SHOULD TYPE 2 DIABETES MANAGEMENT BE MORE OF A PRIORITY IN POST-ACUTE CORONARY SYNDROME PATIENTS?

This symposium took place on 14th September 2015 as part of the 51st Annual Meeting of the European Association for the Study of Diabetes (EASD) in Stockholm, Sweden

Chairperson

Ele Ferrannini[1]

Speakers

Ele Ferrannini,[1] Stephen J Nicholls,[2] Jørgen Rungby,[3] Jean-Claude Tardif,[4] Faiez Zannad[5]

1. University of Pisa School of Medicine, Pisa, Italy
2. SAHMRI and University of Adelaide, Adelaide, Australia
3. Gentofte University Hospital, Hellerup, Copenhagen, Denmark
4. Montreal Heart Institute Research Centre, Montreal, Quebec, Canada
5. Université de Lorraine and CHU, Vandoeuvre-lès-Nancy, France

Disclosures: Ele Ferrannini has served on advisory boards for Boehringer Ingelheim, Eli Lilly, J&J, Sanofi, MSD, GSK, and Metabolon; has received research grants from Eli Lilly and Boehringer Ingelheim; and has served as a speaker for Takeda. Stephen Nicholls has received research support from AstraZeneca, Amgen, Anthera, Eli Lilly, Novartis, Cerenis, The Medicines Company, Resverlogix, InfraReDx, Roche, and LipoScience. He has also served as a consultant for, or received honoraria from, AstraZeneca, Eli Lilly, Anthera, Omthera, Merck, Takeda, Resverlogix, Sanofi-Aventis, CSL Behring, Esperion, and Boehringer Ingelheim. Jørgen Rungby has received research support from Merck, Novo Nordisk, and Servier, and has served as consultant for, or received honoraria from, AstraZeneca, Eli Lilly, Novo Nordisk, Merck, Takeda, Janssen, Sanofi-Aventis, and Boehringer Ingelheim. Jean-Claude Tardif has received research grants or honoraria from Roche, AstraZeneca, Pfizer, Merck, Servier, Eli Lilly, Cerenis, Thrasos, and Sanofi. Faiez Zannad has served as a consultant on steering committees, event committees, or data safety monitoring boards for AstraZeneca, Bayer, Boston Scientific, CardioRenal Diagnostics, CVCT, CVRx, Daiichi Sankyo, Eli Lilly, Janssen, Merck, Mitsubishi, Novartis, Pfizer, Quantum Genomics, Relypsa, Resmed, St Jude, Takeda, and ZS Pharma.
Acknowledgements: Writing assistance was provided by Dr Janet R. Davies, Atlantic Medical Writing, and funded by Takeda Pharmaceuticals International GmbH Limited.
Support: The symposium was organised by Takeda Pharmaceuticals International GmbH. All authors received honoraria for the preparation and delivery of their presentations. The views and opinions expressed are those of the authors and not necessarily of Takeda Pharmaceuticals International GmbH.
Citation: EMJ Diabet. 2015;3[1]:31-38.

MEETING SUMMARY

This symposium aimed to address the current issues in the management of patients with Type 2 diabetes (T2D) post-acute coronary syndrome (ACS), bringing together the views of both cardiologists and diabetologists. T2D increases the risk of ACS and is associated with a poorer prognosis for these patients. Although guidelines provide comprehensive recommendations for patients with ACS, specific guidance is lacking following hospital discharge for those with concomitant T2D. As a result, these patients receive suboptimal treatment compared with patients without T2D. The cardiovascular (CV) benefits of intensive glucose lowering alone for those with T2D are uncertain. However, knowledge of the CV safety profiles of available therapies helps diabetologists to provide individualised treatment for their patients. Currently, three studies have reported on the CV safety of dipeptidyl peptidase-4 (DPP-4) inhibitors in patients with T2D. However, active inclusion of patients who are both post-ACS (15–90 days) and at high risk of CV

disease (CVD) is rare. Only the DPP-4 alogliptin has been assessed in a CV safety outcome study in patients with this specific profile.

Opening Remarks from the Chair

Professor Ele Ferrannini

If the title of this symposium is framed as a question, 'Should T2D management be more of a priority in patients with post-ACS?', this implies that the answer is 'yes'. However, reaching this conclusion requires a much closer look at this topic and we endeavour to conduct such an exploration in this symposium. We will examine the current management of T2D in post-ACS patients from the point of view of both the cardiologist and the diabetologist. Several cardiovascular outcome trials (CVOTs) have assessed the CV safety of oral antidiabetic drugs (OADs) in patients with T2D, and the clinical implications of their findings are discussed. Of particular interest are: 1) the effect that this data may have on the optimal management of T2D, and; 2) gaps in the data that need to be addressed.

The ACS Patient Journey: Where Does T2D Fit In?

Professor Jean-Claude Tardif

Cardiovascular Disease in the Context of T2D

T2D is an independent risk factor for CVD,[1] which accounts for the death of over 70% of those with T2D.[2] Compared with age-matched controls, people with T2D have more than double the risk of developing CVD, even after adjusting for risk factors such as age, sex, systolic blood pressure (SBP), smoking, and body mass index.

ACS

ACS describes a group of disorders caused by acute myocardial ischaemia that results from atherosclerotic coronary disease. ACS is responsible for approximately 50% of all CVD-related deaths,[3] with around 15% of patients with ACS dying or experiencing a re-infarction within a month of diagnosis.[4] In the European Union, this translates to a total economic cost of ACS ranging between 1–3 billion euros per country annually,[5] whereas in the USA costs attributable to ACS account for approximately $150 billion per year.[3] ACS disorders can be divided into three categories distinguishable by electrocardiography and biomarkers (elevated troponin in myocardial infarction [MI]): ST-segment elevation myocardial infarction (STEMI), non-STEMI, and unstable angina.[6]

T2D and ACS

Reasons for T2D being a risk factor for ACS include the high prevalence of subclinical atherosclerosis in individuals with T2D who do not have a clinical history of coronary heart disease,[7] i.e. plaques that are present but are not yet causing symptoms. In addition, coronary disease has been shown to be more severe in patients with T2D,[1,8] in whom elevated levels of fasting blood glucose and glycosylated haemoglobin (HbA1c) contribute to the more rapid progression of coronary disease.[8] Patients with diabetes represent 20–30% of those with non-STEMI or unstable angina, and 23% of those with STEMI.[6,9] Approximately 65% of patients with acute MI, even those not known to have T2D, have impaired glucose regulation upon testing.[10] Hyperglycaemia on admission for ACS is predictive of poorer survival and an increased risk of complications, while persistent hyperglycaemia during acute MI increases the likelihood of in-hospital mortality.[10]

Treatment of ACS

For patients with STEMI, treatment aims to rapidly restore adequate coronary blood flow, primarily via mechanical revascularisation with primary angioplasty or fibrinolysis.[6,11] In patients with non-STEMI, treatment to alleviate ischaemia and associated symptoms is usually achieved by coronary revascularisation on a semi-urgent basis.[6,11] For patients who also have T2D, coronary artery bypass surgery is superior to percutaneous coronary intervention for treatment of complex or multi-vessel coronary disease.[6,11] Treatment of unstable angina should aim to reduce the risk of recurrence and commonly includes: dual antiplatelet therapy, a statin, a renin–angiotensin system (RAS) inhibitor (an angiotensin-converting enzyme [ACE] inhibitor or an angiotensin-receptor blocker [ARB]), and a beta-blocker.[11]

Guidelines provide comprehensive recommendations for the diagnosis and management of STEMI,[12] non-STEMI, and unstable angina,[6] but recommendations for glycaemic

control in patients with T2D and CVD are very general.[13] If hyperglycaemia is substantial, insulin-based regimens should be considered to achieve glycaemic control.[13] Guideline recommendations for patients with T2D following STEMI advocate lifestyle changes in addition to pharmacotherapy to achieve HbA1c <7.0%, but without increasing the risk of hypoglycaemia. All other risk factors, such as dyslipidaemia, blood pressure, obesity, and cessation of smoking, should be intensively monitored in collaboration with a diabetologist. However, there are currently no specific guidelines on the long-term management of T2D after ACS.[12]

The increased risk of short and long-term CV events in post-ACS diabetic patients clearly requires an individualised, intensive approach to treatment management,[6,12] yet treatment for post-ACS diabetic patients is suboptimal compared with non-diabetic patients. This results in higher rates of long-term mortality.[6,12,14]

Diabetes and Cardiovascular Risk Management in Post-ACS T2D patients: The Cardiologist's Perspective

Professor Stephen Nicholls

Dysglycaemia in ACS Patients

In patients with dysglycaemia, systemic therapies targeting metabolic risk factors are an important part of the interventional approach. At discharge from coronary care, treatment typically includes dual antiplatelet therapy, with patients having undergone early invasive revascularisation targeted to the culprit lesion, high-intensity statin therapy, and treatment with a beta-blocker and an ACE inhibitor or ARB.

Although a 2009 meta-analysis[15] showed that a more intensive approach to glucose lowering is favourable from a CV perspective, the studies analysed were heterogeneous in terms of glycaemic control. From the cardiologist's perspective, there is no compelling evidence for an aggressive approach to glycaemic control, and a target HbA1c of 7% rather than 6.5% may be appropriate.

Management of Metabolic Risk Factors Other Than Blood Glucose

Blood pressure lowering is unequivocally beneficial for patients with coronary disease, and particularly for those with T2D.[16] However, whether the optimal blood pressure for patients with T2D is <140 mmHg or 130 mmHg is unclear. In addition, reduction of low-density lipoprotein cholesterol (LDL-C) is crucially important and has unequivocal CV benefit in patients with T2D.[17] Treatment with a statin is the cornerstone of CV risk reduction, but even with aggressive reduction of LDL-C to <1.8 mmol/L (<70 mg/dL) not every patient is protected from a CV event; one of the predictors of progression is T2D, which reflects the pro-atherosclerotic milieu in these individuals. Other predictors are high blood pressure, low high-density lipoprotein cholesterol, and elevated apolipoprotein B. Progression occurs if any single risk factor is poorly controlled, thus increasing the risk of a subsequent CV event.

The benefit of targeting not just one but multiple risk factors has been shown by a small but elegant study, STENO-2, that compared intensive and conventional control of lipids, blood pressure, and glucose.[18] After 13.3 years of follow-up, intensive control resulted in significantly fewer CV events than did conventional control (hazard ratio: 0.41, 95% confidence interval: 0.25–0.67; p=0.0003). In a similar approach in patients with T2D and atheroma, outcome improved with each additional target achieved (HbA1c <7%, LDL-C <2.5 mmol/L, triglycerides <1.7 mmol/L, SBP <130 mmHg, C-reactive protein <2.0 mg/L).[19] From the cardiologist's perspective, the benefits of intensive glucose lowering alone are uncertain, but increasing evidence supports intensive modification of multiple risk factors to reduce CV risk in patients with T2D.

The Diabetologist's Perspective

Professor Jørgen Rungby

Cardiovascular Risk Reduction

As previously mentioned, the risk of CV events is reduced by lowering blood pressure, lowering cholesterol, and, to a certain extent, lowering blood glucose (Figure 1),[20] although further clarity in this area is needed.[15]

Choosing the Right Treatment

The diabetologist has a variety of treatments to select from today, with distinct modes of action to address the lack of glycaemic control. An individualised approach to T2D management is required because patients differ greatly in their insulin sensitivity and insulin production, as well as in their attitude to their diabetes and their ability to cope with episodes of hypoglycaemia.[21,22]

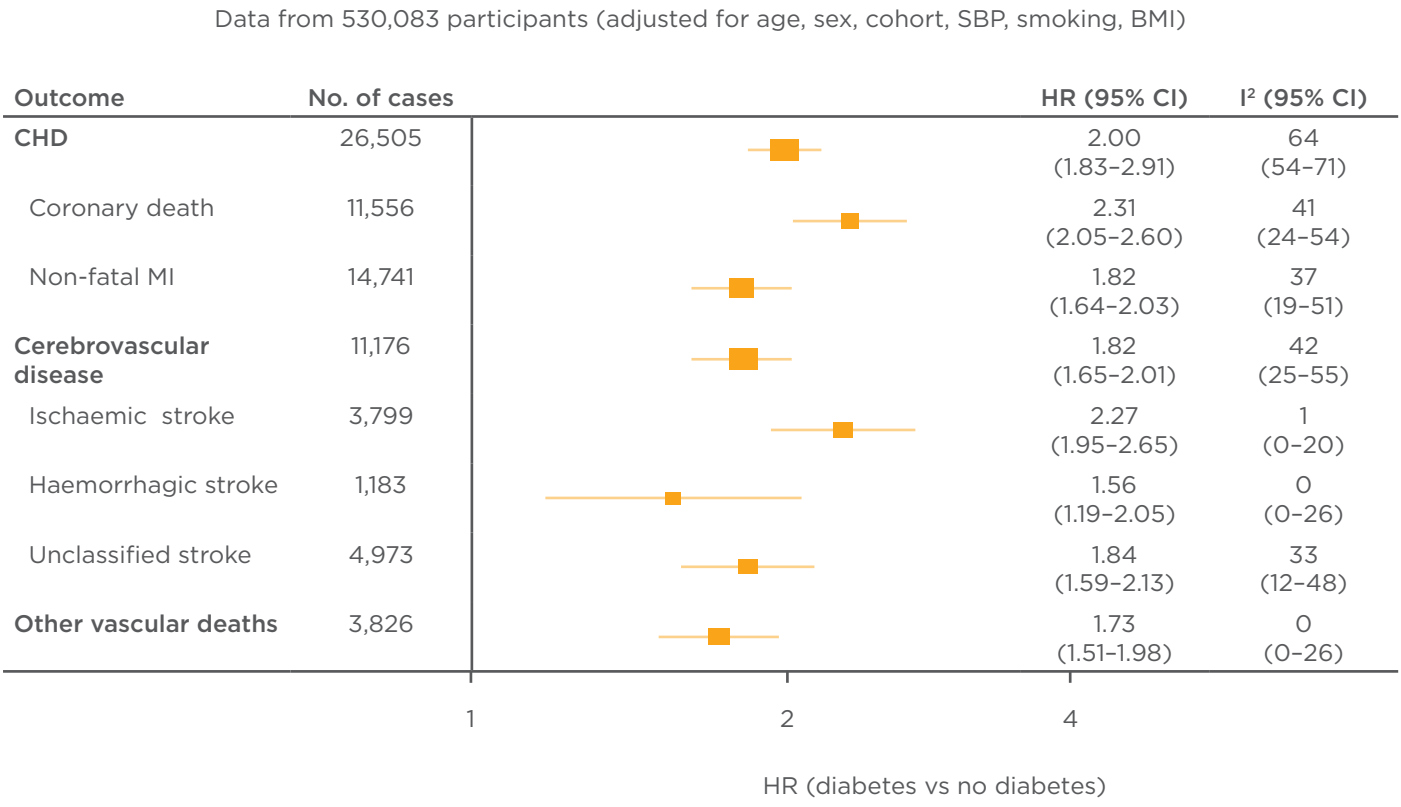

Figure 1: Reasons to achieve glycaemic control.[20]

BMI: body mass index; CHD: coronary heart disease; CI: confidence interval; HR: hazard ratio; MI: myocardial infarction; SBP: systolic blood pressure.

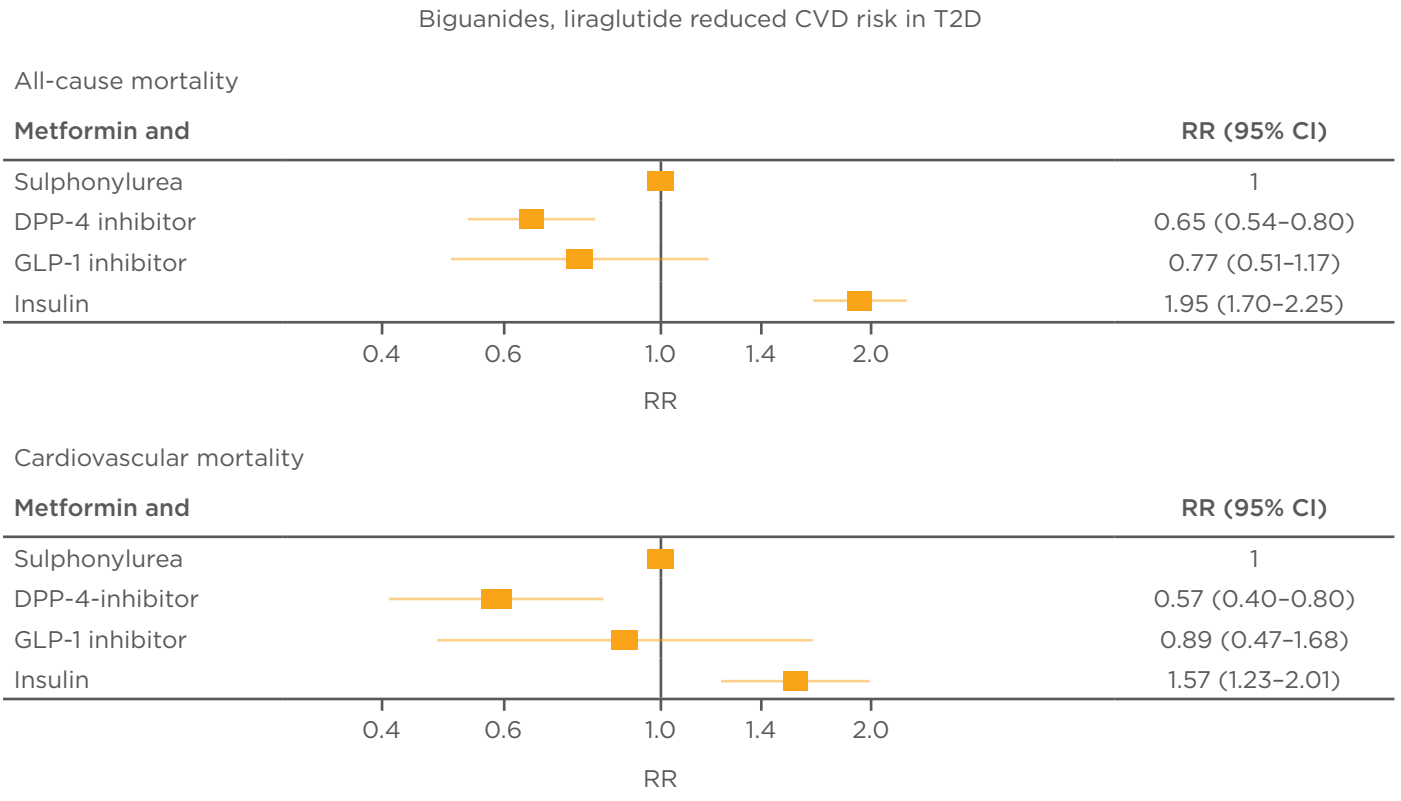

Figure 2: Comparison of T2D treatments: Danish second-line therapies.[28]

CI: confidence interval; CVD: cardiovascular disease; DPP-4: dipeptidyl peptidase-4; GLP-1: glucagon-like peptide-1; RR: risk ration; T2D: Type 2 diabetes.

Treatment decisions are even more complex for the post-ACS patient, for whom the first consideration is to 'do no harm'. Treatment with rosiglitazone has been shown to increase the risks of MI and death from CV causes.[23] The Prospective Pioglitazone Clinical Trial In Macrovascular Events (PROactive) CVOT showed a lower risk of CV events (MI or stroke) with pioglitazone compared with placebo.[24,25] In addition, the ORIGIN study showed that intensive treatment with insulin glargine appears to be neutral for CV risk, but also for treatment benefit.[26]

Using metformin as a reference in post-marketing surveillance data for comparing CV outcomes,[27] comparison of the adjusted risk of MI with various OADs used in Denmark shows that sulphonylureas appear to cause no harm, and indeed they are the most popular second-line post-ACS therapy in Denmark. However, the rate of prescriptions for sulphonylureas is decreasing.[28] Analysis of all-cause and CV mortality rates in patients receiving a sulphonylurea, a DPP-4 inhibitor, a glucagon-like peptide 1 (GLP-1) agonist, or insulin, each with metformin, showed that CV risk was lower with the incretin-based therapies (DPP-4 inhibitor and GLP-1 agonist) than with insulin or sulphonylurea, although it remains unclear whether this finding is true or a result of residual confounding (Figure 2).[28]

As hypoglycaemia prolongs QT interval and predisposes to further complications, treatments likely to cause hypoglycaemia in post-ACS patients should be avoided.[29] Awareness of the complications that post-ACS patients face is essential in order to make the right treatment choice, as is familiarity with the known CV safety profiles of available OADs. In summary, individualised treatment and goals for patients with T2D is key, with provision of multidisciplinary care ensuring that contact with the patient's cardiologist is maintained.

What Do We Know About the Safety of OADs in Post-ACS T2D Patients? Exploring Evidence from Recent Outcomes Studies

Professor Faiez Zannad

Reducing HbA1c has been shown to improve outcomes for patients with T2D and ACS. However, a beneficial effect against macrovascular disease remains unproven. A meta-analysis suggesting a 43% increase in risk of MI and a 64% increase in risk of death from CV causes associated with rosiglitazone use[30] prompted the European Medicines Agency (EMA) to suspend this treatment and launch a prospective, stand-alone study to examine any risks. The results of this study showed that rosiglitazone does not increase the risk of CV morbidity or mortality, but it does increase the risk of heart failure and some bone fractures.[31] Therefore, the EMA and the United States Food and Drug Administration (FDA) ruled that a CVOT was required to rule out unacceptable excess CV risk before approving anti-diabetes therapies.[32,33]

Cardiovascular Outcome Trials in T2D

Five CVOTs of similar but not identical design are assessing DPP-4 inhibitors. They all compare active therapy versus placebo in addition to standard care; changes in HbA1c, however, cannot be compared across trials. An important feature of the EXAMINE trial is that patients were randomised between 2 weeks and 3 months following discharge after hospitalisation due to ACS, and therefore represent a high-risk population.[34,35] The SAVOR-TIMI-53 trial enrolled patients receiving primary or secondary prevention therapy and therefore at lower risk,[36] as did the TECOS trial (Table 1).[37,38]

The result was that 88.4% of patients included in the trial had a history of MI, and 28% of patients had a history of heart failure. Results are similar in terms of the primary outcome (non-inferiority of the drug to placebo), which was met in all three trials. The rate of events in the primary CV endpoint was not increased by treatment with alogliptin[34] or with sitagliptin,[37] and was not increased or decreased by treatment with saxagliptin.[36] The 1-year event rate was around 4–5% in SAVOR-TIMI-53 and TECOS and approximately 8% in EXAMINE, in which the higher rate is explained by the higher-risk post-ACS population experiencing more events during the first 6 months. Looking at secondary endpoints: alogliptin did not increase the rate of events in the main secondary endpoints (CV death, MI, stroke, or urgent revascularisation due to unstable angina);[34] saxagliptin did not increase the rate of events in the secondary CV endpoint (composite of CV death, MI, stroke, hospitalisation for unstable angina, coronary revascularisation, or heart failure);[36] and sitagliptin did not increase the rate of events in the secondary CV endpoint (CV death, MI, or stroke).[37]

Table 1: Baseline characteristics comparison of the EXAMINE,[34,35] SAVOR-TIMI-53,[36] and TECOS[37,38] studies.

	EXAMINE alogliptin population (n=2,701)	SAVOR-TIMI saxagliptin population (n=8,280)	TECOS sitagliptin population (n=7,332)
Mean age (years)	61.0	65.1	65.4
Median/mean duration of diabetes (years)	7.1	10.3	11.6
Median/mean weight (kg)	90.2	87.7	Not reported
Median or mean BMI (kg/m^2)	29.7	31.1	30.2
Average/mean HbA1c at baseline (%)	9.0	8.0	7.2
CV history/risk factors			
Prior MI (%)	99.4	38	42.7
Prior stroke (%)	7.2	Not reported	17.7
Heart failure (%)	28.0	12.8	17.8
Hypertension (%)	92.5	81.2	Not reported
PAD (%)	9.7	11.9	16.6
Dyslipidaemia (%)	27.1	71.2	77
Coronary revascularisation (%)			
Overall	-	43.1	-
PCI	62.5	-	38.9
CABG	12.8	-	25.2

BMI: body mass index; CABG: coronary artery bypass graft; CV: cardiovascular; MACE: major adverse cardiovascular effect; MI: myocardial infarction; PAD: peripheral arterial disease; PCI: percutaneous coronary intervention.

It is unfortunate that heart failure was not a primary endpoint as it is the most common CV event in patients with T2D, but it is included in the secondary endpoint. The risk of hospitalisation for heart failure or the (composite) risk of CV death or hospitalisation for heart failure was not increased by alogliptin[39] or sitagliptin,[37] but more patients receiving saxagliptin (compared with those receiving placebo) were hospitalised for heart failure in the SAVOR-TIMI-53 trial.[40] The reason for this last finding is not clear. In terms of other important adverse events, including pancreatitis and malignancy, all three trials demonstrated the safety of the respective drug.

Rates of hypoglycaemia cannot be compared across the trials as it was defined differently in each trial. Nevertheless, the rates were very low in EXAMINE. This was similar for alogliptin and placebo,[34] and findings for sitagliptin were similar in the TECOS trial.[37] In SAVOR-TIMI-53, however, saxagliptin significantly increased the risk of hypoglycaemia. One may speculate that this higher rate of hypoglycaemia could have driven the increased risk of heart failure seen in this trial.

Overall, all three trials support the CV safety of the DPP-4 inhibitors alogliptin, saxagliptin, and sitagliptin. It must be kept in mind that alogliptin was tested in the highest-risk (post-ACS patient) population, whereas saxagliptin and sitagliptin were tested in patients with stable CVD.

EXAMINE from the Perspective of CVOTs of Other Classes of Antidiabetic Agents

Other CVOTs conducted in high-risk populations include: ELIXA (NCT01147250), for the GLP-1 receptor agonist lixisenatide; EMPA-REG OUTCOME™,[41] for the SGLT-2 inhibitor empagliflozin; and CANVAS (NCT01032629), for the SGLT-2 inhibitor canagliflozin.

The ELIXA trial has a design similar to that of EXAMINE and is addressing a similar post-ACS population. EMPA-REG OUTCOME and CANVAS have patient populations similar to those of TECOS and SAVOR-TIMI-53, and are assessing single and combined doses of the drugs. Early indications are that the results of the ELIXA trial are similar to those of EXAMINE (i.e. neutral: no excess harm, no benefit); full reports are expected soon.

The detailed results of the EMPA-REG-OUTCOME study are going to be made available in 2 days' time, but currently available information states that EMPA-REG OUTCOME met its primary endpoint and demonstrated superiority of empagliflozin in CV risk reduction when added to standard of care. The primary endpoint was defined as time to first occurrence of either CV death, non-fatal MI, or non-fatal stroke.[41,42]

Conclusions

Three trials have assessed the CV safety of DPP-4 inhibitors, although the EXAMINE study was the only one of these to actively include and provide data for patients with ACS at high risk of CVD. Many treatments for T2D now have a good record of CV safety and it may be time to revise the FDA guidance and move on to CV efficacy trials, perhaps with long-term follow-up trials (>10 years) being conducted in preference to multiple super-sized studies.

Optimal Management of Post-ACS T2D Patients: Panel Discussion

Chairperson
Professor Ele Ferrannini

Question: What is the role of baseline cardiovascular risk in trial outcome?

Discussion: Enrolling only high-risk patients would allow a shorter study duration with fewer participants. Because the event rate would be high, the number of events needed to achieve the outcome would be quickly reached. However, use of a high-risk population is important to demonstrate good tolerability, especially in terms of lack of aggravation of heart failure.

This response prompted a comment about the ethical issue of enrolling patients with high-risk disease in order to test a treatment that may prove harmful and to ask whether there are ways to improve CV risk assessment, perhaps using imaging to determine plaque composition. Subsequent discussion included that it would be useful to be able to do that and to be able to triage patients for therapy. However, there are many different kinds of events (e.g. arrhythmia) upon which most interventions will have no effect at all, and not all patients have the same modifiable risk. Therefore, the time frame in which damage may be shown to be reduced by treatment would be long.

Question: Is there any evidence that the degree of glycaemic control after ACS makes any difference to outcome?

Professor Rungby: No, there is no evidence, yet it remains important to control glycaemia and even more important to choose the right treatment and tailor that treatment to the patient's needs. Above all, there must be no risk attributable to the treatment.

Question: When will we move away from 'one-size-fits-all' treatment to individualised treatment?

Professor Nicholls: When we can use a marker or panel of markers to triage patients to a therapy and show that that therapy changes outcomes then we will be able to tailor therapy. Our patients are desperate for this approach because they are not going to take 27 medications on a daily basis, and we cannot afford it. So we need to be smarter in terms of which patients are selected for a specific treatment.

REFERENCES

1. Berry C et al. Coronary heart disease in patients with diabetes: part I: recent advances in prevention and noninvasive management. J Am Coll Cardiol. 2007;49(6):631-42.

2. Laakso M. Cardiovascular disease in type 2 diabetes: challenge for treatment and prevention. J Intern Med. 2001;249(3):225-35.

3. Kolansky DM. Acute coronary syndromes: morbidity, mortality, and pharmacoeconomic burden. Am J Manag Care. 2009;15(2 Suppl):S36-41.

4. Turpie AG. Burden of disease: medical and economic impact of acute coronary syndromes. Am J Manag Care. 2006;12(16 Suppl):S430-4.

5. Taylor MJ et al. Acute coronary syndromes in Europe: 1-year costs and outcomes. Curr Med Res Opin. 2007;23(3):495-503.

6. Hamm CW et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2011;32(23):2999-3054.

7. Goraya TY et al. Coronary atherosclerosis in diabetes mellitus: a population-based autopsy study. J Am Coll Cardiol. 2002;40(5):946-53.

8. Berry C et al. Glycaemic status

influences the nature and severity of coronary artery disease. Diabetologia. 2010;53(4):652-8.

9. Roe MT et al. Treatments, trends, and outcomes of acute myocardial infarction and percutaneous coronary intervention. J Am Coll Cardiol. 2010;56(4):254-63.

10. NICE. Hyperglycaemia in acute coronary syndromes. Available at: http://www.nice.org.uk/guidance/cg130. Last accessed: 21 October 2015.

11. NICE. Acute coronary syndromes (including myocardial infarction). Guidance and guidelines. Available at: http://www.nice.org.uk/guidance/qs68. Last accessed: 21 October 2015.

12. Van de Werf F et al. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. Eur Heart J. 2008;29(23):2909-45.

13. Rydén L et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). Eur Heart J. 2013;34(39):3035-87.

14. Dotevall A et al. Diabetes mellitus: clinical presentation and outcome in men and women with acute coronary syndromes. Data from the Euro Heart Survey ACS. Diabet Med. 2005;22(11):1542-50.

15. Ray KK et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. Lancet. 2009;373(9677):1765-72.

16. Emdin CA et al. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. JAMA. 2015;313(6):603-15.

17. Kearney PM et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet. 2008;371(9607):117-25.

18. Gaede P et al. Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med. 2008;358(6):580-91.

19. Kataoka Y et al. Multiple risk factor intervention and progression of coronary atherosclerosis in patients with type 2 diabetes mellitus. Eur J Prev Cardiol. 2013;20(2):209-17.

20. Sarwar N et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet. 2010;375(9733):2215-22.

21. Beck-Nielsen H. Pathophysiologic phenotypes of patients clinically diagnosed as type 2 diabetes. Available at: https://dd2.nu/media/5545/DD2%20phenotypes%202013%20version%207.pdf. Last accessed: 21 October 2015.

22. Inzucchi SE et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2015;38(1):e128-9.

23. Gerstein HC et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008;358(24):2545-59.

24. Erdmann E et al. The effect of pioglitazone on recurrent myocardial infarction in 2,445 patients with type 2 diabetes and previous myocardial infarction: results from the PROactive (PROactive 05) Study. J Am Coll Cardiol. 2007;49(17):1772-80.

25. Wilcox R et al. Effects of pioglitazone in patients with type 2 diabetes with or without previous stroke: results from PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events 04). Stroke. 2007;38(3):865-73.

26. ORIGIN Trial Investigators. Basal insulin and cardiovascular and other outcomes in dysglycemia. N Engl J Med. 2012;367(4):319-28.

27. Horsdal HT et al. Antidiabetic treatments and risk of hospitalisation with myocardial infarction: a nationwide case-control study. Pharmacoepidemiol Drug Saf. 2011;20(4):331-7.

28. Mogensen UM et al. Cardiovascular safety of combination therapies with incretin-based drugs and metformin compared with a combination of metformin and sulphonylurea in type 2 diabetes mellitus--a retrospective nationwide study. Diabetes Obes Metab. 2014;16(10):1001-8.

29. Chow E et al. Risk of cardiac arrhythmias during hypoglycemia in patients with type 2 diabetes and cardiovascular risk. Diabetes. 2014;63(5):1738-47.

30. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med. 2007;356(24):2457-71.

31. Home PD et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. Lancet. 2009;373(9681):2125-35.

32. FDA. Guidance for Industry. Diabetes mellitus—evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. Available from: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071627.pdf. Last accessed: 21 October 2015.

33. EMA (CHMP). Reflection paper. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/06/WC500187801.pdf. Last accessed: 21 October 2015.

34. White WB et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med. 2013;369(14):1327-35.

35. White WB et al. EXamination of cArdiovascular outcoMes with alogliptIN versus standard of carE in patients with type 2 diabetes mellitus and acute coronary syndrome (EXAMINE): a cardiovascular safety study of the dipeptidyl peptidase 4 inhibitor alogliptin in patients with type 2 diabetes with acute coronary syndrome. Am Heart J. 2011;162(4):620-6.e1.

36. Scirica BM et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013;369(14):1317-26.

37. Green JB et al. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2015;373(3):232-42.

38. Green JB et al. Rationale, design, and organization of a randomized, controlled Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) in patients with type 2 diabetes and established cardiovascular disease. Am Heart J. 2013;166(6):983-9.e7.

39. Zannad F et al. Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial. 2015;385(9982):2067-76.

40. Scirica BM et al. Heart failure, saxagliptin, and diabetes mellitus: observations from the SAVOR-TIMI 53 randomized trial. Circulation. 2014;130(18):1579-88.

41. Zinman B et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015. [Epub ahead of print].

42. Boehringer Ingelheim. Jardiance® demonstrated cardiovascular (CV) risk reduction in people with type 2 diabetes at high risk for CV events. Available at: http://www.boehringer-ingelheim.com/news/news_releases/press_releases/2015/20_august_2015_diabetes.html. Last accessed: 21 October 2015.