THE LANCET

Supplementary webappendix

This webappendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Ismail-Beigi F, Craven T, Banerji MA, et al. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. *Lancet* 2010; published online June 29. DOI:10.1016/S0140-6736(10)60576-4.

Appendix

Microvascular outcomes related to three main clinical areas (kidney function, diabetic eye complications, and peripheral neuropathy) were defined in the ACCORD protocol at study outset. Endpoints included in analyses are shown in Table 1 of the manuscript. Details of measurement for individual components of each clinical area are described below.

Kidney function: microvascular related kidney parameters were based on ACCORD Central Laboratory measurement of serum and urine creatinine, and urine albumin. Serum and urine creatinine were determined enzymaticaly on a Roche Double Modular P Analytics automated analyzer. Inter-assay precision is consistently <1.4% for the high and <2.2% for the low quality control samples. Urine microalbumin was determined by immunonephelometry on a Siemens BNII nephelometer. Sensitivity of the assay is 0.16 mg/dL with inter-assay CV's of 3.0%, 2.6% and 4.9% for control levels of 0.89 mg/dL, 6.6 mg/dL, and 16.1 mg/dL, respectively. All serum and urine samples were analyzed on the day of sample receipt. Estimated glomerular filtration rate (eGFR) was also calculated at each serum creatinine measurement using the 4-variable MDRD Study equation: $eGFR = 186 \times (\text{serum creatinine})^{-1.154} \times \text{age}^{-0.203} \times 1.212$ (if black) × 0.742 (if female).[1] In addition to laboratory assays to measure renal function, follow-up surveillance for dialysis, end-stage renal disease, and renal transplantation was performed by updated medical history at four month clinic visits throughout the trial.

Diabetic eye complications: assessment of eye surgeries for diabetes related conditions (photocoagulation or vitrectomy for retinopathy, and cataract removal) was performed by participant self report at annual follow-up clinic visits. At each annual exam, participants were asked whether or not they "…had eye surgery, including laser photocoagulation, during the past year…" with areas provided to specify "retinal laser photocoagulation for diabetic retinopathy" or "vitrectomy for diabetic retinopathy", and "cataract removal" or "yag laser for cataract capsule".

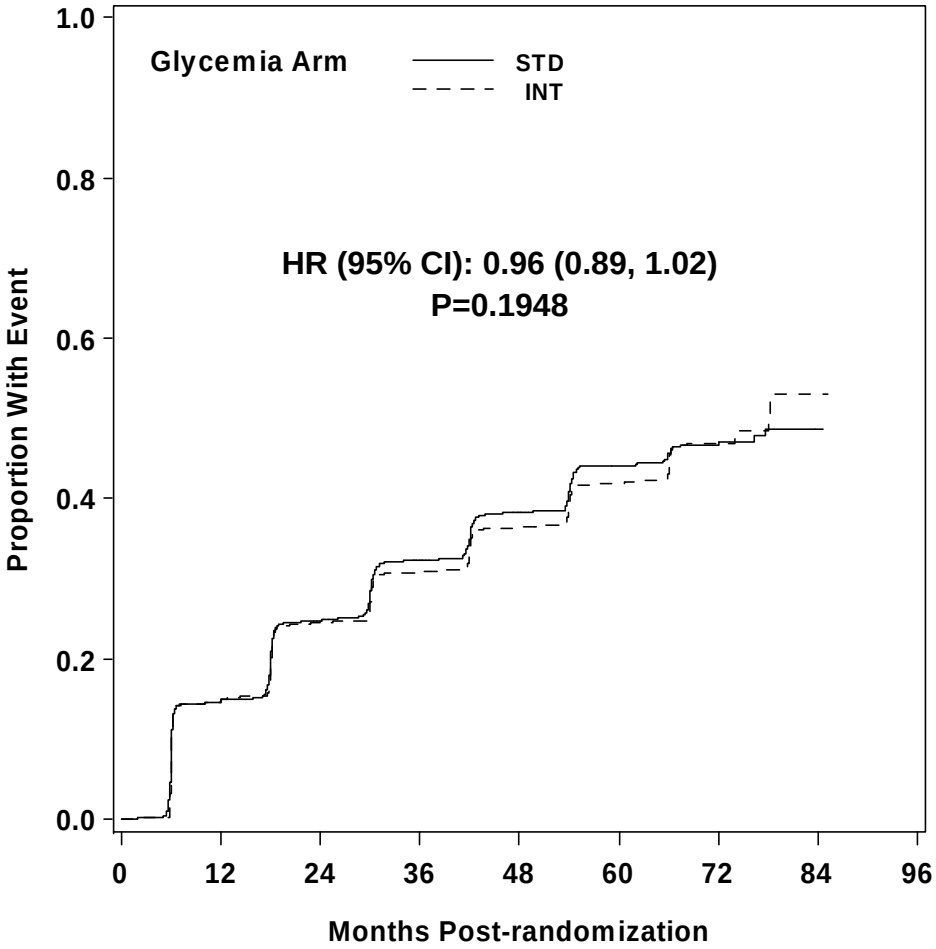
In addition to questions regarding eye surgery within the last year, ACCORD participants had an eye exam to assess visual acuity at baseline, every two years during follow-up, and at exit from the study. This exam included assessment of visual

acuity using the R chart of the Lighthouse Distance Visual Acuity Test charts (Lighthouse Low Vision Products, 36-02 Northern Boulevard, Long Island, New York 11101), which are modified Early Treatment Diabetic Retinopathy Study (ETDRS) charts. Testing was performed at a distance of 4 meters and, for patients with sufficiently reduced vision, at 1 meter. Participants were assessed for "habitual vision" with usual correction for the distance utilizing current distance glasses or contacts. Participants with visual acuity score of 70 or less (Snellen fraction less than 20/40), were referred to their ophthalmologist for follow-up exam. Participants with a decrease in baseline visual acuity score ≥ 15 units in either eye at any follow-up exam were considered to have outcome Eye-3 (a 3-line or greater worsening in visual acuity).

Peripheral Neuropathy: assessment of diabetic neuropathy in the extremities was performed annually via a standardized clinical exam in the ACCORD study sites. Neuropathic signs were assessed using the Michigan Neuropathy Screening Instrument (MNSI) examination, which comprises a structured assessment of the feet to identify deformities, dry skin, calluses, infection, fissure, or ulcers; and evaluation of ankle reflexes and vibration sensation in the great toe. For this study, neuropathy was defined operationally as a score >2.0 on the MNSI examination, a threshold defined by prior validation studies.[2]

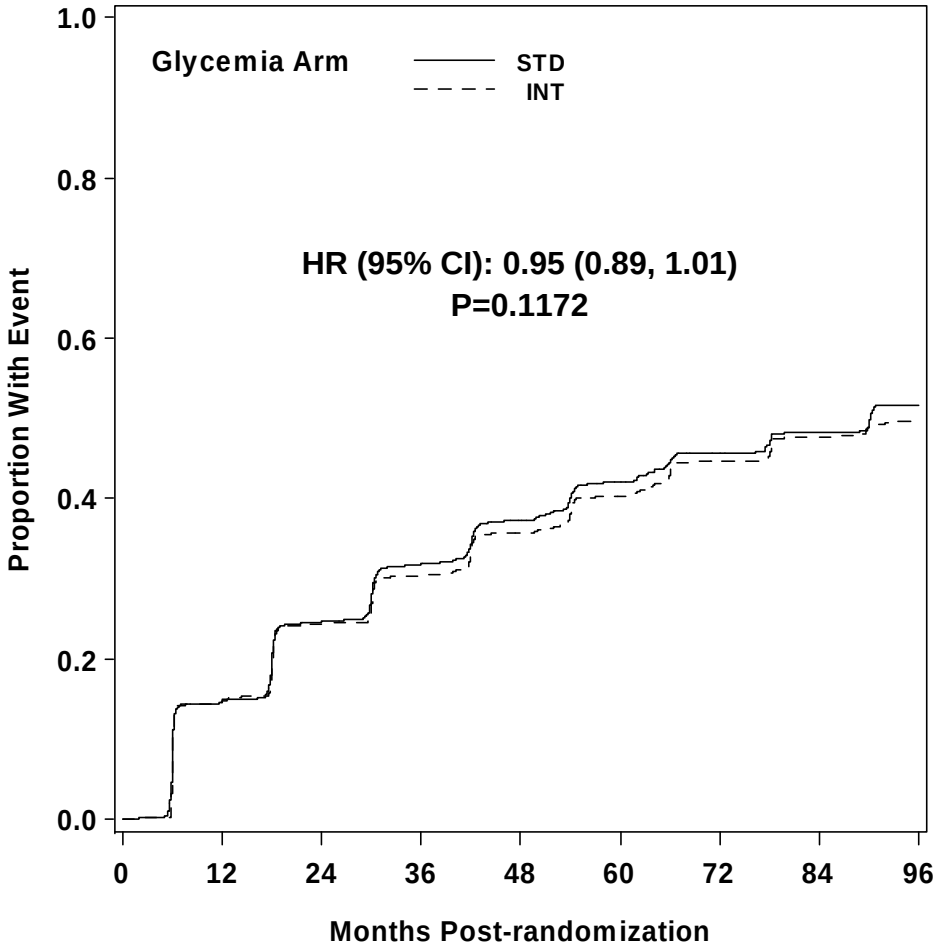
Appendix References

1. Levey AS, Coresh J, Greene T, Stevens LA, Zhang Y, Hendriksen S, Kusek JW, Van Lente F. Using standardized serum creatinine values in the Modification of Diet in Renal Disease study equation for estimating glomerular filtration rate. *Ann Intern Med* 2006; **145:** 247-54.
2. Feldman EL, Stevens MJ, Thomas PK, Brown MB, Canal N, Greene DA. A practical two-step quantitative clinical and electrophysiological assessment for the diagnosis and staging of diabetic neuropathy. *Diabetes Care* 1994; **17:** 1281-9.



Follow-up numbers at risk

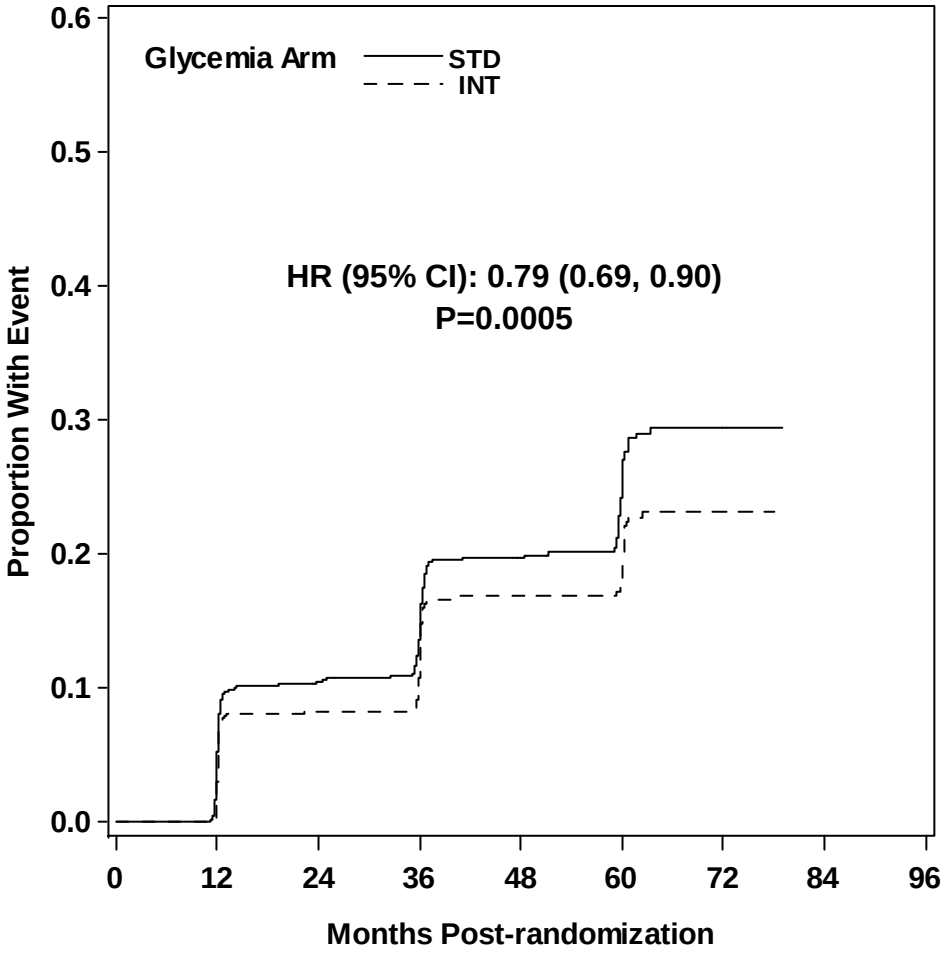
Month	12	24	36	48	60	72	84
	8301	6385	3856	1668	550	280	4

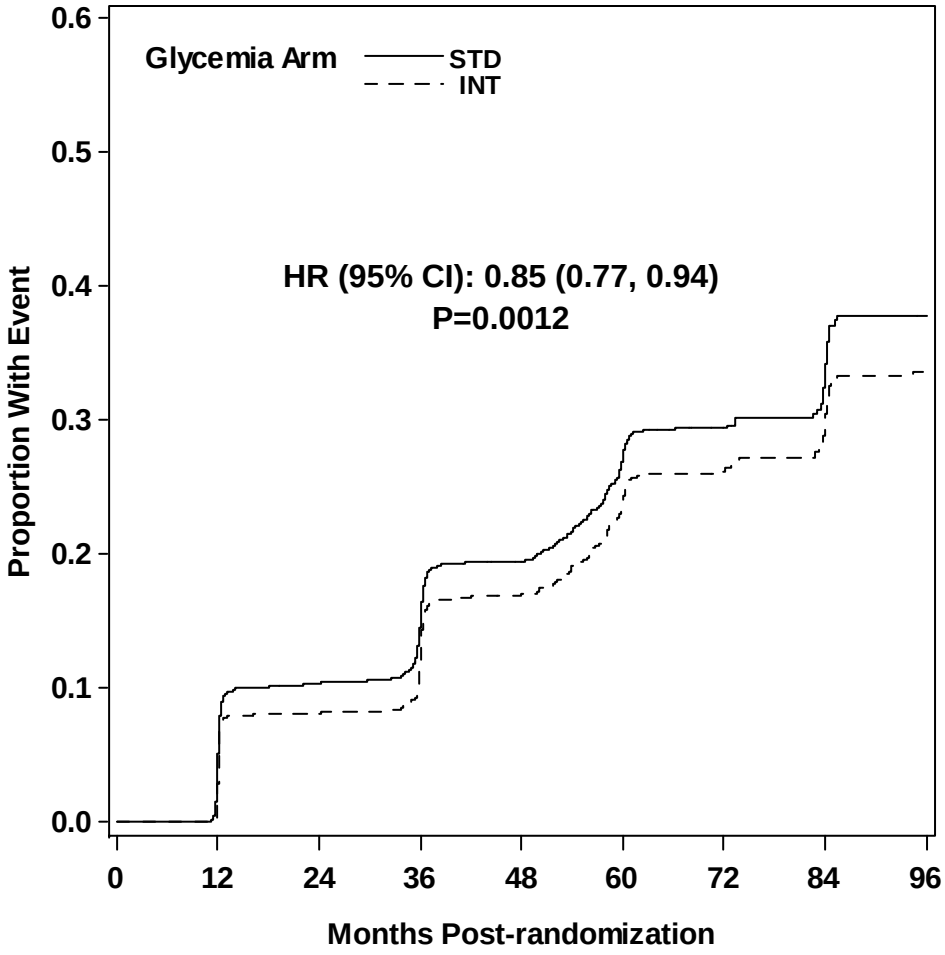


Follow-up numbers at risk

Month	12	24	36	48	60	72	84	96
	8374	7215	6357	4805	2680	803	454	1

Figure A1. Kaplan-Meier curves for the microvascular secondary composite outcome (development of renal failure or retinal photocoagulation or vitrectomy to treat retinopathy, or score >2.0 on MNSI) by glycemia arm. Panel A: data until transition of intensive glycemia arm to standard therapy (N=10215). Panel B: all data through end of study (N=10234). Hazard ratios adjusted for baseline history of clinical cardiovascular disease and second trial treatment arm assignment.





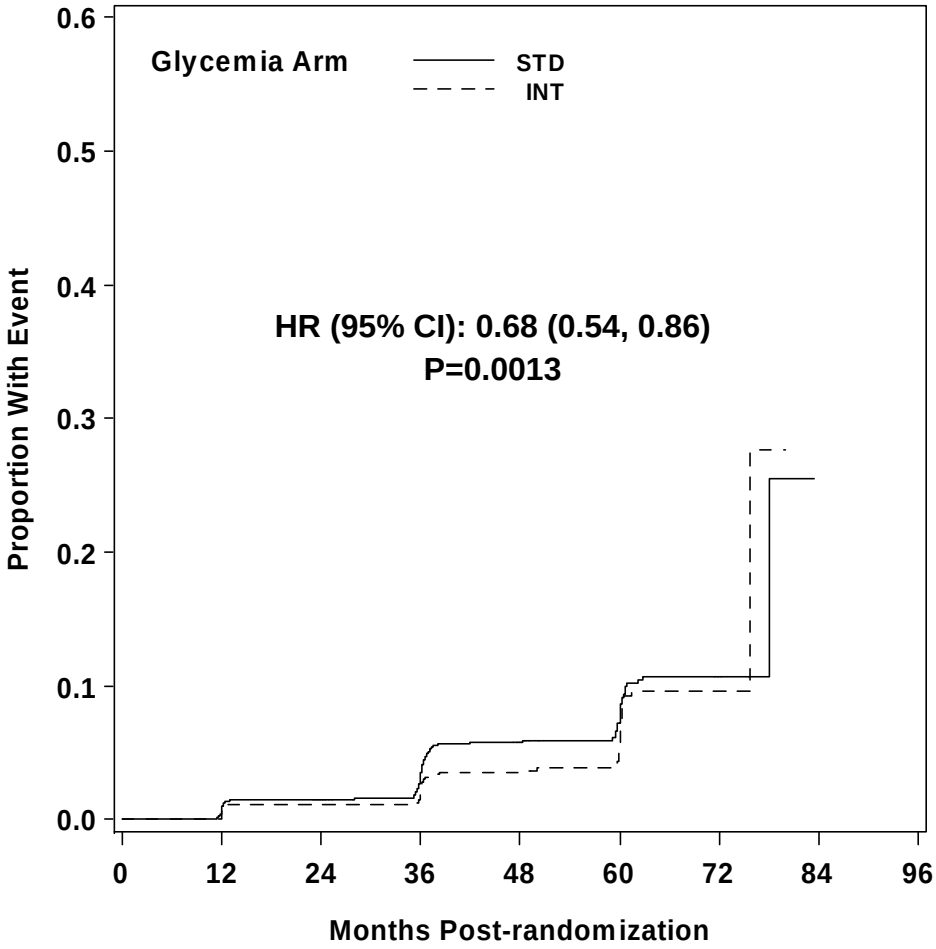
Follow-up numbers at risk

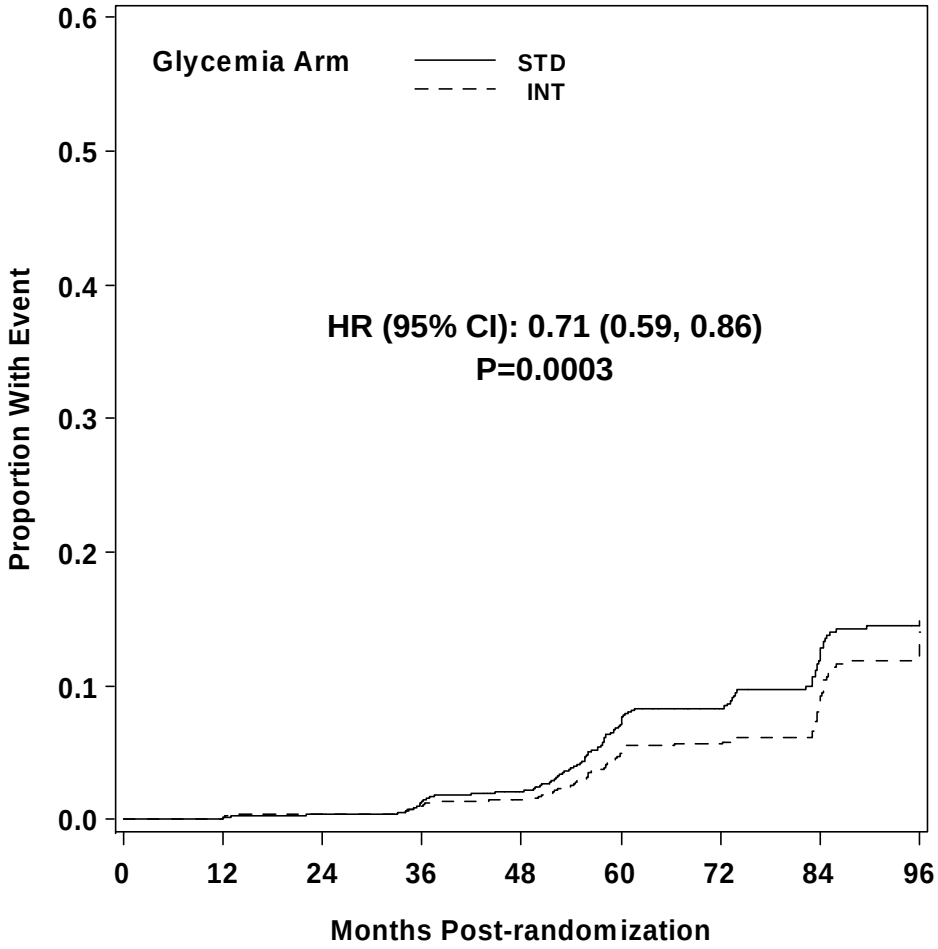
Month	12	24	36	48	60	72	84
	6190	4442	2382	1469	459	259	0

Follow-up numbers at risk

Month	12	24	36	48	60	72	84	96
	6277	5794	5337	4220	2360	736	424	1

Figure A2. Kaplan-Meier curves for microvascular outcome Neph-1 (development of microalbuminuria) by glycemia arm. Panel A: data until transition of intensive glycemia arm to standard therapy (N=6436). Panel B: all data through end of study (N=6523). Hazard ratios adjusted for baseline history of clinical cardiovascular disease and second trial treatment arm assignment.





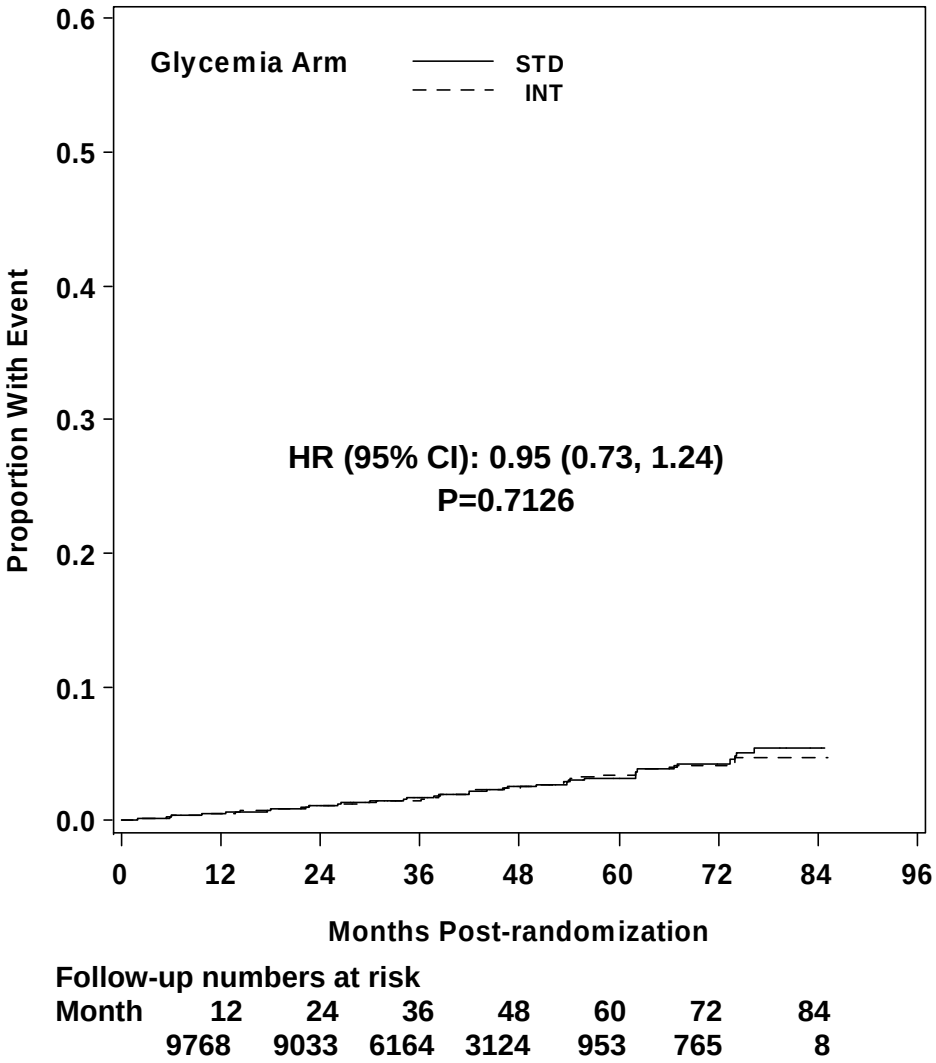
Follow-up numbers at risk

Month	12	24	36	48	60	72	84
	8645	6551	3632	2358	753	424	0

Follow-up numbers at risk

Month	12	24	36	48	60	72	84	96
	8812	8586	8184	6841	4010	1314	749	392

Figure A3. Kaplan-Meier curves for microvascular outcome Neph-2 (development of macroalbuminuria) by glycemia arm. Panel A: data until transition of intensive glycemia arm to standard therapy (N=8695). Panel B: all data through end of study (N=8821). Hazard ratios adjusted for baseline history of clinical cardiovascular disease and second trial treatment arm assignment.



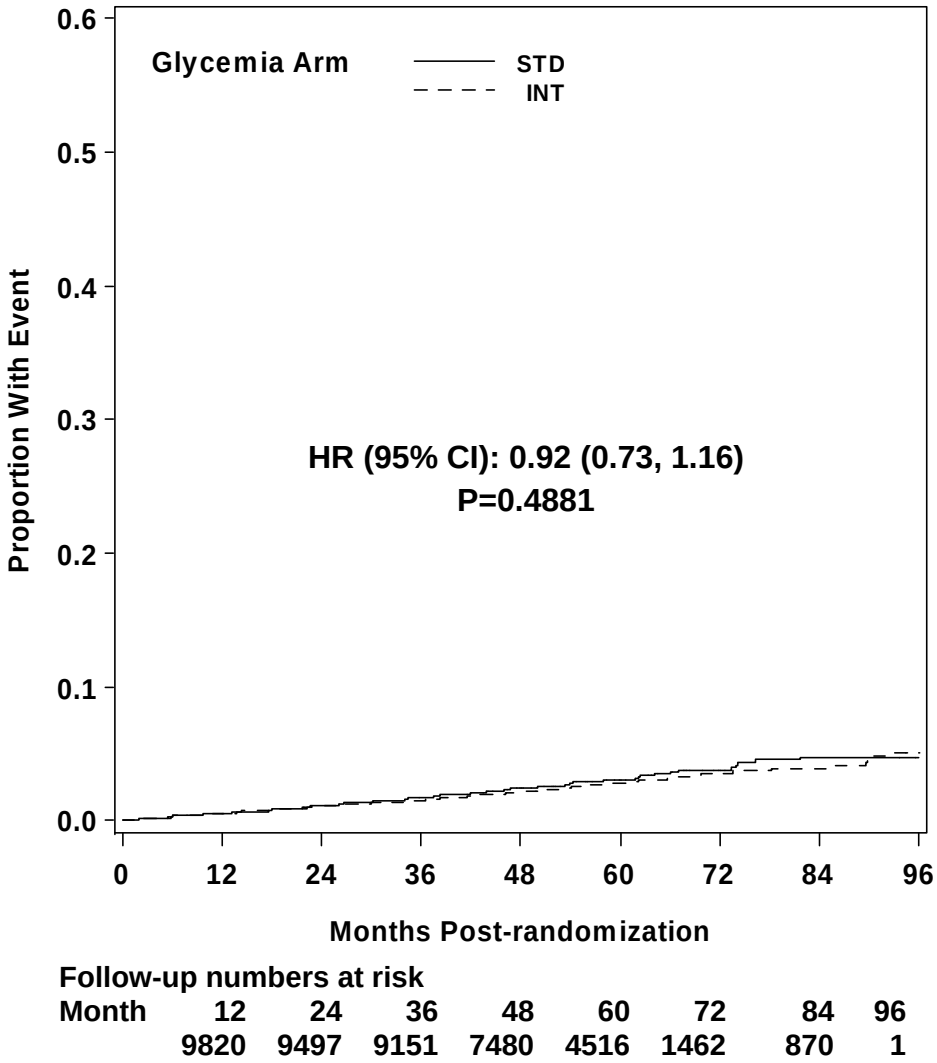
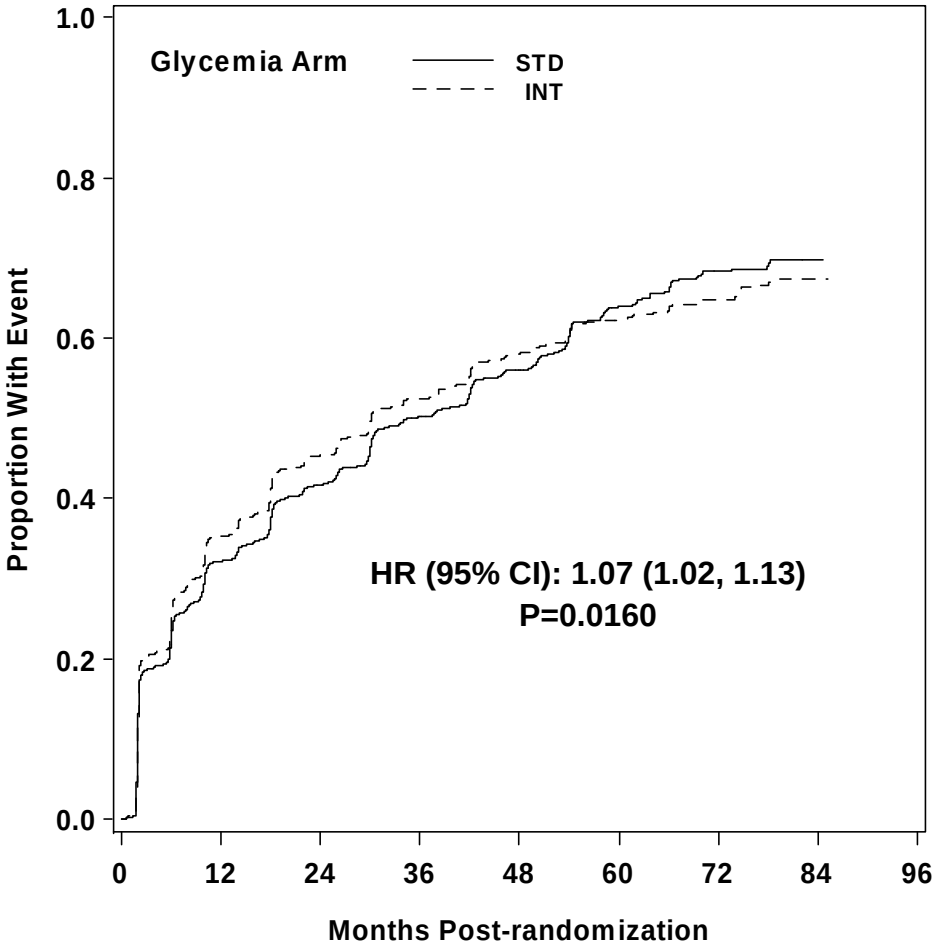
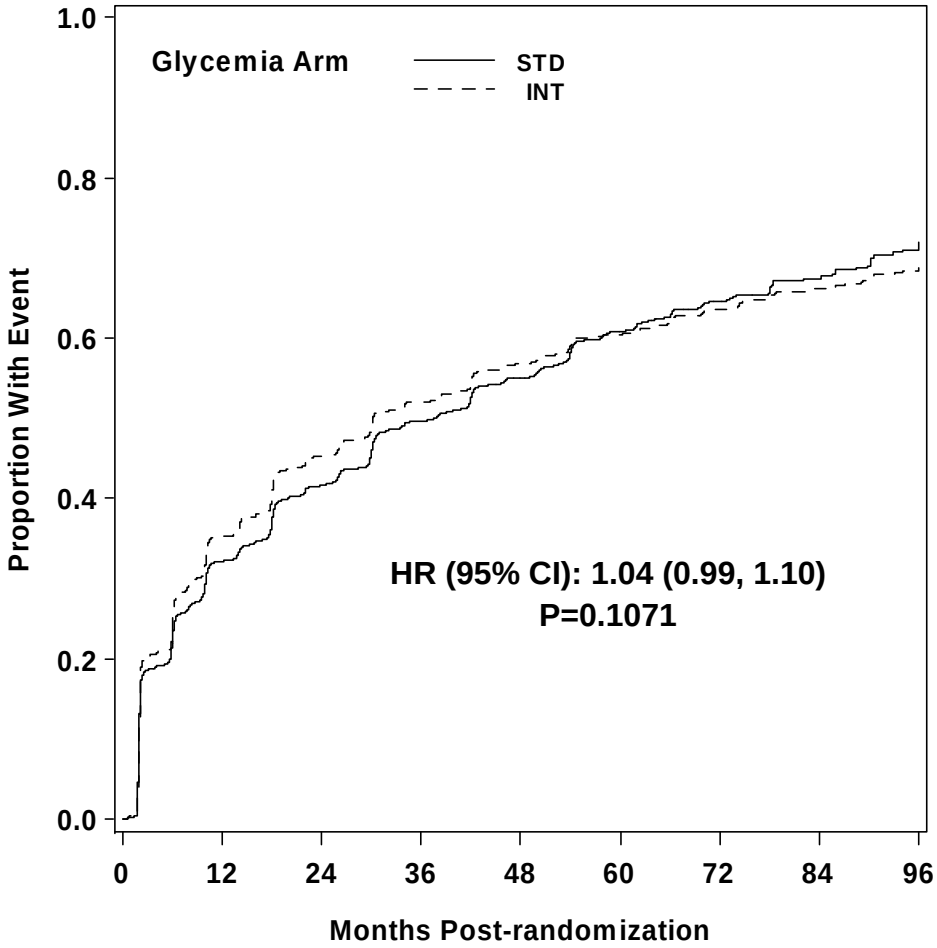


Figure A4. Kaplan-Meier curves for microvascular outcome Neph-3 (development of renal failure, renal transplant, or serum creatinine > 291.7 micomol/L) by glycemia arm. Panel A: data until transition of intensive glycemia arm to standard therapy (N=10215). Panel B: all data through end of study (N=10234). Hazard ratios adjusted for baseline history of clinical cardiovascular disease and second trial treatment arm



Follow-up numbers at risk

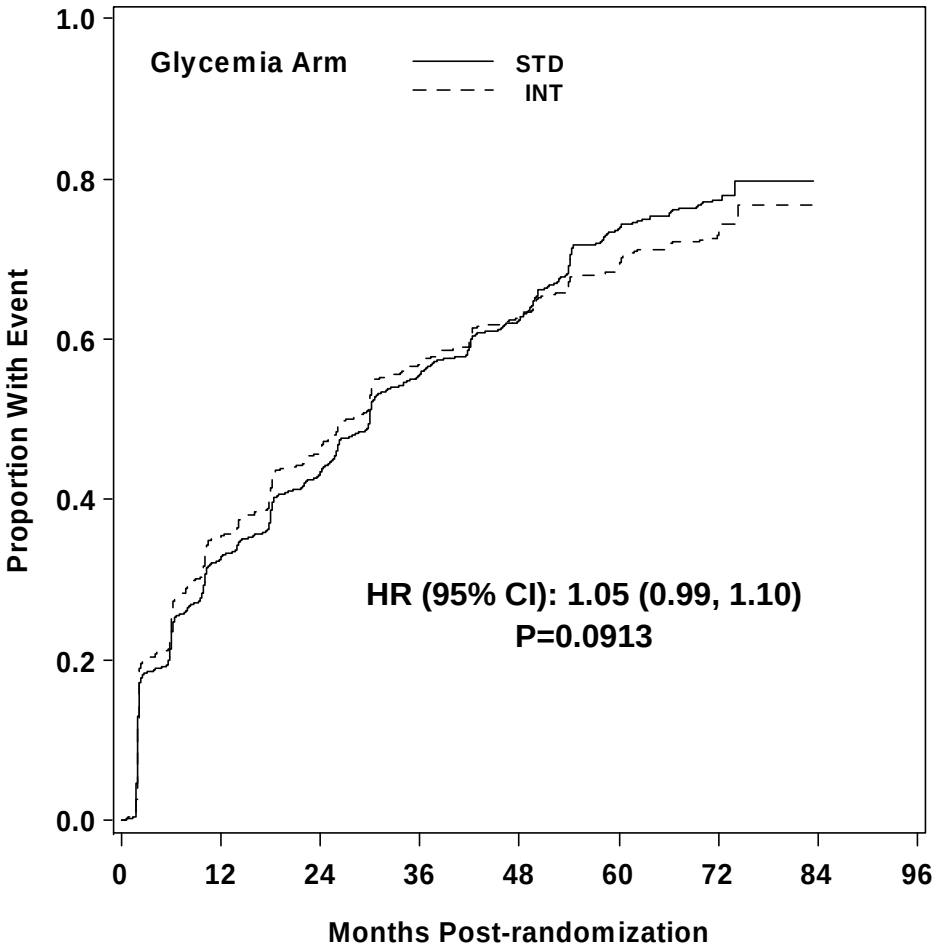
Month	12	24	36	48	60	72	84
	6428	5081	3041	1406	347	249	3



Follow-up numbers at risk

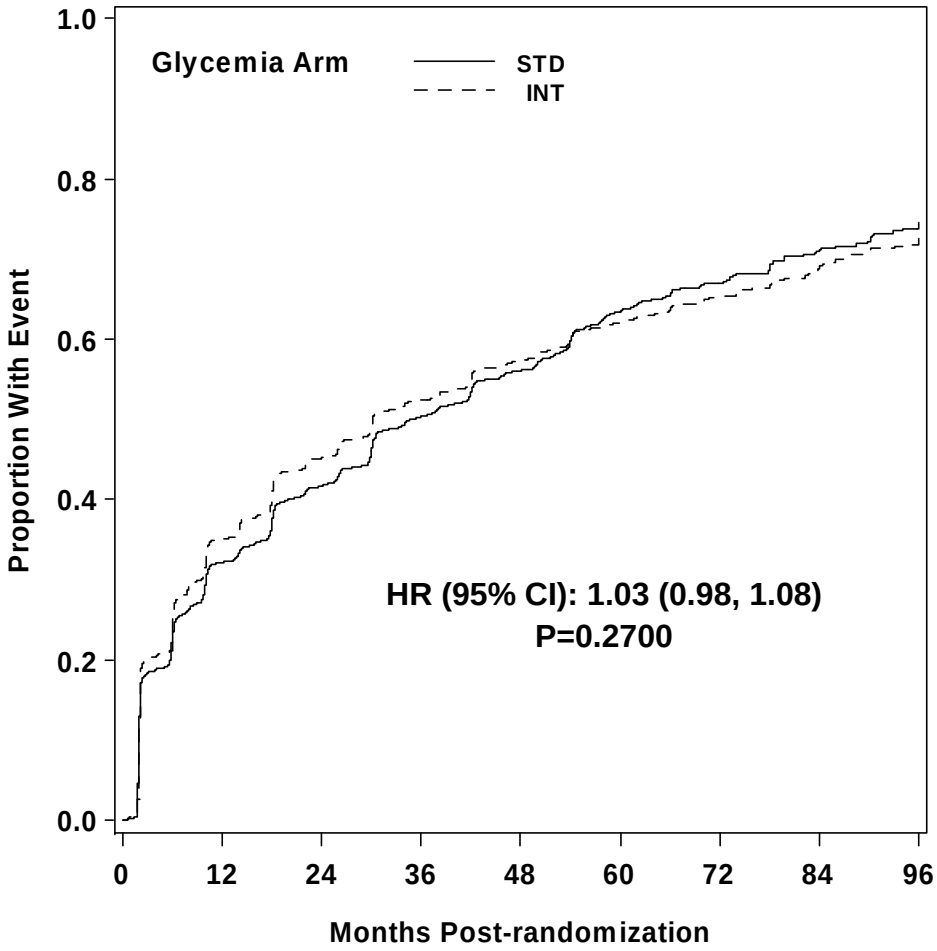
Month	12	24	36	48	60	72	84	96
	6447	5363	4514	3289	1821	536	272	128

Figure A5. Kaplan-Meier curves for microvascular outcome Neph-4 (doubling of serum creatinine or more than 20 mL/min/1.73m^2 decrease in estimated GFR) by glycemia arm. Panel A: data until transition of intensive glycemia arm to standard therapy (N=10069). Panel B: all data through end of study (N=10076). Hazard ratios adjusted for baseline history of clinical cardiovascular disease and second trial treatment arm assignment.



Follow-up numbers at risk

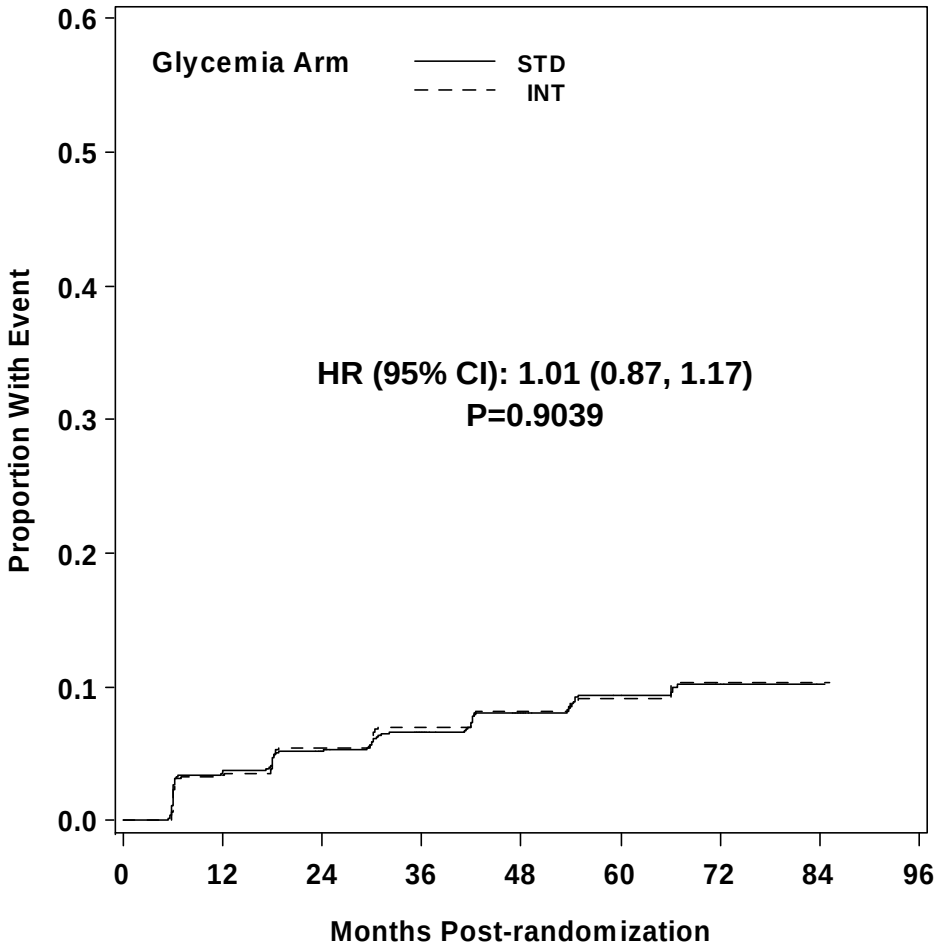
Month	12	24	36	48	60	72	84
	6472	4268	2071	1217	309	169	0



Follow-up numbers at risk

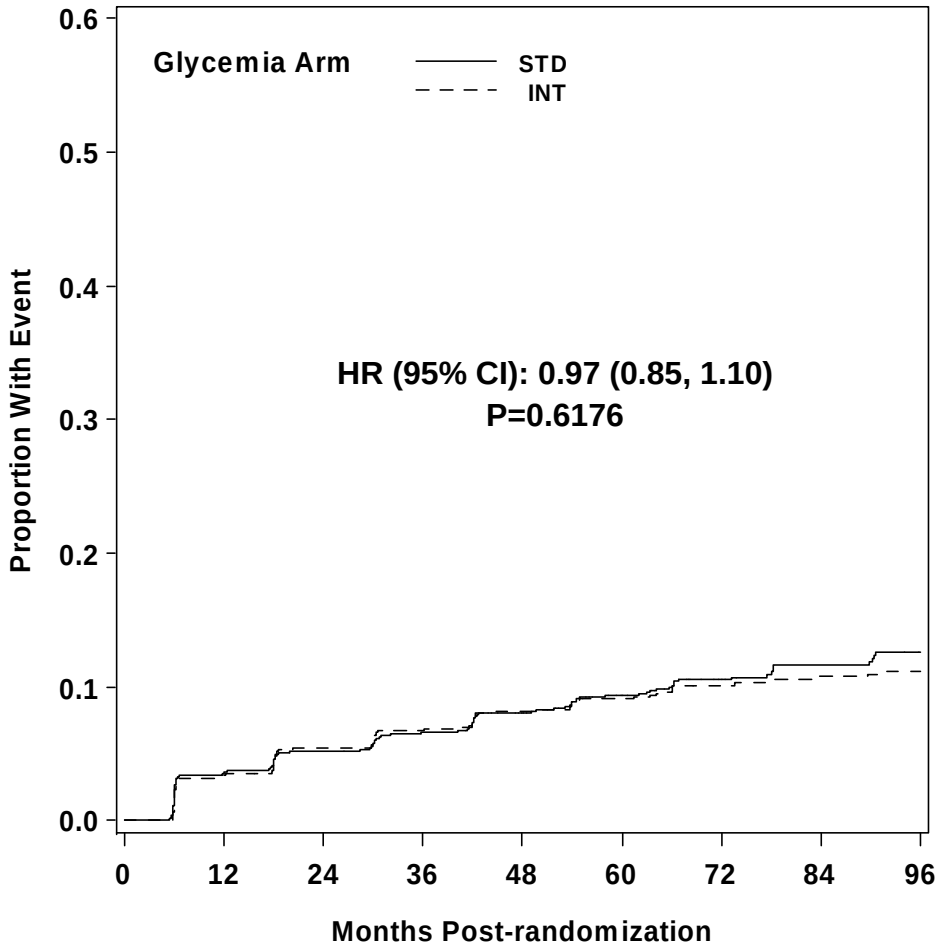
Month	12	24	36	48	60	72	84	96
	6551	5368	4457	3286	1751	530	271	136

Figure A6. Kaplan-Meier curves for microvascular renal composite outcome Neph-5 (development of any of three conditions Neph-2, Neph-3, or Neph-4) by glycemia arm. Panel A: data until transition of intensive glycemia arm to standard therapy (N=10215). Panel B: all data through end of study (N=10234). Hazard ratios adjusted for baseline history of clinical cardiovascular disease and second trial treatment arm assignment.



Follow-up numbers at risk

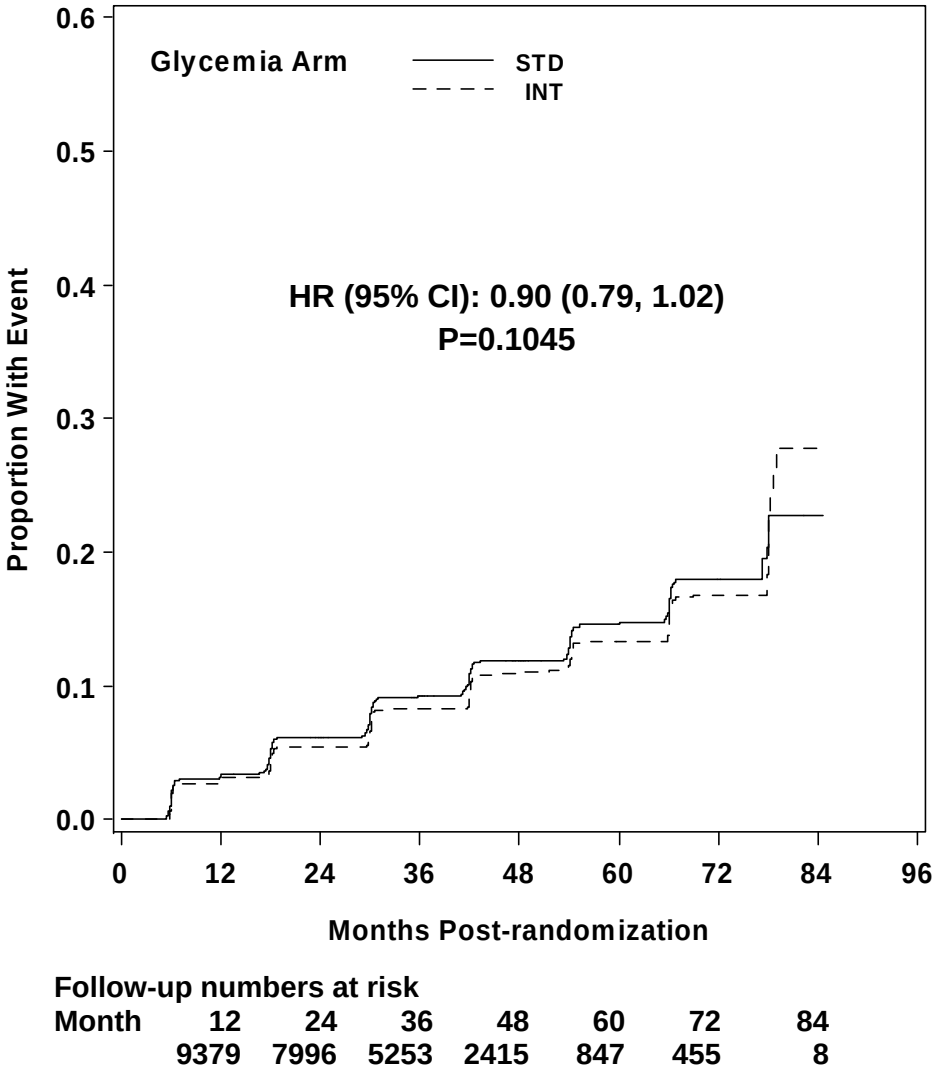
Month	12	24	36	48	60	72	84
	9334	8023	5330	2465	875	479	8



Follow-up numbers at risk

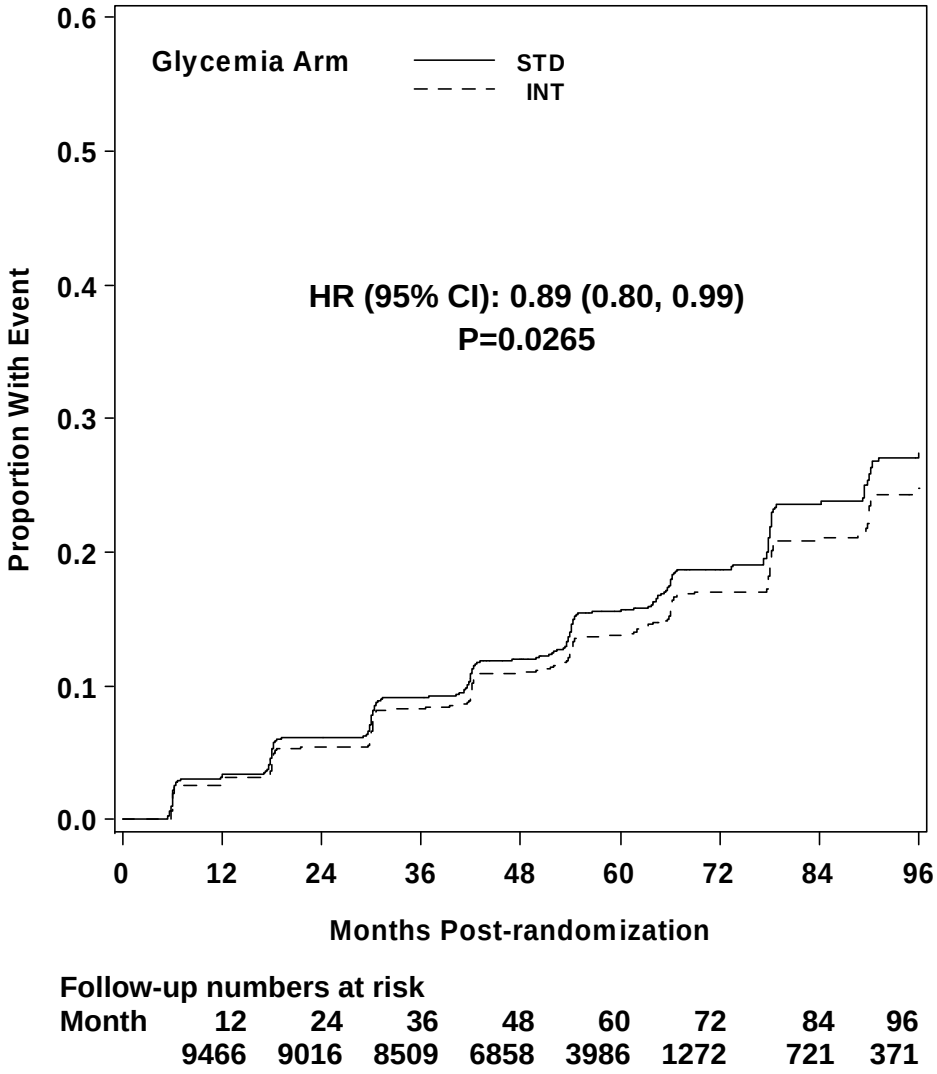
Month	12	24	36	48	60	72	84	96
	9422	9057	8688	7046	4220	1346	800	1

Figure A7. Kaplan-Meier curves for microvascular outcome Eye-1 (retinal photocoagulation or vitrectomy to treat retinopathy) by glycemia arm. Panel A: data until transition of intensive glycemia arm to standard therapy (N=9796). Panel B: all data through end of study (N=9848). Hazard ratios adjusted for baseline history of clinical cardiovascular disease and second trial treatment arm assignment.



Follow-up numbers at risk

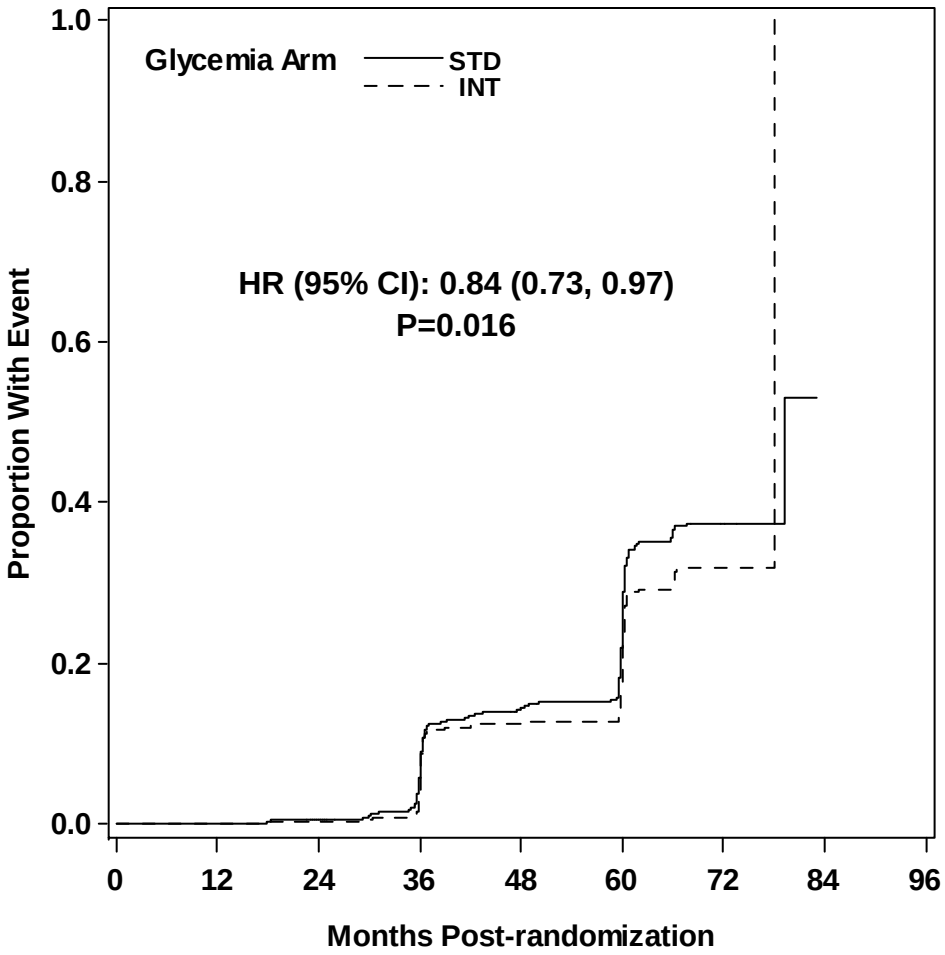
Month	12	24	36	48	60	72	84
	9379	7996	5253	2415	847	455	8

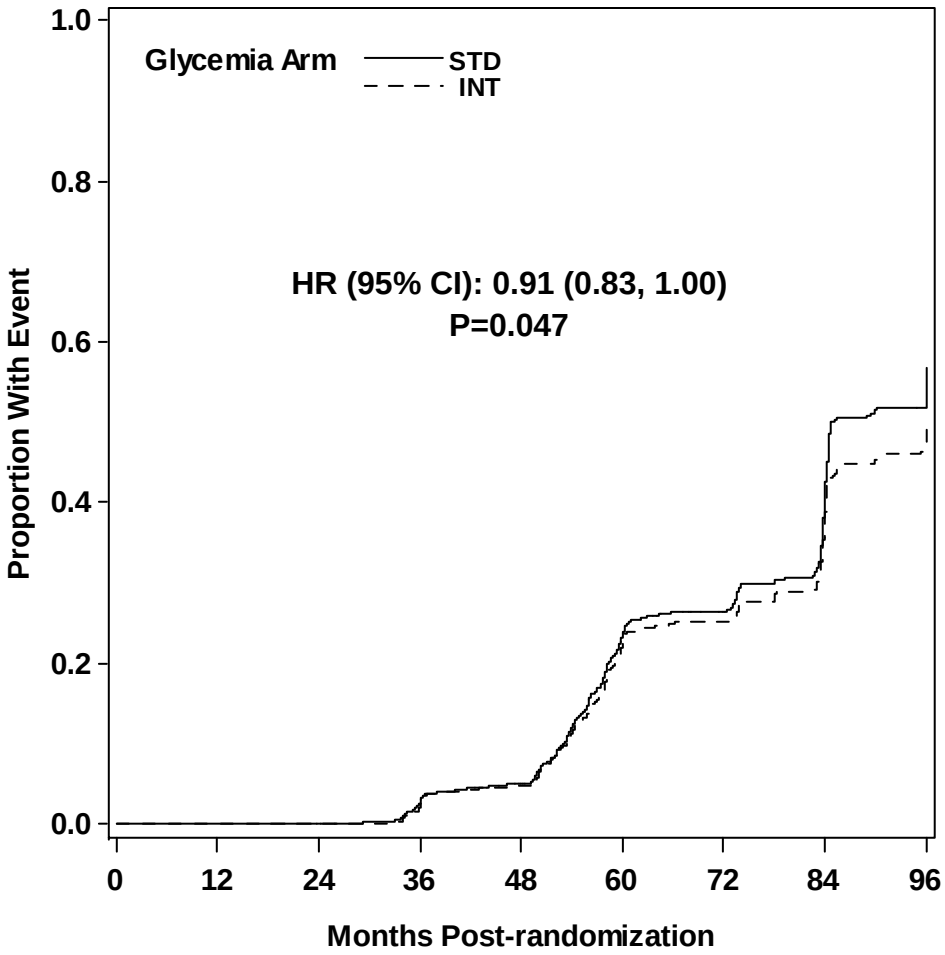


Follow-up numbers at risk

Month	12	24	36	48	60	72	84	96
	9466	9016	8509	6858	3986	1272	721	371

Figure A8. Kaplan-Meier curves for microvascular outcome Eye-2 (surgery for cataract extraction) by glycemia arm. Panel A: data until transition of intensive glycemia arm to standard therapy (N=9796). Panel B: all data through end of study (N=9848). Hazard ratios adjusted for baseline history of clinical cardiovascular disease and second trial treatment arm assignment.





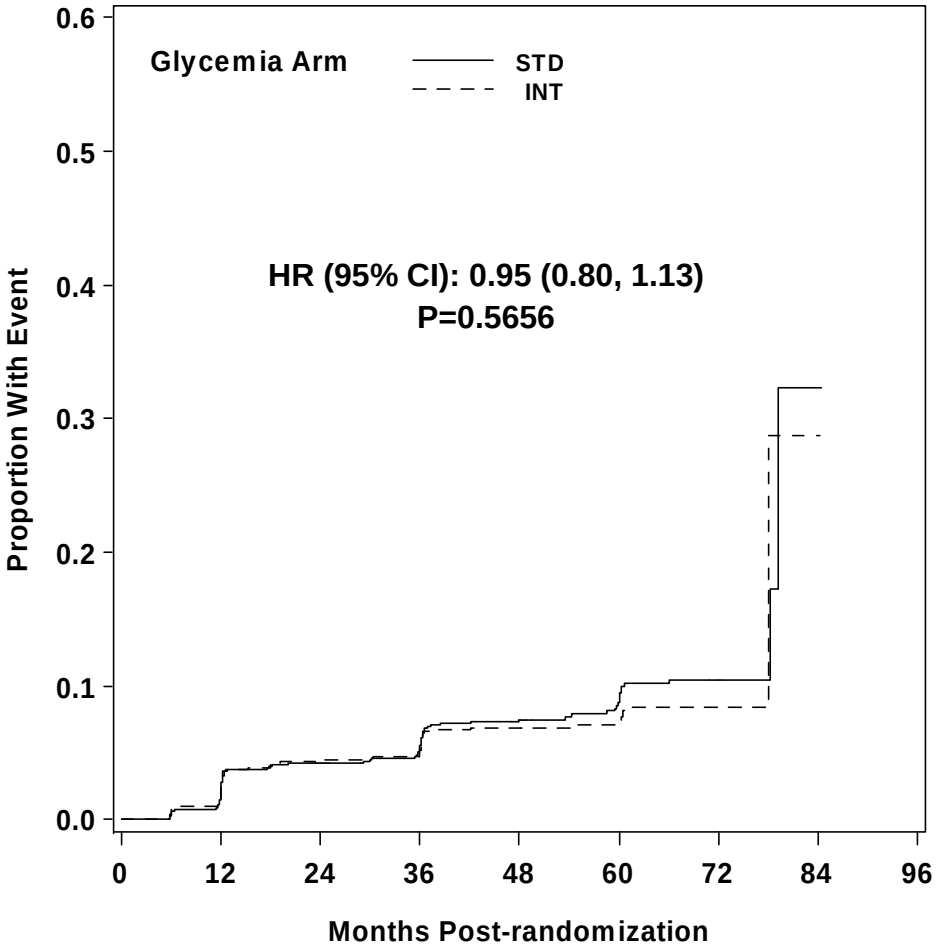
Follow-up numbers at risk

Month	12	24	36	48	60	72	84
	8880	6802	3752	2281	814	379	0

Follow-up numbers at risk

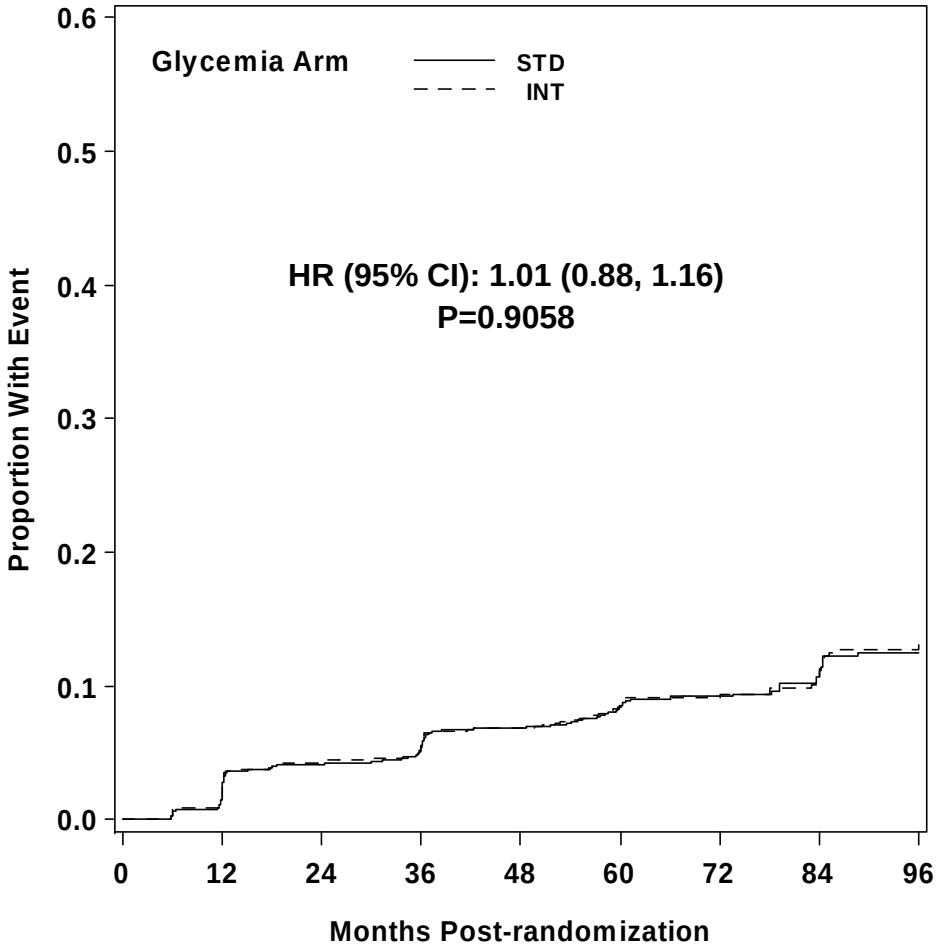
Month	12	24	36	48	60	72	84	96
	9392	9133	8565	7076	3675	1308	702	309

Figure A9. Kaplan-Meier curves for microvascular outcome Eye-3 (three line change in visual acuity) by glycemia arm. Panel A: data until transition of intensive glycemia arm to standard therapy (N=8933). Panel B: all data through end of study (N=9640). Hazard ratios adjusted for baseline history of clinical cardiovascular disease and second trial treatment arm assignment.



Follow-up numbers at risk

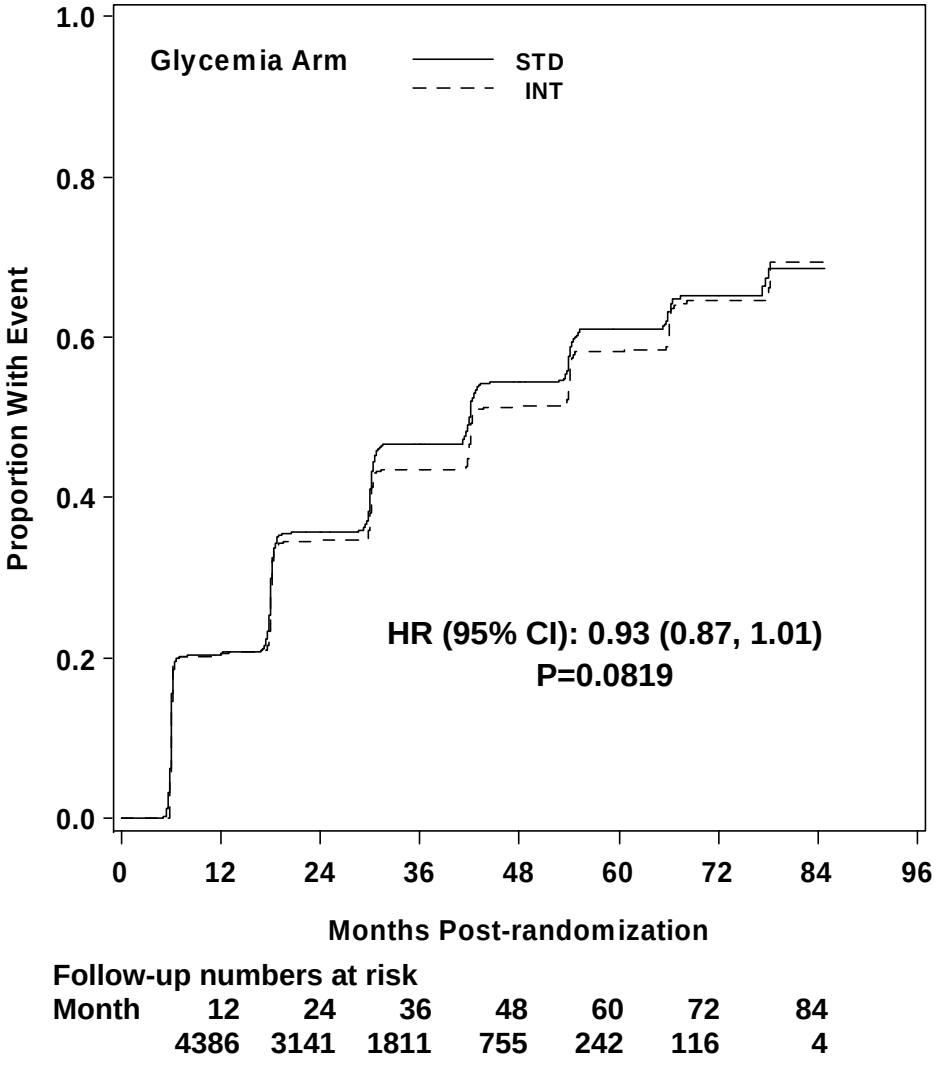
Month	12	24	36	48	60	72	84
	9092	6782	3745	2378	824	452	1



Follow-up numbers at risk

Month	12	24	36	48	60	72	84	96
	9279	8823	8339	6804	3984	1275	723	376

Figure A10. Kaplan-Meier curves for microvascular outcome Eye-4 (severe vision loss) by glycemia arm. Panel A: data until transition of intensive glycemia arm to standard therapy (N=9340). Panel B: all data through end of study (N=9522). Hazard ratios adjusted for baseline history of clinical cardiovascular disease and second trial treatment arm assignment.



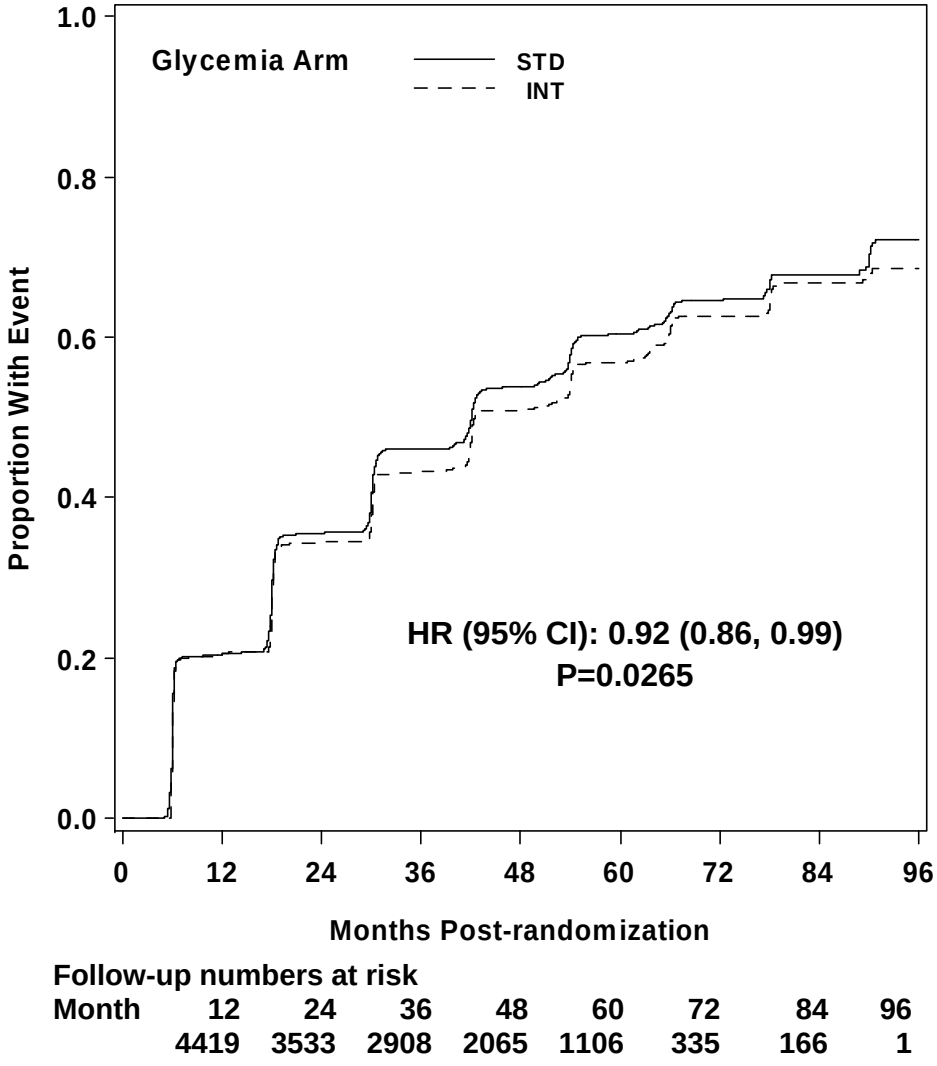
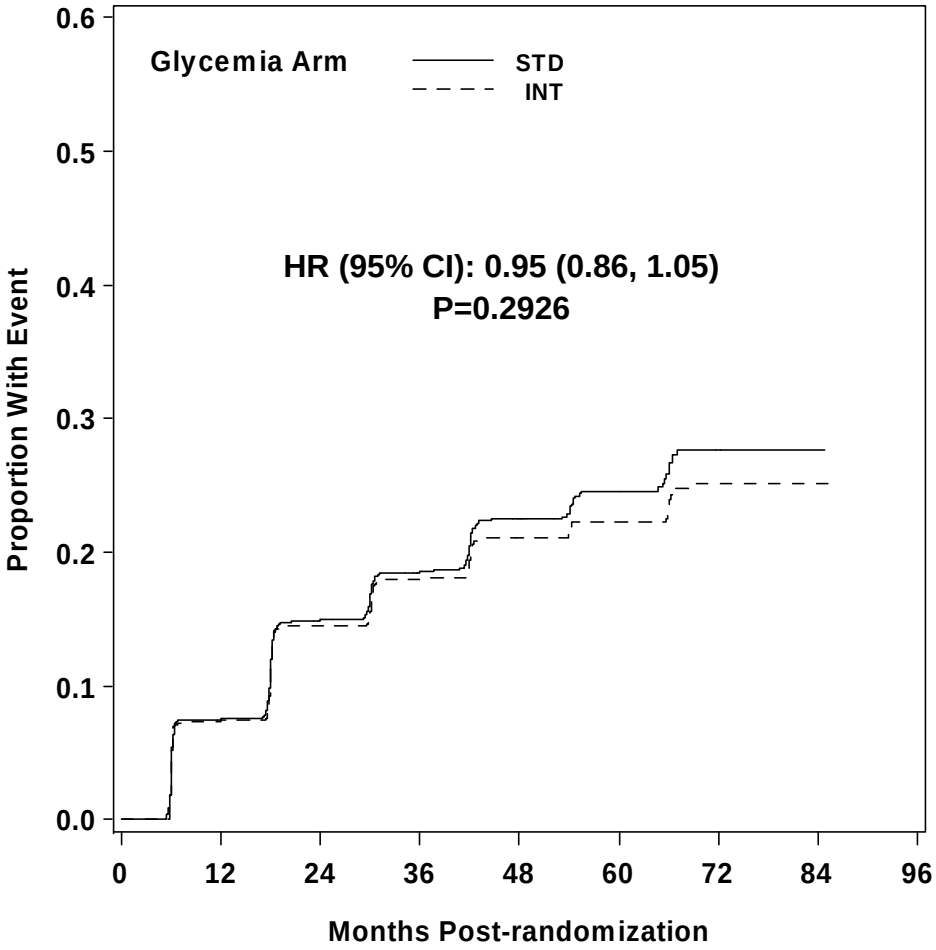
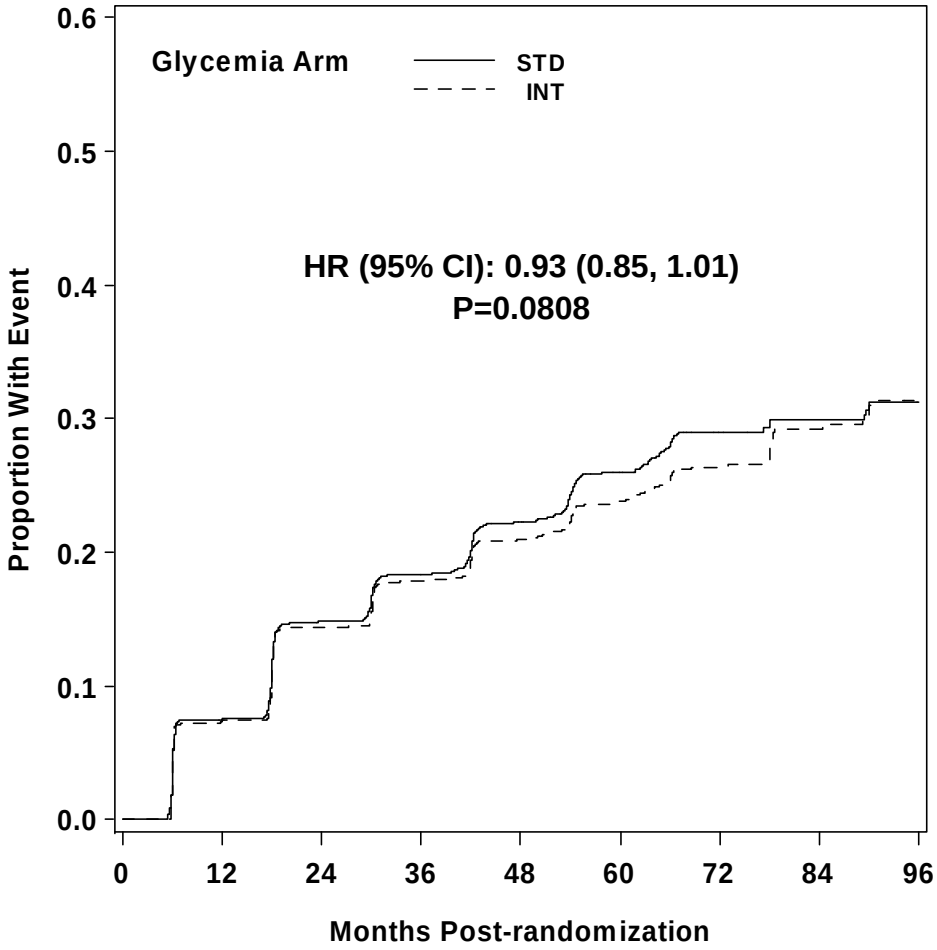


Figure A11. Kaplan-Meier curves for microvascular outcome Neuro-1 (score of >2.0 on the Michigan Neuropathy Screening Instrument) by glycemia arm. Panel A: data until transition of intensive glycemia arm to standard therapy (N=5606). Panel B: all data through end of study (N=5626). Hazard ratios adjusted for baseline history of clinical cardiovascular disease and second trial treatment arm assignment.



Follow-up numbers at risk

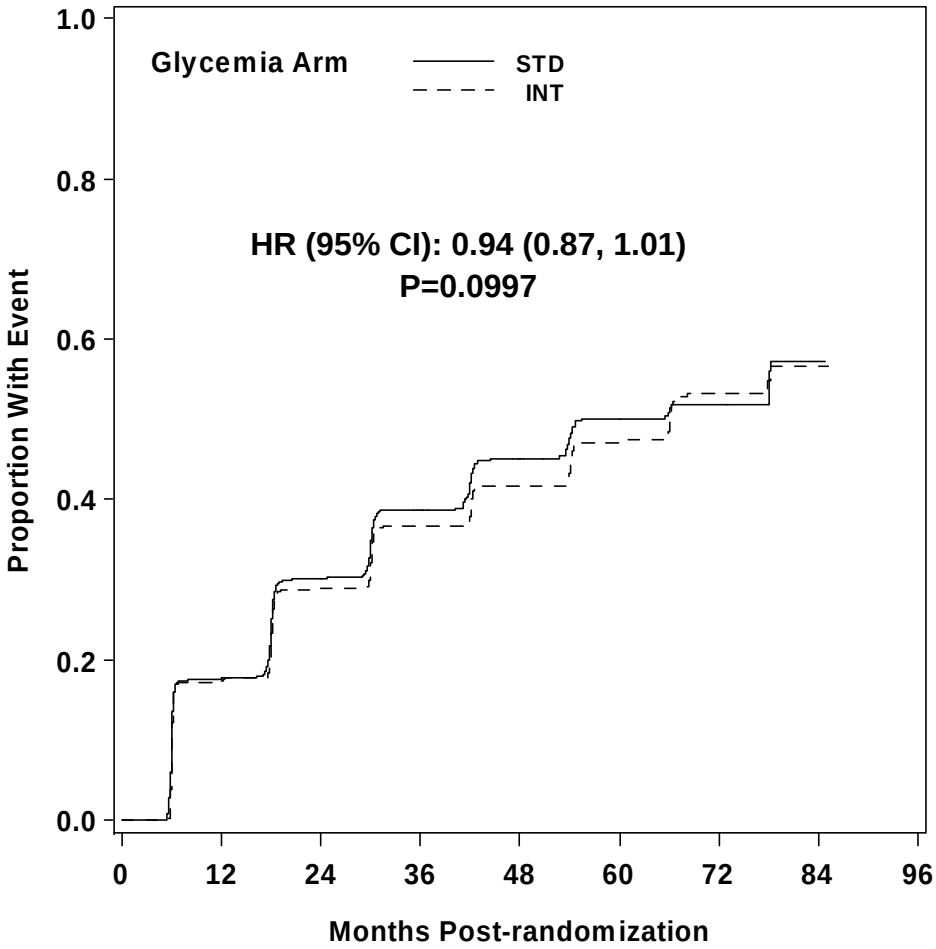
Month	12	24	36	48	60	72	84
	7656	6286	4236	1970	606	331	32



Follow-up numbers at risk

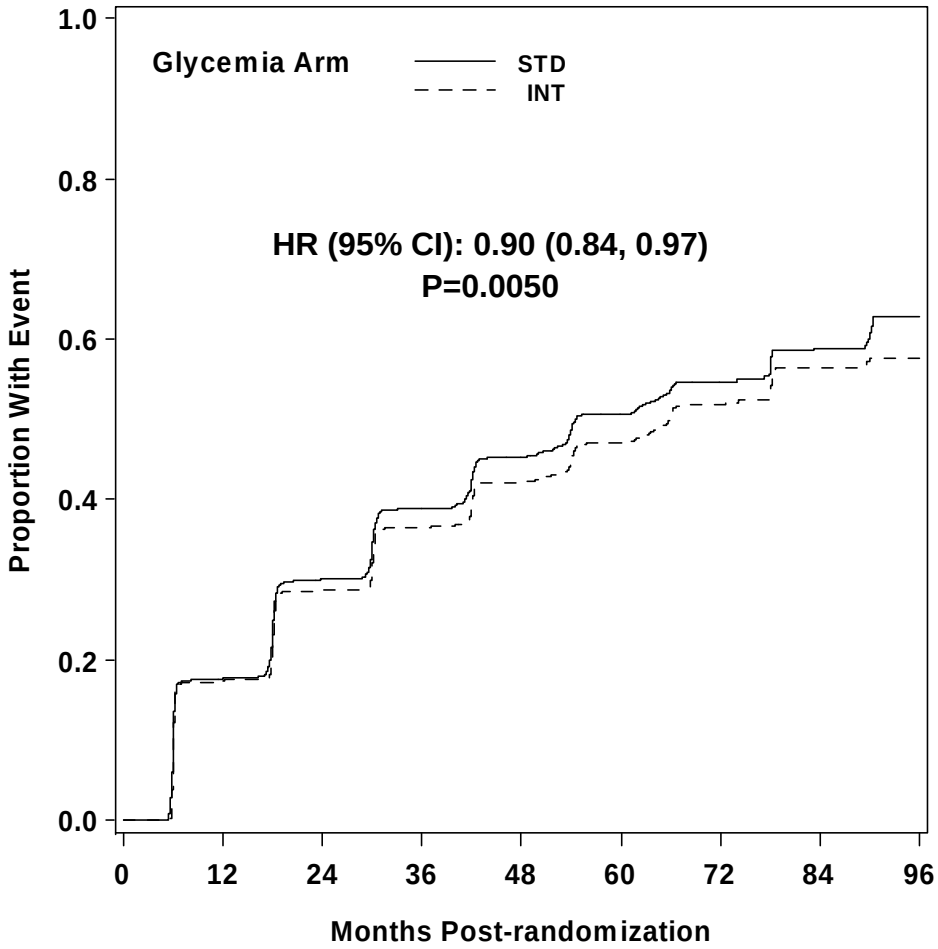
Month	12	24	36	48	60	72	84	96
	7705	6921	6447	5030	2899	851	463	1

Figure A12. Kaplan-Meier curves for microvascular outcome Neuro-2 (loss of vibratory sensation) by glycemia arm. Panel A: data until transition of intensive glycemia arm to standard therapy (N=8418). Panel B: all data through end of study (N=8444). Hazard ratios adjusted for baseline history of clinical cardiovascular disease and second trial treatment arm assignment.



Follow-up numbers at risk

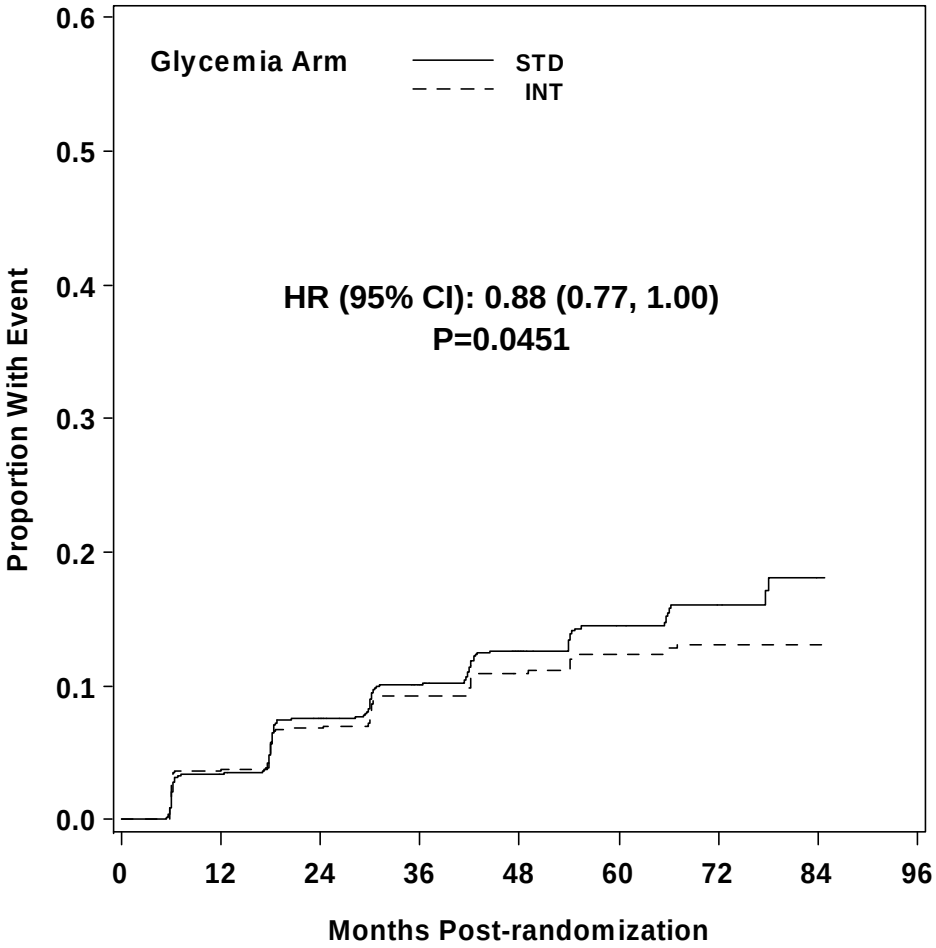
Month	12	24	36	48	60	72	84
	5300	3947	2352	975	310	167	5



Follow-up numbers at risk

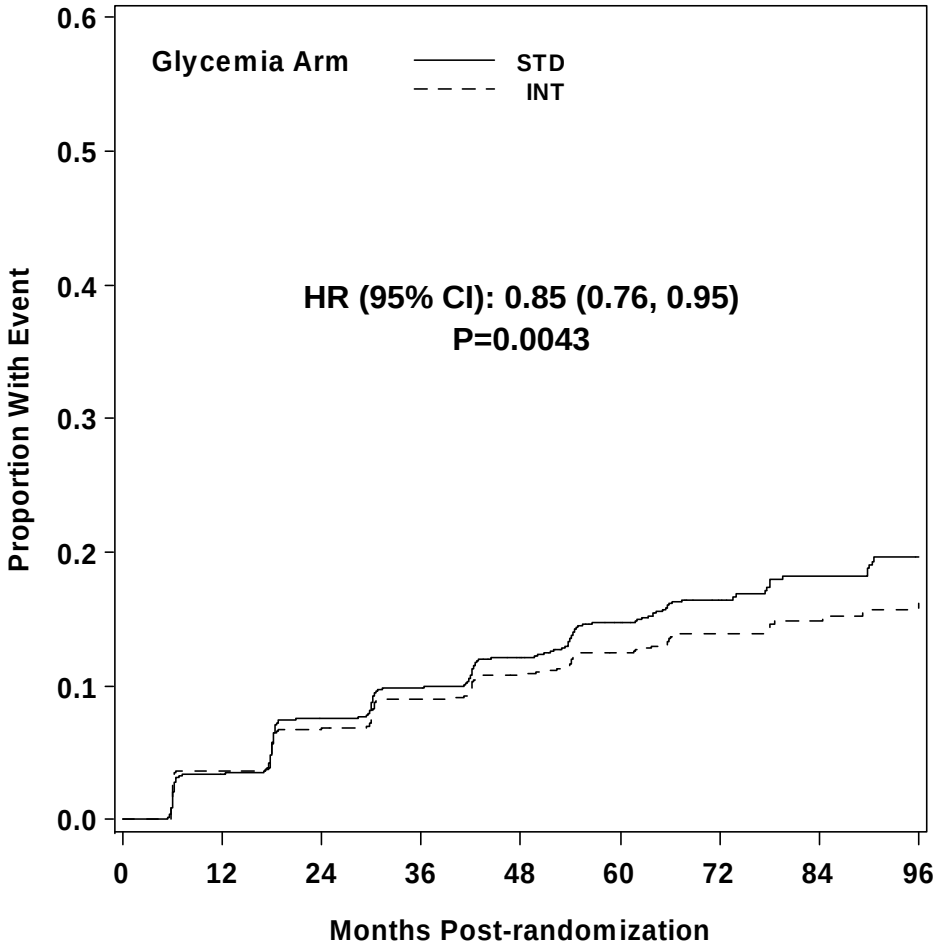
Month	12	24	36	48	60	72	84	96
	5339	4444	3795	2799	1539	455	225	1

Figure A13. Kaplan-Meier curves for microvascular outcome Neuro-3 (loss of ankle jerk during Jendrassic maneuver) by glycemia arm. Panel A: data until transition of intensive glycemia arm to standard therapy (N=6563). Panel B: all data through end of study (N=6583). Hazard ratios adjusted for baseline history of clinical cardiovascular disease and second trial treatment arm assignment.



Follow-up numbers at risk

Month	12	24	36	48	60	72	84
	8659	7288	4754	2128	699	381	5



Follow-up numbers at risk

Month	12	24	36	48	60	72	84	96
	8715	8174	7727	6191	3638	1113	634	320

Figure A14. Kaplan-Meier curves for microvascular outcome Neuro-4 (loss light-touch sensation) by glycemia arm. Panel A: data until transition of intensive glycemia arm to standard therapy (N=9141). Panel B: all data through end of study (N=9169). Hazard ratios adjusted for baseline history of clinical cardiovascular disease and second trial treatment arm assignment.