Executive Highlights

Hello from the beautiful canals of Amsterdam where 30,000 people have flooded the city to attend the European Society of Cardiology's 2013 Congress. Today's agenda featured the highly anticipated results of two DPP-4 inhibitor cardiovascular outcomes trials (CVOTs), BMS/AZ's SAVOR-TIMI 53 for Onglyza (saxagliptin), and Takeda's EXAMINE for Nesina (alogliptin) - we also reported on this session earlier today. The hall for this session was packed to the brim with thousands of people! Results were published concurrently in NEJM, and the full texts of both papers are available online at nejm.org. As we reported earlier with our early highlights of the results and interview with Dr. Itamar Raz (a co-principal investigator for SAVOR; to read the interview, see http://www.closeconcerns.com/knowledgebase/r/549a0f4a), both trials demonstrated CV neutrality with regards to a composite MACE endpoint with hazard ratios near or at 1.00 and CI upper bounds below 1.3, thus satisfying the FDA's CV safety requirement for type 2 diabetes drugs and effectively showing no significant safety issues or benefit. To reiterate our report earlier today, in SAVOR, a slight increase (HR=1.27; 95% CI=1.07-1.51) in hospitalization for heart failure was observed, while heart failure results were not broken out during the presentation for EXAMINE; EXAMINE investigators have informed us that there was no significant difference in heart failure between the alogliptin and placebo groups. See the detailed reports below for more on SAVOR's heart failure risk - since it was increased risk for hospitalization, but that group didn't have more CV events, we suspect it won't ultimately be viewed as a meaningful risk. Importantly, rates of pancreatitis (both acute and chronic) and pancreatic cancer were balanced between treatment and placebo groups in both SAVOR and EXAMINE.

For endocrinologists and diabetes specialists, we believe the pancreatitis and pancreatic cancer news is the biggest to come out of Amsterdam - for them and for patients, to have no pancreatitis and no cancer signals in two large randomized trials with adjudicated events is extremely valuable new information. This new data on safety is much more reliable than much of the alarmist science we have seen over the past several years, and we think this puts to rest much of the speculation that had already been dying down about pancreatitis and pancreatic cancer.

As for what these results mean for the class, SAVOR co-principal investigator and presenter Dr. Deepak Bhatt (Brigham and Women's Hospital, Newton, MA) commented that the SAVOR and EXAMINE results were, at the core, very similar, leading him to speculate that the results could be extrapolated to the rest of the DPP-4 inhibitor class.

With the results of these two studies now available, we are much more aware of how challenging it would have been to show CV benefit. Several factors worked against this result in these trials: 1) In order to definitively establish CV safety in even the highest-risk population (which is often under-studied in phase 2 and 3 trials), and to expedite trial progress, both trials had to enroll populations that were already at severe risk for CVD. As ACCORD, ADVANCE, and VADT suggested, it's hard to change the course of disease once CVD risk has been firmly established. 2) Both trials rigorously administered standard of care for secondary CV prevention. As we heard in our interview with Dr. Itamar Raz, no currently marketed therapy has ever been shown to reduce CV risk as much as statins, so perhaps any potential beneficial CV effects of the DPP-4 inhibitors were masked by the very high statin-use in both trials (about 90% at baseline for EXAMINE and about 90% by trial end for SAVOR). 3) Both trials were relatively short for CVOTs - SAVOR's mean follow up was 2.1 years while EXAMINE's was only 18 months, which likely was not enough time for long-term CV effects to materialize. Investigators remarked that it is hard to speculate whether longer-term follow-up would have yielded different results. 4) Only modest A1c differences were achieved between treatment and

placebo groups - while the relationship between glycemic control and cardiovascular risk has yet to be made crystal clear, we imagine that more exaggerated differences in A1c would make any benefit easier to detect.

Also featured at ESC today was a presentation on the relationship between hypoglycemia and CV risk in ORIGIN where severe hypoglycemia was associated with the composite MACE endpoint, CV mortality, and overall mortality. Finally, ESC held a session to discuss its new diabetes and CVD guidelines that were just released two days ago. See more inside for both!

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Detailed Discussion and Commentary

Hot Line III: Late Breaking Trials on Risk Factors and Diabetes

EXAMINE: EXAMINATION OF CARDIOVASCULAR OUTCOMES WITH ALOGLIPTIN VERSUS STANDARD OF CARE IN PATIENTS WITH TYPE 2 DIABETES MELLITUS AND ACUTE CORONARY SYNDROME

William White, MD (University of Connecticut, Farmington, CT)

Dr. William White discussed the primary results of EXAMINE (n=5,380), the cardiovascular outcomes study for Takeda's DPP-4 inhibitor Nesina (alogliptin) that was commissioned to fulfill the FDA's cardiovascular safety requirement for type 2 diabetes drugs. This was the first time that results of this trial were revealed. The trial demonstrated Nesina's non-inferiority of cardiovascular safety compared to placebo. Superiority was not demonstrated. Dr. White emphasized that this observation occurred in the context of 1) alogliptin also providing a significant A1c reduction over placebo (0.36% placebo-adjusted A1c reduction); 2) a high overall CV event rate of ~11% (suggesting that even in the highest-risk CV patients, alogliptin is safe); and 3) high levels of standard of care for both diabetes and cardiovascular prevention (i.e., with 90% of patients at baseline already on a statin, it would be tough for the addition of a DPP-4 inhibitor to confer much additional benefit). With regard to the primary outcome of MACE (cardiovascular

death, myocardial infarction, and stroke), events occurred in 11.3% of alogliptin and 11.8% of placebo-treated patients (p<0.001 for non-inferiority; HR=0.96 with the upper bound of the one-sided repeated confidence interval at 1.16). Turning to other adverse events of interests, there were no reported cases of pancreatic cancer during the trial. Additionally, the rates of acute and chronic pancreatitis were "low and similar" in each treatment group - 0.4% vs. 0.3% in the alogliptin vs. placebo groups, respectively. There were no differences in hypoglycemia (although hypoglycemia was reported at the discretion of the investigators), measures of renal function, or overall malignancies between the groups. For background, EXAMINE had a mean and median follow-up of 18 months (maximum of 40 months). A short trial indeed, Dr. White noted that the trial actually ended early because it met its primary endpoint during a March 2013 interim analysis. The full text of these results were published concurrently in the New England Journal of Medicine and is available at http://www.nejm.org/doi/full/10.1056/NEJMoa1305889.

- **EXAMINE was a randomized, double-blind, placebo-controlled trial (n=5,380) conducted in 898 sites in 49 countries.** The primary objective was to demonstrate that major CV events (MACE: CV death, nonfatal myocardial infarction, and non fatal stroke) were not higher with alogliptin than with placebo in type 2 diabetes patients with recent acute coronary syndrome (within 15-90 days of randomization), and who are receiving standard of care for diabetes and secondary CV prevention. Secondary objectives included 1) a superiority assessment of the primary end point if non-inferiority were proven; and 2) time to first MACE+ (MACE plus urgent revascularization due to unstable angina). Major exploratory endpoints included cardiovascular death and all-cause mortality.
- **Patients were randomized ~1:1 to alogliptin plus standard of care or placebo plus standard of care.** The mean follow-up length was 18 months, and the maximum follow-up was 40 months. Dr. White disclosed that the trial ended early in March 2013 when, after accruing 550 MACE events, an interim analysis ruled out an upper bound of 1.3 for the hazard ratio using a one-sided alpha value of 0.01, and the data safety monitoring board recommended that the trial be stopped as it had met the primary endpoint. Following the 550th event, 71 additional patients had events prior to the locking of the database, and these were included in the complete analysis. We are curious to know if investigators also felt that superiority would be very unlikely to emerge. We have no information on this.
- **Patient characteristics at baseline were balanced between the alogliptin and placebo groups and were as follows:** median age of 61 years with 35-36% of patients ≥65 years; 68% were male; median diabetes duration was about seven years; BMI was 29 kg/m^2, and mean A1c was 8.0%. The time from initial acute coronary syndrome to randomization was about 45 days. The types of medications being used at baseline was also balanced between groups with 90-91% of patients on statins and 82-83% of patients using ACE inhibitors or ARBs - this demonstrates that secondary cardiovascular prevention was practiced quite intensively in the study population, and this may have masked any potential CV benefit provided by alogliptin. At baseline, about 30% of patients in either group were using insulin.
- **For the primary composite endpoint of major cardiovascular events (MACE) including cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke, rates were similar between alogliptin and placebo groups.** The event rates were 11.3% and 11.8% in the alogliptin and placebo groups, respectively (HR=0.96; one-sided repeated confidence interval bound: 1.16). Broken down into individual components, the hazard ratios were 0.79 (95% CI: 0.60-1.04) for CV death, 1.08 (0.88-1.33) for nonfatal myocardial infarction, and 0.91 (0.55-1.50) for nonfatal stroke. As such, alogliptin was deemed to demonstrate cardiovascular safety; it did not achieve superiority.
- **The secondary MACE+ endpoint was also similar between treatment and placebo groups (HR=0.95, one-sided repeated CI bound: 1.14).** The HR for cardiovascular death was 0.85 (upper bound of 95% CI: 1.10), and the HR for all-cause mortality was 0.88 (upper bound of 95% CI: 1.08).

- **The placebo-adjusted change in A1c from baseline was 0.36% for alogliptin - quite modest, though perhaps not surprising given the fairly high rate of pre-existing insulin treatment (30%).** From a mean baseline A1c of 8.0% in both groups, the placebo group experienced a 0.03% A1c increase compared to the 0.33% A1c decrease in the alogliptin group at the end of follow-up. About 40% of patients in the alogliptin group achieved an A1c ≤7% compared to 29% of the placebo group.
- **Dr. White also highlighted several other adverse events of special interest, including pancreatitis and pancreatic cancer.** There were no imbalances in rates of acute or chronic pancreatitis, though the numbers may have just been too small to tell. There were 12 cases of acute pancreatitis in the alogliptin group (0.4%) compared to 8 cases of acute pancreatitis in the placebo group (0.3%), p=0.50. For chronic pancreatitis, which is type of pancreatitis that researchers believe precedes pancreatic cancer, 5 cases (0.2%) were observed in the alogliptin group compared to 4 in placebo (0.1%), p=1.00. Overall malignancies were balanced at 2.0% and 1.9% in the alogliptin and placebo groups, respectively. Notably, there were zero cases of pancreatic cancer in either group. Hypoglycemia was similar between groups (6.7% vs. 6.5% for alogliptin vs. placebo, respectively), though we learned that hypoglycemia was reported at the discretion of the investigator, which calls the rigorousness of the hypoglycemia findings into question. There were also no differences in measures of renal function or initiation of dialysis.

EXAMINE - DISCUSSANT REVIEW

Eugene Braunwald, MD (Brigham and Women's Hospital, Boston, MA)

Dr. Eugene Braunwald, who was the chair of the steering committee for BMS/AZ's CVOT for Onglyza, SAVOR-TIMI 53, offered his evaluation of EXAMINE. He noted that the trial very clearly achieved the primary safety objective, and he also posed several questions. For example, he wondered which add-on therapies were utilized in the placebo group such that CV outcomes were similar to the alogliptin group. He stated that if generic medications were used to achieve the same outcomes, then a cost-benefit analysis may be warranted for alogliptin in this population. We certainly hope that such an analysis would take into account quality of life measures due to DPP-4 inhibitors' ease of use, weight neutrality, and low risk of hypoglycemia. His line of talking implied he thought that perhaps the DPP-4 inhibitors were not worthwhile, in which case, of course, had they not been developed, there would also be no chance for them ever to become generic.

SAVOR-TIMI 53: SAXAGLIPTIN ASSESSMENT OF VASCULAR OUTCOMES RECORDED IN PATIENTS WITH DIABETES MELLITUS (SAVOR)-TIMI 53 STUDY

Deepak Bhatt, MD, MPH (Brigham and Women's Hospital, Newton, MA)

Dr. Deepak Bhatt presented the primary results of SAVOR-TIMI 53, the cardiovascular outcomes study for BMS/AZ's DPP-4 inhibitor Onglyza (saxagliptin) commissioned to satisfy the US FDA's cardiovascular safety requirement. This is the first presentation of detailed data following BMS/AZ's release of topline results in June 2013. The trial demonstrated Onglyza's non-inferiority of cardiovascular safety compared to placebo in people with type 2 diabetes at high risk for cardiovascular disease. The hazard ratio (HR) for the primary outcome of MACE was exactly 1.00 (95% CI: 0.89-1.12; p<0.001 for non-inferiority; p=0.99 for superiority), and the HR for the secondary endpoint of MACE+ (MACE plus hospitalization for heart failure, unstable angina, or coronary revascularization) was 1.02 (95% CI: 0.94-1.11). There was actually a greater risk of hospitalization due to heart failure in the Onglyza group than the placebo group: HR=1.27 (95% CI: 1.07-1.51; p=0.007), though in the group that exhibited excess heart failure risk, there was no increased risk of all-cause mortality, occurrence of the primary endpoint, or occurrence of the secondary endpoint. The rate of pancreatitis (including both acute and chronic) was identical between Onglyza and placebo groups (0.3%). There was a trend towards reduced pancreatic cancer in the Onglyza group with p=0.095. Onglyza also reduced and prevented progression of microalbuminuria, which suggests that it may have positive effects on microvascular outcomes, although the trial was not designed to adequately assess this. Dr. Bhatt strongly emphasized that even though Onglyza did not demonstrate CV benefit, prescribers should not

forget that A1c-lowering is vital for prevention of microvascular complications, and it has now been shown that Onglyza can lower A1c safely with regard to CV events while also providing the benefits of weight neutrality, delaying insulin initiation, ease of use, and relatively low hypoglycemia. The median follow up for this very large 16,492-person, 700+ site trial was 2.1 years, and the maximum follow-up was 2.9 years. The full text of the results are available online at http://www.nejm.org/doi/full/10.1056/NEJMoa1307684.

- **For background, Dr. Bhatt reminded the audience that a prior pooled analysis of phase 2b/3 saxagliptin studies had suggested cardiovascular benefit (Frederich et al., *Postgraduate Medicine* 2010).** The hazard ratio (HR) for the study was 0.44 with a 95% confidence interval of 0.24-0.82. However, the study included only 41 events.
- **SAVOR was a randomized, placebo-controlled, double-blind trial of 16,492 patients with type 2 diabetes and established CV disease or multiple risk factors.** The criterion of high risk for a CV event could be satisfied one of two ways: 1) having established CV disease, or 2) having multiple risk factors (being a male ≥55 years old or female ≥60 years old and have an additional risk factor such as dyslipidemia, hypertension, or current smoking). In the final study population, ~80% were enrolled through criterion #1, and ~20% through #2, suggesting that it was primarily a secondary CV prevention population with others at very high risk for developing CVD. At baseline, patients were on average 65 years old, had an average diabetes duration of 10 years, and a BMI of 31 kg/m^2.
- **For the primary composite endpoint of major cardiovascular events (MACE), which included cardiovascular death, myocardial infarction, and ischemic stroke, were similar, rates were similar between saxagliptin and placebo groups (7.3% vs. 7.2%, respectively; HR=1.00; 95% CI: 0.89-1.12).** The Kaplan Meier curves appeared to perfectly overlap. The secondary composite MACE+ endpoint (MACE plus hospitalization for unstable angina, hospitalization for heart failure, and hospitalization for coronary revascularization) also showed no difference between saxagliptin and placebo groups. When broken down into individual component endpoints, there was no difference in the rates of CV death, myocardial infarction, ischemic stroke, hospitalization for coronary revascularization, hospital for unstable angina, or all-cause mortality. However, there was a slightly increased risk of hospitalization for heart failure (HR=1.27; 95% CI: 1.07-1.51; p=0.007).
    - **Dr. Bhatt relayed that in the group that had an increased risk of hospitalization for heart failure, there was no concomitant increased risk of mortality, or for either the primary or secondary composite outcomes.** A preliminary analysis of this group revealed that the people with excess risk of hospitalization for heart failure were largely confined to the people with highest levels of BNP (the upper-most quartile) - a protein associated with increased risk for heart failure. Even in this quartile, there was no excess in all-cause mortality or in the primary or secondary outcomes. Therefore, Dr. Bhatt concluded that the excess risk of heart failure was highest in those who were already at elevated baseline risk for heart failure.
    - **All subgroups analyzed showed the same non-inferior (HR near 1.0) result for the primary endpoint.** Patients were subdivided by age, gender, across strata of renal function, by criterion used to satisfy the elevated CV enrollment requirement, diabetes duration, baseline A1c, and baseline diabetes medication use.
- **The A1c reduction after two years of 0.5% (0.3% placebo-adjusted) was modest, similarly to EXAMINE (see above).** The A1c difference converged even more to just 0.2% by the end of the trial. However, with 40% of patients on insulin at baseline, and with a good proportion of patients starting with a low baseline A1c of ≤6.5%, this modest mean reduction may not be unexpected. Furthermore, Dr. Bhatt remarked that since treatment intensification for loss of glycemic control had to be allowed in both arms for ethical reasons and was significantly greater in placebo, this also served to minimize differences in A1c between the two groups. Dr. Bhatt also emphasized that the modest A1c reduction took place in the context of also reducing the

intensification of antihyperglycemic medications by 23% in the saxagliptin group compared to the control group as well as a 30% reduction in insulin initiation in the saxagliptin group.

- **Other adverse of events of special interest included pancreatitis and pancreatic cancer (which were balanced between the groups), hypoglycemia (which was minimally increased with saxagliptin), and progression of microalbuminuria (which was lower in the saxagliptin group).** The overall rate of pancreatitis was identical between the two groups (0.3%). There were also no differences when broken down into acute or chronic pancreatitis. Pancreatic cancer was very low (0.1% in placebo vs. 0.08% in saxagliptin; p=0.095). Minor, major, and overall hypoglycemia was slightly higher in the saxagliptin group (14.2% vs. 12.5%, 2.1% vs. 1.7%, and 15.3% vs. 13.4%, respectively), though there was no difference in hypoglycemic events requiring hospitalization. Dr. Bhatt remarked that the definition of hypoglycemia was more sensitive in SAVOR than the definition used in EXAMINE, which resulted in a higher overall rate in SAVOR compared to EXAMINE. Although SAVOR was not powered to investigate hard microvascular outcomes, it was reassuring that fewer people in the saxagliptin group experienced worsening of microalbuminuria compared to placebo (13% vs. 16%) and a more people experienced improvement of microalbuminuria compared to placebo (11% vs. 9%).
- **Similar to EXAMINE, there was a high rate of statin use at baseline (78%), which was increased to 90% by the end of the trial,** reflecting that many patients were already receiving standard of care for secondary prevention of cardiovascular events. As such, it seems it would be quite challenging for DPP-4 inhibitors to show additional benefit on top of statins.
- **We noticed a general disappointment in the cardiology community with these results - some questioned whether a diabetes drug had any place in the treatment paradigm at all if it did not have a CV benefit since most people with diabetes die of CVD.** Dr. Bhatt provided a very well-articulated response, acknowledging that he is fairly certain that the class as a whole will not show CV-benefit. He noted that the impact of safely lowering A1c has a strong impact on very clinically relevant microvascular outcomes such as blindness, kidney failure, and amputation. He remarked that endocrinologists largely saw this as "terrific" data since the safety of a widely-utilized glucose-lowering drug has been reinforced.

SAVOR-TIMI 53 - DISCUSSANT REVIEW

Michel Komajda, MD (Pierre and Marie Curie University, Paris, France)

Dr. Michel Komajda, past President of the ESC, emphasized seven points for audience members to take away from SAVOR and keep in mind when interpreting results:

1. *Because SVOR was primarily designed to assess CV safety, the population enrolled was elderly and at high CV risk, as recommended by the FDA. This is reflected by high rate of MACE - roughly 3.6% per year, which is significantly higher than the rate observed in ACCORD, according to Dr. Komajda. In addition more than 40% of patients were on insulin therapy, and average diabetes duration was 12 years.*
2. *The were "remarkably" well treated for their CV risk, which makes it hard to show additional benefit.*
3. *The modest A1c reduction should not be misinterpreted since investigators were allowed to intensify treatment in the control arm whenever needed.*
4. *Saxagliptin was associated with a lower rate of insulin initiation and a lower rate of intensification of other diabetes medications. So, despite the lack of benefit on CV outcomes, it provided benefits for diabetes control.*
5. *Saxagliptin's CV safety was confirmed in all prespecified subgroups, and particularly in patients over the age of 70, a population often ignored in randomized controlled trials. He characterized the modest but significant increase in heart failure hospitalizations as "intriguing," noting that since DPP-4 inhibitors do not influence heart rate, do not induce fluid retention, and do not modify cardiac function,*

this is surprising. He questioned the rigorousness of the procedure for classifying heart failure in the study since echography, which is the diagnostic standard for heart failure, was not invoked. He speculated that one could still not exclude chance and that the results of future DPP-4 inhibitor cardiovascular outcomes trials will be interesting to supplement this result.

6. *SAVOR's failure to show CV benefit was not unexpected. Despite the positive results of previously published pooled analyses, the patients' advanced diabetes, documented severe CVD risk, and two-year follow up may have been inadequate.*
7. *Finally, he remarked that SAVOR brought reassurance on non-CV safety concerns as well since there were no increases in observed rates of infections, malignancies, hone fractures, pancreatitis, or pancreatic cancer.*

Clinical Trial Update Hot Line I: Updates on Hypertension, Heart Failure, and Diabetes

ORIGIN: ASSOCIATION BETWEEN HYPOGLYCEMIA AND RISK OF CARDIOVASCULAR EVENTS WITH TITRATED INSULIN GLARGINE OR STANDARD CARE

Linda Mellbin, MD (Karolinska Institute, Stockholm, Sweden)

Dr. Linda Mellbin presented results of an analysis of the relationship between hypoglycemia and cardiovascular outcomes in the ORIGIN trial. As a reminder, ORIGIN's primary result found that insulin glargine had a neutral effect on CV outcomes vs. standard therapy for people with high CV risk and impaired glucose tolerance, impaired fasting glucose, or early type 2 diabetes. See http://www.closeconcerns.com/knowledgebase/r/10be2669 for our full coverage of the primary ORIGIN results. This new analysis of hypoglycemia, which has now been published in the European Heart Journal, demonstrated that non-severe hypoglycemia (symptoms confirmed by a glucose reading of ≤54 mg/dl) was associated with increased risk of mortality (HR=1.21; p<0.001) and cardiovascular death (HR=1.16; p=0.049), but not arrhythmic death or the composite MACE endpoint. Severe hypoglycemia (symptomatic hypoglycemia needing assistance and documented glucose ≤35 mg/dl or prompt recovery with oral carbohydrate, intravenous glucose, or glucagon) was associated with increased risk for the MACE composite (HR=1.77) as well as all-cause mortality (HR=2.05), cardiovascular death (HR=2.02), and arrhythmic death (HR=2.14); p<0.001 for all. After adjusting for propensity scores (which took into account pre-existing conditions and therapies [e.g., SFUs] that might predispose patients to hypoglycemia), the relationship between non-severe hypoglycemia and CV risk disappeared, and the relationship between severe hypoglycemia remained, although it was slightly blunted. Very interestingly, the risk associated with severe hypoglycemia was more pronounced in the standard care group than the insulin glargine group by about 1.7 times. This led us to wonder about rates of SFU use between the standard care and insulin glargine groups and whether, if there was a higher rate of SFUs in the standard care group, this could account for the excess CV risk. Dr. Mellbin concluded that there does seem to be a relationship between severe hypoglycemia and CV outcomes in this population, but that this relationship may be due to confounding unmeasured risk factors.

ESC Guidelines on Diabetes, Pre-Diabetes, and Cardiovascular Disease

GUIDELINES 2013 - WHAT'S HOT AND WHAT'S NOT

Lars Ryden, MD, PhD (Karolinska Institute, Stockholm, Sweden)

Outgoing president of the European Society for Cardiology and renowned cardiologist Dr. Lars Ryden reviewed highlights from the recently updated ESC/EASD guidelines on diabetes, pre-diabetes, and cardiovascular disease (available at www.escardio.org/guidelines and released just two days prior to the presentation). The last such guidelines were published in 2007. One big change is that A1c has been introduced as a diagnostic criterion for diabetes. However, since A1c "does not cover it all," the guidelines also recommend that people with cardiovascular disease who do not meet A1c diagnostic criteria also perform an OGTT (since about 60% of people with coronary artery disease do have glucose perturbations, the yield of performing OGTTs in this group is quite high). The new guidelines have also simplified CV risk assessment for people with diabetes - they no longer recommend using risk scores since they were not

developed for this category of patients, or, like the Oxford risk score, were based on outdated UKPDS data (back then few people were on statins, blood pressure therapy, or aspirin therapy). The new guidelines simply recommend classifying diabetes patients as "high" or "very high" risk CV patients based on presence of concomitant risk factors. Another big change was the relaxation of A1c targets to allow for individualization (general goal of ≤7%; more stringent goal of 6.0-6.5% for younger patients with no significant CVD and a long life expectancy; and a more relaxed goal for those with a shorter life expectancy and at CV risk), though Dr. Ryden was very quick to warn that glycemic control is essential for preventing microvascular complications so this broadening of acceptable A1c goals did not constitute permission to ignore A1c "completely".

-- by Jessica Dong and Kelly Close