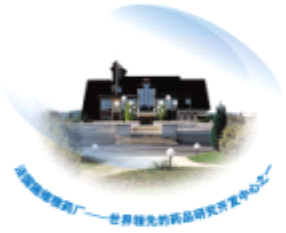

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专家介绍

Professor Ken Shaw is Honorary Consultant Physician, specialising in general medicine, diabetes, endocrinology and metabolism; based at Queen Alexandra Hospital, Portsmouth Hospitals NHS Trust and Emeritus Professor of Medicine, University of Portsmouth, Hants, UK. Drawing on a deep personal empathy for people with diabetes and a passionate commitment to developing and delivering high quality diabetes care, Professor Shaw has led an internationally recognised and award winning, multidisciplinary, professional diabetes team in Portsmouth, UK.

Ken Shaw，普兹茅斯大学皇家亚历山大医院医学系教授，系荣誉医学顾问专家，专长于全科医学、糖尿病、内分泌和代谢。
Ken Shaw 教授领导的糖尿病专业研究小组，秉承解救糖尿病疾患之苦的精神，致力于提供高水准糖尿病医疗。
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Intensive Glycaemic Control and the Prevention of Cardiovascular Events in the Treatment of Type 2 Diabetes

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The rapidly changing environment of modern world living has resulted in a global expansion of the number of people suffering from Type 2 diabetes and its distressing consequences to health. In particular, it is recognised that with change from traditional to modernised lifestyle, the overall prevalence of diabetes in China has increased dramatically in recent years, presenting major problems in both human and economic terms[1]. Type 2 Diabetes has a number of important characteristics, which in turn create challenges for determining best medical management. By its nature Type 2 diabetes remains a progressive disorder as beta-cell function declines with time. But the rate of decline varies between individuals raising the therapeutic prospect of protecting the beta-cell and potentially preventing or delaying progression. The pathogenesis of Type 2 diabetes is complex and multifactorial,such that optimal management is likely to require multiple therapeutic interventions. Cardiovascular disease, and coronary heart disorder in particular, is now the biggest complication challenge. Reducing long-term cardiovascular risk has been a key objective of several recent studies that have been published in the last year.

Medical management of Type 2 diabetes requires a combination of treatment to target with that appropriate to the individual .The therapeutic aim should consider present quality of life and well being, whilst addressing future good health and longevity – "getting the balance right" . A healthy lifestyle should be encouraged for all. The China Da Qing study[2] has shown that for those with impaired glucose tolerance an intensive diet and exercise programme can effectively reduce the future risk of developing diabetes

Coronary disease is much increased with Type 2 diabetes. Epidemiological data from the United Kingdom Prospective Diabetes Study (UKPDS) identified a linear relationship between the degree of hyperglycaemia and risk of myocardial infarction, but evidence that optimising glucose control can reduce this risk has proved difficult to determine. However, following on from the encouraging longer-term observations of the Diabetes Control and Complications Trial (DCCT/EDIC Study) in Type 1 diabetes, similar outcome has recently been reported[3] from UKPDS for Type 2 diabetes with 10 year post trial follow-up data indicating a significant risk reduction in myocardial infarction and all-cause mortality. This has been described as a **"Legacy Effect"** arising from earlier intensified glucose control, and has been similarly observed in the Steno-2 Study[4] where after a mean follow-up period of 13.3 years, intensified, multifactorial intervention was associated with a 54% relative risk and a 20% absolute risk reduction in mortality. Both of these studies emphasise the importance of early tight glycaemic control if long-term cardiovascular benefits are to be achieved.Three recent major studies (ACCORD, VADT & ADVANCE) set out specifically to address whether, with newer treatment glucose-lowering regimens, such intensified glycaemic control could result in reduced adverse cardiovascular outcomes. ACCORD[5] treated high risk individualsintensively to tight target (HbA1c < 6.0%) and was discontinued prematurely because of a high rate of serious hypoglycaemia and apparent increased mortality. VADT[6] similarly reported increased severe hypoglycaemia and weight gain. No significant difference in cardiovascular endpoints was observed in either ACCORD or VADT.

The ADVANCE Collaborative Group study of intensive blood pressure & blood glucose control and vascular outcomes in Type 2 Diabetes was specifically designed to extend beyond UKPDS findings and to determine whether tighter glucose control (<6.5% HbA1c vs 7% in the UKPDS intensive arm), based on a gliclazide MR regimen, could reduce major micro and macrovascular complications. **Results[7] from the blood glucose lowering arm showed that intensive treatment with gliclazide MR (Diamicron MR), in combination with other drugs as required, lowered blood glucose levels progressively and safely to HbA1c 6.5% and that serious microvascular complications of diabetes could be reduced, including reduction of kidney disease by 21% and also of proteinuria, a predictor of cardiovascular risk, by 30%.** After a median 5 years of follow-up no significant change in cardiovascular outcomes had been observed. However, **when the joint effects of blood pressure lowering and intensive glucose control, although independent of each other, were taken into consideration, substantial additive benefit was observed, including a 24% reduction in cardiovascular death.**

The reduction in HbA1c to target was much less rapid and significantly less severe hypoglycaemia was observed. **has shown that pragmatic and progressive glucose reduction can safely achieve a target HbA1c of 6.5% with an acceptable rate of hypoglycaemia and minimal weight gain.**

A recent consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes[8] has advised that medical management of hyperglycaemia in Type 2 diabetes should be based on a combination of clinical trial evidence and clinical judgement, **recommending that choice of treatment should be individualised with considerations of potential long-term benefits, safety & tolerability, long-term adherence, cost-effectiveness and additional non-glycaemic properties of the medication.** An algorithm is proposed, reinforcing life-style interventions, with prescribed glucose-lowering drugs divided as either Tier 1: well-validated core therapies or Tier 2: less well-validated therapies. **Tier 1 is seen "to represent the best established, most effective & cost-effective therapeutic strategy for achieving target glycaemic goals".**

Within this ADA/EASD guidance, medical management of Type 2 diabetes includes a continuing and important role for the use of sulphonylureas as Tier 1 therapy. Clinical Trial evidence combined with a long-standing clinical experience has confirmed that gliclazide MR offers established efficacy and high patient acceptability. Additional anti-oxidant and endothelial protective properties provide further prospect of potential cardiovascular benefit. ADVANCE has shown that it is possible to achieve intensifed glycaemic control (HbA1c < 6.5%) with safety, and with significant reduction in serious long-term complications of diabetes. The combined joint effects of blood pressure lowering and intensive glucose control are particularly striking with substantial benefits, including reduction by one quarter of deaths from cardiovascular causes.

Prof Ken Shaw
27th Jan 2009
(www.Profkenshaw.com)

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2型糖尿病患者严格血糖控制和心血管事件的预防

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现代社会生活方式和生活节奏的迅速变化，导致了全球范围内越来越多的人罹患上2型糖尿病。而其并发症也严重地威胁着人类的健康。特别是近年来，随着传统生活方式向现代生活方式的转变，中国2型糖尿病患病率呈全面流行的趋势，患者数量激增，这也反映出人和经济社会之间存在的主要矛盾。（参考文献1）。2型糖尿病自身有很多的疾病特点，让医生根据这些特点来决定最佳的治疗方案是一件非常有挑战性的事情。随时间进展，β细胞的功能呈进行性衰竭的趋势。但是每个患者β细胞功能降低的程度是不一致的，因此要求在制定治疗方案时尽可能的保护β细胞功能，阻止或延缓β细胞功能的降低。2型糖尿病的发病机理非常复杂且与很多因素有关。所以，优化血糖管理很可能需要进行多因素的干预治疗。2型糖尿病患者的并发症，特别是心血管疾病与冠状动脉疾病两大并发症，是目前我们面临的最大挑战。减少2型糖尿病患者长期的心血管风险已经成为最近几项研究的一个主要目标，而这几项研究的结果已经在去年得到公布。

2型糖尿病患者的血糖管理需要制定个体化的联合治疗方案，以达到适合的血糖控制目标。治疗的目的应既考虑患者目前的生活质量，同时又要寻求未来的健康长寿　并且在这两者之间“达到恰当的平衡”。对所有的人来说，都应该提倡一个健康的生活方式。中国的大庆研究（参考文献2）表明，那些糖耐量受损的患者进行强化的饮食控制和运动治疗的方案，可以有效地减少这些人群未来罹患糖尿病的风险。

越来越多的2型糖尿病患者出现冠状动脉疾病等并发症。来自英国前瞻性糖尿病研究（UKPDS）的流行病学数据确定了一定程度的高血糖与心肌梗死风险之间的线性关系，但因为证据不足，还难以确定优化血糖控制可以减少这种风险。然而，下列长期的观察结果还是很鼓舞人心的：1型糖尿病患者的糖尿病控制与并发症试验（DCCT / EDIC研究）以及最近报道（参考文献3 ）的UKPDS对2型糖尿病患者10年后的随访资料表明：强化血糖控制能够明显减少心肌梗死及全因死亡的风险。我们能够在早期进行强化血糖控制的2型糖尿病患者身上看到这种被称为**“延迟效应”**的现象，在Steno– 2研究（参考文献4）中我们同样可以观察到这种延迟效应。经过平均随访时间为13.3年，可以观察到多因素强化干预可以使2型糖尿病患者死亡率相对危险减少 54 %；绝对风险下降20 %。这些研究非常重要，因为其强调了早期严格的血糖控制能够使长期心血管获益。最近三个主要的大型研究(ACCORD,VADT和ADVANCE)的目的是观察新的强化血糖控制方案是否可能会减少心血管不良后果。ACCORD（参考文献5）研究对可能存在心血管疾病风险的高危2型糖尿病患者采取了强化血糖控制的治疗方案，目标非常严格（HbA1c < 6.0%），但由于严重的低血糖发生率和明显增加的死亡率，强化组的研究被迫停止。VADT研究（参考文献6）同样报告了严重低血糖发生率增加和体重增加。遗憾的是，无论在ACCORD 研究还是 VADT.研究中，心血管终点都没有得到显著的统计学差异。

ADVANCE研究协作组开展了针对2型糖尿病患者进行强化降压和降糖以观察血管结局的研究。该研究是专门设计（2×2析因设计）、在UKPDS 结果基础上又进一步延伸的大型临床研究。目的是确定以格列齐特缓释片（达美康缓释片）为基础的治疗方案、采用更严格的血糖控制措施是否能够减少主要大血管和微血管并发症。（ADVANCE 强化组HbA1c < 6.5 %VS UKPDS强化组HbA1c 7 %），**降糖分支的研究结果表明（参考文献7 ），以格列齐特缓释片（达美康缓释片）为基础的强化治疗组，联合其他必要的降糖药物，可以安全有效的使HbA1c达到 6.5%，并减少肾脏疾病达21%，大量蛋白尿达30%，而大量蛋白尿是心血管事件的独立预测因子。**经过5年的随访，未发现强化治疗组在心血管事件上有显著的统计学差异。然而，**当分析常规降压和强化降糖组的结果时，能看到心血管死亡下降24%，这种额外的益处的确是存在的，而且降压和降糖的结果是彼此独立，互不干扰的。**

ADVANCE研究和ACCORD研究在很多地方存在不同之处。ADVANCE研究设立了循序渐进的治疗方案，糖化血红蛋白降低的速度比较舒缓，没有那么激进，而且严重低血糖的发生率很低。此外，两个研究在选择其他降糖药物上也存在明显差异。ACCORD研究中有相当大比例的患者使用了格列酮类药物和胰岛素进行治疗。**ADVANCE研究结果则表明，务实渐进的降糖策略可以安全地降低血糖，实现目标糖化血红蛋白达到6.5 %，且低血糖的发生率是在可以接受的、体重的增加也很轻微。**

最近美国糖尿病协会和欧洲糖尿病研究协会（参考文献8 ）的一项共识声明表示， 2型糖尿病高血糖的医疗管理应该以临床试验的证据和临床经验相结合为基础，**建议治疗药物的选择应充分考虑其潜在的长期效益、安全与耐受性、依从性、成本效益，还有降糖作用之外的药物特性，使之对患者更具有针对性。**该共识的治疗流程如下：在加强生活方式干预的同时，把降糖药物分为一级推荐 – 有充分循证依据的核心治疗药物和二级推荐 – 循证依据较少或不充分的治疗药物。**一级推荐的药物代表已经确立的、最有效的及最高性价比的血糖达标治疗策略。**

ADA/ EASD 关于2型糖尿病的治疗管理明确指出，磺脲类药物是具有重要地位的、有充分循证依据的1级推荐核心治疗药物。临床试验证据，再加上长期的临床经验证实，格列齐特缓释片（达美康缓释片）具有确定的疗效、病人的接受程度高。其额外的抗氧化特性和内皮保护功能为2型糖尿病患者在今后能够获得进一步的、潜在的心血管益处带来了希望。ADVANCE研究结果已经表明，以达美康缓释片为基础的治疗方案有可能实现强化控制血糖安全达标(HbA1c < 6.5%)，并显著降低长期严重的糖尿病并发症。强化降压和强化降糖的联合作用成果显著，能够使四分之一的2型糖尿病患者避免因心血管疾病而死亡的风险。

Prof Ken Shaw
27th Jan 2009
(www.Profkenshaw.com)

Intensive Glycaemic Control & the Prevention of Cardiovascular Events in the Treatment of Type 2 Diabetes

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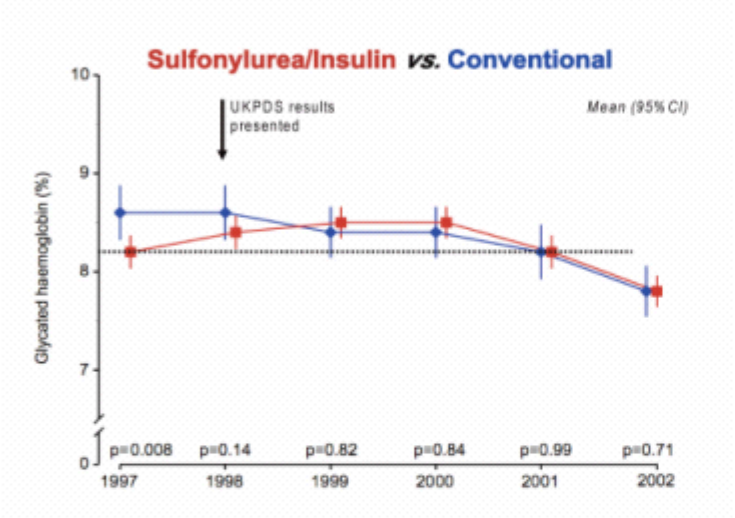
Type 2 Diabetes & Characteristics & Challenges

Characteristic	Challenge
Progressive Nature	*Prevention*
Declining Beta-cell function	*Protection*
Multifactorial Pathogenesis	*Multiple Interventions*
Coronary/Heart Risk	*Reducing Vascular Risk*
Multiple Treatments	*Optimising Therapy*

notes

UKPDS Post-Trial Changes in HbA 1c



Legacy Effect of Earlier Glucose Control

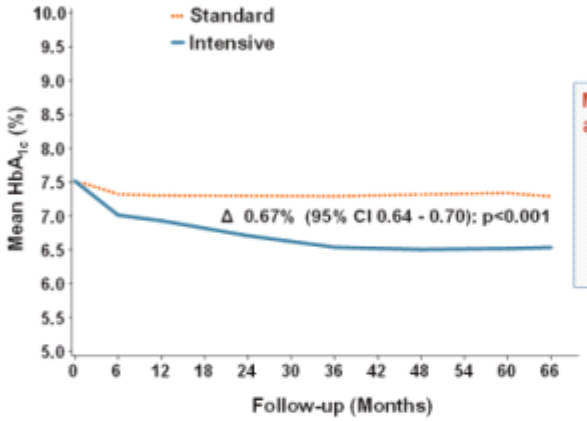
After median 8.5 years post-trial follow-up

Intensive (SU/Ins) vs. Conventional

Aggregate Endpoint		1997	2007
Any diabetes related endpoint	*RRR:*	12%	**9%**
	P:	0.029	**0.040**
Microvasculadisease	*RRR:*	25%	**24%**
	P:	0.0099	**0.001**
Myocardial infarction	*RRR:*	16%	**15%**
	P:	0.052	**0.014**
All - cause mortality	*RRR:*	6%	**13%**
	P:	0.44	**0.007**

RRR = Relative Risk Reduction, P = Log Rank

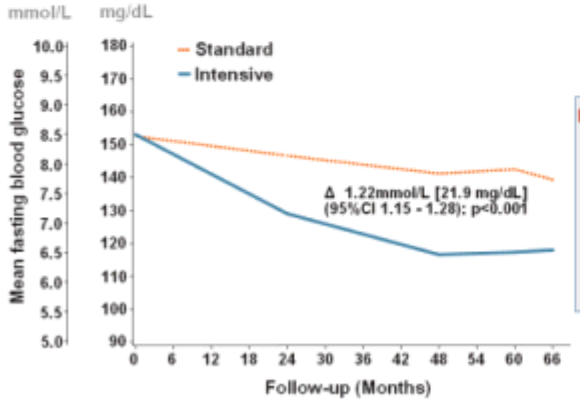
ADVANCE: Glycaemic Results



Mean HbA_{1c} at final visit

7.3 %

6.5%



Mean FBG at final visit

7.7 mmol/L
139 mg/dL

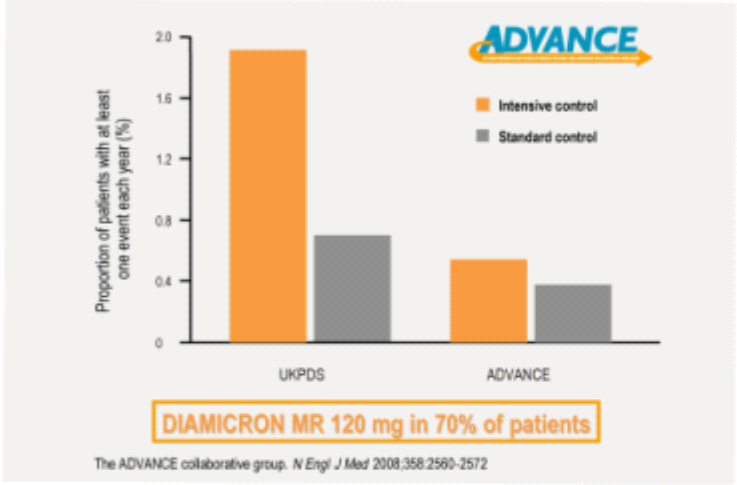
6.2 mmol/L
112 mg/dL

Comparison: ACCORD, ADVANCE & VADT studies

characteristic	ACCORD	ADVANCE	VADT
Baseline:			
Age (yr)	*62*	*66*	*60*
DM duration (yr)	*10*	*8*	*11*
CVS disease (%)	*35*	*32*	*41*
Intervention:			
target HbA1c (%)	*6.0*	*6.5*	*6.0*
Trial duration (yr)	*3.4*	*5.0*	*5.6*
insulin (%)	*77*	*41*	*89*
Outcome:			
HbA1c (%)	*6.4*	*6.5*	*6.9*
CVS Death (% Int. v Std.)	*2.6 v 1.8 **	*4.5 v 5.2*	*4.5 v 3.7*
Severe Hypo (%)	*16.2*	*2.7*	*21.2*

notes

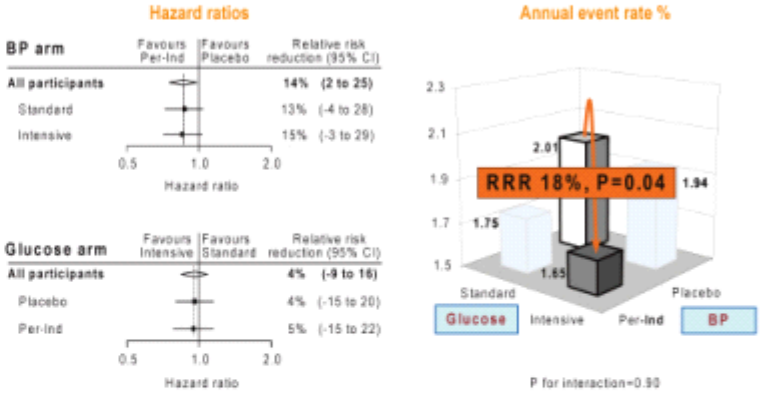
Comparative rates of severe hypoglycemia in ADVANCE and UKPDS



The ADVANCE collaborative group. *N Engl J Med* 2008;358:2560-2572

notes

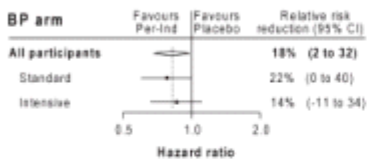
ADVANCE BP/BG Arm Joint AnalysisAll cause mortality

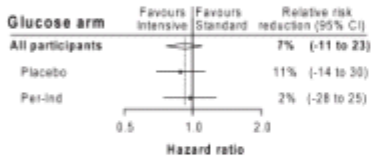


notes

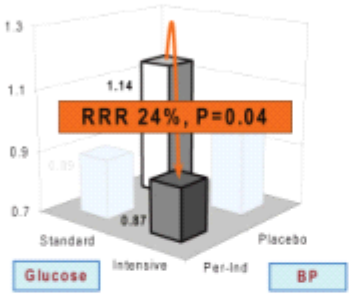
ADVANCE BP/BG Arm Joint Analysis
Cardiovascular death

Hazard ratios





Annual event rate %



P for interaction=0.62

notes

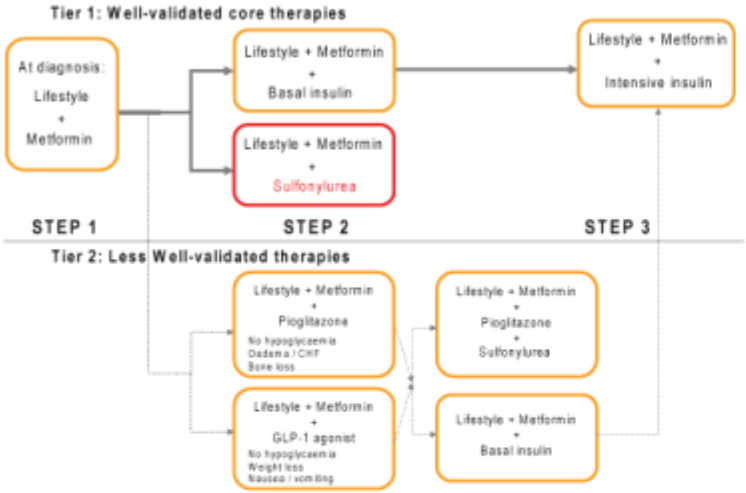
Rationale for the choice of DIAMICRON MR

- Innovative formulation for an effective 24-hour coverage in a single intake at breakfast [1]
- Effective and long-lasting glycemic control [2,3,4]
- Well tolerated even at higher doses [2,3]
- Antioxidant properties and direct vascular protection [5,6,7]

1. Guillausseau PJ and Greb W. Diabetes Metab. 2001;27:133-137 - 2. Schernthaner G, et al. Eur J Clin Invest. 2004;34:535-542 3. data on file - 4. Satoh J, et al. Diabetes Res Clin Pract. 2005;70:291-297 - 5. O'Brien RC , et al. J Diabetes Complications. 2000;14:201-206 - 6. Katakami N, et al. Diabetologia. 2004;47:1906-1913 - 7. Johnsen SP, et al. Am J Ther. 2006;13:134-140

notes

Algorithm from the ADA/EASD



Hypoglycemic episodes

with blood glucose < 3.0 mmol/L