Drugs of the Future 2010, 35(7): 593-604

CCC: 0377-8282/2010
DOI: 10.1358/dof.2010.35.7.1524797

MEETING REPORT

A REPORT FROM THE 59TH ANNUAL SCIENTIFIC SESSION OF THE AMERICAN COLLEGE OF CARDIOLOGY

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SUMMARY

This meeting report summarizes the most important data presented at the 59th Annual Scientific Session of the American College of Cardiology (ACC.10 & I2 Summit), which was held at the Georgia World Congress Center in Atlanta, Georgia, USA, on March 14-16, 2010. Besides focusing on themes such as heart failure, coronary artery disease, valvular heart disease, cardiac arrhythmia, cardiovascular risk factors and lifestyle, several ways to prevent cardiovascular disease were discussed, including whether or not use of the Metropolitan Atlanta Rapid Transit Authority (MARTA) buses is advisable.

PREVENTION OF CARDIOVASCULAR DISEASE

Making greater use of public transportation rather than traveling by private vehicle is crucial if we want to save our planet. Thinking heartwise, however, walking is even better, and for moving between the Georgia World Congress Center –site of this year's American College of Cardiology (ACC) meeting– and the many hotels in down- and midtown Atlanta, walking may be preferred over using the Metropolitan Atlanta Rapid Transit Authority (MARTA) buses and trains, or even the designated congress shuttle service. Obviously, this is not to say that public transportation is not a priority, but walking is one of the most cost-effective options for preventing cardiovascular diseases, metabolic syndrome and diabetes, and spending 30-45 min to walk to work, shopping malls or entertainment areas is time well invested. The same could be said for walking to restaurants and eating places, especially if eating outside the home (at least in the case of children who eat at school rather than at home) results in poor dietary habits and higher LDL cholesterol levels (Smith, C.A. et al., Abst 1001-20).

Prevention of cardiovascular disease can also be achieved with pharmacological tools, and everybody is aware of the benefits of aspirin. A novel meta-analysis presented this year during ACC.10, however, revealed that low-dose aspirin modestly reduces nonfatal coronary events, but also moderately increases the risk of bleeding, not offering strong support for its use in preventing heart disease in men or stroke in women, as currently indicated by guidelines (Das, J.R. et al., Abst 1002-30). However, if preventing cardiovascular diseases is of increasing importance, so is treating established cardiac and vascular diseases, and important new information in this regard was discussed during the meeting. Although, as demonstrated in the DIANA study in Japan, lifestyle intervention may be as effective as pharmacological therapies for preventing adverse cardiovascular events in patients with early-stage diabetes and established coronary artery disease (Kataoka, Y. et al., Abst 1129-101), pharmacological therapies continue to be the major asset for saving lives and preventing cardiovascular mortality, and important news was also discussed to that end during this year's meeting in Atlanta, as summarized below.

HEART FAILURE

β-Adrenoceptor blockers are a major asset in the treatment of heart failure, with additional benefits, at least considering nonselective agents, in reducing thrombotic events (De Peuter, O.R. et al., Abst 1123-58). According to additional observations, many patients show a progressive decline in the left ventricular ejection fraction after 1 year of treatment with these agents (Hourani, P. et al., Abst 1235-74), while others achieve no beneficial effects on myocardial glucose uptake, despite showing improvements in ejection fraction (Bozkut, B. et al., Abst 1235-75). Carvedilol is among the most extensively studied β-adrenoceptor blockers for the treatment of heart failure,

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with new studies revealing better responses in patients with higher neurohormonal activation (Spoladore, R. et al., Abst 1235-73), while a comparative study suggested similar improvements in intra- and interventricular synchronization and left ventricular remodeling as those achieved with metoprolol (Kaya, M. et al., Abst 1235-69) (Fig. 1). Carvedilol also prevented the proarrhythmogenic profile during atrial tachycardia remodeling in experiments in animals (Motoda, H. et al., Abst 1246-153). Also, regarding new findings on β-adrenoceptor blockers, nebivolol was shown to prevent chemotherapy-induced cardiomyopathy in patients with breast cancer (Kaya, M. et al., Abst 1235-76).

Diuretics are also widely used in the management of heart failure, and new studies were discussed this year on the mortality benefit of a combination of hydralazine hydrochloride and isosorbide dinitrate in black and non-black patients with diastolic heart failure (Mazurek, J.A. et al., Abst 1123-57) (Fig. 2). However, the DOSE trial could not demonstrate a benefit for intensified and/or continuous dosing with furosemide compared to lower-dose therapy regarding cardiac or renal function in patients with chronic heart failure (Felker, G.M., Abst 3019-8). Aldosterone antagonism is another option in the treatment of heart failure, with newly demonstrated benefits for spironolactone on systolic myocardial motion recruitment after exertion (Wang, Y.C. et al., Abst 1236-84).

Novel agents under development for the treatment of heart failure include the soluble guanylate cyclase activator cinaciguat, which demonstrated potential for rapidly improving pulmonary capillary wedge pressure, pulmonary vascular resistance and cardiac output in a placebo-controlled trial in patients with acute decompensated heart failure, without negatively affecting cardiac or renal function, although hypotension developed in a minority of the participants (Erdman, E. et al., Abst 0910-04). Another placebo-controlled study demonstrated that rolofylline had no impact on worsening renal function in subjects with acute heart failure, volume overload and renal dysfunction (Voors, A.A. et al., Abst 1179-65). Furthermore, a retrospective observational study concluded that patients with heart failure and chronic kidney disease showed an increased risk of mor-

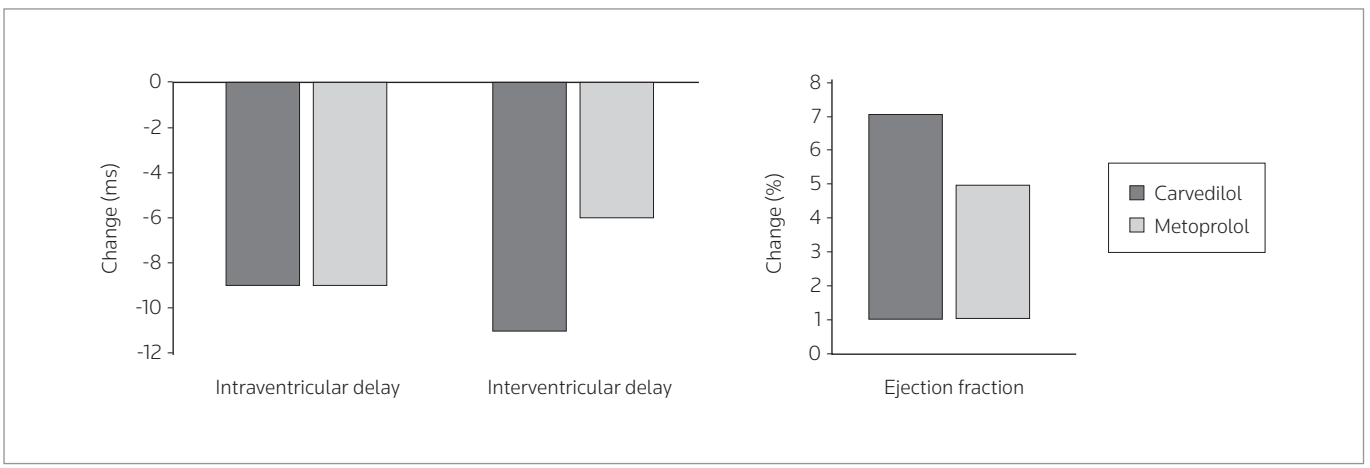

Figure 1. Change in intra- and interventricular delay and left ventricular ejection fraction after 6 months of treatment with carvedilol or metoprolol (Kaya, M. et al., Abst 1235-69).

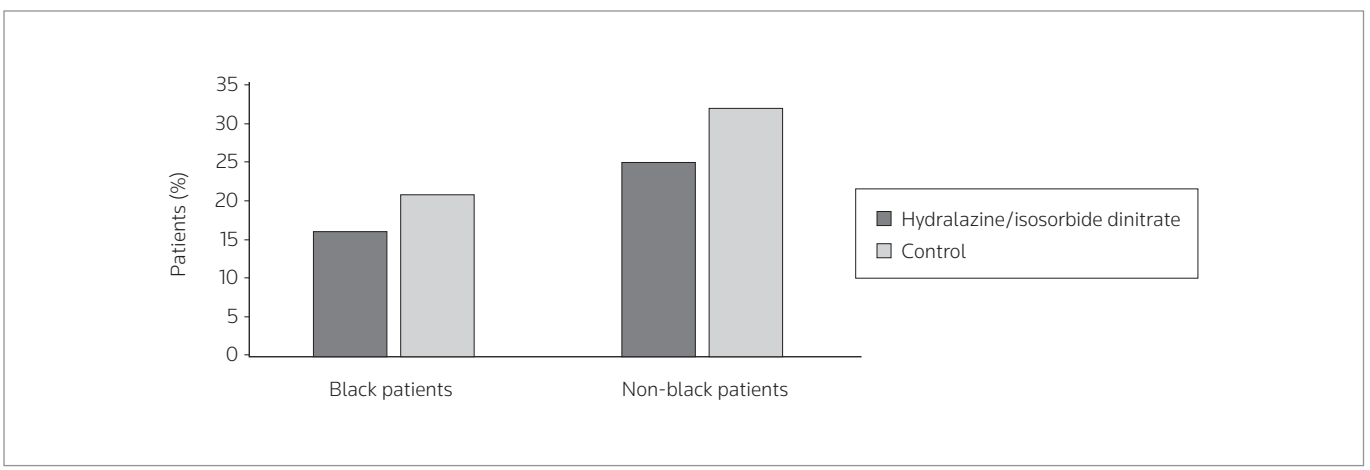

Figure 2. The 1-year death rates in black and non-black patients receiving hydralazine/isosorbide dinitrate, or not (Mazurek, J.A. et al., Abst 1123-57).

tality upon treatment with epoetin (Jackevicius, C. et al., Abst 1179-64).

In the experimental setting, cardioprotective activity was attributed to the selective β_3-adrenoceptor agonist BRL-37344, which reduced overload-induced ventricular hypertrophy and recovered left ventricular function in animal models (Niu, X. et al., Abst 1003-549), and to the adenosine-regulating agent GP-531, which improved left ventricular diastolic function in models of chronic heart failure (Sabbah, H.N. et al., Abst 1236-79). Also in the preclinical arena, fasudil hydrochloride demonstrated antifibrotic activity in animal models of diabetes (Ameenuddin, S. et al., Abst 1016-84), while rosuvastatin decreased hypertrophic and proinflammatory protein levels in the left ventricle of animals with moderate heart failure (Mishra, S. et al., Abst 1016-81). Treatment with hydrogen sulfide attenuated ischemic heart failure through an effect on signaling involving the nuclear respiratory factors NRF-1 and NRF-2 (Calvert, J.W. et al., Abst 1014-61), whereas the black bean extract BBTMH-007 inhibited cardiac fibrosis and preserved cardiac function in models of cardiomyopathy (Torre-Amione, G. et al., Abst 1013-53). Functional improvements in animal models of heart failure were also obtained with i.v. poloxamer-188 (Ilsar, I. et al., Abst 0910-03) and a sustained-acting atrial natriuretic peptide$_{1\text{-}28}$ product, which offered concomitant benefits on left ventricular function, blood pressure and renal function (McKie, P.M. et al., Abst 1072-90). In the in vitro laboratory, coexposure to hydralazine and nitroglycerin reduced calcium leaks in cardiomyocytes lacking nitric oxide synthase (Dulce, R.A. et al., Abst 1070-69).

Cardiac transplantation is the last resort for patients with failing hearts, and may require additional pharmacological therapy, notably with immunosuppressants to prevent rejection. In this context, desensitization with rituximab combined with intravenous immunoglobulin facilitated transplantation in highly sensitized transplant candidates with high levels of HLA antibodies (Czer, L.S.C. et al., Abst 1012-50). Also, conversion from calcineurin inhibitor- to everolimus-based immunosuppression had no significant impact on the development of chronic allograft vasculopathy, but significantly attenuated the progression of established chronic allograft vasculopathy in heart transplant recipients also receiving azathioprine (Arora, S. et al., Abst 1012-48). In addition, a further study confirmed the safety and efficacy of regadenoson for stress myocardial perfusion imaging in patients with renal failure and orthotopic heart transplant recipients (Cavalcante, J.L. et al., Abst 1012-51; Ananthasubramanian, K. et al., Abst 1206-245). Also, a study in pediatric heart transplant recipients suggested functional benefits for sildenafil, which improved right ventricular dysfunction and pulmonary vascular resistance even after weaning from i.v. and inhaled vasodilators (Singh, R. et al., Abst 1281-405).

CORONARY ARTERY DISEASE

Dual antiplatelet therapy with aspirin and clopidogrel remains the cornerstone maintenance treatment for patients with or with a history of coronary artery disease, although with an acceptable risk of bleeding (greater in patients with lower baseline hemoglobin levels [Rossini, R. et al., Abst 2502-533] and possibly unacceptable in patients requiring coronary artery bypass graft surgery [Miceli, A. et al., Abst 0924-06], and significant in the case of upper gastrointestinal bleeding in patients at risk requiring proton pump inhibitor therapy [Garcia Rodriguez, L.A. et al., Abst 1192-154]). Noncompliance with, discontinuation of or underresponse to clopidogrel was associated with an increased risk for stent thrombosis and adverse outcomes after drug-eluting stent implantation (Cox, D.A. et al., Abst 2501-523; Hawkins, B.M. et al., Abst 1107-320; Petr, R. et al., Abst 0919-06; Palacio, A. et al., Abst 1141-181). Dual therapy was confirmed to be superior to antiplatelet therapy with aspirin alone in preventing adverse outcomes in high-risk patients with cardiovascular disease (Kamireddy, S. et al., Abst 1107-319), and preexposure to clopidogrel before coronary artery bypass graft surgery had no negative impact on reoperation for bleeding or mortality, although it increased the need for packed red blood cell transfusion (Bhuriya, R. et al., Abst 2501-419), whereas postprocedural low- and high-dose aspirin showed no difference in the risk of stent thrombosis, death or myocardial infarction (Harjai, K.J. et al., Abst 2504-456). However, resistance to aspirin and clopidogrel, resulting in an increased risk for cardiovascular events, has been reported (Kim, C.H. et al., Abst 1073-92; Sung, J.K. et al., Abst 2504-439; Beigel, R.S. et al., Abst 1100-280), especially in the case of aspirin, upon concomitant treatment with proton pump inhibitors (Würtz, M. et al., Abst 0908-05), and, in the case of clopidogrel, with concomitant administration of cytochrome P-450 CYP3A4-metabolized statins (Jeong, Y.H. et al., Abst 1073-95) and in carriers of the CYP2C19*2 allele (So, D.Y.K. et al., Abst 2504-453). Concomitant proton pump inhibitor therapy with clopidogrel attenuated its pharmacodynamic effects without affecting clinical efficacy (Oshima, S. et al., Abst 1021-110; Shimomura, H. et al., Abst 1074-99; Harjai, K.J. et al., Abst 2903-07; Hakeem, A. et al., Abst 1139-167); in the case of worsened outcomes, this was because patients receiving concomitant proton pump inhibitors had more severe comorbidities, rather than being due to a negative interaction with clopidogrel (Siller-Matula, J.M. et al., Abst 2504-437). On the contrary, hyporesponsiveness to clopidogrel was improved by cotreatment with St. John's wort in healthy volunteers (Lau, W.C. et al., Abst 1221-352). Furthermore, new results reported this year indicated that increasing the dose of clopidogrel to 150 mg/day did not overcome resistance related to CYP2C19 polymorphisms (Jeong, Y.H. et al., Abst 1022-117), although the use of a higher 600-mg loading dose of clopidogrel improved pre- and postprocedural patency and shortened the need for anticoagulation and hospital stay as compared to the standard 300-mg loading dose, without increasing the risk of serious bleeding complications in patients undergoing percutaneous coronary interventions (Sim, D.S. et al., Abst 2504-435). This finding was not corroborated in all studies: according to at least one randomized trial, the high dose was not associated with a reduced risk for major adverse cardiovascular events (Kwon, O.S. et al., Abst 1154-272), whereas an additional study in patients with S-T segment elevation myocardial infarction (STEMI) suggested impaired responses to clopidogrel and suboptimal platelet inhibition after prehospital upfront therapy with the thienopyridine, resulting in higher cardiovascular event rates (Schäfer, A. et al., Abst 0406-5). New studies indicated that high-dose clopidogrel was safe and feasible when administered less than 2 h before the procedure (Feldman, D.N. et al., Abst 2504-426), and that reloading in patients on chronic clopidogrel was safe but devoid of effect on in-hospital and 1-year events after percutaneous coronary interventions for acute coronary syndrome (Syed, A.I. et al., Abst 2504-438). In addition, low-dose aspirin has been associated with a prevalence of dyspeptic complaints of approximately 26%,

despite the use of buffered formulations (Focks, J.J. et al., Abst 0908-04), although this untoward effect was effectively attenuated or prevented by esomeprazole cotherapy (Scheiman, J. et al., Abst 1131-113). Observations in a large cohort of 1,286 patients with significant coronary artery disease on treatment with low-dose aspirin identified such treatment as an independent risk factor for coronary artery spasm, without translating into an increased risk of death or myocardial infarction (Park, J.Y. et al., Abst 0908-07), although the use of aspirin as secondary cardiovascular prevention offered overall benefits overweighing any possible risks (Das, J.R. et al., Abst 1195-173). Regarding clopidogrel, an increase in the risk of minor bleeding upon concomitant enoxaparin was demonstrated, with increased anticoagulant activity for the low-molecular-weight heparin (Yang, S.C. et al., Abst 1073-93), whereas low-dose aspirin was described as feasible for improving outcomes in patients with coronary spastic angina (Takano, H. et al., Abst 1217-320). Besides aspirin and clopidogrel, the range of available antiplatelet therapies that can be used to treat acute coronary syndromes also includes glycoprotein IIb/IIIa (gpIIb/IIIa) blockers, in which regard early use of eptifibatide with upfront clopidogrel was demonstrated to reduce ischemic risk during angiography without an unacceptable risk of bleeding in the EARLY ACS trial (Wang, T. et al., Abst 0908-06) (dose-adjusted eptifibatide remains safe in patients with reduced renal function, although it seems to be frequently overdosed, resulting in excess bleeding [Melloni, C. et al., Abst 1046-285]). According to a meta-analysis, high-dose tirofiban and abciximab were effective without increasing bleeding risk in patients undergoing primary percutaneous coronary intervention for STEMI (Dong, L. et al., Abst 2504-455), both agents being equieffective regarding 1-year cardiovascular outcomes in the MULTISTRATEGY study (Valgimigli, M. et al., Abst 1100-277) (Fig. 3). However, an overall analysis could not demonstrate improved short-term clinical outcomes upon the addition of gpIIb/IIIa blockers to clopidogrel before percutaneous coronary interventions (Sim, D.S. et al., Abst 2504-429), but upstream therapy improved initial epicardial patency without increasing the risk of bleeding (Dong, L. et al., Abst 1047-290). Other alternatives include ticagrelor, which was associated with much reduced rates of high platelet reactivity compared to clopidogrel in patients with stable coronary artery disease (Gurbel, P.A. et al., Abst 1073-94), and lower cardiovascular mortality, also compared to clopidogrel, in patients undergoing coronary artery bypass graft surgery (Held, C. et al., Abst 1264-266; Held, C. et al., Abst 3020-11) (Fig. 4); compared to the standard thienopyridine, it had no detrimental effects on pulmonary function (Storey, R.F. et al., Abst 1100-276), although it was associated with a greater likelihood for predominantly asymptomatic ventricular pauses (Scirica, B.M. et al., Abst 1100-274). Another alternative is cilostazol, which significantly reduced late loss and restenosis after coronary stent implantation (Ueda, H. et al., Abst 2502-490), and in a direct comparison achieved greater platelet aggregation than high-dose clopidogrel in clopidogrel-underresponding diabetic patients (Ferreiro Gutierrez, J.L. et al., Abst 2504-457). However, a triple antiplatelet regimen of aspirin, clopidogrel and cilostazol offered no additional benefit over standard dual therapy in patients undergoing percutaneous coronary interventions with drug-eluting stent implantation (Poddar, K.L. et al., Abst 1072-89; Nakao, T. et al., Abst 2504-459; Kim, H.S. et al., Abst 3016-12), despite improving platelet responsiveness during the peri- and postprocedural phases (Kim, M.H. et al., Abst 2504-458), especially in patients with CYP2C9 gene variants associated with underresponse to clopidogrel (Jeong, Y.H. et al., Abst 1028-163), and improving outcomes in higher-risk patients, such as those with type 2 diabetes who commonly show an underresponse to clopidogrel (Ha, S.J. et al., Abst 1154-268). In a similar way, upstream use of abciximab with high-dose clopidogrel did not reduce the incidence of major adverse cardiovascular events after percutaneous coronary interventions for STEMI (Kim, J.S. et al., Abst 2504-461).

Besides antiplatelet therapy, anticoagulant agents are also required in the treatment of acute coronary syndromes, and in this context, bivalirudin monotherapy was as effective as heparin combined with gpIIb/IIIa inhibitors, but was associated with a reduced risk of major bleeding at all body mass index sextiles. The addition of gpIIb/IIIa inhibitors to bivalirudin did not add to the benefits of the agent (Choi, S.Y. et al., Abst 2903-10; Delhaye, C. et al., Abst 2504-418; Dhoot, J.S. et al., Abst 2504-420; Kim, L. et al., Abst 2504-422; Kesserwane, R. et al., Abst 2504-421; Pinto, D.S. et al., Abst 1045-

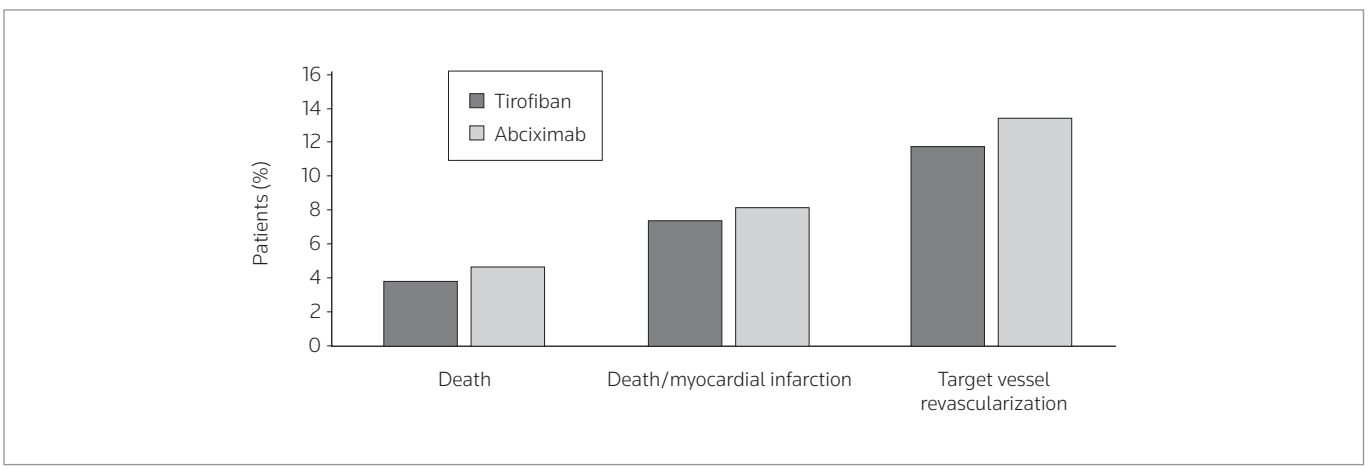

Figure 3. Rates of death, death/myocardial infarction and target vessel revascularization at 1 year in patients with S-T segment elevation myocardial infarction undergoing sirolimus-eluting stent implantation and receiving tirofiban or abciximab (Valgimigli, M. et al., Abst 1100-277).

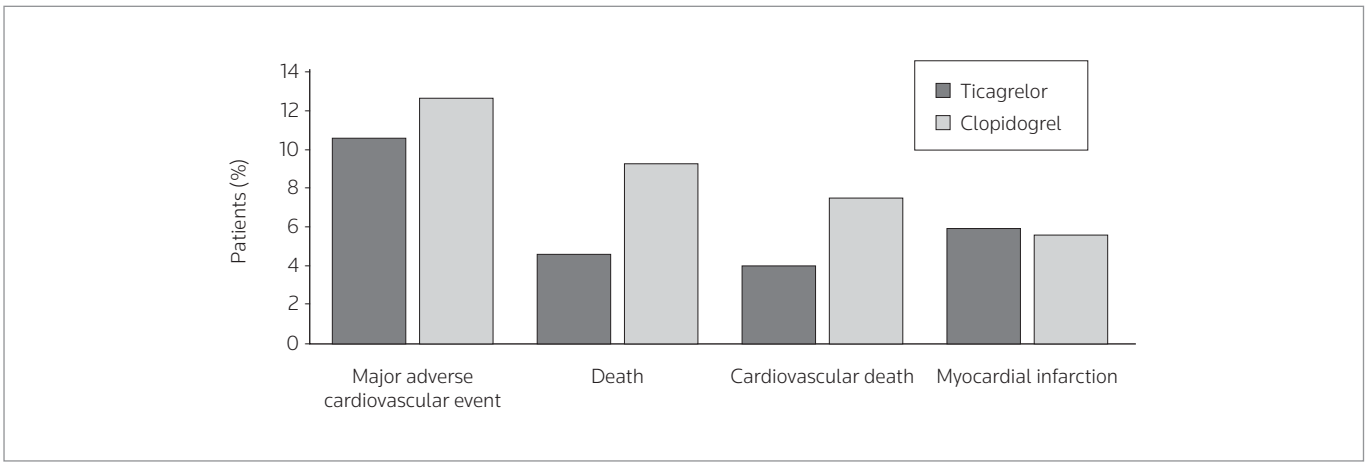

Figure 4. Cardiovascular death, myocardial infarction and/or major adverse cardiovascular event rates in patients undergoing coronary artery bypass graft surgery less than 7 days after receiving ticagrelor or clopidogrel (Held, C. et al., Abst 1264-266; Held, C. et al., Abst 3020-11).

274). However, the situation may be different in patients not pretreated with clopidogrel, as, according to a meta-analysis, in this particular case the use of bivalirudin was associated with higher major adverse cardiovascular event rates compared to heparin plus gpIIb/IIIa inhibitors (Kim, L. et al., Abst 2504-419), whereas pretreatment with clopidogrel had no impact on ischemic complications upon bivalirudin therapy in additional studies (Amin, A.P. et al., Abst 2903-06). Furthermore, no differences in outcomes comparing bivalirudin and heparin alone could be demonstrated in patients with chronic kidney disease on dialysis undergoing percutaneous coronary interventions (Delhaye, C. et al., Abst 2903-09). Moreover, according to the HORIZONS-AMI trial, administration of heparin prior to bivalirudin or heparin/gpIIb/IIIa inhibitors further reduced ischemic complications, especially in patients on bivalirudin alone, without increasing the risk of bleeding complications (Nikolsky, E. et al., Abst 2501-421). Significant benefits were likewise reported with the direct factor Xa inhibitor apixaban, which, compared to placebo, reduced D-dimer and fragment 1+2 levels in patients with acute coronary syndrome also treated with clopidogrel and aspirin (Becker, R.C. et al., Abst 1045-277). As an alternative, use of the regulatable RNA aptamer RB-006 (a direct factor IX inhibitor) and RB-007 (control antidote) also demonstrated potential, with rapid, adjustable anticoagulation during percutaneous coronary interventions (Cohen, M.G. et al., Abst 2504-433).

Fibrinolytic therapy may also be helpful in the initial treatment of acute coronary syndromes, and in fact, a study demonstrated that prehospital fibrinolysis was associated with smaller infarcts and less microvascular obstruction compared to primary percutaneous coronary intervention, without increasing the risk of bleeding (Weirick, T. et al., Abst 2501-422).

Antianginal therapies have an established role in the management of angina, without a clear role during acute coronary syndromes. An example reported during this year's meeting was the lack of benefit for nitroprusside regarding infarct size or coronary blood flow in patients with STEMI (Sakamoto, H. et al., Abst 1048-298). Other examples were the demonstrated benefit of ranolazine in patients with stable angina, reducing hospitalization, percutaneous coronary intervention and coronary artery bypass graft rates and total healthcare costs (Phelps, C.E. et al., Abst 1213-300), and the reported effect of ivabradine in reducing angina and nitrate consumption after percutaneous coronary interventions (Koester, R. et al., Abst 1213-298). However, intracoronary administration of nicorandil in patients undergoing percutaneous coronary interventions improved microvascular function more effectively than nitroglycerin in patients suffering from the same acute coronary syndrome (Ito, N. et al., Abst 1048-296).

A further, currently experimental strategy for improving outcomes in patients with acute coronary syndrome is varespladib, a secretory phospholipase A_2 ($sPLA_2$) inhibitor with potential for improving inflammation through an effect on proatherogenic enzymes and lipoprotein remodeling. This was demonstrated in a randomized, placebo-controlled trial in which varespladib, added to high-dose atorvastatin, improved LDL cholesterol, C-reactive protein and $sPLA_2$ levels over the effect of placebo, although with only nonsignificant trends in reducing unstable angina and myocardial infarction rates (Rosenson, R.S. et al., Abst 1155-274). In addition, at least in women without significant macrovascular coronary artery disease, treatment with sildenafil improved microvascular dysfunction (Denardo, S.J. et al., Abst 1272-337).

In addition to the above-mentioned pharmacological interventions, red ginseng extract was described to improve angiogenic cell mobilization and decrease inflammation during an acute myocardial infarction compared to placebo (Shin, D. et al., Abst 1043-260), and plasmid-mediated vascular endothelial growth factor gene therapy improved signs and symptoms, myocardial ischemia and left ventricular ejection fraction in patients with no-option chronic angina (Favaloro, L.E. et al., Abst 1266-289). Subcutaneous injections of granulocyte colony-stimulating factor also demonstrated therapeutic potential by mobilizing endothelial progenitor cells, although without improving blood flow or angina in patients with ischemic heart disease (Chih, S.S. et al., Abst 1267-303).

In the experimental laboratory, exogenous administration of α_1-antitrypsin was noted to preserve the myocardium during and prevent adverse cardiac remodeling after an acute myocardial infarction (Abbate, A. et al., Abst 1104-304), whereas treatment with VEGF165

plasmid improved cardiac function by enhancing cardiomyocyte proliferation (Bourji, M. et al., Abst 1158-298). Furthermore, the hydrogen sulfide donor diallyl trisulfide showed cardioprotective activity during myocardial ischemia (Predmore, B.L. et al., Abst 1159-305), and sildenafil was active in limiting infarct expansion when added to the angiotensin-converting enzyme (ACE) inhibitor perindopril (Sim, D.S. et al., Abst 1158-300). On the contrary, stimulation of angiotensin AT_2 receptors with CGP-42112A was associated with worsened mortality after experimental infarction, independent of blood pressure and cardiovascular remodeling (Benndorf, R.A. et al., Abst 1158-299), whereas blockade of stretch-activated channels with GsMTx-4 did not prevent coronary occlusion-induced ventricular arrhythmia (Barrabes, J.A. et al., Abst 1161-315).

New experimental studies corroborated the potential of cardiac-derived stem cell transplantation for improving myocardial function and mechanics after an acute myocardial infarction (Bonios, M. et al., Abst 1001-10). Endothelium-derived stem cell transplantation was also reported to be of benefit in the experimental arena, protecting against the deterioration of ischemic myocardial remodeling in models of stable chronic myocardial ischemia and suggesting potential as a treatment for no-option chronic heart disease (Pedrosa, D.J. et al., Abst 1002-27). In a similar way, bone marrow-derived stem cells showed potential for preventing doxorubicin-induced cardiotoxicity (Sanganalmath, S.K. et al., Abst 1176-42), while cardiogenic cells obtained by differentiation from mesenchymal stem cells showed cardioregenerative potential in models of myocardial ischemia (Hwang, K.C. et al., Abst 1103-297). Advancements were also reported in the clinical arena, with intracoronary bone marrow-derived stem cell injection improving left ventricular ejection fraction and infarct size compared to placebo in patients with myocardial infarction (Wöhrle, J. et al., Abst 1043-262). In a similar way, the APOLLO study concluded on the benefits of adipose tissue-derived stem cells in patients with STEMI (Duckers, H.J. et al., Abst 1043-257). However, an additional study could not demonstrate benefits of bone marrow- or peripheral blood-derived mononuclear cells on myocardial perfusion after reperfused acute myocardial infarction (Afsharzada, F. et al., Abst 1103-296). In addition, cotreatment with oxytocin facilitated cardiac repair through enhanced migration of umbilical blood-derived mesenchymal stem cells (Ahn, Y. et al., Abst 1160-308).

Drug-eluting stents

Although new studies and clinical observations confirming the potential of standard and novel sirolimus- and paclitaxel-eluting stents were presented during the meeting (Botelho, R. et al., Abst 2505-524; Nakatani, D. et al., Abst 2505-523; Vorpahl, M.M. et al., Abst 2505-522; De Ribamar Costa, J. et al., Abst 2904-05; Wöhrle, J. et al., Abst 2909-08; Vagaonescu, T.D. et al., Abst 2909-06; Witzenbichler, B. et al., Abst 2909-05; Nasu, K. et al., Abst 2503-422; Nasu, K. et al., Abst 2911-08; Tamura, T. et al., Abst 2503-429; Nakamura, S. et al., Abst 2503-444; Vaquerizo, B. et al., Abst 2503-435; Zhang, F. et al., Abst 2530-437; De Ribamar Costa, J. et al., Abst 2504-493; De Ribamar Costa, J. et al., Abst 2504-466; Marroquin, O.C. et al., Abst 2910-06; Kawaguchi, R. et al., Abst 2503-439; Magni, V. et al., Abst 2503-438; Lee, J.M. et al., Abst 2501-517; Schafer, P. et al., Abst 2501-512; Wakabayashi, K. et al., Abst 2501-532; Kim, Y.H. et al., Abst 2501-524; Lichtenwalter, C. et al., Abst 2502-435; Ko, Y.G. et al., Abst 2502-430; Birkmeier, K.A. et al., Abst 2501-534; Rodés-Cabau, J. et al., Abst 2502-436; Yamaguchi, H. et al., Abst 2502-453; Amano, H. et al., Abst 2502-446; Kadota, K. et al., Abst 2502-444; Shirai, S. et al., Abst 2502-447; Rodriguez, A.E. et al., Abst 2502-437; Rossi, J. et al., Abst 2909-10; Cannon, L.A. et al., Abst 2910-07; Byrne, R.A. et al., Abst 2910-10; Tada, T. et al., Abst 2504-501; Nakamura, S. et al., Abst 2504-508; Maeng, M. et al., Abst 2911-05; Takagi, K. et al., Abst 2502-501; Hassan, W. et al., Abst 2504-504; Shiomi, H. et al., Abst 2906-08; Nakamura, S. et al., Abst 2502-504; Ito, T. et al., Abst 2504-514; Toutouzas, K. et al., Abst 2504-521; Nakao, K. et al., Abst 2502-489; Challa, K.K. et al., Abst 1215-309; Han, Y. et al., Abst 1058-366; Buszman, P.P. et al., Abst 1058-367), including an innovative fully bioabsorbable salicylate-based sirolimus-eluting stent that tested positive in experimental animal models (Matsumoto, D. et al., Abst 2505-521), data were also reported on the incomplete endothelialization of most stents (Kim, T.H. et al., Abst 2503-461; Her, A.Y. et al., Abst 2502-450), the risk of edge restenosis (Ichimoto, E. et al., Abst 2503-504), late stent malapposition (Soo-Jin, K. et al., Abst 2908-05), restenosis (Kuriyama, N. et al., Abst 2502-429; Ino, Y. et al., Abst 2502-451) and thrombosis (Kuriyama, N. et al., Abst 2501-515; Costa, R.A. et al., Abst 2501-522), transient stent-related endothelial dysfunction (Kitahara, H. et al., Abst 2502-443) or stent-related coronary aneurysm formation (Kim, U. et al., Abst 2501-510; Imai, M. et al., Abst 2904-08), and on the adverse outcomes in terms of cardiovascular risk in case of stent fracture (Kim, U. et al., Abst 2503-447), and an overall decline in the use of medicated stents was reported (Marcoff, L. et al., Abst 2501-521). Comparing sirolimus- and paclitaxel-eluting stents, the latter were associated with poorer stent coverage, greater lumen loss and higher thrombogenicity (Hara, M. et al., Abst 2908-10; Nakamura, S. et al., Abst 2503-446), while the former were reported to be more effective overall (Yamawaki, M. et al., Abst 2503-431). In contrast, favorable neointimal coverage was reported after everolimus- compared to sirolimus-eluting stent implantation in a 9-month follow-up (Choi, H.H. et al., Abst 2503-490), the stent proving equivalent to first- and second-generation drug-eluting stents in terms of major adverse cardiovascular event and stent thrombosis rates (Lee, K. et al., Abst 2501-461), while uncovered stent struts after sirolimus-eluting stent implantation resulted in an increased likelihood for clinically relevant thrombosis (Ozaki, Y. et al., Abst 2908-08). New medicated stents, positive results with which were presented in experimental animal models, included everolimus- (Onuma, Y. et al., Abst 2505-520; Byrne, R.A. et al., Abst 2910-08; Calfon, M.A. et al., Abst 2501-462; Onuma, Y. et al., Abst 1214-302; Applegate, R.J. et al., Abst 1266-286; Kereiakes, D.J. et al., Abst 1195-174), zotarolimus- (Kandzari, D.E. et al., Abst 2502-431; Kandzari, D.E. et al., Abst 2502-432; Nakatani, D. et al., Abst 2502-449; Kirtane, A. et al., Abst 2504-503; Koh, Y.S. et al., Abst 1050-309), bevacizumab- (Toutouzas, K. et al., Abst 2505-533), biolimus A9- (Lansky, A.J. et al., Abst 2503-421; Costa, R.A. et al., Abst 2501-531; Costa, R.A. et al., Abst 2501-421; Kim, B.K. et al., Abst 2501-419; Hagiwara, H. et al., Abst 2502-438; Danzi, J.B. et al., Abst 2502-439) and, in the experimental arena, ramiprilat-eluting stents (Hong, Y.J. et al., Abst 1166-350), with the biolimus A9-, sirolimus- and everolimus-eluting stents being associated, according to some data, with comparable or superior efficacy but a reduced risk for restenosis compared to other drug-eluting stents (Nakamura, S. et al., Abst 2503-443; Kim, H.K. et al., Abst 2501-535;

Muramatsu, T. et al., Abst 2502-420; Hermiller, J.B. et al., Abst 2501-533; Nakamura, S. et al., Abst 2502-502; Nakamura, S. et al., Abst 2906-05; Jo, S.H. et al., Abst 2504-516; Yamamoto, M.H. et al., Abst 1214-305) (Fig. 5). An interesting research program comparing percutaneous coronary intervention with drug-eluting stent placement versus coronary artery bypass graft surgery, specifically for unprotected left main coronary artery disease, suggested encouraging results for drug-eluting stent implantation, with favorable long-term outcomes and no differences in the occurrence of death, cardiac death or death/myocardial infarction/cerebrovascular disease between the two groups, although open surgery fared better regarding exclusively target vessel revascularization rates (Meliga, E. et al., Abst 1001-6; Park, D.W. et al., Abst 2906-09). In this context, it should be emphasized that a cost–effectiveness analysis suggested superiority for percutaneous coronary intervention over medical therapy alone for severe stable angina, although medical therapy could be optimally used against less severe disease (Zhang, Z. et al., Abst 1001-19). Note that discrepant results comparing drug-eluting versus bare metal stents in saphenous vein graft lesions, indicating delayed healing and higher thrombosis rates (Yazdani, S.K. et al., Abst 2501-508) or safety and effectiveness (Hakeem, A. et al., Abst 2501-509) with the medicated stents, complicated decisions regarding what type of intervention to use.

VALVULAR HEART DISEASE

Other than pharmacological control of the risk of thrombosis and endocardiac infections, valvular heart disease is largely a surgical condition. However, adjuvant pharmacotherapy may be required in specific instances. As adjuvant therapy, the addition of candesartan to conventional therapy after aortic valve replacement resulted in accelerated reverse left ventricular and atrial remodeling, expanding the therapies of benefit for such patients (Dahl, J.S. et al., Abst 1001-14). On the other hand, although elevated C-reactive protein levels are common in patients with aortic stenosis, the marker has no impact on disease progression, and treatment with rosuvastatin offered no benefit in the disease (Chan, K.L. et al., Abst 1170-376).

CARDIAC ARRHYTHMIA

Although electrical cardioversion is considered the most effective means for terminating atrial fibrillation, resistant fibrillation has been reported, and in such patients ranolazine appears to provide a useful alternative, as noted in a series of 15 patients discussed during this year's meeting in a poster presentation (Murdock, D.K. et al., Abst 1023-120). In fact, further studies also documented the safety and rapid onset of action of ranolazine used for converting new or paroxysmal atrial fibrillation (Murdock, D.K. et al., Abst 1081-146). Dofetilide is another antiarrhythmic agent potentially useful against atrial fibrillation, provided accurate measurement of the Q-T interval, which is significantly longer during fibrillation, is obtained and the agent is titrated accordingly (Musat, D.L. et al., Abst 1023-121). Interestingly, one predictor of dofetilide success was the presence of underlying coronary artery disease (Bavikati, V.V. et al., Abst 1135-138). Dronedarone also demonstrated modest efficacy for maintaining sinus rhythm compared to placebo in patients with atrial fibrillation, as demonstrated in a meta-analysis of four major trials (Kaul, S. et al., Abst 1023-123), while rapid switch from amiodarone to dronedarone was reported to be safe and well tolerated in a subgroup of patients from the EURIDIS and ADONIS studies, the agent reducing the frequency of atrial fibrillation/flutter recurrence compared to placebo without an excess incidence of adverse events, including serious events and torsades de pointes (Kowey, P.R. et al., Abst 0903-05). Another agent, ivabradine, also demonstrated benefits by controlling heart rate and improving heart function during myocardial ischemia, thus reducing in-hospital event rates in patients with acute myocardial infarction (Rajagopal, J. et al., Abst 1045-273), and reducing heart rate and preventing acute angina attacks in elderly people, without causing significant bradycardia or other tolerability concerns (Koester, R. et al., Abst 1217-323). Furthermore, in combination with bisoprolol, ivabradine demonstrated superior antianginal and left ventricular dysfunction-preventing effects than bisoprolol uptitration, the latter being ineffective as an anti-ischemic agent (Amosova, E.N. et al., Abst 1217-322). In addition to electrical and pharmacological cardioversion, data were reported to indicate that ω_3-polyunsaturated fatty acids have potential for helping maintain sinus rhythm and preventing recur-

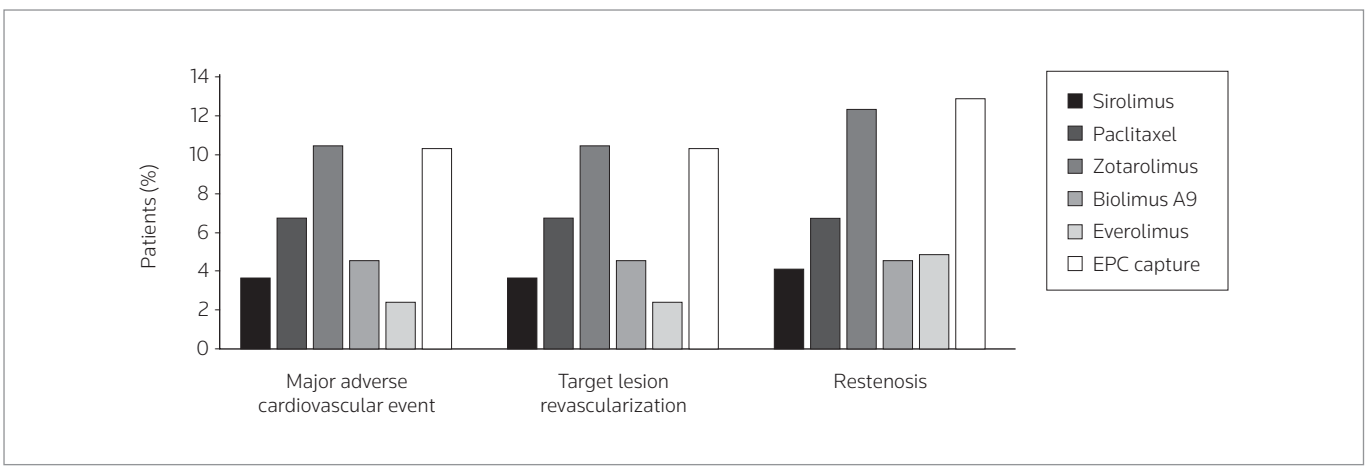

Figure 5. Major adverse cardiovascular event, target lesion revascularization and restenosis rates at 9 months after sirolimus-, paclitaxel-, zotarolimus-, biolimus A9- or everolimus-eluting or endothelial progenitor cell (EPC) capture stent implantation (Nakamura, S. et al., Abst 2503-443).

rences after cardioversion from persistent atrial fibrillation (Nodari, S. et al., Abst 1023-124; Bianconi, L. et al., Abst 1081-152), while also preventing adverse atrial remodeling and preserving left ventricular function in heart failure in human patients and experimental animal models (Ghio, S. et al., Abst 0910-05; Lau, D.H. et al., Abst 1244-136) (Fig. 6) (in fact ω_3-polyunsaturated fatty acids were identified as predictors of mortality in patients with depression and heart failure [Fiuzat, M. et al., Abst 1069-67]). They also dose-dependently lowered insulin resistance while dose-independently reducing systemic inflammation in patients with metabolic syndrome (Kim, J.Y. et al., Abst 1018-95). Chronic renin–angiotensin system blockade with either ACE inhibitors or angiotensin receptor blockers was also associated with a reduced likelihood for atrial fibrillation recurrence (Bhuriya, R. et al., Abst 1081-153). In addition, although no efficacy data were reported, the activity of the antiarrhythmic agent cibenzoline on left ventricular diastolic function in patients with hypertrophic cardiomyopathy was attenuated in the presence of fibrosis (Saito, M. et al., Abst 1067-48).

Anticoagulant therapy is required for preventing stroke in patients with atrial fibrillation, although the use of clopidogrel/aspirin in patients unsuitable for vitamin K antagonist therapy was suggested to be equieffective at neutral additive cost, as it was offset by the prevention of costly strokes (Lamy, A. et al., Abst 3014-14). A favorable risk:benefit profile was demonstrated with dabigatran compared to warfarin in the RE-LY trial. The results indicated benefits for dabigatran regardless of age or renal function, dabigatran being associated with a lower risk for major bleeding in patients under 65 years of age (Oldgren, J. et al., Abst 0903-04; Koti, M.J. et al., Abst 1078-124; Healey, J.S. et al., Abst 1078-120). A late-breaking clinical trial presentation on the direct factor Xa inhibitor betrixaban also demonstrated the potential of the agent for preventing stroke, with a low risk for major/clinically relevant bleeding complications compared to warfarin (Ezekowitz, M.D. et al., Abst 3015-12). Similarly, although totally unrelated with atrial fibrillation and the risk of stroke, rivaroxaban exhibited a favorable risk:benefit ratio compared to enoxaparin in the prevention of deep vein thrombosis and thromboembolism in patients undergoing knee arthroplastic surgery (Kaul, S. et al., Abst 1224-371), whereas the antithrombotic REG-1 system, comprising the factor IXa inhibitor RB-006 and the reversal inhibitor RB-007, demonstrated pharmacodynamic potential in experimental animals (Rusconi, C.P. et al., Abst 1224-373). Overall, anticoagulant therapy was reported to be effective without an excess bleeding risk as prophylaxis of thromboembolic events in patients with chronic kidney disease developing atrial fibrillation after a percutaneous coronary intervention (Iwasaki, Y. et al., Abst 1127-87).

CARDIOVASCULAR RISK FACTORS

Hypertension

Diuretics remain a popular therapy for hypertension, although they are largely relegated to combination therapy for resistant hypertension. Among diuretics, thiazides are the most frequently used drugs, with no negative impact on bone mineral density, as demonstrated in a new study in elderly African American women (Javed, F. et al., Abst 1130-106). In addition to their use in heart failure, β-blockers are also popular as antihypertensive drugs, with, at least in the case of nebivolol, additional benefits on oxidative stress, endothelial nitric oxide availability and inflammation biomarkers even in high-risk African American subjects undergoing exercise stress testing (Merchant, N. et al., Abst 1127-89; Mason, R.P. et al., Abst 1218-329); nebivolol showed cardioprotective potential in experimental models of myocardial ischemia (Aragon, J.P. et al., Abst 1159-306). In addition, landiolol proved cardioprotective during elective percutaneous coronary interventions (Haengnam, P., Abst 1217-319) and was demonstrated to inhibit the expansion of myocardial injury during an acute myocardial infarction, widening the usefulness of β-blockers to additional patient circumstances (Higuchi, H. et al., Abst 1045-280). Calcium channel blockers also remain a popular antihypertensive strategy, with renewed interest based on the superiority of amlodipine over atenolol in preventing stroke and acute coronary events associated with active lowering of systolic blood pressure, as demonstrated in the ASCOT trial (Sever, P. et al., Abst 3014-12).

Among the ACE inhibitors, renal vasodilating responses to captopril were noted to be enhanced in obese diabetic patients on a high-salt diet, probably because of hyperactivation of the renin–angiotensin system in such patients (Moukarbel, G.V. et al., Abst 1242-115).

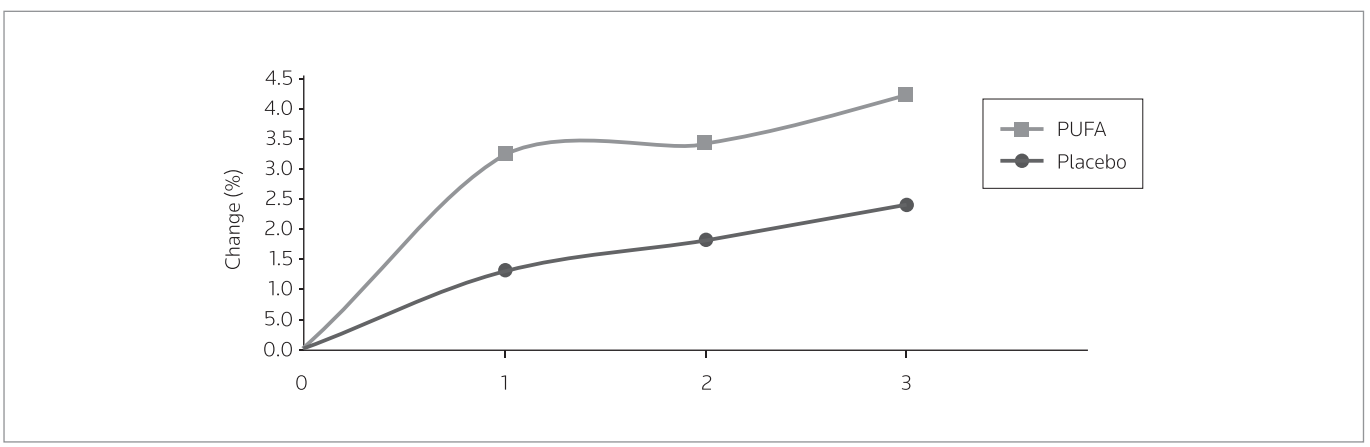

Figure 6. Change in left ventricular ejection fraction during 3 years of treatment with ω_3-polyunsaturated fatty acids (PUFA) or placebo (Ghio, S. et al., Abst 0910-05).

Benefits on endothelial function and inflammation resulted from treatment with another ACE inhibitor, quinapril, combined with lipoic acid in obese patients with metabolic syndrome (Khan, B.V. et al., Abst 1077-118). A combination of ramipril and the calcium channel blocker felodipine was reported to induce plaque regression without changes in plaque composition in patients with hypertension, angina and mild to moderate coronary atherosclerosis (Hong, Y.J. et al., Abst 2503-449).

Angiotensin receptor blockers have gained a well-established role in the treatment of hypertension and increased cardiovascular risk, with effects well beyond a simple reduction in blood pressure. As an example, administration of candesartan to experimental animals with myocardial infarction resulted in suppression of secreted frizzled-related protein 2 levels and fibrosis during the post-reperfusion healing phase (Judgutt, B.I. et al., Abst 1216-316). A combination of candesartan and pioglitazone was further demonstrated to protect against vascular inflammation and improve endothelial function after experimental sirolimus-eluting stent implantation (Dohi, T. et al., Abst 1271-329). Also in the preclinical arena, telmisartan, like resveratrol, demonstrated activity against TNF-α-induced monocyte recruitment and endothelial adhesion molecule expression, suggesting potential antiatherosclerotic activity (Garlichs, C.D. et al., Abst 1273-346).

The direct renin inhibitor aliskiren reduced brain natriuretic peptide levels in patients with heart failure already optimally treated with ACE inhibitors (McMurray, J.J.V. et al., Abst 1125-75), accelerating compensation during hospitalization in patients with acute decompensated disease (Volkova, A.L. et al., Abst 0406-2). However, according to the ASPIRE trial, the addition of aliskiren to optimal medical therapy including ACE inhibitors or angiotensin receptor blockers did not improve ventricular remodeling compared to placebo after an acute myocardial infarction in high-risk patients (Solomon, S.D. et al., Abst 3019-10) (Fig. 7). Combined with hydrochlorothiazide, aliskiren was at least as effective as amlodipine or atenolol/hydrochlorothiazide in lowering peripheral systolic blood pressure, but proved superior to both comparator therapies in lowering central pressure, which is an important additional risk factor, at least in African Americans (Ferdinand, K. et al., Abst 1240-103; Fogari, R. et al., Abst 1240-106).

Important news was also reported during this year's meeting regarding new putative therapies for hypertension, including the marked blood pressure-lowering activity exerted by the novel dual angiotensin receptor blocker and neprilysin inhibitor LCZ-696 in a placebo-controlled trial, with good tolerability and superiority compared to the pure angiotensin receptor blocker valsartan and the pure neprilysin inhibitor AHU-377 (Böhm, M. et al., Abst 1239-101). Also regarding new putative therapies, the aldosterone synthase inhibitor LCI-699 demonstrated superiority over placebo and equivalent efficacy compared to the mineralocorticoid receptor blocker eplerenone in lowering blood pressure in patients with essential hypertension (White, W.B. et al., Abst 1239-99), offering additional avenues to explore in the treatment of hypertension and associated cardiovascular risk. LCI-699 was also confirmed to be pharmacodynamically active in dose-dependently lowering plasma and urinary aldosterone levels and increasing plasma renin levels (Menard, J. et al., Abst 1239-100).

Regarding general topics, and specifically related to blood pressure control in patients with type 2 diabetes, the results of the ACCORD blood pressure trial presented during a late-breaking clinical trial session could not demonstrate that targeting a systolic blood pressure goal of 120 mmHg compared to the standard 140 mmHg reduced major cardiovascular event rates in such high-risk patients (Cushman, W.C., Abst 3010-8), although in the INVEST trial, tight blood pressure control aimed at systolic values of < 130 mmHg translated into improved outcomes compared to values of 140 mmHg, but lower values resulted in increased mortality (Cooper-Dehoff, R.M. et al., Abst 3010-10).

Diabetes and glucose intolerance

In addition to the known cardiovascular risk of diabetes, new data reported during this year's ACC meeting in Atlanta indicated that diabetes is also a major risk factor for heart failure in older adults (Deedwania, P.C. et al., Abst 1178-59). However, except for gliclazide, all sulfonylureas used concomitantly with metformin in the treat-

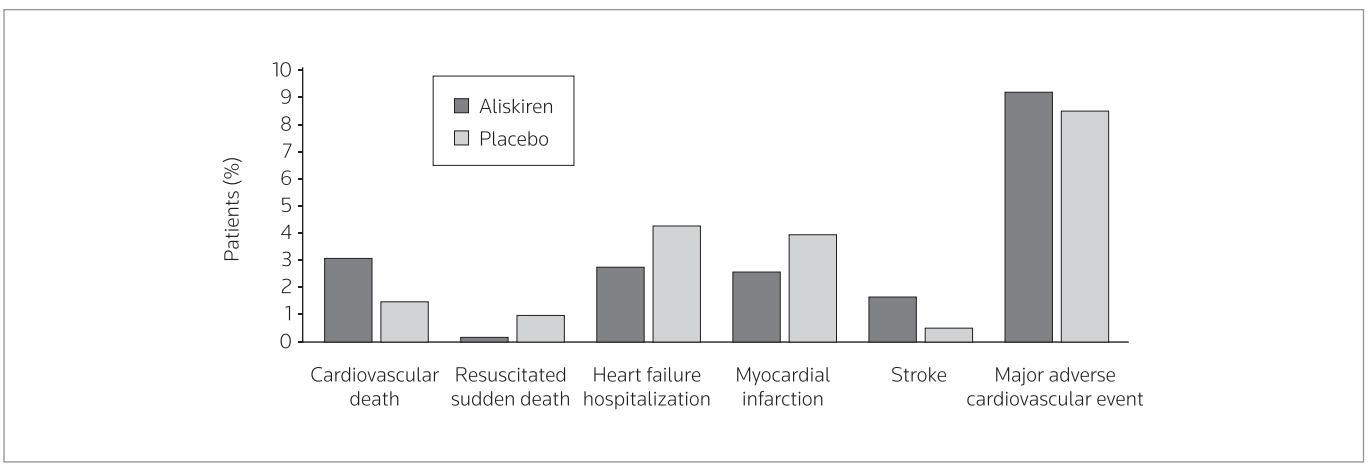

Figure 7. Cardiovascular death, resuscitated sudden death, heart failure hospitalization, myocardial infarction, stroke or total major adverse cardiovascular event rates in patients receiving aliskiren or placebo in addition to optimal medical therapy (Solomon, S.D. et al., Abst 3019-10).

ment of type 2 diabetes were associated with an increased risk of myocardial infarction (Jorgensen, C.H. et al., Abst 1049-305). While inducing regression of coronary artery atherosclerotic plaques and neointima formation and preserving lumen diameter even without reducing LDL cholesterol levels in non- and early diabetic individuals and patients with established type 2 diabetes (Komiyama, N. et al., Abst 1018-93; Choi, J.H. et al., Abst 1169-373) in the POPPS study, treatment of diabetic patients with symptomatic ischemic heart disease undergoing percutaneous coronary interventions with pioglitazone resulted in improvements in ventricular filling pressure without worsening left ventricular systolic or diastolic function (Okura, H. et al., Abst 0910-07). With results from the GATE study suggesting improvements in glycemic control and insulin resistance, but not endothelial function (Hubacek, J. et al., Abst 1220-345), experimental studies with rosiglitazone indicated potential for vasoprotection and improved re-endothelialization after coronary stent implantation (Utchil, S.I. et al., Abst 1221-350), although switching ventricular fibrillation to a higher frequency through blockade of ATP-dependent potassium channels impaired the success of defibrillation in the case of ventricular fibrillation (Sarraf, M. et al., Abst 1052-323). Regarding the use of thiazolidinediones, pharmacogenomic variability of response was indicated depending on the presence of single nucleotide polymorphisms of the *PIK3R1*, *ACACA*, *GNAO1*, *EDN1*, *INSR* and *UCP3* genes (Seip, R.L. et al., Abst 2504-490). Going beyond thiazolidinediones, the dual peroxisome proliferator-activated receptor PPARα/γ agonist muraglitazar improved left ventricular ejection fraction, left ventricular mass index and cardiac volumes as effectively as glimepiride in patients with type 2 diabetes, with a similar risk of peripheral, but not central, edema (Rao, V.U. et al., Abst 1055-347). In addition, although the GATE study revealed no benefit for rosiglitazone on endothelial function, potent activity against insulin resistance-related endothelial dysfunction was demonstrated with exenatide, an effect related to opening of ATP-dependent potassium channels (Ha, S.J. et al., Abst 1219-337), whereas the dipeptidyl peptidase 4 inhibitor saxagliptin improved nitric oxide bioavailability in experimental models of insulin-resistant obesity (Mason, R.P. et al., Abst 1273-348). On the contrary, the results of the NAVIGATOR trial did not demonstrate any impact of nateglinide on the risk of progression to overt diabetes or cardiovascular morbidity and mortality in patients with impaired glucose tolerance and/or at risk for cardiovascular disease, whereas treatment with valsartan prevented diabetes without reducing cardiovascular morbidity or mortality (Califf, R.M. et al., Abst 3010-14).

An interesting additional report comparing insulin-sensitizing therapies for diabetes, predominantly metformin and/or thiazolidinediones, to insulin-providing therapy with insulin secretagogues and/or insulin demonstrated more favorable increases in LDL particle size and subclass profile after 1 year with the former strategy, without a change in total LDL particle levels (Orchard, T.J. et al., Abst 1018-96).

Dyslipidemia and hypercholesterolemia

Although data from the CARE study demonstrated a reduced risk of cardiovascular events with pravastatin in carriers of the *KIF6* ^{719}Arg allele, but not in noncarriers (Shiffman, D. et al., Abst 1028-161), new results from the IDEAL trial indicated that high-dose atorvastatin prevented peripheral arterial disease compared to standard-dose simvastatin, while also preventing coronary events in patients with peripheral arterial disease at baseline (Larsen, M.L. et al., Abst 1002-31). Compared to a dose of 10 mg/day, atorvastatin 40 mg/day also improved stem cell mobilization and decreased inflammatory cytokine and LDL cholesterol levels and microvascular integrity during and after acute myocardial infarction (Park, J.H. et al., Abst 1043-261), and was also reported to rapidly reduce vascular superoxide generation and increase nitric oxide bioavailability independent of LDL cholesterol levels in human arteries and vein grafts (Bakogiannis, C. et al., Abst 1022-118; Antoniades, C.A. et al., Abst 1217-321), while a higher dose of 80 mg reduced cardiovascular event rates regardless of the presence of obesity or chronic kidney disease (Deedwania, P.C. et al., Abst 1131-110). At a dose of 80 mg/day, atorvastatin significantly reduced lipoprotein-associated PLA_2 and $sPLA_2$ levels and activity in patients with acute coronary syndrome (Ryu, S.K. et al., Abst 1164-339). Greater anti-inflammatory potential for atorvastatin was similarly described upon combination with clopidogrel and either perindopril or valsartan in patients with unstable angina (Grabrielyan, A. et al., Abst 1155-277). However, additional randomized, placebo-controlled data indicated that atorvastatin use in hypercholesterolemia, metabolic syndrome and/or type 2 diabetes worsens glucose metabolism and insulin sensitivity (Koh, K.K. et al., Abst 1018-92; Koh, K.K. et al., Abst 1169-370), although according to another study, doubling the dose of atorvastatin or adding ezetimibe to lower-dose atorvastatin improved insulin resistance in patients with metabolic syndrome (Goshima, K. et al., Abst 1019-99), so that making definite conclusions is not possible at the present time. Furthermore, the finding that the combination of ezetimibe and atorvastatin in other independent studies decreased buoyant and oxidized LDL cholesterol without increasing LDL particle size (Azar, R.R. et al., Abst 1019-100) indicated that new studies are required to clarify the impact of such treatment on the atherogenic lipid profile. New clinical trial results were also reported with rosuvastatin, which lowered triglyceride levels and improved the atherogenic lipid profile (Talavera, J.O. et al., Abst 1076-112), and prevented cardiovascular events and total mortality regardless of the presence of chronic kidney disease in the JUPITER trial (Ridker, P.M. et al., Abst 1077-117; Ridker, P.M. et al., Abst 1077-116); combined with ezetimibe, it proved superior to cotreatment with simvastatin plus the cholesterol absorption inhibitor in lowering total, LDL and non-HDL cholesterol and apolipoprotein B levels, resulting in higher LDL cholesterol goal attainment rates (Ballantyne, C.M. et al., Abst 1019-98). In the experimental arena, rosuvastatin increased growth factor and stem cell marker expression in the left ventricle during heart failure (Rastogi, S. et al., Abst 0910-06). New data were similarly reported with simvastatin, which in a placebo-controlled study improved endothelial function and endothelium-dependent vasodilatation, while reducing adiponectin levels and insulin sensitivity (Koh, K.K. et al., Abst 1164-334), and, like aspirin, inhibiting angiogenesis by increasing the expression of vascular endothelial cadherin (Khaidakov, M. et al., Abst 1166-356). In addition, concomitant statin therapy in patients with pulmonary hypertension was associated with a statistically significant reduction in the risk of all-cause mortality according to an open-label survey (Bader, E.M. et al., Abst 1001-2), whereas pretreatment with pravastatin (Fukunaga, M. et al., Abst 2503-518), atorvastatin (Gatto, L. et al., Abst 2501-464) or in general any statin reduced microvascular dysfunction during percutaneous coronary interventions, at least in the latter case due

to attenuation of endothelial inflammation, resulting in a reduced risk for periprocedural infarction (Zhang, F. et al., Abst 2504-464). Statin administration before percutaneous coronary interventions for myocardial infarction improved cardiac event rates overall, but especially in patients with elevated C-reactive protein levels (Auguadro, C. et al., Abst 2504-463), and resulted in a reduced risk for peri- and postprocedural atrial fibrillation and long-term adverse outcomes (Winchester, D.E. et al., Abst 1072-86); although postdischarge statin adjusted to LDL cholesterol levels under 70 mg/dL had no major impact on the risk of death or myocardial infarction at 1 year, according to additional data (Kim, H.K. et al., Abst 1072-87), statin therapy after coronary artery bypass graft surgery was clearly associated with reduced all-cause mortality (Philip, F. et al., Abst 1131-112). In addition, it should be emphasized that a meta-analysis demonstrated a benefit for statin therapy in preventing heart failure in patients with coronary artery disease, but not in patients without coronary artery disease or overt heart failure at treatment onset (Silva Enciso, J.E. et al., Abst 1131-109), and overall, analysis of the JUPITER trial suggested cost–effectiveness for statins in the prevention of vascular events in individuals with elevated C-reactive protein levels (Slejko, J.F. et al., Abst 1030-172).

Statins are not the only drugs used in the treatment of dyslipidemia and hypercholesterolemia, however, and studies were also discussed on other drug families during the meeting. In one such study, adding dalcetrapib to prior pravastatin therapy resulted in improvements in the atherogenic profile and lipoprotein particle size distribution profile in patients with low baseline HDL cholesterol levels (Ballantyne, C.M. et al., Abst 0904-03), although a related compound, torcetrapib, induced endothelial dysfunction in animal models of hypertension (Simic, B. et al., Abst 1166-353). In a similar way, dual combination of fenofibrate and rosuvastatin (Jones, P.H. et al., Abst 1019-101), pravastatin (Farnier, M. et al., Abst 1076-110) or niacin (Wi, J. et al., Abst 1076-109), or a triple combination of fenofibrate and extended-release niacin with low-dose atorvastatin (Dunbar, R.L. et al., Abst 0904-05; Dunbar, R.L. et al., Abst 0904-06) induced significant additional benefits on the HDL cholesterol, triglyceride and overall lipid profile, although, at least in the case of the triple combination, without improving apolipoprotein A1 kinetics or levels. Note in that regard that the results of the ACCORD-Lipid trial did not support the use of fenofibrate combined with simvastatin for reducing cardiovascular events in patients with type 2 diabetes, despite improvements in HDL cholesterol and triglyceride levels (Ginsberg, H.N., Abst 3010-6). In addition, a fixed-dose combination of extended-release niacin and laropiprant was reported to lower phosphorus levels in dyslipidemic conditions, regardless of baseline estimated glomerular filtration rate (Bostom, A.G. et al., Abst 1127-88), although extended-release niacin alone improved the lipid profile without this translating into benefits on endothelial function (Hubaceck, J. et al., Abst 1164-336). As an investigational approach, the orally bioavailable apolipoprotein A1 production inhibitor RVX-208 improved apolipoprotein A1 and HDL cholesterol levels and induced regression of atherosclerotic plaque in a phase I study (Wong, N.C. et al., Abst 1164-333). In the experimental arena, addition of the liver X receptor agonist and ABCA1 expression enhancer LXR-623 to treatment with simvastatin induced synergistically enhanced regression of atherosclerotic plaque (Giannarelli, C. et al., Abst 1163-330), while the anti-ETS-1 microRNA products MIR-155 and -221/222 attenuated angiotensin II-induced endothelial inflammation (Zhu, N. et al., Abst 1166-354), widening the field of potential antiatherosclerotic therapies.

LIFESTYLE AND CARDIOVASCULAR RISK

Although it is not the main scope of this report, a few new findings related to different aspects of lifestyle discussed during the ACC 2010 are worth mentioning as suggestions to improve the cardiovascular health of the population. One such report indicated an inverse correlation between alcohol consumption, particularly wine, and carotid intima–media thickness, with the effect modulated by socioeconomic, behavioral and familial factors (Shah, A.J. et al., Abst 1129-98), while additional data suggested potential for resveratrol for reversing the atherogenic effect of interferon-γ on cholesterol efflux in monocytes and macrophages (Hai, O.Y. et al., Abst 1164-337). Another study related with diet and cardiovascular health compared the impact of low- versus moderate-fat diet on insulin resistance and endothelial function in patients with metabolic syndrome, and demonstrated the benefits of a moderate-fat diet in improving atherogenic dyslipidemia, with no differences in the two mentioned outcomes (Paramsothy, P. et al., Abst 1184-98). In this same context, a third study documented improvements in metabolic syndrome parameters with a low-carbohydrate, high-protein diet enriched with mono- and polyunsaturated fatty acids (Lopez-Jimenez, F. et al., Abst 1183-95). Additional studies confirmed the benefit of the so-called Mediterranean diet on several parameters, notably, renal function (Chrysohoou, C.A. et al., Abst 1132-117).

MISCELLANEOUS

Sildenafil was reported to improve ventilator efficiency during exercise in young children and adults undergoing Fontan's operation (Goldberg, D. et al., Abst 1002-33). Beneficial effects were reported with vardenafil on arterial stiffness and function in patients with erectile dysfunction (Terentes-Printzios, D. et al., Abst 1021-109).

The arrhythmogenicity of melphalan was described, with an incidence of atrial arrhythmia of 11% (Feliz, V. et al., Abst 1135-142).

Troponin I was identified as a reliable predictor and marker of trastuzumab-induced cardiotoxicity (Cipolla, C.M. et al., Abst 1181-84).

Patch contraception with ethinylestradiol/norelgestromin and oral contraception with ethinylestradiol/norgestimate had no effect on serum amyloid A or plasminogen activator inhibitor 1 levels in healthy women, although both were associated with increases in C-reactive protein levels and the total antioxidant capacity because of the intrinsic antioxidant effects of estrogens (Paramsothy, P. et al., Abst 1130-103).

Nurse-administered propofol sedation was considered a safe and effective option for implantable cardioverter defibrillator implantation, although it was associated with common nonserious adverse events (Sayfo, S. et al., Abst 1191-148).

Treatment of epilepsy with valproate brought about decreases in the risk of myocardial infarction (Olesen, J.B. et al., Abst 1127-90).

The use of telgacepant in the treatment of migraine in patients with exercise-induced myocardial ischemia had no negative impact on exercise tolerance (Chaitman, B.R. et al., Abst 1043-263).

The use of the iso-osmolar contrast medium iodixanol did not result in reduced nephrotoxicity compared to the low-osmolar nonionic agent iomeprol in diabetic patients with impaired renal function (Koppara, T. et al., Abst 2504-522).

While clinical trial data supported the use of cilostazol (Soga, Y. et al., Abst 1057-358), improvements in reperfusion were demonstrated with recombinant interleukin-11 in experimental models of limb ischemia (Aitsebaomo, J. et al., Abst 1057-360).

Bosentan therapy in patients with Eisenmenger's syndrome improved pulmonary artery pressure and right ventricular function, resulting in effective symptom relief (Kaya, M. et al., Abst 1223-364).

The EPIC study confirmed the maintained cardiac iron-removing effect of deferasirox over 2 years in patients with cardiac siderosis secondary to thalassemia β (Pennell, D.J. et al., Abst 1150-239).

DISCLOSURES

The author states no conflicts of interest.