REVIEW ARTICLE

Necessity of Baseline Diabetic Autonomic Neuropathy Screening to Start Cardiovascular Safety Outcome Trials: A Focus on Antidiabetic Agents and Autonomic Neurointegrity

Shambo Samrat Samajdar[1], Shatavisa Mukherjee[2], Shashank Joshi[3], Santanu Kumar Tripathi[4]

Abstract

Diabetic autonomic neuropathy (DAN) is an individual risk factor for nonfatal myocardial infarction, nonfatal stroke, cardiovascular death, other major cardiovascular events like hospitalization for angina, hospitalization for heart failure, urgent revascularization for unstable angina, and death from any cause. Diabetic autonomic neuropathy screening is of paramount importance for cardiovascular risk stratification in patients with and without cardiovascular disease; as a marker for patients requiring more intensive monitoring during the perioperative period and other physiological stresses; and as an indicator for more intensive pharmacotherapeutic and lifestyle management of comorbid conditions. The present review highlights the necessity of DAN screening in starting cardiovascular outcome trials for antidiabetic agents.

Keywords: Antidiabetic agents, Cardiovascular outcome trials, Cardiovascular risk factors, Diabetic autonomic neuropathy.

Bengal Physician Journal (2022): 10.5005/jp-journals-10070-7069

Introduction

Diabetic autonomic neuropathy (DAN), one of the most neglected complications of diabetes, has significant negative impact on survival and quality of life in patients with diabetes apart from contributing to increased healthcare cost. Diabetic autonomic neuropathy is well prevalent in patients with type 2 diabetes (1–90%) and type 1 diabetes (20–73%).[1] Diabetic patients presenting with signs and symptoms of unexplained tachycardia, orthostatic hypotension, poor exercise tolerance etc. should be examined for detection of cardiovascular autonomic neuropathy (CAN).[2] Cardiovascular autonomic neuropathy is an important cause of morbidity and mortality in diabetic patients. High risk of cardiac arrhythmias and sudden death and silent myocardial ischemia are possible detrimental associates with CAN.[3] Screening for CAN is thus recommended to all asymptomatic type 2 diabetic patients at diagnosis and all type 1 diabetic patients after 5 years of disease, in particular those at greater risk for CAN because of a history of poor glycemic control (hemoglobin A1c >7%) or the presence of one major cardiovascular risk factor (among hypertension, dyslipidemia, and smoking), or the presence of macro or microangiopathic complications.[4]

CAN and Mortality

The Detection of Ischemia in Asymptomatic Diabetic Subjects[5] study showed a diminished Valsalva heart rate ratio being strongly associated with silent myocardial ischemia, independent of risk factors like age, sex, hypertension, and smoking. In the European Epidemiology and Prevention of Diabetes[6] study, autonomic dysfunction was present in one-third of type 1 diabetic patients, and was strongly associated with coexisting cardiovascular disease (CVD) after adjustment for age, hemoglobin A1c, and duration of diabetes. The association of CAN and mortality has also been established by observations from the Action to Control Cardiovascular Risk in Diabetes[7] trial, where death from CVD [including that related to arrhythmia, myocardial infarction (MI), heart failure, cardiovascular interventions, and stroke] was even more likely (1.94–2.95 times) in subjects with CAN. Furthermore, CAN in the presence of peripheral neuropathy was the highest predictor of CVD mortality [i.e., hazard ratio (HR) 2.95, p <0.008].

Cardiovascular Outcome Trials

Cardiovascular safety outcome trials (CVOTs) define their outcomes as a combination of major adverse cardiovascular events, which include nonfatal MI, nonfatal stroke, and cardiovascular death. Other major cardiovascular events of interest are hospitalization for angina, hospitalization for heart failure, urgent revascular post parandialization for unstable angina, and death from any cause.[8]

After rosiglitazone saga, the Food and Drugs Administration has suggested guidelines on conduct of studies on antidiabetic drugs to ascertain acceptable CV risk. Based on the CV risks of pre-approval clinical trials, guidelines have been made to conduct cardiovascular safety outcome trials prior to the drug approval or

[1,4]Department of Clinical Pharmacology, School of Tropical Medicine, Kolkata, West Bengal, India

[2]Department of Clinical and Experimental Pharmacology, School of Tropical Medicine, Kolkata, West Bengal, India

[3]Joshi Clinic, Indian College of Physicians, Mumbai, Maharashtra, India

Corresponding Author: Shambo Samrat Samajdar, Department of Clinical Pharmacology, School of Tropical Medicine, Kolkata, West Bengal, India, e-mail: shambo_sa2001@yahoo.co.in

How to cite this article: Samajdar SS, Mukherjee S, Joshi S, *et al*. Necessity of Baseline Diabetic Autonomic Neuropathy Screening to Start Cardiovascular Safety Outcome Trials: A Focus on Antidiabetic Agents and Autonomic Neurointegrity. Bengal Physician Journal 2022;9(1):9–12.

Source of support: Nil

Conflict of interest: None

after the drug has been approved, examining the cardiovascular safety of a drug in comparison to standard of care. Salient features of the guidelines are as follows:[9–11]

- An upper bound of the two-sided 95% CI for the risk ratio is less than 1.3 should be used as a key criterion for excluding unacceptable CV risk for new treatments of type 2 diabetes.
- Study subjects must include individuals with relatively advanced disease, elderly patients, and patients with some degree of renal impairment.
- A minimum of 2 years of CV safety data must be provided.
- All phase 2 and phase 3 studies should include a prospective independent adjudication of CV events. Adjudicated events should include CV mortality, MI, and stroke and can include hospitalization for acute coronary syndrome, urgent revascularization procedures, and possibly other end points.
- To satisfy the new statistical guidelines, the analysis of CV events may include a meta-analysis of all placebo-controlled trials, add-on trials (i.e., drug vs placebo, each added to standard therapy), and active-controlled trials, and/or an additional single, large safety trial may be conducted that alone, or added to other trials, would be able to satisfy this upper bound before a new drug application/biologics license application (NDA/BLA) is approved.

Major CVOTs in patients with diabetes namely LEADER, EMPA REG, TECOS, SAVOR-TIMI, EXAMINE, EXSCEL have not focused on CAN screening as a part of baseline measure, which may have been a confounding factor in the assessed CV outcomes.[12]

The assessment of CAN is thus of paramount importance for CV risk stratification in patients with and without CVD, as a marker for patients requiring more intensive monitoring during the perioperative period and other physiological stresses and as an indicator for more intensive pharmacotherapeutic and lifestyle management of comorbid conditions.[13]

Diabetic autonomic neuropathy (specially CAN) is an individual risk factor for nonfatal myocardial infarction, nonfatal stroke, cardiovascular death, and other major cardiovascular events like hospitalization for angina, hospitalization for heart failure, urgent revascularization for unstable angina, and death from any cause. From the major CV safety outcome trials in diabetes, it has been observed that there is no screening of autonomic neuropathy done in the trial subjects. Before subject recruitment for trial, it is imperative to match the baseline autonomic neuropathy status to definite statistical considerations in results. Instances like placebo arm having more patients with autonomic neuropathy (placebo arm thereby showing falsely more HR than active arm), or active arm having more patients with autonomic dysfunction (drugs thereby showing falsely more HR than placebo) may chance thus influencing the results. Emphasizing autonomic neuropathy screening of the recruited patients in CV safety trials is thus a need.

Antidiabetic Agents and Autonomic Neurointegrity

Antidiabetic drugs and their interactions with the autonomic nervous system are very interesting. Though there is dearth of clinical studies probing the same, with a brief view of the molecular mechanisms involved, certain clinical pharmacological concerns can be proposed.

For drug class like sulfonylureas, hypoglycemia is a significant concern as each hypoglycemic episode leads to hypoglycemia-associated autonomic failure. And in autonomic neuropathy patient's hypoglycemia unawareness is a challenge. Sulfonylurea produces positive inotropic action. It also increases blood pressure without influencing glucagon, insulin, or adrenaline in dogs.[14] In humans, studies suggest that glibenclamide therapy produces higher nocturnal blood pressures, where glibenclamide treatment arm has shown significantly higher plasma insulin levels. Increased insulin level is therefore responsible for insulin-mediated sympathetic stimulation and which contributes to hypertension. Using sulfonylurea may contribute to sympathovagal disharmony; however, more clinical studies need to validate the same. Newer sulfonylureas like gliclazide and glimiperide have no documented effects on autonomic nervous system (ANS) in diabetics. However, in healthy volunteers, during both euglycemia and hypoglycemia increased pancreatic polypeptide responses have been observed in glimepiride arm compared to placebo or glyburide arm. Pancreatic polypeptide (PP) which is released from specific cells in islets is a marker for parasympathetic nervous system activity. Parasympathetic nervous system activation by glimepiride by increasing PP response is thus an important hypothesis. More clinical studies on diabetic individuals shall ensue, which can demonstrate beneficial effects to sympathovagal balance.

Repaglinides have no direct interaction with autonomic nervous function. However, a pharmacogenomic study showed that although repaglinide treatment produces similar extent of glucose lowering among all type 2 diabetic patients tested, the variant of rs10494366 in NOS1AP had more serious insulin resistance before treatment, but repaglinide decreased HOMA-IR more effectively in this group than other genotype carriers. Repaglinide in that subset of type 2 diabetic patients might attenuate autonomic neuropathy.[15] In general, repaglinide increases insulin in the system and hyperinsulinemia is a cause of autonomic dysfunction. Apart from that hypoglycemia is an adverse effect of repaglinide which may aggravates hypoglycemia-associated autonomic failure and thus cannot be considered as an autonomic nervous system friendly drug.

Metformin targets insulin resistance and presumptively ameliorates autonomic neuropathy. Intravenous metformin produces reduction in arterial pressure and sympathetic nerve activity. Meta-analysis suggests that metformin therapy causes reduction in systolic and diastolic pressure and is associated with a significant improvement in cardiac sympathovagal balance.[16] However, more clinical studies are required to be watchful regarding the beneficial effects. Metformin-related gastrointestinal adverse effects may also aggravate autonomic neuropathy-related complications like night time diarrhea, constipation, and gastroparesis.

Pioglitazone significantly decreased muscle sympathetic nerve activity and homeostasis model assessment of insulin resistance index in type 2 diabetic patients with recent MI compared with alpha-glucosidase inhibitors.[17] Improvement in insulin resistance is associated with reduction in sympathetic nerve activity and drugs like pioglitazone which ameliorates insulin resistance is beneficial in producing sympathoinhibitory effects thus helping to attain sympathovagal balance.

Alpha glucosidase inhibitors like acarbose, miglitol, and voglibose may ameliorate autonomic neuropathy-related gastric

complications. In one study it has been seen that 100 mg acarbose significantly improves postparandial hypotension in autonomic failure but no mechanism is established which suggests these molecules improve dysautonomia. Glycemic variability leading to fluctuation of plasma glucose level is related with heart rate variability and activation of the sympathetic nervous system. In one study, miglitol shows reduction in glucose fluctuation and reducing heart rate variability and inhibition of sympathetic nervous system. There are no evidences that suggest direct interaction between the autonomic nervous system and alpha glucosidase inhibitors.

Unfavorable autonomic interactions with incretin-based therapy have created quite uproar in recent times. Short-acting GLP1 analogues like exenatide and lixisenatide are shown to cause modest and transient increase in heart rate, while more potent longer-acting GLP1 analogues like dulaglutide and liraglutide have shown sustainable rise in heart rate up to 10 bpm.[18] Supra physiologic concentration of GLP1 analogue stimulates the sympathetic nervous system and inhibits the parasympathetic nervous system. Few studies showed that due to sympathetic nervous system stimulation liraglutide increases the heart rate. GLP1RA-related increase in heart rate has been associated with relative sympathetic stimulation compared to the inhibition of parasympathetic nervous system. It is also proposed to be associated with direct stimulation of sinoatrial node. Another study interestingly showed that GLP1R agonists increase heart rate via regulating the autonomic nervous system function, and stimulation of the atrial GLP1R. But following exposure to GLP1R agonists in the intact heart, isolated atrial GLP1R not produces direct chronotropic effect. Hence, cardiac GLP1R-mediating heart rate control needs autonomic neural involvement and do not depend on heart's autonomy. However, more clinical studies should probe the effect of incretin-based therapy on sympathovagal relationship. GLP1 analogues also aggravate gastroparesis in already diagnosed autonomic neuropathic patients. It is imperative to exercise caution in treating autonomic dysfunction in patients receiving incretin-based therapy specially GLP1 analogue.

SGLT2 inhibitors like empagliflozin, dapagliflozin, and canagliflozin are showing remarkable cardiovascular benefits; however, the underlying mechanism still remains unclear. BP reduction seen in all cardiovascular outcome trials is not associated with compensatory rise in heart rate, which suggests possibility of inhibition of sympathetic nervous system by this class of drugs. Recent studies have shown that SGLT2 inhibitors inhibit sympathetic nerve activity by decreasing insulin level and leptin and plasma glucose value. They also decrease insulin resistance and hyperinsulinemia, which in turn inhibit the activation of carotid body. SGLT2 inhibitors lower sodium volume leading to the inhibition of activating organum vasculosum laminae terminalis.[19] Scientists are in search of some other unexplored mechanisms by which this class of drugs inhibit sympathetic nerve activity. SGLT2 inhibitors therefore improve sympatho-vagal relationship by inhibiting sympathetic nervous system. Inhibition of SGLT2 has also been hypothesized to cause sympatho-inhibitory class-effect during the sleeping time leading to improvement of the circadian rhythm of sympathetic nervous activity. But it is essential to take a vigilant approach using SGLT2 inhibitors in patients who have already advanced cardiac autonomic neuropathy (associated with postural hypotension) as it may worsen postural blood pressure drop by inhibiting further sympathetic nervous activity.

In insulin therapy, hypoglycemic unawareness is a serious concern, which may contribute to autonomic neuropathy. Type 2 diabetic patients demonstrate higher sympathetic nerve activity than normal subjects. A study by Anderson et al. showed the acute rise in plasma insulin increasing muscle sympathetic nerve activity in healthy young volunteers.[20] Three prime mechanisms postulated were direct effect on the central nervous system, hypoglycemia by insulin, and feedback mechanism against vasodilatation induced by insulin.[20] So, insulin therapy also possesses some risks regarding increase in sympathetic activity and therefore creating imbalance between sympathetic and parasympathetic functional status. Early and timely initiation of insulin would help in intensive glycemic control leading to reduce beta cell stress. Good glycemic memory in early days could produce legacy effect and prevent complications of diabetes, reduce the need of antidiabetic medicine number to maintain glycemic control.[21] It is important to explore autonomic functional status in this group of patients.

In India drug regulators are not stringent regarding CVOT of newer antidiabetic drugs. Considering high prevalence of CVD in India especially the involvement of younger patient population, it is high time for regulators to consider CVOT in Indian aspect. Different adaptive designs (considering subsequent CV safety study during seamless phase II/III trials), factorial designs would increase efficiency by reducing the timeline and cost. But we need to get equipoise baseline autonomic functions also in the study population before initiating CVOT, which was overlooked by the USFDA.[22]

Conclusion

Glycemic control is extremely important to control autonomic neuropathy. So, it is important to control glucose value by any suitable patient-specific antidiabetic agents with special attention for avoiding hypoglycemia. It is important to understand the effect of antidiabetic drugs on function of autonomic nervous system and need to emphasize on prospective observational studies to explore this. Each CVOT must consist of baseline autonomic neuropathy screening and baseline parameters should be matched before conducting.

Highlights

- Glycemia control is imperative in controlling autonomic neuropathy.
- Emphasizing autonomic neuropathy screening of the recruited patients in CV safety trials is a need.
- Before subject recruitment, baseline neuropathy status should be matched to definite statistical considerations in results.

References

1. Rebrina SV, Barada A, Duvnjak LS. Diabetic Autonomic Neuropathy. Diabetologia Croatica 2013;42(3):73–79.
2. Serhiyenko VA, Serhiyenko AA. Cardiac Autonomic Neuropathy: Risk Factors, Diagnosis and Treatment. World J Diabet 2018;9(1):1–24. DOI: 10.4239/wjd.v9.i1.1.
3. Vinik AI, Erbas T, Casellini CM. Diabetic Cardiac Autonomic Neuropathy, Inflammation and Cardiovascular Disease. J Diabet Investigat 2013;4(1):4–18. DOI: 10.1111/jdi.12042.

4. Tesfaye S, Boulton AJM, Dyck PJ, et al. Diabetic Neuropathies: Update on Definitions, Diagnostic Criteria, Estimation of Severity, and Treatments. Diabet Care 2010;33(10):2285–2293. DOI: 10.2337/dc10-1303.
5. Wackers FJ, Young LH, Inzucchi SE, et al. Detection of Silent Myocardial Ischemia in Asymptomatic Diabetic Subjects: The DIAD Study. Diabet Care 2004;27:1954–1961. DOI: 10.2337/diacare.27.8.1954.
6. Kempler P, Tesfaye S, Chaturvedi N, et al., the EURODIAB IDDM Complications Study Group. Autonomic Neuropathy is Associated with Increased Cardiovascular Risk Factors: The EURODIAB IDDM Complications Study. Diabet Med 2001;19:900–909. DOI: 10.1046/j.1464-5491.2002.00821.x.
7. Pop-Busui R, Evans GW, Gerstein HC, et al. Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of cardiac autonomic dysfunction on mortality risk in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Diabetes Care 2010;33(7):1578–1584. DOI: 10.2337/dc10-0125.
8. Marso SP, McGuire DK, Zinman B, et al. Design of DEVOTE (Trial Comparing Cardiovascular Safety of Insulin Degludec vs Insulin Glargine in Patients With Type 2 Diabetes at High Risk of Cardiovascular Events)–DEVOTE 1. Am Heart J 2016;179:175–183. DOI: 10.1016/j.ahj.2016.06.004.
9. US Food and Drug Administration Guidance for industry: Diabetes mellitus—Evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. Available from: https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071627.pdf
10. Hirshberg B, Raz I. Impact of the U.S. Food and Drug Administration Cardiovascular Assessment Requirements on the Development of Novel Antidiabetes Drugs. Diabet Care 2011;34:S101–S106. DOI: 10.2337/dc11-s202.
11. John M, Unnikrishnan AG, Kalra S, et al. Cardiovascular Outcome Trials for Anti-Diabetes Medication: A Holy Grail of Drug Development? Ind Heart J 2016;68(4): 564–571. DOI: 10.1016/j.ihj.2016.02.017.
12. Schnell O, Rydén L, Standl E, et al; D&CVD EASD Study Group. Updates on cardiovascular outcome trials in diabetes [published correction appears in Cardiovasc Diabetol 2017 Nov 15;16(1):150]. Cardiovasc Diabetol 2017;16(1):128. DOI: 10.1186/s12933-017-0610-y.
13. Maser RE, Mitchell BD, Vinik AI, et al. The Association between Cardiovascular Autonomic Neuropathy and Mortality in Individuals with Diabetes: A Meta-Analysis. Diabet Care 2003;26:1895–1901. DOI: 10.2337/diacare.26.6.1895.
14. Williams S, Abbott D, Morfis L, et al. Effects of Glibenclamide on Blood Pressure and Cardiovascular Responsiveness in Non-Insulin Dependent Diabetes Mellitus. J Hypertens 1998;16:705–711. DOI: 10.1097/00004872-199816050-00019.
15. Wulffelé MG, Kooy A, de Zeeuw D, et al. The Effect of Metformin on Blood Pressure, Plasma Cholesterol and Triglycerides in Type 2 Diabetes Mellitus: A Systematic Review. J Intern Med 2004;256:1–14. DOI: 10.1111/j.1365-2796.2004.01328.x.
16. Kobayashi D, Takamura M, Murai H, et al. Effect of Pioglitazone on Muscle Sympathetic Nerve Activity in Type 2 Diabetes Mellitus with α-Glucosidase Inhibitor. Auton Neurosci 2010;158:86–91. DOI: 10.1016/j.autneu.2010.05.003.
17. Gill A, Hoogwerf BJ, Burger J, et al. Effect of Exenatide on Heart Rate and Blood Pressure in Subjects with Type 2 Diabetes Mellitus: A Double-Blind, Placebo-Controlled, Randomized Pilot Study. Cardiovasc Diabetol 2010;9:6. DOI: 10.1186/1475-2840-9-6.
18. Nakatani Y, Kawabe A, Matsumura M, et al. Effects of GLP-1 Receptor Agonists on Heart Rate and the Autonomic Nervous System Using Holter Electrocardiography and Power Spectrum Analysis of Heart Rate Variability. Diabet Care 2016;39:e22–e23. DOI: 10.2337/dc15-1437.
19. Guyenet PG. Putative Mechanism of Salt-dependent Neurogenic Hypertension: Cell-Autonomous Activation of Organum Vasculosum Laminae Terminalis Neurons by Hypernatremia. Hypertension 2017;69:20–22. DOI: 10.1161/HYPERTENSIONAHA.116.08470.
20. Anderson EA, Hoffman RP, Balon TW, et al. Hyperinsulinemia Produces both Sympathetic Neural Activation and Vasodilation in Normal Humans. J Clin Invest 1991;87:2246–2252. DOI: 10.1172/JCI115260.
21. Samajdar SS, Mukherjee S, Tripathi SK, et al. Early Initiation of Insulin Therapy in Newly Diagnosed Patients with Type 2 Diabetes and Exploring the Legacy Effect—A Single-arm Prospective Observational Study. Bengal Phys J 2020;7(3):52–54. DOI: 10.5005/jp-journals-10070-7031.
22. Samajdar SS, Mukherjee S, Joshi S, et al. Cardiovascular Outcome Trials in Indian Perspective: A Call to Indian Drug Regulators. J Indian Med Assoc 2020;118(6):70–72.