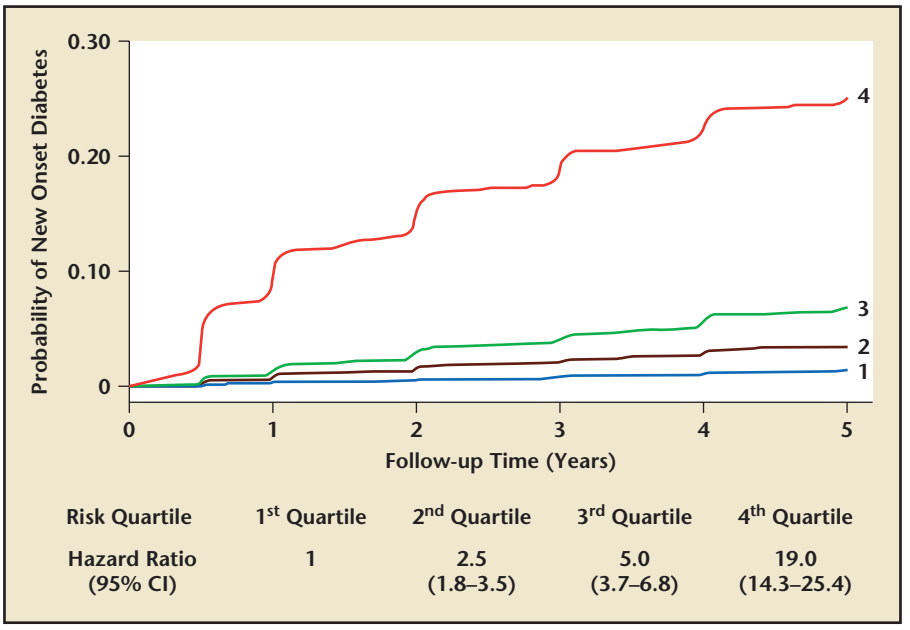

Figure 1. *Data from the Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm (ASCOT-BPLA). Probability of new onset diabetes by risk quartile. Reprinted with permission from Gupta AK.*[25]

Rosuvastatin Plus Ezetimibe for Achieving Low-Density Lipoprotein and C-Reactive Protein Goals

The Examination of Potential Lipid-Modifying Effects of Rosuvastatin in

Table 10
Proportion of Patients Achieving Treatment Goals in the EXPLORER Trial

	Rosuvastatin 40 mg/d (n = 230)	Rosuvastatin 40 mg + Ezetimibe 10 mg/d (n = 235)	*P* Value
LDL-C < 100 mg/dL (%)	79.1	94	< .001
LDL-C < 70 mg/dL (%)	35	79.6	< .001
LDL-C < 100 mg/dL or < 70 mg/dL (depending on risk category) and CRP < 2 mg/L (%)	23.9	58.2	< .001
LDL-C < 70 mg/dL and CRP < 2 mg/L (%)	18.6	55	< .001

EXPLORER, Examination of Potential Lipid-Modifying Effects of Rosuvastatin in Combination with Ezetimibe versus Rosuvastatin Alone; LDL-C, low-density lipoprotein cholesterol; CRP, C-reactive protein. Data from Ballantyne CM et al.[26,27]

Combination with Ezetimibe versus Rosuvastatin Alone (EXPLORER) study aimed to evaluate the effectiveness of rosuvastatin plus ezetimibe as compared with rosuvastatin alone for achieving goal LDL levels. The study also evaluated the proportion of patients who achieved combined LDL and C-reactive protein (CRP) goals at 6 weeks. A total of 469 patients at high risk of coronary heart disease were randomized to rosuvastatin 40 mg/d monotherapy or the combination of rosuvastatin 40 mg/d and ezetimibe 10 mg/d. More patients randomized to combination therapy achieved LDL and dual LDL/CRP goals as compared with patients randomized to rosuvastatin monotherapy (Table 10).[26,27] The investigators concluded that combination therapy may enable high-risk patients to achieve cholesterol and inflammatory marker goals, particularly if those patients have not achieved these goals on statin monotherapy. ■

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Main Points

- Data suggest that fondaparinux may be preferred over enoxaparin and unfractionated heparin as a medical treatment in patients with acute coronary syndrome.
- In a recent study, hospital transfer for percutaneous coronary intervention in patients with acute myocardial infarction improved outcomes as compared with immediate thrombolysis.
- Patients with viable myocardium after myocardial infarction who undergo stenting of the infarct-related artery have a lower rate of clinical events, particularly unstable angina, within 6 months after the myocardial infarction.
- Data suggest that warfarin should not be added to aspirin for the treatment of peripheral artery disease.
- Add-on therapy with aliskiren effectively lowered systolic and diastolic blood pressure without the adverse effects associated with increasing amlodipine doses.
- A recent study showed that pioglitazone was associated with a significant reduction in the risk of recurrent stroke among patients with type 2 diabetes.
- Combination therapy of rosuvastatin plus ezetimibe may enable high-risk patients to achieve cholesterol and inflammatory marker goals, particularly if those patients have not achieved these goals on statin monotherapy.

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