Drugs of the Future 2012, 37(5): 379-387

CCC: 0377-8282/2012
DOI: 10.1358/dof.2012.37.5.1813664

MEETING REPORT

HIGHLIGHTS FROM THE AMERICAN COLLEGE OF CARDIOLOGY 2012 ANNUAL MEETING

MARCH 24-27, 2012 – CHICAGO, ILLINOIS, USA

X. Rabasseda

Thomson Reuters, Barcelona, Spain

CONTENTS

SUMMARY

During four busy days, McCormick Plaza become the centerpoint of cardiology as ACC.12 smoothly but busily channeled news on drugs for cardiovascular diseases and risk factors, and very specifically informed on novel antiplatelet agents, anticoagulants and lipid-lowering drugs, the information on which is summarized in the following report.

Key words: Heart failure – Coronary artery disease – Atrial fibrillation – Cardiovascular risk factors – Peripheral arterial disease – Valvular heart disease

HEART FAILURE

β-Blockers have a well-established role in the management of heart failure, although differences exist between individual agents regarding efficacy and safety issues. For example, data was presented in the McCormick convention center demonstrating that switching from carvedilol to bisoprolol helped continue therapy and increase the dose in patients with adverse events, most of whom were able to reach target doses [Taniguchi, T. et al., Abst 1214-102]. Nevertheless, carvedilol was reported to be effective on heart failure and systolic and diastolic pressure in patients with dilated cardiomyopathy on maintenance dialysis [Sharma, A. & Herzog, Ch., Abst 1214-104]. Effective was also the adjective applied to bucindolol after the results of a trial that demonstrated additional benefits in preventing new-onset atrial fibrillation in patients with advanced heart failure [Aleong, R. et al., Abst 1238-256] (Fig. 1).

Considering aldosterone blockers, which according to a meta-analysis improved ejection fraction and the functional class independently of baseline severity [Phelan, D. et al., Abst 1229-601], spironolactone prevented cardiac and sudden death in patients with class I/II heart failure accompanied by elevated cardiac sympathetic nerve activity [Kondo, T. et al., Abst 1105-273], and the combined use of spironolactone and loop diuretics further reduced the risk of sudden death [Iwasaki, Y. et al., Abst 1214-100]. However, the benefits of spironolactone were greater in patients with reduced glomerular fil-

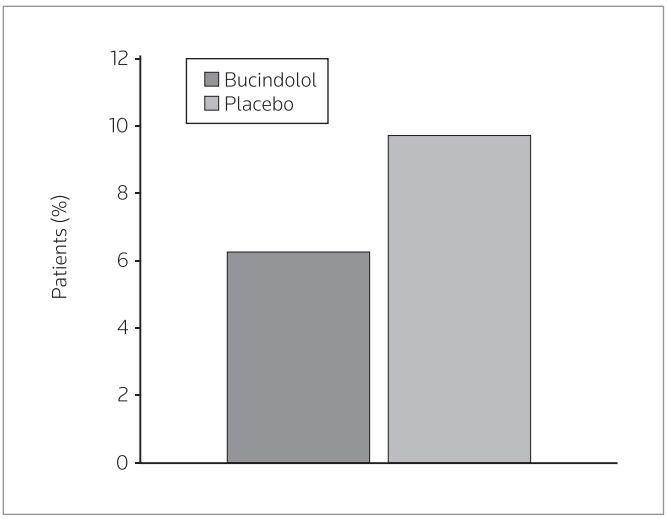

Figure 1. New-onset atrial fibrillation rates in patients receiving bucindolol or placebo [Aleong, R. et al., Abst 1238-256].

Correspondence: X. Rabasseda, MD, Thomson Reuters, Provença 398, 08025 Barcelona, Spain. E-mail: xavier.rabasseda@thomsonreuters.com.

tration rate, in whom the drug maintained benefits on mortality despite a negative prognosis [Vardeny, O. et al., Abst 921-6]. Overall, spironolactone was found to be underutilized, although it was not associated with hyperpotassemia or 30-day mortality and readmission outcomes [Hameed, M.M. et al., Abst 1229-597].

Another established therapy for heart failure, levosimendan, reduced mortality, new-onset renal failure and ischemic morbidity in patients with heart failure undergoing cardiac surgery [Harrison, R. et al., Abst 1229-604].

Natriuretic peptides have become an area of intensive research as a treatment for heart failure. Among these agents, nesiritide improved symptoms of congestion without adding tolerability concerns, although without lowering short-term mortality either [Leiming, L. et al., Abst 1229-602], while cenderitide was well tolerated and dose-dependently lowered blood pressure in patients with stable systolic heart failure [Neutel, J. et al., Abst 1228-628]. An additional study indicated benefits of sildenafil on pulmonary hemodynamics and right ventricular function in patients with dilated cardiomyopathy [Saurav, A. et al., Abst 1229-600]. In fact, mechanistic studies demonstrated inhibition of vascular smooth muscle cell proliferation and platelet aggregation by sildenafil through activation of protein kinase G and reduction of neointimal hyperplasia [Yang, H.M. et al., Abst 1195-146].

Concerning additional miscellaneous therapies reported to be beneficial in patients with heart failure, a proof-of-concept study indicated improvements in cardiopulmonary hemodynamics in patients with preserved ejection fraction treated with ranolazine [Maier, L. et al., Abst 921-8], while dual therapy with isosorbide dinitrate and hydralazine not only reduced mortality but also prolonged time to readmission in patients with heart failure [Salamon, J.N. et al., Abst 1228-625; Win, S. et al., Abst 1228-633; Salamon, J.N. et al., Abst 1228-634], and digoxin improved renal function in patients with chronic heart failure [Testani, J.M. et al., Abst 1228-632] (and in preclinical animal models improved ventricular performance through an effect on collagen deposition and fibrosis [Mady, C. et al., Abst 1231-553]). In preclinical animal models, selective blockade of adenosine A_{2B} receptors with GS-6201 improved cardiac remodeling after myocardial ischemia through an effect on caspase-1 activity [Toldo, S. et al., Abst 1220-333]. On the contrary, high-dose furosemide, which was frequently associated with acute kidney injuries [Tisdale, J. et al., Abst 1228-627], arose as an independent risk factor for death in patients with chronic heart failure [Terrovitis, J. et al., Abst 1214-103], although the risk, which is common to loop diuretics, depended on serum albumin levels and was increased by hypoalbuminemia, which correlated with increased dose of diuretics [Cauthen, C. et al., Abst 1214-105]. However, in patients with acute decompensated heart failure furosemide with hypertonic saline infusion nonsignificantly improved diuresis, although with an untoward effect on blood urea nitrogen compared to intravenous furosemide [Engelmeier, R.S. et al., Abst 1229-603]. On the other hand, administration of epoetin alfa to patients with heart failure with preserved ejection fraction resulted in improved hemoglobin levels without an apparent effect on left ventricular structure or function [Green, P. et al., Abst 1222-423].

Regarding biomarkers for heart failure, higher levels of galectin-3 (a marker of fibrosis) identified patients at higher risk for new-onset heart failure and all-cause death [Ho, J. et al., Abst 905-3], serum neutrophil gelatinase-associated lipocalin and cystatin-C (markers of renal function) were associated with arterial stiffness and cardiac remodeling in patients with heart failure [Michalea, S. et al., Abst 1119-303], increased soluble Fms-like tyrosine kinase 1 was associated with worse outcomes [Kalogeropoulos, A.P. et al., Abst 1227-596] and elevated copeptin was related to an increased likelihood of noncardiac death [Xue, Y. et al., Abst 1227-590]. A novel sensitive biomarker in heart failure, YKL-40, also identified patients at higher risk for all-cause death [Harutyunyan, M. et al., Abst 1198-45; Harutyunyan, M. et al., Abst 1227-587]. On the other hand, in patients with established heart failure, pulmonary uptake of [^{123}I]-metaiodobenzylguanidine predicted adverse cardiac events [Gerson, M.C. et al., Abst 1105-268], whereas a higher heart:mediastinum ratio was associated with lower rates of serious arrhythmic events [Al Badarin, F.J. et al., Abst 1105-267], but a lower heart:mediastinum ratio correlated with increased hospitalization rates and the need for aggressive therapy for heart failure [Parker, M.W. et al., Abst 1105-266]. Furthermore, an abnormal washout rate of the tracer identified patients at increased risk for death [Nakata, T. et al., Abst 1105-272], regardless of the presence or absence of metabolic syndrome [Yamamoto, H. et al., Abst 1105-271].

CORONARY ARTERY DISEASE

Aspirin remains the basic approach for treating and preventing coronary artery disease, with a higher risk of bleeding in women compared to men, despite no differences in ischemic outcomes comparing both genders [Yu, J. et al., Abst 2536-631]. New mechanistic data for the agent indicated protection against endothelial injury by oxidized LDL particles through an effect on fibroblast growth factor 2 expression, enhancing endothelial cell survival [Chang, P.Y. et al., Abst 1181-147].

Clopidogrel is extensively used in the setting of dual antiplatelet therapy for coronary artery disease, and novel results indicated reductions in readmission rates and costs related to cardiovascular endpoints in clopidogrel-compliant compared to -noncompliant patients [Ciniglio, C. et al., Abst 1164-86], as well as reductions in microvascular obstruction after upstream therapy before catheterization in patients with ST segment-elevated myocardial infarction [de Waha, S. et al., Abst 902-8]. Moreover, clopidogrel exerted direct protective effects on endothelial cell and platelet microparticles and endothelial progenitor cell mobilization [Izar, M.C. et al., Abst 1211-612]. However, the agent is generally underused in patients with acute coronary syndrome [Zhang, Q. et al., Abst 1164-79], and although increased loading and maintenance doses improved antiplatelet responses [Fefer, P. et al., Abst 1160-630], underresponsiveness to clopidogrel is not uncommon, especially in patients with diabetes or reduced renal function, smokers, females and subjects receiving upstream treatment after an ST segment-elevated myocardial infarction [Xanthopoulou, I. et al., Abst 1160-631; Cubero, J.M. et al., Abst 1160-634; Hou, X.M. et al., Abst 1197-39], as well as during concomitant treatment with omeprazole (but not pantoprazole or famotidine) [Arbel, Y. et al., Abst 1197-44], and, if mediated by poor cytochrome P450 2C19 metabolism, is partially but not completely overcome by higher loading or maintenance doses [Rossi, J. et al., Abst 1197-40; Jeong, Y.H. et al., Abst 2501-12], although in responders, maintaining dual antiplatelet therapy with aspirin and

clopidogrel for 12 months after a primary percutaneous coronary intervention was associated with a reduced risk for subsequent ischemic events [Vlachojannis, G.J. et al., Abst 2501-6]. On the other hand, high-fat meals did not impact on the antiplatelet efficacy of clopidogrel, at least in healthy subjects [Dobesh, P.P. et al., Abst 1160-632].

Further analysis of the TRITON-TIMI 38 and additional trials confirmed the superior antiplatelet activity of prasugrel compared to clopidogrel [Beigel, R. et al., Abst 1160-626; Beigel, R. et al., Abst 1164-83; Tam, C.C. et al., Abst 1168-258], leading to reduced cardiovascular events [Scirica, B. et al., Abst 902-3], while prasugrel loading after upstream clopidogrel resulted in potent antiplatelet activity, similar to direct prasugrel administration [Koul, S. et al., Abst 1168-262], and switch to prasugrel reduced the risk of stent thrombosis in patients with high on-treatment platelet reactivity during treatment with clopidogrel [Sibbing, D. et al., Abst 2536-624]. Doses of 60 mg prasugrel also resulted in faster and greater platelet inhibition than lower doses [Tello-Montoliu, A. et al., Abst 2536-629]. Furthermore, real-world data indicated the predominant use of prasugrel in younger patients with ST segment-elevated myocardial infarction, in whom it was not associated with an increased risk of bleeding compared to clopidogrel [Damman, P. et al., Abst 2536-630]. In that context, aspirin maintains a predominant role as an antiplatelet approach to the treatment and prevention of acute coronary syndromes, although the dose of aspirin did not impact on the effectiveness or safety of concomitant prasugrel [Kohli, P. et al., Abst 902-5], in which regard, a lower dose (5 mg) of prasugrel in lean individuals reduced platelet reactivity as effectively as the standard 10-mg dose in patients with greater body weight [Erlinge, D. et al., Abst 902-4]. Also in relation to prasugrel, partial recovery of platelet function was attained within 6 hours by platelet transfusion, although full restoration of platelet function was not attained before 24 hours post-dosing [Zafar, M.U. et al., Abst 902-6].

As another alternative, cilostazol effectively reduced platelet reactivity compared to clopidogrel reloading in patients with an acute myocardial infarction already on dual antiplatelet therapy [Tanaka, A. et al., Abst 1160-625], and adding cilostazol enhanced the antiplatelet efficacy of dual therapy with aspirin and clopidogrel in patients with acute myocardial infarction simultaneously receiving omeprazole more effectively than doubling the dose of the thienopyridine [Jeong, Y.H. et al., Abst 1168-257]. Moreover, triple therapy adding cilostazol to aspirin/clopidogrel significantly lowered on-treatment platelet reactivity [Singh, A. et al., Abst 1168-263; Jeong, Y.H. et al., Abst 1209-476], with non-inferiority compared to doubling the dose of clopidogrel [Park, K.W., Abst 304-11], and magnified the protection against major adverse cardiovascular events compared to dual therapy alone, with variability depending on patient and stent characteristics [Singh, A. et al., Abst 1164-81; Suh, J.W. et al., Abst 1210-545], although no effect remained at 2 years when cilostazol was added for 6 months to dual antiplatelet therapy [Kim, H.L. et al., Abst 1197-38].

Ticagrelor exerted greater antiplatelet activity than clopidogrel, resulting in a reduced likelihood for stent thrombosis regardless of gender, baseline inflammatory biomarker levels, smoking status and clopidogrel metabolism genotype in patients with acute coronary syndromes [Cornel, J.H. et al., Abst 1162-641; Wallentin, L. et al., Abst 1164-80; Kohli, P. et al., Abst 1164-84; Storey, R.F. et al., Abst 1164-85; Husted, S. et al., Abst 1164-87]. In patients underresponding to clopidogrel, ticagrelor inhibited platelet aggregation more effectively than prasugrel [Alexopoulos, D. et al., Abst 903-7], although an indirect comparison in a systematic review and meta-analysis confirmed the superiority of both over clopidogrel, but indicated better protection against stent thrombosis and recurrent ischemic events with prasugrel [Chatterjee, S. et al., Abst 1160-627]. Ticagrelor plus aspirin arose as an optimal antiplatelet therapy regardless of genotype in a cost-effectiveness analysis focusing on patients undergoing percutaneous coronary interventions for acute coronary syndrome [Kazi, D. et al., Abst 903-5]. Furthermore, compared to clopidogrel, ticagrelor was associated with a lower risk for respiratory tract infection-related sepsis and death [Storey, R.F. et al., Abst 1160-628]. On the other hand, dyspnea induced by ticagrelor was blocked by theophylline, and hence suggested to be mediated by adenosine [Gan, L. et al., Abst 902-7], and in fact, ticagrelor was shown to induce ATP release from red blood cells through an effect on multidrug resistance protein 1 [Ohman, J. et al., Abst 1174-506].

Glycoprotein IIb/IIIa blockers are also commonly used during acute treatment in patients with acute coronary syndromes, resulting, as demonstrated in a cohort of patients with non-ST segment-elevated myocardial infarction, in reduced infarct size and improved ischemic outcomes [Rasoul, S. et al., Abst 1162-644]. Furthermore, direct intracoronary administration of abciximab modestly but significantly reduced 30-day reinfarction rates in a similar cohort of patients [Stone, G.W. et al., Abst 304-9] (Fig. 2). However, although the use of glycoprotein IIb/IIIa inhibitors during percutaneous coronary interventions did not increase the risk of bleeding upon loading with clopidogrel [Huff, C.M. et al., Abst 1168-260], glycoprotein IIb/IIIa blockers did not offer protection against stent thrombosis in patients with drug-eluting stents requiring interruption of thienopyridine therapy [Alshawabkeh, L. et al., Abst 1164-82].

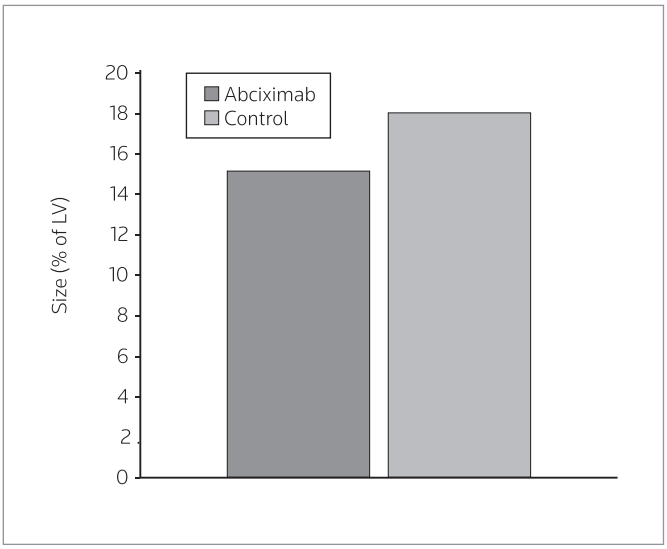

Figure 2. Thirty-day infarct size in patients treated or not with intracoronary abciximab [Stone, G.W. et al., Abst 309-4].

News was also discussed during the meeting on anticoagulants, with a particular observation indicating prolongation of activated clotting time with a single heparin 5000 U bolus prior to a percutaneous coronary intervention in most patients [Nosair, M. et al., Abst 1158-563]. Among novel anticoagulants, bivalirudin significantly improved 3-year outcomes compared to unfractionated heparin/glycoprotein IIb/IIIa inhibitors after percutaneous coronary interventions in high-risk patients [Woehrle, J. et al., Abst 2502-15]. Bivalirudin, which in the real world was noted to be increasingly used in patients with an intermediate to higher risk for bleeding [Rao, S. et al., Abst 2501-8], was also associated with lower rates of hemorrhagic and ischemic outcomes than unfractionated heparin in patients submitted to carotid artery stenting [Wayangankar, S.A. et al., Abst 2535-562] or valvular procedures [Yu, J. et al., Abst 2533-321; Kini, A.S. et al., Abst 2536-625].

A novel anticoagulant thrombin receptor blocker, vorapaxar, proved effective for inhibiting platelet aggregation in response to thrombin agonists, but not after stimulation with ADP [Jennings, L.K. et al., Abst 903-8], resulting in effective prevention of recurrent thrombosis in patients with a prior myocardial infarction [Morrow, D.A., Abst 300-15] (Fig. 3). Furthermore, as demonstrated in the placebo-controlled TRACER trial, vorapaxar reduced spontaneous, and to a lesser extent periprocedural, myocardial infarctions in patients with non-ST segment-elevated acute coronary syndromes [Leonardi, S. et al., Abst 1164-88]. An additional novel protease-activated receptor PAR1 blocker, atopaxar, decreased platelet activation while also increasing levels of interleukin-18 and lipoprotein-associated phospholipase A2 [O'Donoghue, M.L. et al., Abst 1211-614]. However, similarly acting dabigatran was associated with a trend towards an increased risk for myocardial infarction compared to warfarin in patients with atrial fibrillation, the effect seeming to be not exclusive of the drug, but a class effect [Benjo, A.M. et al., Abst 1251-66]. On the other hand, dabigatran was found to be effective and safe as a substitute for warfarin in patients with thrombophilia refractory to the standard anticoagulant [Sharifi, M. et al., Abst 1192-603].

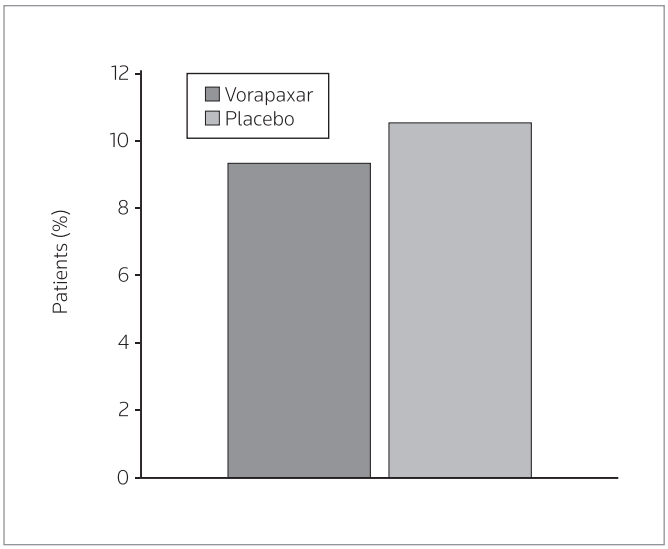

Figure 3. Cardiovascular death, myocardial infarction and/or stroke rates in patients receiving vorapaxar or placebo [Morrow, D.A. et al., Abst 300-15].

Regarding antianginal agents, intracoronary nitroprusside prior to a percutaneous intervention prevented no/slow reflow and attenuated left ventricular remodeling, resulting in improved functional recovery [Sato, T. et al., Abst 110-349; Shinozaki, N. et al., Abst 2520-63], while administration of ivabradine after a previous myocardial infarction in patients with early left ventricular systolic dysfunction improved systolic and diastolic function and decreased *N*-terminal pro-atrial-type natriuretic peptide more effectively than uptitrating prior metoprolol doses [Amosova, K. et al., Abst 1174-504]. Add-on ivabradine also improved diastolic function and exercise capacity in patients with heart failure with normal ejection fraction [De Masi de Luca, G., Abst 1222-424].

Among miscellaneous additional therapies in the setting of coronary artery disease, doxycycline after an acute ST segment-elevated myocardial infarction attenuated left ventricular remodeling and reduced infarct size and severity [Cerisano, G. et al., Abst 903-6], whereas a randomized, retrospective chart review suggested worse outcomes in patients with acute coronary syndromes receiving intravenous morphine [Agarwal, N. et al., Abst 1159-587], while randomized, controlled trials could not demonstrate benefits for intracoronary bone marrow-derived stem cells on left ventricular ejection fraction, volume or infarct size in patients with acute myocardial infarction [Woehrle, J. et al., Abst 903-3; Nasseri, B.A. et al., Abst 921-7], although two discrepant open-label observations indicated benefits for autologous mesenchymal stem cells in patients with severe coronary artery disease and refractory angina [Mathiasen, A.B. et al., Abst 923-5; Rodrigo, S. et al., Abst 1158-565], and a meta-analysis indicated improvements in cardiac function after intracoronary stem cell delivery [Singh, P.P. et al., Abst 1170-350].

Besides pharmacotherapy, supplementation with ethyl icosapentate in patients with low LDL cholesterol levels was associated with prevention of atheroma fibrous cap disruption during an acute coronary syndrome, facilitating plaque stabilization [Yamano, T. et al., Abst 1161-639]. Additional data suggested a beneficial effect of pure ω_3-polyunsaturated fatty acids in stabilizing coronary plaques independently of the effect in lowering LDL cholesterol [Shintani, Y. & Kawasaki, T., Abst 1181-152]. Moreover, eicosapentaenoic acid added to statin therapy resulted in further improvements in the endothelial function of patients with a history of old myocardial infarction [Toyama, K. et al., Abst 1189-486].

Regarding stent therapy for coronary artery disease, everolimus-, biolimus- and sirolimus-eluting stents were comparably effective [de Waha, A. et al., Abst 1204-313; Park, D.W. et al., Abst 1204-316; Chen, K.Y. et al., Abst 2520-23; Magro, M. et al., Abst 2520-29; Nakamura, S. et al., Abst 2525-376; Hougaard, M. et al., Abst 2531-315] (with better initial neointimal stent coverage with biolimus compared to everolimus stents [Kuramitsu, S. et al., Abst 2527-555], but better coverage with everolimus than sirolimus stents [Awata, M. et al., Abst 2527-531], greater suppression of neointimal formation with biolimus- compared to everolimus-eluting stents [Kitahara, H. et al., Abst 2531-402], and lower major adverse cardiovascular event rates in at least two studies with everolimus- compared to sirolimus-, paclitaxel- and zotarolimus-eluting stents [Simsek, C. et al., Abst 1209-475; Hong, S.J. et al., Abst 2531-388]) and superior to paclitax-

el- [Chen, K.Y. et al., Abst 2520-21; Li, Y.J. et al., Abst 2520-22; Chen, K.Y. et al., Abst 2520-66; de la Torre Hernandez, J. et al., Abst 2520-153; Sonoda, S. et al., Abst 2527-556; Kitano, D. et al., Abst 2527-606] and zotarolimus-eluting stents [Velders, M.A. et al., Abst 2520-117; Tada, T. et al., Abst 2527-598] (despite similar outcomes in one direct comparison each between everolimus- or sirolimus- and zotarolimus-eluting stents [Lee, J.M. et al., Abst 1169-274; Im, E. et al., Abst 1204-318]) in reducing target lesion failure, although new-generation biopolymer-based zotarolimus-eluting stents were as effective as everolimus-eluting stents [Lee, K., Abst 2520-113], and a particular observational registry did not reveal differences between everolimus- and paclitaxel-eluting stents [Woehrle, J. et al., Abst 25322-148]. However, distinct advantages in terms of vascular healing were demonstrated with a novel, rapidly biodegradable sirolimus-eluting stent compared to a durable polymer everolimus-eluting stent [Tada, T. et al., Abst 2503-9].

Concerning diagnostic issues, ioxilan was safer than iodixanol regarding contrast-induced vascular dysfunction, while also offering contrast resolution and image quality [Ahmadi, N. et al., Abst 1114-640]. In addition, biomarker studies identified a relationship between increased levels of fibroblast growth factor 23 and a higher risk of cardiovascular death and heart failure in patients with coronary artery disease, independently from clinical status and other disease markers [Udell, J.A. et al., Abst 1198-51]. Increases in osteopontin and osteoprotegerin were also documented in patients with coronary artery disease, possibly predicting multivessel disease [Maniatis, K. et al., Abst 1198-48].

ANTICOAGULATION FOR ATRIAL FIBRILLATION

While additional systemic reviews confirmed the superiority of novel anticoagulants over warfarin [Miller, C.S. et al., Abst 1235-97], and studies with individual drugs such as dabigatran confirmed their efficacy and relative safety [Eitel, C. et al., Abst 1235-96; Parikh, V. et al., Abst 1235-95], a meta-analysis of studies with the oral coagulation factor X inhibitors rivaroxaban, apixaban and darexaban confirmed the benefits in lowering ischemic cardiovascular events at the cost of increasing bleeding events, but not fatal bleeding [Singh, M. et al., Abst 1168-261], and overall pharmacoeconomic assessments indicated benefits for the novel agents (apixaban, dabigatran and rivaroxaban) as an alternative to warfarin [Deitelzweig, S. et al., Abst 1235-92], while specific cost–effectiveness analysis suggested feasibility for rivaroxaban as an alternative to dose-adjusted warfarin [Lee, S. et al., Abst 1235-93], and apixaban as an alternative to aspirin [Lee, S. et al., Abst 1235-89], at least in selected patients. Moreover, the results of EINSTEIN PE, presented as a late-breaking clinical trial, confirmed the non-inferiority versus enoxaparin/vitamin K antagonist, but a reduced likelihood for major bleeding using rivaroxaban as a treatment for pulmonary embolism [Büller, H.R. et al., Abst 305-11]. However, further pooled data pointed towards not only the superiority of apixaban and dabigatran over warfarin, but to better safety and tolerability of apixaban [Roversi, S. et al., Abst 1235-91], and in fact, adding apixaban to aspirin in the AVERROES trial did not significantly increase the risk of bleeding, except for superficial bleeding and hematomas at puncture site, and no subgroup of patients at risk or not benefiting from apixaban was identified [Flaker, G.C. et al., Abst 904-9]. In fact, details from the ARISTOTLE trial indicated benefits for apixaban compared to warfarin regardless of background aspirin therapy [Alexander, J.H. et al., Abst 1192-600]. However, in experimental animals, the bleeding effect of apixaban was not counteracted by recombinant activated coagulation factor VII, prothrombin complex concentrate and fibrinogen concentrate [Martin, A.C. et al., Abst 904-8].

However, warfarin remains an effective option for the control of thromboembolic risk in patients with atrial fibrillation [Agarwal, S. et al., Abst 1256-286], and a study comparing enoxaparin bridging to non-bridged warfarin interruption demonstrated no differences in periprocedural thrombotic complication rates, but a higher incidence of bleeding during bridged procedures [Wilson, W.W. et al., Abst 1235-98].

In addition to anticoagulants, antiarrhythmics are required in patients with atrial fibrillation, in which regard dronedarone appeared to be less effective than amiodarone and propafenone in terms of success rates after electrical cardioversion [Ajmal, M.S. et al., Abst 1238-264]. Furthermore, retrospective data indicated no association between amiodarone and mortality in patients with atrial fibrillation and renal impairment requiring hemodialysis [Turakhia, M. et al., Abst 1238-258]. On that subject, dofetilide was reported to be effective not only against persistent atrial fibrillation, but also as off-label treatment for paroxysmal atrial fibrillation [Brumberg, G.E. et al., Abst 1238-259]. Improved outcomes after catheter ablation for atrial fibrillation were reported using eplerenone [Ito, Y. et al., Abst 1238-260]. No efficacy, but rather the opposite, was reported using digoxin in patients with atrial fibrillation, as the drug was independently associated with an increased risk of death, especially in patients on maintenance hemodialysis [Turakhia, M. et al., Abst 1238-261].

CARDIOVASCULAR RISK FACTORS

Combination therapies have become standard for controlling hypertension, with two and three drugs offering an increased likelihood of blood pressure control and additional improvements in risk factors at a lower risk for adverse events. As an example, besides lowering blood pressure, the combination of losartan, which in patients with heart failure improved renal function [Kiernan, M. et al., Abst 1228-631], and hydrochlorothiazide improved left ventricular relaxation in patients with coronary artery disease, suggesting a reduced risk for progression to heart failure [Oe, H. et al., Abst 1180-112]. In addition, adding valsartan to amlodipine/hydrochlorothiazide induced left ventricular mass reduction significantly more than the addition of ramipril to the calcium channel blocker/thiazide combination, independently of the effect of the two drugs on blood pressure [Fogari, R. et al., Abst 1179-61] (Fig. 4). While an alternative angiotensin receptor blocker, candesartan, prevented age-related left ventricular remodeling and dysfunction and kidney remodeling and fibrosis in experimental animals [Jugdutt, B.I. et al., Abst 1231-554], preclinical data with another angiotensin receptor blocker, the novel compound fimasartan, indicated sympathetic-mediated cardioprotective activity comparable to other renin–angiotensin system blockers [Sim, D.S. et al., Abst 1176-576]. Also at the preclinical level, the addition of LBQ-657, the active metabolite of the neprolysin inhibitor AHU-377, to valsartan resulted in enhanced antifibrotic and antihypertrophic effects, suggesting benefits yet to be tested in the clinical setting [Wang, B.H. et al., Abst 1219-276].

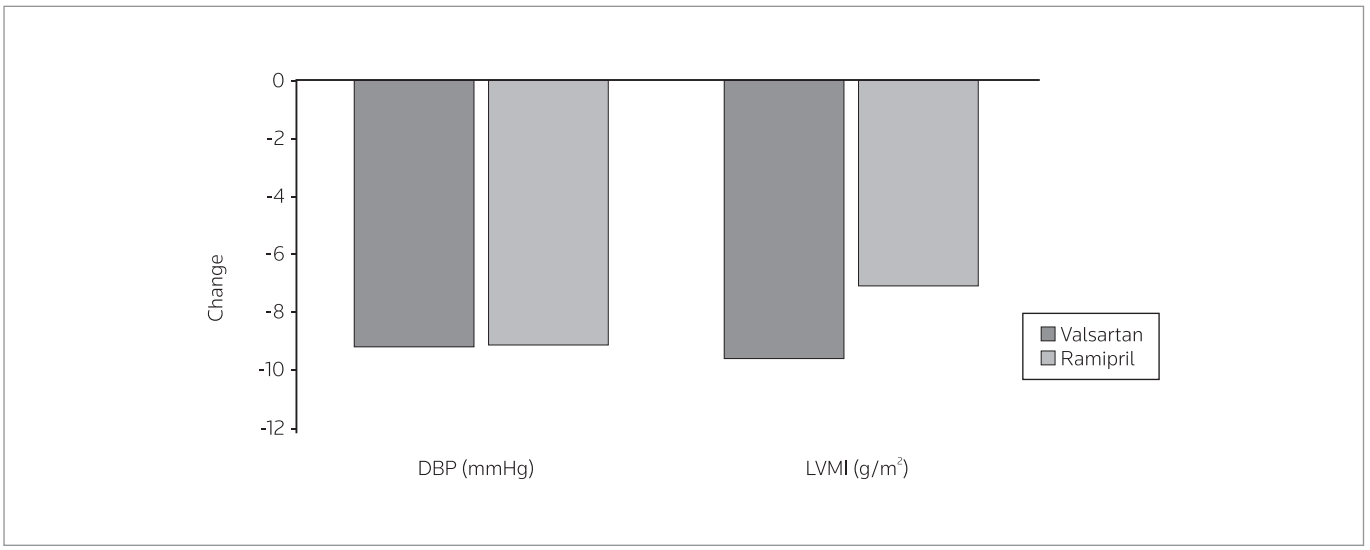

Figure 4. Change in diastolic blood pressure (DBP) and left ventricular mass index (LVMI) after 12 months of adding valsartan or ramipril to amlodipine/hydrochlorothiazide [Fogari, R. et al., Abst 1179-61].

Even after short-term therapy, atorvastatin was able to improve endothelial function, reduce arterial stiffness and increase endothelial progenitor cell counts in patients with coronary artery disease [Oikonomou, E. et al., Abst 1121-220], resulting in improved neointimal coverage and endothelial function after sirolimus-eluting stent implantation [Wang, T. et al., Abst 1196-209]. In mesenchymal stem cells, the protection against hypoxic injuries and apoptosis brought about by atorvastatin was related to activation of autophagy [Zhang, Q. et al., Abst 1173-449]. At high doses of 80 mg, atorvastatin markedly improved arterial stiffness and endothelial function in patients with heart failure, through an effect on inflammatory pathways [Oikonomou, E. et al., Abst 1124-52]. Using rosuvastatin, while data from SATURN indicated enhanced regression of coronary atheroma volume compared to atorvastatin [Nichols, S.J. et al., Abst 1202-229], analysis of patients attaining LDL cholesterol levels < 30 mg/dL in the JUPITER trial did not reveal safety or tolerability concerns [Everett, B. et al., Abst 911-4]. Furthermore, rosuvastatin exhibited a favorable drug–drug interaction with clopidogrel, resulting in increased vascular protection by the latter [Izar, M.C. et al., Abst 1211-608]. Turning to pitavastatin, while the agent reduced LDL cholesterol levels more effectively than pravastatin, without affecting glucose metabolism [Kryzhanovski, V. et al., Abst 1190-536], a study in patients with or without diabetes suffering from an acute myocardial infarction demonstrated similar outcomes, regardless of the presence of diabetes, despite the worse disease and procedural characteristics of these patients. However, rates of target vessel revascularization and major adverse cardiovascular events remained higher in diabetic patients [Rha, S.W. et al., Abst 1159-589]. Furthermore, in patients with metabolic syndrome, the lipid benefits of pitavastatin were not associated with untoward effects on fasting plasma glucose, which increased after treatment with simvastatin [Kryzhanovski, V. et al., Abst 1184-288] (Fig. 5). In addition, in vivo preclinical studies suggested an effect in preventing the progression of heart failure in models of myocardial hypertrophy [Kameda, Y. et al., Abst 1231-555], while in vitro studies showed enhanced survival of isolated mesenchymal stem cells through an effect on heme oxygenase 1 and endothelial nitric oxide synthase [Tsubokawa, T. et al., Abst 1228-630].

Regarding fibrates, although fenofibrate and ω_3-polyunsaturated fatty acid supplementation resulted in similar decreases in triglyceride levels and improvements in endothelium-dependent vasodilation, fenofibrate offered greater benefits on HDL and non-HDL cholesterol, insulin and adiponectin levels [Koh, K.K. et al., Abst 1190-538].

While a meta-analysis confirmed the benefit of niacin for reducing the risk of coronary artery disease in patients at risk [Lavigne, P.M. et al., Abst 1190-531], a new clinical study was reported this year on the use of niacin combined with ezetimibe/simvastatin, resulting in incremental benefits on HDL and LDL cholesterol levels [Le, A. et al., Abst 1190-535]. Furthermore, ezetimibe exerted direct antiplatelet effects and modulated the expression of proatherosclerosis mediators in the endothelium [Stach, K. et al., Abst 1191-555], decreased paraoxonase and aryltransferase activity, indicating atheroprotective activity, while niacin exerted no activity in these tests [Tang, W.H. et al., Abst 1202-224] and magnified the LDL cholesterol reduction brought about by concomitant statins [Okada, K. et al., Abst 1211-611].

As an alternative or complementary approach to the treatment of dyslipidemia, aleglitazar reduced the triglyceride:HDL cholesterol ratio compared to placebo and more effectively than pioglitazone in the phase II SYNCHRONY trial, suggesting delayed progression of atherosclerosis in this population of patients with type 2 diabetes [Nicholls, S.J. et al., Abst 1184-290] (Fig. 6). Moreover, aleglitazar did

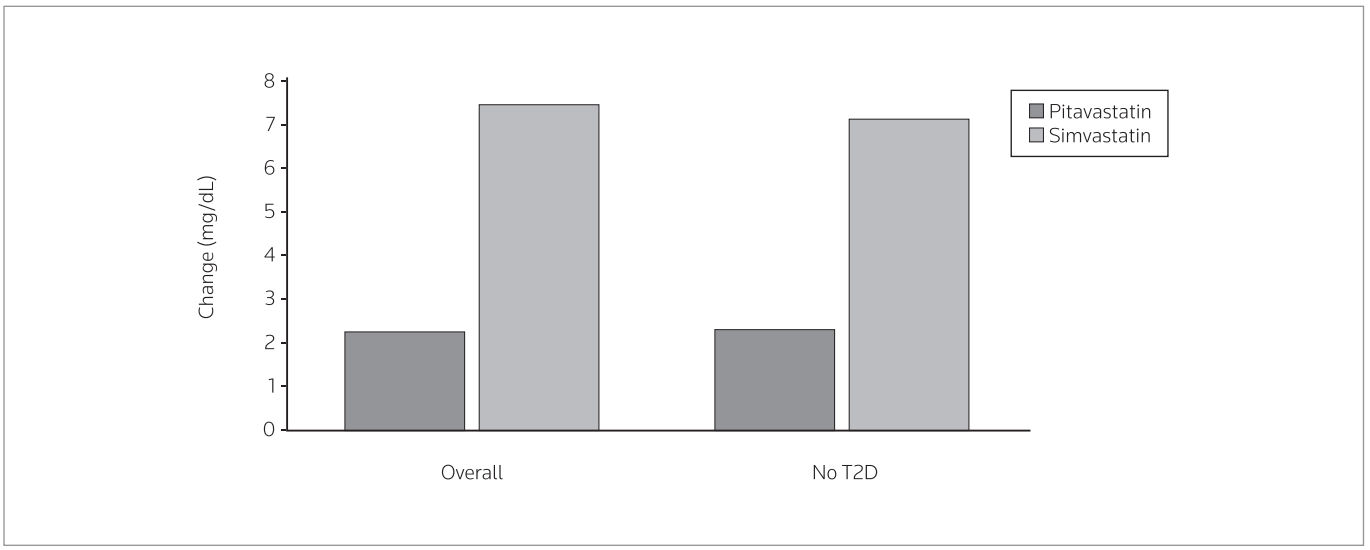

Figure 5. Change in fasting plasma glucose levels after 56 weeks of treatment with pitavastatin or simvastatin. Data plotted for the overall population and patients without type 2 diabetes (T2D) [Kryzhanovski, V. et al., Abst 1184-288].

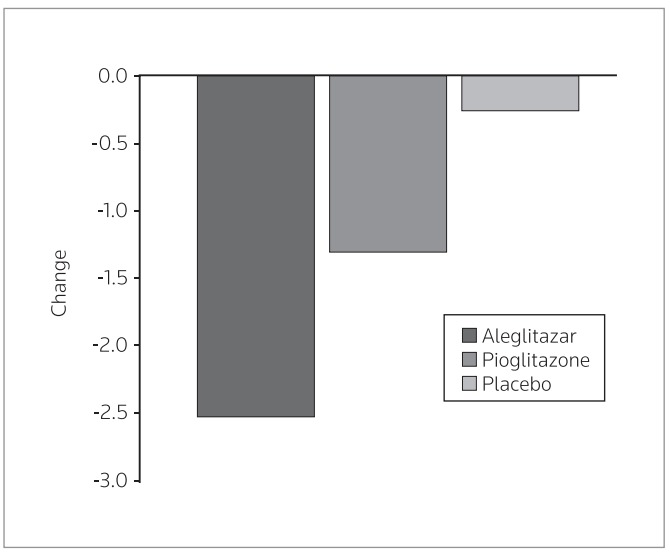

Figure 6. Change in the triglyceride:HDL cholesterol ratio after 16 weeks of treatment with aleglitazar 150 µg, pioglitazone 45 mg or placebo [Nichols, S.J. et al., Abst 1184-290].

not worsen renal function in patients on low-dose aspirin and did not impair the antiplatelet effect of aspirin [Pellanda, C. et al., Abst 1192-606].

Another lipid-lowering alternative, anacetrapib alone or combined with atorvastatin, brought about significant decreases in LDL and increases in HDL cholesterol levels with good tolerability in patients with dyslipidemia [Teramoto, T. et al., Abst 1190-533] (Fig. 7).

Also regarding dyslipidemia, REGN-727 dose-dependently reduced LDL cholesterol and other lipid markers when added to ongoing statin therapy [McKenney, J.M. et al., Abst 306-10], while a study in hypercholesterolemic subjects demonstrated greater LDL cholesterol-lowering activity upon adding REGN-727 to atorvastatin 10 mg compared to atorvastatin 80 mg in patients not successfully controlled with low-dose atorvastatin, and an even greater decrease with REGN-727 combined with atorvastatin 80 mg [Roth, E.M. et al., Abst 911-5] (Fig. 8). Another anti-proprotein convertase subtilisin/kexin type 9 monoclonal antibody, AMG-145, also proved to be well tolerated compared to placebo in patients on stable statin therapy, and resulted in marked reductions in LDL cholesterol levels [Dias, C. et al., Abst 923-4].

As a novelty in the area of lipid-lowering therapies, the small-molecule metabolic regulator ETC-1002 dose-dependently improved LDL cholesterol levels and other atherogenic lipid levels in dyslipidemic patients, regardless of the presence of hypertriglyceridemia [Ballantyne, C. et al., Abst 911-10] (Fig. 9). Focusing on apolipoprotein(a), the antisense apolipoprotein B-100 synthesis inhibitor mipomersen exhibited effective lowering activity in patients with familial or severe hypercholesterolemia and high cardiovascular risk [Tsimikas, S. et al., Abst 1202-221].

As a last topic regarding drug therapy for dyslipidemia, a first-in-man study with a novel antisense oligonucleotide inhibiting apolipoprotein C3 synthesis in the liver demonstrated potent, dose-dependent reductions in apolipoprotein C3 and triglyceride levels in healthy volunteers, with a favorable safety and tolerability profile [Alexander, V. et al., Abst 1190-529]. In addition, preclinical studies indicated enhanced cholesterol efflux from cells and activation of reverse transport and esterification with CSL-112, an apolipoprotein A1 concentrate [Easton, R. et al., Abst 1161-636; Easton, R. et al., Abst 1161-637; Easton, R. et al., Abst 1161-638].

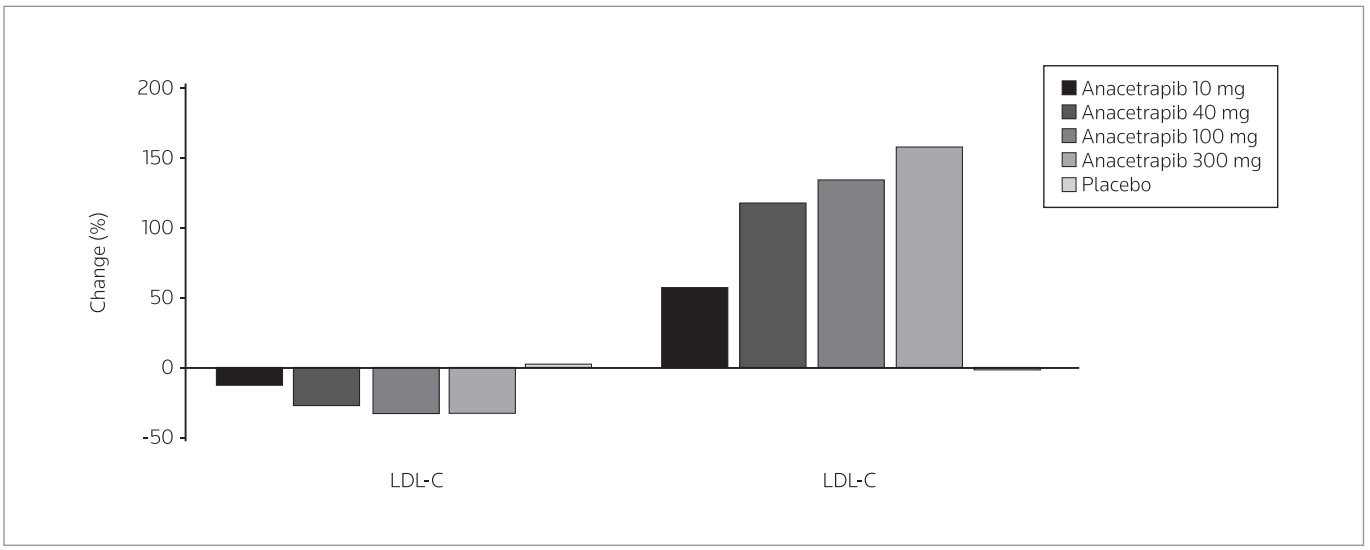

Figure 7. Changes in LDL (LDL-C) and HDL cholesterol (HDL-C) levels after 8 weeks of treatment with anacetrapib or placebo [Teramoto, T. et al., Abst 1190-533].

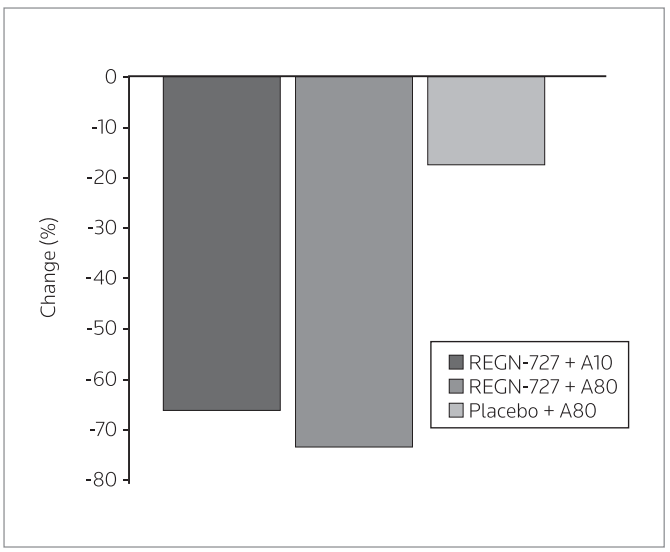

Figure 8. Percent change in LDL cholesterol levels after 8 weeks of treatment with REGN-727 combined with atorvastatin 10 or 80 mg or placebo combined with atorvastatin 80 mg [Roth, E.M. et al., Abst 911-5].

With direct benefits on inflammation, but no effect on the risk of periprocedural myocardial injury during percutaneous interventions in diabetic individuals [Poerner, T.C. et al., Abst 1209-478], the addition of pioglitazone to dual antiplatelet therapy with aspirin and clopidogrel did not impact on platelet inhibition through $P2Y_{12}$ signaling pathways [Suryadevara, S. et al., Abst 2536-595]. Also in relation with antidiabetic therapies, phase I clinical trial data indicated safe use of exenatide in patients undergoing percutaneous coronary interventions for acute myocardial infarction, resulting in a trend towards increased myocardial salvage [Bernink, F. et al., Abst 2536-594]; the infarct size-limiting effect of exenatide and the dipeptidyl peptidase 4 inhibitor MK-0626 was amplified by concomitant cilostazol, at least in experimental animal models [Birnbaum, Y. et al., Abst 1172-432; Birnbaum, Y. et al., Abst 1177-583]. A related agent, liraglutide, exhibited antioxidant and antiinflammatory activity in endothelial cells, also suggesting benefits on the cardiovascular risk profile [Shiraki, A. et al., Abst 1219-277]. Another antidiabetic agent, sitagliptin, demonstrated improved regional myocardial contractility and overall myocardial performance in diabetic patients with coronary artery disease, especially in ischemic myocardial areas [McCormick, L.A. et al., Abst 923-7; McCormick, L.M. et al., Abst 1209-473], whereas a direct comparison between vildagliptin and repaglinide indicated maintained ischemic preconditioning with the former, compared to a loss of preconditioning with repaglinide [Rahmi Garcia, R.M. et al., Abst 1202-228], and mechanistic observations with an additional agent, saxagliptin, indicated blood pressure-lowering activity in hypertensive conditions through increased endothelial nitric oxide synthase coupling and nitric oxide availability [Mason, R.P. et al., Abst 1211-613].

Turning to smoking, a study confirming the high efficacy of varenicline combined with a brief smoking cessation program [Clavario, P. et al., Abst 1185-324] offered hopes for improved control of this highly relevant cardiovascular risk factor.

PERIPHERAL ARTERIAL DISEASE

While preclinical data indicated benefits for granulocyte colony-stimulating factor, but not sildenafil, in models of limb ischemia, although both improved blood flow in the nonischemic limb [Valatsou, A. et al., Abst 1196-231], MultiGeneAngio (an autologous, transduced cell-based gene therapy) proved safe and well tolerated

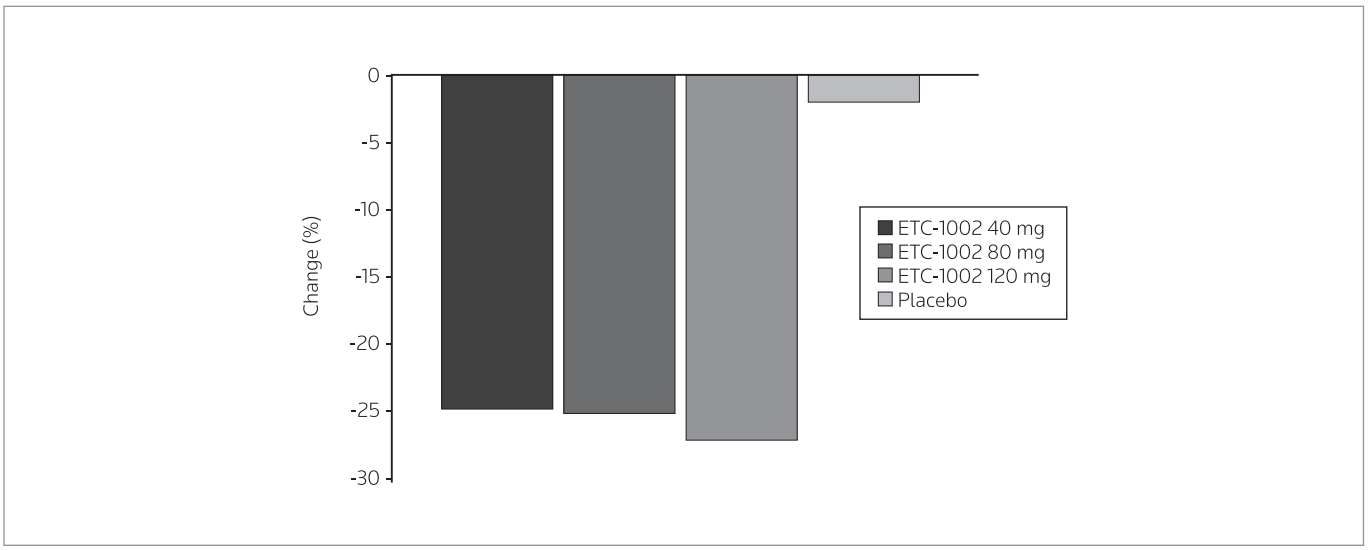

Figure 9. Percent change in LDL cholesterol levels after 12 weeks of treatment with ETC-1002 or placebo [Ballantyne, C. et al., Abst 911-10].

in a phase I trial in patients with claudicating lower limb peripheral arterial disease [Grossman, P.M. et al., Abst 1121-211].

VALVULAR HEART DISEASE

A number of clinical observations on the subject of medical therapies for valvular heart disease indicated improvements in pulmonary and systemic hemodynamics and ventricular function, with good safety and tolerability, in patients with severe aortic stenosis treated with sildenafil [Lindman, B. et al., Abst 1152-339], as well as the feasibility of enoxaparin bridging in patients with mechanical valve prostheses on chronic warfarin undergoing invasive procedures, although with an increased risk of minor periprocedural bleeding [Wilson, W.W. et al., Abst 1152-333]. Another clinical study concluded that, by decreasing heart rate, ivabradine improved exercise tolerance and hemodynamics as effectively as metoprolol in patients with moderate mitral stenosis [Saran, R.K. et al., Abst 1150-252].

MISCELLANEOUS

Imidapril prevented calcium chloride-induced experimental abdominal aortic aneurysm more effectively than losartan and hydralazine, despite similar effects for the three treatments on blood pressure [Miyoshi, T. et al., Abst 1117-131].

A meta-analysis of five randomized, controlled trials confirmed the reduction in the risk for recurrent pericarditis and post-cardiotomy syndrome brought about by colchicine [Alam, M. et al., Abst 925-6].

Mechanistic data suggested an effect for the ρ/ρ kinase pathway inhibitor fasudil in protecting the endothelium against hyperglycemia by reducing monocyte adhesion to endothelial cells [Li, H. et al., Abst 1195-120].

B-cell depletion with rituximab in patients with rheumatoid arthritis resulted in improved endothelial function and reduced inflammation [Hsue, P. et al., Abst 1211-610]. Vascular benefits were also demonstrated with canakinumab, which reduced C-reactive protein, interleukin-6 and fibrinogen levels, without affecting LDL or HDL cholesterol, suggesting benefits on atherosclerosis-related inflammation [Ridker, P.M. et al., Abst 1211-609].

DISCLOSURES

The author states no conflicts of interest.