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IMPORTANCE OF SERUM POTASSIUM IN RISK OF TYPE-2 DIABETES (10-1)

TRICYCLIC ANTI-DEPRESSANTS FOR MIGRAINE AND TENSION HEADACHE (10-2)

**THE THROMBIN-INHIBITOR DABIGATRAN FOR PREVENTION OF EMBOLIC STROKE
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SEVERE HYPOGLYCEMIA AND RISK OF VASCULAR EVENTS AND DEATH (10-5)

**INTENSIVE TREATMENT OF HYPERGLYCEMIA AND RISK OF MICRO-VASCULAR
OUTCOMES IN TYPE-2 DIABETES (10-6)**

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This document is divided into two parts

1) The **HIGHLIGHTS AND EDITORIAL COMMENTS SECTION**

HIGHLIGHTS condenses the contents of studies, and allows a quick review of pertinent points of each article.

EDITORIAL COMMENTS are the editor's assessments of the clinical practicality of articles based on his long-term review of the current literature and his 25-year publication of Practical Pointers.

2) The main **ABSTRACTS** section is designed as a reference. It presents structured summaries of the contents of articles in much more detail.

I hope you will find *Practical Pointers* interesting and helpful. The complete content of all issues for the past 10 years can be accessed at www.practicalpointers.org

Richard T. James Jr. M.D.
Editor/Publisher.

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HIGHLIGHTS AND EDITORIAL COMMENTS OCTOBER 2010

“Serum Potassium Levels -- An Independent Predictor Of Incident DM-2.”

10-1 SERUM AND DIETARY POTASSIUM AND RISK OF INCIDENT TYPE-2 DIABETES

Hypokalemia may be a risk factor for type-2 diabetes (**DM-2**): 1) In studies of thiazide diuretics, lower K levels were associated with higher serum glucose levels. This effect was blunted by oral K supplementation. 2) Experimental studies provide biological plausibility by showing that thiazide-induced hypokalemia leads to diminished insulin secretion. 3) ACE inhibitors, which increase serum K levels, are associated with a decreased risk of DM-2. 4) A reanalysis of the Systolic Hypertension in the Elderly Program (**SHEP**) identified hypokalemia as a mediator of thiazide-related risk of incident DM-2.

This study analyzed data from ARIC study to test the hypothesis that adults with lower serum K levels (in the normal range) are at higher risk for DM-2, even without diuretic use. It also sought to determine whether higher dietary K intake is associated with lower risk. ARIC is a prospective study of over 15 000 adults age 45-65 (mean 54) at baseline (1986-89) from 4 population probability samples in the US. None had diabetes at baseline. All had serum K determined.

Categorized serum K into 4 clinically meaningful groups: < 4.0 mEq/L; 4.0 to 4.4; 4.5 to 4.9; and 5.0 to 5.5.

Follow-up to 2008. In the first 9 years, subjects were followed by clinic visits; thereafter by telephone consultation.

Mean serum K at baseline was 4.4 mEq/L (range 2.4 to 5.5)

There was a significant inverse relationship between serum K and fasting insulin levels.

	Serum K levels at baseline			
	<4.0	4.0 - 4.4	4.5 - 4.9	5.0 -5.5
Number of participants	1619	4903	4178	1509
Fasting insulin pIU/mL	13.72	11.10	10.76	9.67
Incident DM-2 during the first 9 years of follow-up (n = 1475)				
Rate per 1000 person-years	24.6	16.6	14.2	11.8
Adjusted hazard ratio (HR)	2.05	1.52	1.37	1.00 (referent)

After excluding participants who were prescribed diuretics, beta-blockers, ACE inhibitors, K supplements, and magnesium supplements there was a graded increase in HR of incident DM-2 with lower serum K levels.

Hazard ratios	1.57	1.49	1.38	1.00
HRs were higher in those receiving diuretics.				
	2.91	2.85	1.93	1.00

The gradient was less evident over 20+ years, but incidence of DM-2 remained higher in those with K levels lower than 5.0

Dietary analysis: Mean K dietary intake was 2655 mg/day (recommended = 4700) The correlation between serum K and dietary intake was modest. But there was a significant graded increase in risk of incident DM-2 with lower dietary K intake. HRs for incident DM-2 by lower to higher K intake quartiles were 1.37; 1.19; and 0.95 compared with the reference highest intake (1.00).

This study is limited by only a single K determination at baseline. However the National Health and Nutrition Examination Survey (NHANES) found that serum K levels have an individual variability of about 5% based on repeated measurements.

I enjoyed this article. It was difficult to cull out the various hazard ratios.

The study emphasizes the importance of a healthy diet--higher intake of fruits and vegetables, the sources of K. The American diet is high in Na and lacking in K. We often forget the importance of K in the pathogenesis of hypertension as well as DM-2.

A study in NEJM May 10, 2007 (See Practical Pointers May 2007) states that "sodium is necessary for development of hypertension, but is not sufficient."

"Potassium is the main intracellular cation. Abundant evidence indicates that a potassium deficit has a critical role in the pathogenesis of hypertension.

"Excess sodium and a deficit of potassium are dominant environmental factors in the pathogenesis.

"Potassium restriction causes a deficit in cellular potassium. This triggers cells to gain sodium in order to maintain their tonicity and volume.

"Sodium retention increases sodium concentration and decreases potassium concentrations in the intra-cellular fluid. This results in a rise in intra-cellular calcium, which triggers contraction of vascular smooth muscle.

"Forms of potassium that do not contain chloride, such as found in fruits and vegetables, offer larger cellular entry in exchange for sodium and greater anti-hypertensive effects.

"Potassium depletion inhibits insulin secretion and is associated with glucose intolerance.

"Thiazide-induced hypokalemia worsens glucose intolerance in type-2 diabetes. Correction of hypokalemia ameliorates the glucose intolerance.

“ Primary hypertension and age-related increases in blood pressure are virtually absent in populations in which individual consumption of sodium chloride is less than 50 mmol/day (~3 grams of NaCl). It appears then, that sodium intake in excess of 50 to 100 mmol/day is necessary, but not sufficient for the development of primary hypertension.

“Isolated populations that eat natural foods (in which hypertension affects less than 1% of the people) have an individual potassium intake that exceeds about 6 grams per day and a sodium intake of 0.5 to 1.0 grams.

“People in industrialized countries ingest 1.2 to 2.7 grams of potassium per day and as much as 9 grams of sodium.

“Differences in prevalence of hypertension have been attributed to the sodium intake, but could also reflect differences in potassium intake.

“A modified diet that approaches the high potassium /sodium ratio of the diets of our human ancestors is a critical strategy for primary prevention and treatment of hypertension.”

The DASH diet is rich in fruits and vegetables.

“Substantially Reduced The Pain From Both Migraine And Tension-Type Headache.”

10-2 TRICYCLIC ANTIDEPRESSANTS AND HEADACHES: Systematic Review and Meta-analysis

This inclusive literature search included published randomized clinical trials that evaluated the efficacy of tricyclic anti-depressant drugs in reducing the frequency and severity of migraine headache (MHA) and tension-type headaches. (THA)

A total of 3176 participants were included in 37 studies., which lasted an average of 10 weeks.. Most studies titrated drug dose. Maximum doses: amitriptyline 150 mg; clomipramine 150 mg; doxepin 100 mg; Mean pooled doses: amitriptyline 80 mg; clomipramine 116 mg; doxepin 50 mg;.

1. Tricyclics vs placebo:

A. Tension-type HA (8 studies)

At baseline, participants averaged 16 headaches per month

Tricyclics were more effective than placebo in reducing the burden of THA by an average standard mean difference of 0.99, a clinically large effect.

The number of THA was reduced by an average of 7 per month .

The beneficial effect increased over time.

Participants taking tricyclics for THA were more likely to experience a 50% improvement than those taking placebo.

2. Migraine headache (9 studies)

At baseline, participants averaged 5 headaches per month.

Tricyclics were more effective than placebo in reducing the burden of migraine by an average standard mean difference of 1.00, a clinically large effect.

The number of MHA was reduced an average of 1.4 per month.

The beneficial effects increased over time.

Participants taking tricyclics for MHA were more likely to experience a 50% improvement than those taking placebo

3. Tricyclics reduced the number of doses of analgesics taken for acute HA pain.

4. Adverse effects vs placebo

Relative risk (**RR**)

Those taking tricyclics reported “any” side effect 1.89

Dry mouth 2.91

Drowsiness 1.87

(The only adverse effects that were statistically significant.)

The likelihood of withdrawing due to adverse effects did not differ between groups

4. Tricyclics vs SSRIs.

Despite a low dose (average 50 mg) tricyclics were more likely than SSRIs to produce at least a 50% improvement in THA and MHA .

5. Tricyclics vs other drugs

There were few studies. Three studies compared tricyclics with beta-blockers. There was no difference in reduction in number of HAs. Two studies did not differ in likelihood of experiencing at least a 50% reduction in HA.

Two studies comparing tricyclics with buspirone (an anxiolytic) found no difference.

One study found amitriptyline better than dihydroergotamine for MHA.

6. “We found that tricyclic antidepressants substantially reduced the pain from both migraine and tension-type headache.” Compared with placebo, patients with THA were 40-70% more likely to report at least a 50% improvement. Patients used fewer analgesics.

Tricyclics seem equally effective for MHA. This is useful clinically because differentiation of the two types may not always be straightforward, especially when HAs are frequent.

The benefit seems to increase over time. Clinical practice recommendations suggest that

tricyclics be taken for several months before reaching any conclusions on effectiveness for any given patient.

Many clinicians encourage patients to take tricyclics for several months during which the dose is

increased before deciding to try a different prophylactic agent.

It is impossible to differentiate whether treatment effect is independent of depression. The relation between depression and physical symptoms is well described. Patients with depression have more physical symptoms and report those symptoms are more serious and more severe and disabling than patients without depression. Depressed patients experience improvements in somatic problems when underlying depression is successfully treated.

7. “Meta-analysis is limited by the problem of aggregate data.” “Heterogeneity in our results was considerable.” “This analysis should be viewed as exploratory rather than definitive.”

Conclusion: Tricyclic antidepressants are effective in preventing migraine and tension-type headache.

Benefits of tricyclics have been described for a half-century.

This is a long, complex article. Abstracting meta-analyses is often unsatisfactory because of heterogeneity between studies. You end up calculating averages.

In eight studies of tension HA, 4 were statistically significant; of 9 studies of migraine, 5 were statistically significant favoring tricyclics over placebo. I believe this adds to the validity of the author's conclusions.

I felt this article was worthy. It deals with patients who are severely afflicted. Some, I am sure, were incapacitated by HA. Tricyclics may be a boon; certainly worth a therapeutic trial. They have the advantage of being effective for tension headaches as well.

It might be reasonable to add short-acting drugs to treat and abort, while patiently continuing amitriptyline. (Eg aspirin with or without metoclopramide.)

Beta-blockers (eg, propranolol) are also effective in prevention of MHA.

Fortunately, amitriptyline is inexpensive. Some pharmacies sell the generic, at any dose for \$4.00 for a monthly supply.

“May Be An Option To Replace Warfarin”

10-3 DABIGATRAN ETEXILATE IN PEOPLE WITH ATRIAL FIBRILLATION

Dabigatran (*Pradaxa*; Boehringer Ingelheim) has been approved for use in the US by the FDA for preventions of stroke in patients with non-valvular AF. It is a direct thrombin inhibitor.

A large trial in September 2009 (*See Practical Pointers Sept 2009*) reported that, in patients with atrial fibrillation (AF), dabigatran is associated with rates of stroke similar to those of warfarin.

ADVANTAGES COMPARED TO WARFARIN

Taken orally. No monitoring. Dose is constant. Long half-life. More predictable anticoagulant

effect. Wide therapeutic range. Much simpler regimen. No interference by foods and other drugs.

Compared with warfarin when used in patients with AF:

Reduces rates of stroke and peripheral embolization as well as, or better than warfarin.

Reduced deaths due to cardiovascular disease.

Fewer intracranial hemorrhage.

Fewer life-threatening bleeds.

Possible use by patients who cannot or will not take warfarin and whose INR is unstable.

DISADVANTAGES

Dose not settled.

Taken twice daily.

Excreted by the kidney. Care when kidney function is impaired.

No antidote. May take several days for effect to lessen.

Possible increased risk of myocardial infarction. May be contraindicated in patients with history of cardiovascular disease.

Increased g.i. bleeding.

Dyspepsia may cause withdrawals.

Generalizability not settled.

Cost \$8.00 a day.

Use for reasons other than AF must be validated.

I believe we require more experience before Pradaxa is used in primary care practice. Other anticoagulants are now approaching approval. We await comparisons for use in indications other than AF.

Increases Incidence And Death From Breast Cancer

10-4 ESTROGEN PLUS PROGESTIN AND BREAST CANCER INCIDENCE AND MORTALITY IN POSTMENOPAUSAL WOMEN

The Women's Health Initiative (WHI) followed a total of 16 608 postmenopausal women, age 50-79 (mean age 63) randomly assigned to: 1) 0.625 mg/d of conjugated equine estrogen + 2.5 mg/d medroxyprogesterone acetate (*Prempro*; Wyeth) or 2) placebo. The intervention period lasted from 1993

to 2002, when participants were instructed to stop CHT. Follow-up of 12 788 participants continued until 2009.

During a mean follow-up of 11 years, a total of 678 cases of BC were identified.

In the intention-to-treat analysis, CHT compared with placebo, was associated with an increased incidence of BC: 385 cases (0.42% per year) vs 293 cases (0.35% per year). Hazard ratio (**HR**) = 1.25.

In the CHT group, a significantly larger fraction of BCs presented with positive nodes: 81 vs 43; HR = 1.78.

Some women prior to entering the trial were taking CRT. These women had a higher risk for BC. HR = 1.85, compared with 1.16 for those without prior use.

More women in the CHT group died of BC: 25 deaths vs 12 deaths. (2.6 deaths per 10 000/year vs 1.3 deaths per 10 000/year. (HR = 1.96)

Following the initial report of the WHI trial, a substantial reduction in use of CHT occurred, followed by a reduction in incidence of BC. Reproductive hormones, especially progestin, are potent stimulators of angiogenesis. Because increased angiogenesis increases both lung and BC metastasis, these findings suggest that angiogenesis stimulation by CHT may facilitate growth and metastatic spread of already-established cancers.

Conclusion: Use of estrogen plus progestin increases the incidence of BC. The cancers are more commonly node positive. Mortality was increased.

I believe the terms hormone replacement therapy (HRT) and hormone therapy (HT) should be abandoned in favor of using the specific terms: estrogen and progestin. HRT and HT are too non-specific. Estrogen and progestin have different benefits and harms. There is good evidence that progestins are the major risk factor for BC.

For discussion, see the following editorial.

Informed Patient-Decisions Are Not Valid When The Information Underlying The Decision Is Speculative

POSTMENOPAUSAL HORMONE THERAPY AND BREAST CANCER

(This editorial comments and expands on the preceding article.)

In 2002, the WHI was stopped early because of evidence of harm. (The WHI reported increased risk of myocardial infarction in addition to BC.) Sales of CHT subsequently fell by 32%.

This contradicted decades of observational studies suggesting that hormone therapy was associated with strong protective effects on the cardiovascular system. The WHI undermined a long and successful campaign by hormone replacement advocates to prescribe hormone therapy as a panacea against heart disease, loss of femininity, and other perils of aging.

This proved once again that only randomized trials can yield insights into harms and benefits.

After many subgroup analyses, a more nuanced explanation emerged. Among the few women who enrolled around the time of menopause, CHT did not increase the risk of cardiovascular disease, and may have reduced it slightly. However, most women in the trial were well past menopause when enrolled.

Ultimately, the only long-term benefit of CHT the FDA allows manufacturers to claim is a reduction in osteoporotic fractures.

It is probable that BC deaths due to CHT has been underestimated. At the end of the study (11 years) the mortality curves appear to be widening, and the difference in cumulative BC between women on CHT and the placebo group appears to be growing.

Since the number of deaths from BC is relatively small, clinicians might conclude that a brief period of treatment given near menopause to relieve symptoms is safe. This is consistent with some guidelines and with the FDA labeling. However, the study does not address the effects of short periods of CHT therapy on risk of BC. The deleterious effects may be underestimated.

Clinicians who prescribe brief courses of CHT for relief of symptoms should be aware that this approach has not been proven to be harmless and the downstream consequences for patients are uncertain. Discussing the risk-benefit with a patient, in pursuit of an informed decision, may seem, at first blush, to be a reasonable approach, given the lack of evidence. The reality is that informed patient-decisions are not valid when the information underlying the decision is itself speculative. This includes advice to take CHT at lower doses for shorter periods, which assumes that enough is known about how CHT modulates disease risk to be confident that a safe dose is determined.

JAMA October 20, 2010| 304: 1719-20 Editorial by Peter B Bach, Memorial Sloan-Kettering Cancer Center, New York

I enjoyed this editorial The editorialist takes an interesting conservative view.

How duty bound are primary clinicians to discuss all possible harmful effects of drugs they prescribe even when the harm is very infrequent? (eg, 1 to 2 per 10 000 per year)

All drugs have harmful effects. Many medications we prescribe have adverse effects that occur more frequently than 1 to 2 in 10 000. Discussing all adverse effects would place an unacceptable time-burden on primary care clinicians.

In the case of CHT, I believe it is reasonable to believe that harms of short-low-dose treatment in women near the menopause are likely to be infrequent.

Much depends on the benefit of CHT in reducing symptoms. I believe many women would willingly accept rare risk of harms to gain relief of symptoms of menopause.

While contemplating the editorialist's comments about the often changing fashions of medicine I thought of the current enthusiasm for vitamin D. Enthusiastic endorsement at one period may be withdrawn as more solid evidence becomes available. I await randomized trials for confirmation of benefits of D. Meanwhile, I will continue to recommend oral replacement doses because D is not harmful and costs little.

Adding To the Uncertainty About The Direct Causal Relationship Between Hypoglycemia And Vascular Outcomes.

10-5 SEVERE HYPOGLYCEMIA AND RISKS OF VASCULAR EVENTS AND DEATH:

The ADVANCE Study

This 5-year, multicenter, multicountry open-label study examined the relationship between severe hypoglycemia and the subsequent risk of vascular complications and death in patients with DM-2.

Followed a total of 11 140 community-dwelling patients over age 55. All had DM-2 diagnosed after age 30, and had a history of major macro-vascular events or micro-vascular disease, or at least one cardiovascular risk factor in addition to DM-2. (A very high-risk group.)

Compared the effects of intensive glucose-lowering (target HbA1c of 6.5% or lower) with the use of modified-release gliclazide and other glucose-lowering drugs as required, vs standard guideline-based glucose-lowering on the risks of vascular outcomes and death.

Defined hypoglycemia as blood glucose less than 50 mg/dL, or the presence of typical symptoms and signs of hypoglycemia without other apparent cause. Patients with transient symptoms of the central nervous system who were unable to treat themselves (requiring help of another person) were considered to have severe hypoglycemia.

Severe hypoglycemia was uncommon, but more common in the intensive group. Minor hypoglycemia was common:

	Intensive (n = 5571)	Standard (n = 5569)
Severe hypoglycemia	150 (2.7%)	81 (1.5 %)
Minor hypoglycemia	2898 (52%)	2077 (37%)

The unadjusted risks of a major macro-vascular event, a major micro-vascular event, death from any cause, and death from a CVD cause were significantly increased among patients who had severe hypoglycemia compared with those who did not.

Hazard ratios severe hypoglycemia vs no severe hypoglycemia:

	HR
Major vascular event	3.51
Death (any cause)	3.27
Cardiovascular disease	3.79
Major microvascular event	2.19

But, relatively few patients with severe hypoglycemia had vascular outcomes and death. And outcomes were not closely related to episodes of severe hypoglycemia.

A. During follow-up, 2125 patients had a major macro-vascular or micro-vascular event:

87 of these patients reported severe hypoglycemia (40 before the event, and 47 after the event).

B. Vascular events and death were not closely related to the time of a severe hypoglycemic event. The median time from the episode of severe hypoglycemia to the first major micro-vascular event was 1.56 years and to the first micro-vascular event was 1 year. The median time from severe hypoglycemia to death was 1.05 years; 1.31 years for death from a CVD event and 0.74 years to death from a non-cardiac cause.

C. There was no evidence of a dose-response relationship between repeated episodes of severe hypoglycemia and vascular outcomes and death.

Severe hypoglycemia was associated with increased risks of vascular events and death.

However, neither a close temporal relationship nor a dose-response was observed.

In junction with the absence of a clear dose-response relationship between repeated episodes of hypoglycemia and subsequent macro-vascular events or death, these observations add to the uncertainty about the direct causal relationship between hypoglycemia and vascular outcomes.

In either case, severe hypoglycemia should raise suspicion of adverse outcomes and prompt action to address this possibility.

Severe hypoglycemia was strongly associated with increased risks of adverse clinical outcomes. It is possible that severe hypoglycemia contributes to adverse outcomes, but these analyses indicate that hypoglycemia is just as likely to be a marker of vulnerability to such events.

This is a complex and (to me) a confusing study.

The study began with a group at very high risk for CVD. The mortality rate was high.

The investigators identified many major vascular events. But few were recorded as being associated with severe hypoglycemia. Naturally, patients at very high risk for CVD who do not have DM-2 will die over a short period. The investigators felt that hypoglycemia was not the cause of many of the deaths.

CVD deaths were not related in time with severe hypoglycemia.

There was no evidence of a dose-response relationship between repeated episodes of severe hypoglycemia and death.

They conclude that, although some deaths might have been associated with severe hypoglycemia, many were not associated, and were due to the high risk of CVD in the cohort at baseline.

Nevertheless, the HRs of adverse events in those experiencing severe hypoglycemia (vs those without) were high.

A HbA1c Target Of 6.0% Or Less With Present Strategies Seems Imprudent.

10-6 EFFECT OF INTENSIVE TREATMENT OF HYPERGLYCEMIA ON MICRO-VASCULAR OUTCOMES IN TYPE-2 DIABETES; An Analysis of the ACCORD Randomized Trial

Epidemiological studies of type-2 diabetes (**DM-2**) have shown that high HbA1c levels are associated with increased risk of diabetic retinopathy and neuropathy.

ACCORD investigated the effects of standard vs intensive control of hyperglycemia on cardiovascular events over 10 years in a large population with DM-2. It also assessed the effect of intensive control on incidence and progression of retinopathy and neuropathy. The study aimed to reduce HbA1c levels to less than 6.0% in the intensive control group vs 7.0-7.9% in the standard group.

Entered 10 251-- 5125 in the intensive group and 5126 in the standard group. At baseline HbA1c levels averaged 8.1% in both groups.

At 4 years, HbA1c levels averaged 6.3% in the intensive group, and 7.6% in the standard group.

Intensive control was stopped at 4 years because of a 22% increase in all-cause mortality. The intensive-control patients were then transferred to standard control and the study continued for another 6 years (total of 10 years) .

At 10 years there were still some benefits remaining in the former intensive group: modest reductions in albuminuria and manifestations of diabetic neuropathy. (*A legacy effect.*) Serum creatinine levels rose equally in both groups.

There was no significant effect of intensive glycemic control on the composite primary micro-vascular outcome. (Renal and retinal)

Analysis of the secondary renal endpoints showed that the risk of development of micro-albuminuria was 20% lower in the intensive group --at both transition and at endpoint.

Targeting HbA1c to 6.0% is not recommended on the basis of micro-vascular benefits. Any benefits should be weighed against the recorded increase in total and CVD-related mortality.

Caution should be exercised in pursuing a strategy of intensive glycemia control for prevention of micro-vascular complications. A HbA1c target of 6.0% or less with present strategies seems imprudent.

Micro-vascular benefits should be weighed against the increase in total and CVD-related mortality, increased weight gain and high risk of severe hypoglycemia

What may primary care clinicians reasonably deduce from ACCORD AND ADVANCE?

- 1. Severe hypoglycemia may occur in those receiving standard treatment. It is more common in those receiving intensive treatment.*
- 2. Adverse CVD effects are more common in patients experiencing severe hypoglycemia.*
- 3. Hypoglycemia is a patho-physiologic stressor. It may be a cause of CVD events and death in patients with DM-2, especially in those at high risk for CVD.*
- 4. Adverse CVD effects and death may occur in patients with DM-2 who are at high risk of CVD, unrelated to occurrence of hypoglycemia. (Participants in both studies were at high risk at baseline.) Take extra care to avoid hypoglycemia in these patients. Young patients who have no CVD risk factors may better withstand hypoglycemia. Nevertheless, severe hypoglycemia should be avoided at any age.*
- 5. Benefits of intensive glycemic control are much less in older patients with DM-2 than younger patients. Good control starting at an early age and continued will reduce incidence of both micro- and macro-vascular complications*
- 6. There may be considerable benefit offered by the new glucagon-like-peptide drugs (eg, liraglutide) which avoid hypoglycemia and weight gain.*

ABSTRACTS OCTOBER 2010

“Serum Potassium Levels -- An Independent Predictor Of Incident DM-2.”

10-1 SERUM AND DIETARY POTASSIUM AND RISK OF INCIDENT TYPE-2 DIABETES

Hypokalemia may be a risk factor for type-2 diabetes (**DM-2**): 1) In studies of thiazide diuretics, lower K levels were associated with higher serum glucose levels. This effect was blunted by oral K supplementation. 2) Experimental studies provide biological plausibility by showing that thiazide-induced hypokalemia leads to diminished insulin secretion. 3) ACE inhibitors, which increase serum K levels, are associated with a decreased risk of DM-2. 4) A reanalysis of the Systolic Hypertension in the Elderly Program (**SHEP**) identified hypokalemia as a mediator of thiazide-related risk of incident DM-2.

However, no epidemiological studies have evaluated the risk of DM-2 associated with serum K, independent of thiazide use.

This study analyzed data from ARIC¹ study to test the hypothesis that adults with lower serum K levels (in the normal range) are at higher risk for DM-2, even without diuretic use. It also sought to determine whether higher dietary K intake is associated with lower risk.

If a low serum K is indeed a risk factor, then a strategy to increase serum K might represent a novel approach to DM-2 prevention.

STUDY

1. ARIC is a prospective study of over 15 000 adults age 45-65 (mean 54) at baseline (1986-89) from 4 population probability samples in the US. None had diabetes at baseline. All had serum K determined.
2. None had a serum K > 5.5 mEq/L at baseline or an elevated serum creatine.
3. After exclusions, 12 209 remained for follow-up.
4. Categorized serum K into 4 clinically meaningful groups: < 4.0 mEq/L; 4.0 to 4.4; 4.5 to 4.9; and 5.0 to 5.5.
6. The main outcome was incident DM-2 assessed at periodic follow-up visits.
7. Follow-up to 2008. In the first 9 years, subjects were followed by clinic visits; thereafter by telephone consultation.

RESULTS

1. Baseline characteristics:

A. Mean serum K at baseline was 4.4 mEq/L (range 2.4 to 5.5)

B.	Serum K levels at baseline			
	<4.0	4.0 - 4.4	4.5 - 4.9	5.0 -5.5
Number of participants	1619	4903	4178	1509
Fasting insulin pIU/mL	13.72	11.10	10.76	9.67

C. Lower K levels were associated with higher BMI, larger waist circumference, lower magnesium levels, higher fasting insulin levels, and higher use of beta-blockers and diuretics.

D. There was a significant inverse relationship between serum K and fasting insulin levels.

2. Incident DM-2 during the first 9 years of follow-up (n = 1475)

A.	<4.0	4.0 - 4.4	4.5 - 4.9	5.0 -5.5
Rate per 1000 person-years	24.6	16.6	14.2	11.8
Adjusted hazard ratio (HR) (Adjusted for multiple covariates)	2.05	1.52	1.37	1.00 (Referent)

B. The crude rate of incident DM-2 was highest in those with serum K lower than 4.0. Those with higher K had progressively lower rates of DM-2.

C. A similar inverse relationship was evident when K levels were categorized as quintiles and deciles.

D. After excluding participants who were prescribed diuretics, beta-blockers, ACE inhibitors, K supplements, and magnesium supplements, there was a graded increase in HR of incident DM-2 with lower serum K levels.

	<4.0	4.0 - 4.4	4.5 - 4.9	5.0 -5.5
Hazard ratios	1.57	1.49	1.38	1.00
E. Among those prescribed diuretics: (HRs were higher in those receiving diuretics.)	2.91	2.85	1.93	1.00

3. Over the entire study period. (Over 20 years)

	Hazard Ratios of DM-2			
Total cases (incident DM-2)				
Self reported DM-2 12 209 (2552)	1.24	1.28	1.31	1.00
Prescribed diuretics 1835 (357)	2.91	2.85	1.93	1.00
Not prescribed diuretics 9353 (1118)	1.41	1.51	1.35	1.00

(The gradient was less evident over the years, but incidence of DM-2 remained higher in those with K levels lower than 5.0)

4. Dietary analysis:

Mean K dietary intake was 2655 grams /day (recommended = 4700)

The correlation between serum K and dietary intake was modest.

There was a significant graded increase in risk of incident DM-2 with lower dietary K intake.

HRs for incident DM-2 by lower to higher K intake quartiles were 1.37; 1.19; and 0.95 compared with the reference highest intake. (1.00)

DISCUSSION

1. “Our study suggests an inverse relationship between serum potassium levels and incidence of DM in middle aged adults.”
2. The relationship was independent of a wide array of potential confounding factors; was strongest in thiazide users, but present in non-thiazide -users.
3. The association was still detectable more than 20 years after baseline.
4. In contrast, there was not a robust association with dietary intake of K and incident DM-2.
5. Since 2000, a few large epidemiological studies have found inconsistent relationships between thiazides and glucose metabolism.
6. Analysis of data from 59 clinical trials found a significant inverse correlation between glucose and potassium levels, and K supplements were associated with a smaller increase in glucose levels.
9. A recent analysis of the SHEP trial found that low K was a primary mediator of the association between thiazide diuretics and increased risk of DM-2. But no trial has looked at the association of K levels, independent of diuretic use, and the risk of DM-2 (the aim of this study),
10. This study is limited by only a single K determination at baseline. However the National Health and Nutrition Examination Survey (NHANES) found that serum K levels have an individual variability of about 5% based on repeated measurements.
11. Assessing a causal relationship between dietary K intake and DM-2 is difficult.
12. “An observational study cannot prove causality.”

CONCLUSION

“A Serum potassium level is an independent predictor of incident DM-2.”

JAMA October 25, 2010; 170:1745-51 Original investigation, first author Ranee Chatterjee, Johns Hopkins University, Baltimore MD

1 The Atherosclerosis Risk in Communities (ARIC) Study

“Substantially Reduced The Pain From Both Migraine And Tension-Type Headache.”

10--2 TRICYCLIC ANTIDEPRESSANTS AND HEADACHES: Systematic Review and Meta-analysis

This inclusive literature search included published randomized clinical trials that evaluated the efficacy of tricyclic anti-depressant drugs in reducing the frequency and severity of migraine headache (MHA) and tension-type headaches. (THA)

Treatment groups were required to receive a tricyclic anti-depressant drug regularly at any dose as a single intervention for at least 4 weeks.

Comparison groups could receive a placebo or a specific alternative drug, or non-drug treatment.

Participants had to be at least 18 years old, with MHA or THA.

Excluded secondary headache such as those related to drug overuse, concussion, or lumbar puncture.

Classified HA according to the most recent criteria of the International Headache Society.

STUDY

1. After reviewing 1471 articles, 37 met inclusion criteria: 13 on MHA; 17 of THA; and 6 on chronic mixed HA. (For this analysis, mixed HA was classified as MHA,)
2. A total of 3176 participants were included in the 37 studies, which lasted an average of 10 weeks. A mean of 70 participants took part in the studies; 70% were women, mean age 40.
3. Twenty studies compared tricyclic anti-depressant drugs (chiefly amitriptyline, a few with clomipramine and doxepin) with placebo. Eight studies compared tricyclic anti-depressant drugs with selective serotonin reuptake inhibitors (SSRI) ; 3 with beta-blockers; a few with other drugs. Others compared amitriptyline with cognitive behavior therapy, spinal manipulation, and transcranial brain stimulation.
4. Measures of HA included frequency, intensity and headache index.
5. Most studies titrated drug dose. Maximum doses: amitriptyline 150 mg; clomipramine 150 mg; doxepin 100 mg; Mean pooled doses: amitriptyline 80 mg; clomipramine 116 mg; doxepin 50 mg;.
6. Studies ran from 1964 to 2009.

RESULTS

1. Tricyclics vs placebo:

- A. Tension-type HA (8 studies)

At baseline, participants averaged 16 headaches per month

Tricyclics were more effective than placebo in reducing the burden of THA by an average standard mean difference of 0.99, a clinically large effect.

Efficacy did not differ among those with infrequent episodes, frequent episodes and chronic THA.

The number of THA was reduced by an average of 7 per month.

The beneficial effect increased over time.

Participants taking tricyclics for THA were more likely to experience a 50% improvement than those taking placebo.

B. Migraine headache

At baseline, participants averaged 5 headaches per month.

Tricyclics were more effective than placebo in reducing the burden of migraine by an average standard mean difference of 1.00, a clinically large effect.

The number of MHA was reduced an average of 1.4 per month.

The beneficial effects increased over time.

Participants taking tricyclics for MHA were more likely to experience a 50% improvement than those taking placebo

C. Tricyclics reduced the number of doses of analgesics taken for acute HA pain.

D. Adverse effects vs placebo

Those taking tricyclics reported “any” side effect

Dry mouth

Drowsiness

(The only adverse effects that were statistically significant.)

The likelihood of withdrawing due to adverse effects did not differ between groups

3. Tricyclics vs SSRIs.

Despite a low dose (average 50 mg) tricyclics were more likely than SSRIs to produce at least a 50% improvement in THA and MHA

4. Tricyclics vs other drugs

There were few studies.

Three studies compared tricyclics with beta-blockers. There was no difference in reduction in number of HAs. Two studies did not differ in likelihood of experiencing at least a 50% reduction in HA.

Two studies comparing tricyclics with buspirone (an anxiolytic) found no difference.

One study found amitriptyline better than dihydroergotamine for MHA.

5. Tricyclics vs non-drug treatments.

Two studies found no difference from spinal manipulation.

Three studies of cognitive behavior therapy found no difference.

6. Assessment of bias and sensitivity analyses:

The authors found no difference in effects between studies meeting and not meeting Cochrane criteria for bias.

DISCUSSION

1. “We found that tricyclic antidepressants substantially reduced the pain from both migraine and tension-type headache.”
2. Compared with placebo, patients with THA were 40-70% more likely to report at least a 50% improvement. Patients used fewer analgesics.
3. Tricyclics seem equally effective for MHA. This is useful clinically because differentiation of the two types may not always be straightforward, especially when HAs are frequent.
4. The benefit seems to increase over time. Clinical practice recommendations suggest that tricyclics be taken for several months before reaching any conclusions on effectiveness for any given patient.
5. Dry mouth, drowsiness, and abdominal distress were more likely to occur with tricyclics, but did not lead to greater withdrawal from treatment. This implies that the side effects were tolerable given the benefit.
6. Tricyclics were more effective than SSRIs in achieving a 50% reduction in THA and MHA.
7. A recent Cochrane review found that SSRIs were no more effective than placebo for THA. They found some indication that SSRIs were less effective than tricyclics for MHA. They concluded that tricyclics were favored over SSRIs, consistent with the findings of this meta-analysis.
8. It is difficult to reach conclusions on the relative efficacy of tricyclics compared with other treatment modalities. There are few studies. Most are underpowered.
9. Many clinicians encourage patients to take tricyclics for several months during which the dose is increased before deciding to try a different prophylactic agent.
10. It is impossible to differentiate whether treatment effect is independent of depression. The relation between depression and physical symptoms is well described. Patients with depression have more physical symptoms and report those symptoms are more serious and more severe and disabling than patients without depression. Depressed patients experience improvements in somatic problems when underlying depression is successfully treated.
11. “Meta-analysis is limited by the problem of aggregate data.” “Heterogeneity in our results was

considerable.”

12. “This analysis should be viewed as exploratory rather than definitive.”

CONCLUSION

Tricyclic antidepressants are effective in preventing migraine and tension-type headache. They are more effective than SSRIs, although with greater adverse effects

BMJ 2010;341:c5222 First author Jeffrey L Jackson General Medical Division VA Milwaukee, WI
A short version was printed in BMJ October 23, 2010:869

May Be An Option To Replace Warfarin

10-3 DABIGATRAN ETEXILATE IN PEOPLE WITH ATRIAL FIBRILLATION

Atrial fibrillation (AF) affects millions of people in the US. Prevalence increases with age: 0.5% in those age 50-59; 10% in those over 80. AF accounts for 15% of stroke. Strokes are more disabling when due to embolization from AF.

The population burden of AF will increase with time.

When compared with placebo, warfarin reduces risk of stroke by about two-thirds in patients with AF. But warfarin is underused because it is inconvenient and causes bleeding. Antiplatelet treatment with aspirin is much less effective than warfarin. Aspirin reduces risk of stroke by 20% compared with placebo. Adding clopidogrel to aspirin improves effectiveness, but the combination remains significantly less effective than warfarin.

Current guidelines recommend warfarin for patients with AF at high-risk of stroke:

Previous stroke or embolism;

Or more than one risk factor: age > 75; hypertension; diabetes; congestive heart failure.

And either aspirin or warfarin for those at moderate risk (only one stroke risk factor)

and aspirin for those at low risk (no stroke risk factors).

Dabigatran is an oral pro-drug that inhibits thrombin. It has a half-life of 12 to 17 hours. 50% is excreted by the kidneys. Unlike warfarin, it has a predictable anticoagulant effect, and does not require routine coagulant monitoring.

The RE-LY trial¹ (2009) compared dabigatran (*Pradaxa*; Boehringer Ingelheim) 110 and 150 mg twice daily with open-label warfarin (adjusted INR 2.0 to 3.0) in over 18 000 patients with AF. The primary outcome was stroke or systemic embolization.

Withdrawals: At a median of 2 years, 21% of dabigatran participants had withdrawn, mainly for dyspepsia, vs 17% of those taking warfarin.

Compared with warfarin, 150 mg dabigatran twice daily significantly reduced stroke and systematic embolization. (Relative risk = 0.66). Deaths from cardiovascular disease were also reduced in the dabigatran group. (RR = 0.85 despite the higher discontinuation rate)

Both doses of dabigatran were associated with fewer intracranial and life-threatening bleeds than warfarin. However, the 150 mg dose increased g.i. bleeding compared with low dose dabigatran and warfarin. The high dose significantly increased risk of myocardial infarction (mechanism not clear).

The INR in the warfarin group was within therapeutic range 64% of the time.

Conclusion: Dabigatran is at least as effective as warfarin for prevention of stroke in patients with AF. The rate of g.i. bleeding was higher with 150 mg dose (excess of 5 bleeds per 1000 patients per year) and myocardial infarction (2 per 1000 per year). But fewer cardiac deaths (5 fewer per 1000 per year) and strokes (5 fewer per 1000 per year with the higher dose). And fewer intracranial bleeds (4 fewer events per 1000 per years).

What are the implications for clinical practice?

1. The participants were a selected group. The results may not be generalisable.
2. As an alternative anticoagulant, dabigatran has limitations and safety concerns. (higher risk of g.i bleeds and myocardial infarction).
3. Possible accumulation of the drug in the presence of renal dysfunction. (Function should be evaluated before starting dabigatran.)
4. Dabigatran has the advantage of a wide therapeutic window, but drug compliance may influence safety and efficacy, a particular concern for vulnerable patients.

“The 150 mg twice daily dose of dabigatran etexilate may be an option to replace warfarin for most patients with atrial fibrillation who are at moderate or high-risk for stroke and who meet the eligibility criteria for the RE-LY trial.”

Lower doses will probably be reserved for patients at increased risk of bleeding and for elderly people.

Warfarin should continue to be the preferred drug for those with severe renal insufficiency who were not eligible for inclusion in the RE-LY trial, and people with known cardiovascular disease. Patient's values and preference should be considered.

Unanswered questions:

1. The relative safety and efficacy of dabigatran compared with warfarin are uncertain for

patients with renal impairment and those at high risk of bleeding who were not eligible for inclusion in the RE-LY trial.

2. The long-term effects of dabigatran beyond the average 2-year duration of the trial.
3. The efficacy of dabigatran compared with other new anticoagulants (rivaroxaban, apixaban, and edoxaban).

BMJ 2010;341Lc3784 doi:10.1135/bmj.c3784

BMJ October 2, 2010; 341:682-83 Editorial, first author Nina C Raju, MvMaster University, Ontario, Canada

1 Randomized Evaluation of Long Term Anticoagulation Therapy. See Practical Pointers September 2009 for an abstract of RE-LY

Increases Incidence And Death From Breast Cancer

10-4 ESTROGEN PLUS PROGESTIN AND BREAST CANCER INCIDENCE AND MORTALITY IN POSTMENOPAUSAL WOMEN

In the Women's Health Initiative trial (**WHI**) breast cancer (**BC**) incidence (vs placebo) was increased among women who received combined hormone therapy (**CHT**).

This study updates information from the WHI on BC incidence and mortality related to CHT.

STUDY

1. The WHI followed a total of 16 608 postmenopausal women, age 50-79 (mean age 63) randomly assigned to: 1) 0.625 mg/d of conjugated equine estrogen + 2.5 mg/d medroxyprogesterone acetate (*Prempro*; Wyeth) or 2) placebo.
2. None had a previous hysterectomy. All received mammography at baseline to rule out BC, Mammograms and clinical breast examinations were done periodically during the intervention phase.
3. The intervention period lasted from 1993 to 2002, when participants were instructed to stop CHT. Follow-up of 12 788 participants continued until 2009.

RESULTS

1. During a mean follow-up of 11 years, a total of 678 cases of BC were identified.
2. In the intention-to-treat analysis, CHT compared with placebo, was associated with an

increased incidence of BC (385 cases (0.42% per year) vs 293 cases (0.35% per year). Hazard ratio (**HR**) = 1.25.

3. In the CHT group, a significantly larger fraction of BCs presented with positive nodes: 81 vs 43; HR = 1.78.
4. There was no evidence of a difference in receptor-positive vs receptor-negative tumors
5. Some women prior to entering the trial were taking CRT. These women had a higher risk for BC. HR = 1.85, compared with 1.16 for those without prior use.
6. More women in the CHT group died of BC: 25 deaths vs 12 deaths. (2.6 deaths per 10 000/y vs 1.3 deaths per 10 000/y (HR = 1.96).

DISCUSSION

1. CHT increased incidence of invasive BC. The cancers were more commonly node positive.
2. More deaths were attributed to BC: 2.6 per 10 000/year vs 1.3 per 10 000/year.
3. All cause deaths in those receiving CHT were also higher following diagnosis of BC (5.3 vs 3.4 per 10 000/year)
4. CHT interferes with the diagnosis of BC, (*denser breasts*) leading to diagnosis at more advanced stages.
5. These findings are consistent with the observational Million Women Study, which reported a HR of 1.22 for BC in women taking CHT.
6. Following the initial report of the WHI trial, a substantial reduction in use of CHT occurred, followed by a reduction in incidence of BC.
7. Reproductive hormones, especially progestin, are potent stimulators of angiogenesis.
8. Because increased angiogenesis increases both lung and BC metastasis, these findings suggest that angiogenesis stimulation by CHT may facilitate growth and metastatic spread of already-established cancers.
9. Unless the mortality risks of lung cancer and BC can be mitigated, use of CHT--other than short term therapy in women with menopausal symptoms not ameliorated by other therapies--seems unwarranted.
10. "A safe interval for combined hormone therapy use cannot be reliably defined."

CONCLUSION

Use of estrogen plus progestin increases the incidence of BC. The cancers are more commonly node positive. Mortality was increased.

JAMA October 2010; 304: 1684-92 Original investigation, first author Rowan T Chlebowski, Harbor-UCLA Medical Center, Torrance California.

Should Raise Suspicion Of Adverse Outcomes And Prompt Action To Address This Possibility.

10-5 SEVERE HYPOGLYCEMIA AND RISKS OF VASCULAR EVENTS AND DEATH:

The ADVANCE¹ Study

In patients with diabetes treated with insulin or insulin secretagogues, severe hypoglycemia is more common when glucose control is intensified. Although most episodes of severe hypoglycemia resolve without apparent permanent injury, there are anecdotal reports of acute coronary syndromes coinciding with hypoglycemia in people with type-2 diabetes (**DM-2**)

Observational studies have suggested that hypoglycemia and reduced levels of HbA1c are associated with increased risk of death in patients with diabetes who have been hospitalized for myocardial infarction.

Recently completed trials investigating the effect of intensive glucose control in patients with long-standing DM-2 have *failed* to demonstrate reductions in cardiovascular events or mortality. The excess mortality observed with intensive glucose control in the ACCORD² study has fueled speculation about the adverse effects of intensive control. Post-hoc analyses of ACCORD suggest that the excessive mortality in the intensively treated group was *not* directly explained by the high rate of hypoglycemia.

The study examined the relationship between severe hypoglycemia and the subsequent risk of vascular complications and death in patients with DM-2.

STUDY

1. This 5-year, multicenter, multicountry open-label study followed a total of 11 140 community-dwelling patients over age 55. All had DM-2 diagnosed after age 30, and had a history of major macro-vascular events or micro-vascular disease, or at least one cardiovascular risk factor in addition to DM-2. (A very high-risk group.)
2. Compared the effects of intensive glucose-lowering (target HbA1c of 6.5% or lower) with the use of modified-release gliclazide and other glucose-lowering drugs as required, vs standard guideline-based glucose-lowering on the risks of vascular outcomes and death.
3. Defined hypoglycemia as blood glucose less than 50 mg/dL, or the presence of typical

symptoms and signs of hypoglycemia without other apparent cause. Patients with transient symptoms of the central nervous system who were unable to treat themselves (requiring help of another person) were considered to have severe hypoglycemia.

- The primary clinical outcomes were the first major macro-vascular event (death from a cardiovascular cause, nonfatal myocardial infarction, or nonfatal stroke), and the first major micro-vascular event (new or worsening nephropathy or retinopathy).

RESULTS

- Severe hypoglycemia was more common in the intensive group.

	Intensive (n = 5571)	Standard (n = 5569)
Severe hypoglycemia	150 (2.7%)	81 (1.5 %)
One episode	120	64
Two episodes	22	13
Three or more episodes	3	4
Minor hypoglycemia	2898 (52%)	2077 (37%)
One episode	1529	1081
Two episodes	397	274
Three or more episodes	972	722

- Risk factors for severe hypoglycemia:

Many variables were independent risk factors for severe hypoglycemia: older age, long duration of DM-2, lower BMI, use of two or more drugs, and assignment to the intensive group.

- The unadjusted risks of a major macro-vascular event, a major micro-vascular event, death from any cause, and death from a CVD cause were significantly increased among patients who had severe hypoglycemia compared with those who did not. After adjustment, for a number of possible confounders, the associations were markedly attenuated, but remained significant.
- Hazard ratios severe hypoglycemia vs no severe hypoglycemia:

	HR
Major vascular event	3.51
Death (any cause)	3.27
Cardiovascular disease	3.79
Major microvascular event	2.19

- But, relatively few patients had vascular outcomes and death. And outcomes were not closely related to episodes of severe hypoglycemia

- A. During follow-up, 2125 patients had a major macro-vascular or micro-vascular event:
Only 87 of these patients reported severe hypoglycemia (40 before the event, and 47 after the event).
- B. Vascular events and death were not closely related to the time of a severe hypoglycemic event. The median time from the episode of severe hypoglycemia to the first major micro-vascular event was 1.56 years and to the first micro-vascular event was 1 year. The median time from severe hypoglycemia to death was 1.05 years; 1.31 years for death from a CVD event and 0.74 years to death from a non-cardiac cause.
- C. There was no evidence of a dose-response relationship between repeated episodes of severe hypoglycemia and vascular outcomes and death.

DISCUSSION

1. Severe hypoglycemia was clearly associated with increased risks of macro-vascular events, micro-vascular events, and death from both cardiovascular and non-cardiovascular causes.
2. Possible explanations by which hypoglycemia might cause CVD or death include: sympatho-adrenal activation, abnormal cardiac repolarization, and increased thrombogenesis, inflammation and vasoconstriction.
3. The effects of confounding were substantial. The presence of coexisting conditions could increase vulnerability to both severe hypoglycemia and adverse clinical outcomes.
4. Severe hypoglycemia was strongly associated with increased risks of vascular events and death. However, neither a close temporal relationship nor a dose-response was observed.
5. In junction with the absence of a clear dose-response relationship between repeated episodes of hypoglycemia and subsequent macro-vascular events or death, these observations add to the uncertainty about the direct causal relationship between hypoglycemia and vascular outcomes.
6. In either case, severe hypoglycemia should raise suspicion of adverse outcomes and prompt action to address this possibility.

CONCLUSION

Severe hypoglycemia was strongly associated with increased risks of adverse clinical outcomes. It is possible that severe hypoglycemia contributes to adverse outcomes, but these analyses indicate that hypoglycemia is just as likely to be a marker of vulnerability to such events.

NEJM October 7, 2010; 1310-18 Original investigation by the ADVANCE Collaboration Group, first author Sophia Zoungas, International Health University of Sydney, Australia.

1 ADVANCE “Action in Diabetes and Vascular Disease” NEJM 2008; 358: 2560-72

2 ACCORD “Action to Control Cardiovascular Risk in Diabetes” NEJM 2008; 358: 2545-59

A HbA1c Target Of 6.0% Or Less With Present Strategies Seems Imprudent.

10-6 EFFECT OF INTENSIVE TREATMENT OF HYPERGLYCEMIA ON MICRO-VASCULAR OUTCOMES IN TYPE-2 DIABETES; An Analysis of the ACCORD Randomized Trial

Epidemiological studies of type-2 diabetes (**DM-2**) have shown that high HbA1c levels are associated with increased risk of diabetic retinopathy and neuropathy. Several clinical trials of intensive glycemic control have reported a reduction in micro-vascular complications (mostly in albuminuria).

ACCORD¹ investigated the effects of standard vs intensive control of hyperglycemia on cardiovascular events over 10 years in a large population with DM-2. It also assessed the effect of intensive control on incidence and progression of retinopathy and neuropathy. At baseline, participants were at very high risk of cardiovascular disease, having already had a CVD or two or more risk factors for CVD.

The study aimed to reduce HbA1c levels to less than 6.0% in the intensive control group vs 7.0-7.9% in the standard group.

The composite primary outcome was dialysis or renal transplantation, high serum creatinine (> 292 umol/L; 3.3 mg/dL) or retinal photocoagulation or vitrectomy. Secondary outcomes were 13 prespecified measures of eye and kidney disease, and peripheral nerve function.

RESULTS

1. Entered 10 251-- 5125 in the intensive group and 5126 in the standard group. At baseline HbA1c levels averaged 8.1% in both groups.
2. At 4 years, HbA1c levels averaged 6.3% in the intensive group, and 7.6% in the standard group.
3. Intensive control was stopped at 4 years because of a 22% increase in all-cause mortality. The intensive-control patients were then transferred to standard control and the study continued for another 6 years (total of 10 years) .
4. At 4 years, there were some benefits noted in the intensive group: modest reductions in incident albuminuria, and comparatively better visual acuity and reduction in cataract surgery.

5. At 10 years, HbA1c levels in the transitioned intensive group averaged 7.2% vs 7.6% in the standard group. (*Some legacy effect in lowering HbA1c.*)
6. At 10 years there were still some benefits remaining in the former intensive group: modest reductions in albuminuria and manifestations of diabetic neuropathy. (*A legacy effect.*) Serum creatinine levels rose equally in both groups.

DISCUSSION

1. There was no significant effect of intensive glycemic control on the composite primary micro-vascular outcome. (Renal and retinal)
2. Analysis of available epidemiological evidence suggests that hyperglycemia is an important contributor to development of micro-vascular complications of DM-2. But recent trials showed less benefit in elderly patients and those with long-term diabetes than in young patients and those with short-term diabetes.
3. Analysis of the secondary renal endpoints showed that the risk of development of micro-albuminuria was 20% lower in the intensive group --at both transition and at endpoint.
4. Intensive therapy increased body mass index and caused more frequent episodes of hypo-glycemia.
5. Targeting HbA1c to 6.0% is not recommended on the basis of micro-vascular benefits. Any benefits should be weighed against the recorded increase in total and CVD-related mortality.
6. Caution should be exercised in pursuing a strategy of intensive glycemic control for prevention of micro-vascular complications. A HbA1c target of 6.0% or less with present strategies seems imprudent.

CONCLUSION

Micro-vascular benefits should be weighed against the increase in total and CVD-related mortality, increased weight gain and high risk of severe hypoglycemia.

Lancet August 2, 2010; 376: 419-30 Original investigation by the ACCORD group, first author Faramarz Ismail-Beigi, Case Western Reserve University, Cleveland, Ohio

1 ACCORD: Action to Control Cardiovascular Risk in Diabetes

