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Target blood pressure levels in diabetes mellitus: are the changes reasonable?

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Abstract

The prognosis of patients in diabetes mellitus associated with hypertension can be improved if target blood pressure is achieved. Based on the results of the large-scale, multicenter trials, the target blood pressure levels have been modified in the recent guidelines on the management of hypertension, and in various countries different approaches have been reported. Lower target blood pressure might be reasonable provided with the optimal safety. A personalized approach is important for the choice of antihypertensive therapy.

Key words: diabetes mellitus, hypertension, blood pressure, target blood pressure, target organ damage

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Оправдано ли изменение целевых значений артериального давления при сахарном диабете?

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Резюме

Достижение целевых значений артериального давления (АД) у больных сахарным диабетом (СД) является важным элементом терапии для улучшения прогноза дальнейшего течения заболевания и его осложнений. За последние годы на основании результатов крупных, многоцентровых исследований в рекомендациях кардиологических сообществ различных стран были пересмотрены целевые уровни АД. Стремление к более низким значениям АД при СД 2-го типа оправдывает себя, однако при условии безопасного достижения этих уровней, и требуется более персонализированный подход к определению целей антигипертензивной терапии у пациентов с СД 2-го типа и артериальной гипертензией.

Ключевые слова: сахарный диабет, артериальная гипертензия, артериальное давление, целевые уровни артериального давления, поражение органов-мишеней

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«When it is obvious that the goals cannot be reached,
don't adjust the goals, adjust the action steps.»
Confucius

Reaching target blood pressure (BP) is as much important for the prognosis in diabetes mellitus (DM) and its complications as glycemic control. But the target BP values in DM are still under discussion. The traditional postulate was «the lower the better». Since the late 90-s of XX century up to 2013, according to the majority of international and national professional societies, target BP for the general population the level below 140/90 mm Hg., but for diabetic patients — below than 130/80 mm Hg in

the absence of chronic kidney disease (CKD), and below 125/75 mm Hg when concomitant kidney pathology is identified [1–4]. However, the completion of several large-scale prospective randomized trials (ACCORD, INVEST, HOT, VALUE) called for discussion considering BP control:

1) There is no evidence of clinical benefits of reaching target BP <130/80 mm Hg in comparison with BP <140/85–90 mm Hg regarding the final cardiovascular outcomes;

**TARGET BP ACCORDING TO THE INTERNATIONAL
AND NATIONAL GUIDELINES IN DIFFERENT POPULATIONS
(DIABETES MELLITUS, CHRONIC KIDNEY DISEASE, ELDERLY PATIENTS)**

| Recommendations / country / year | Target BP (mm Hg) | | |
|---|---|--|--|
| | General population | DM | CKD |
| ESH/ESC Europe / 2013(5) | < 140/90 Older than 80 years old: 140–150 | < 140/85 | < 140/90 |
| JNC 8/ USA/2014 (6) | <60 years old: < /90 ≥60 years old: < 150/90 | < 140/90 | < 140/90 |
| ASH/ISH / USA/ 2014 (7) | < 80 years old: < 140/90 ≥ 80 years old: < 150/90 | < 140/90 | < 140/90 |
| AHA/ACC/CDC USA/2014 (8) | < 140/90 Lower targets can be considered | <140/90 Lower targets can be considered | <140/90 Lower targets can be considered |
| ADA / USA 2015 (9) | Not specified | < 140/90 Can be considered < 130/80 for young | < 140/90 Can be considered < 140/80 |
| AACE / ACE / USA/2016 (10) | | <130/80 (for the majority) <120/80 (if it is safe) | < 130/80 |
| KDIGO / Europe / 2013 (11) | ≤ 140/90 | In case of albuminuria < 30 mg per day: < 140/90: In case of albuminuria > 30 mg per day or after renal transplantation, regardless of the albuminuria level: < 130/80 | |
| CHEP / 2016 / Canada (12) | < 80 years old: < 140/90 ≥ 80 years old: < 150/ not specified | < 130/80 | < 140/90 |
| The Russian Association of Endocrinologists / Russian Federation/2015 (13) | Not specified | ≤ 140/85 Not less than 120/70* * when antihypertensive therapy is ongoing | ≤ 130/85 Not less than 120/70* * when antihypertensive therapy is ongoing |
| The Russian Society of Cardiology (RSC) / 2015 (14) | SBP <140–150 Not less than 110–115 / 70–75 | < 140/85 | САД < 130–140 |

2) There is a potential risk of the adverse cardiovascular events of reaching low BP levels due to the J-shaped association, especially in elderly patients;

3) The target BP level <130/80 mm Hg in patients with DM is difficult to achieve and requires the prescription of the multicomponent combination antihypertensive therapy, which is very expensive.

With regard to above-mentioned reasons, in 2013–2014, the majority of international and national societies of cardiologists, nephrologists and endocrinol-

ogists revised BP targets in order to increase them in general population in general and among patients with DM and for individuals with CKD (Table 1).

The opinions of various professional communities in relation to BP targets in general population and in DM patients after 2013 have been divided: in the USA cardiologists and diabetologists refused to establish lower BP target values for patients with DM and they recommend the common target BP to the whole population <140/90 mm Hg. The European

and Russian recommendations have also raised the target systolic BP to < 140 mm Hg. At the same time they suggested the lower target diastolic BP (< 85 mm Hg). Only Canadian hypertensiologists (CHEP) and the American Association of Clinical Endocrinologists (AAACE) keep the position of stricter BP control for patients with DM, as it has been before 2013 (< 130/80 mm Hg).

I would like to discuss the validity of BP target change in patients with DM, based on the analysis of the same study, the ACCORD and INVEST, which caused changes in the recommendations and mitigation of the therapy goals in DM patients below 140/90 mm Hg.

Milder over stricter BP control in DM: pro

Altogether 4733 people with non-insulin dependent diabetes mellitus were included in the ACCORD BP study [15]. They were randomized into two groups depending on the achievement of target systolic BP (SBP): the group, which reached SBP <120 mm Hg, and the group, which achieved SBP <140 mm Hg. After 1 year of follow-up the average SBP level was 119.3 and 133.5 mm Hg in the first and second groups, respectively. Despite significant differences in the achieved SBP levels, the frequencies of cardiovascular endpoints in the two groups did not differ: death from cardiovascular causes, non-fatal myocardial infarction and non-fatal stroke (HR: 0.88, 95 % CI: 0.73–1.06, $p = 0.20$). Similar data were obtained in the INVEST study [16], in which 6400 patients with non-insulin dependent DM were randomized (28 %

of all included patients). Patients were divided into groups depending on the reached average SBP levels: the strict control group (average SBP < 130 mm Hg), the standard control group (130 mm Hg < average SBP < 140 mm Hg) and the poor BP control group (average SBP > 140 mm Hg). However, there was no significant between-group differences in the incidence of the final cardiovascular outcomes. Moreover, exactly in the strict SBP control group (<130 mm Hg) the rate of overall mortality was significantly higher than in the group, which reached the standard average SBP (from 130 to 140 mm Hg), but lower than in the group with inadequate control of SBP (>140 mm Hg). These data confirmed the hypothesis about the J-shaped mortality curve dependent on SBP level.

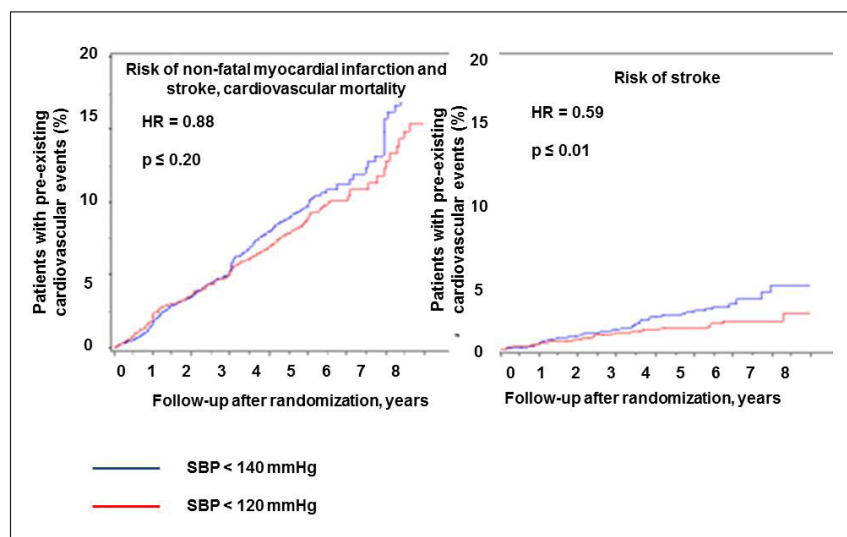
The INVEST study also demonstrated the risks of excessive reduction in diastolic BP (DBP). Thus, in the group, which reached the average DBP <60 mm Hg, cardiovascular outcomes were more common than in the group with DBP from 80 to 90 mm Hg.

Based on these data, the experts concluded that the strict BP targets in DM patients are not appropriate and even dangerous!

Milder over stricter BP control in DM: contra

On the other hand, the ACCORD and INVEST studies provide many arguments for a stricter BP targets in DM. Thus, the ACCORD study showed that reaching SBP <120 mm Hg, though had no advantages in reducing rates of cardiovascular outcomes in general, but reduced (almost by 40 %) the incidence of strokes (HR = 0.59, $p < 0.01$) (15) (Fig. 1).

Figure 1. The ACCORD trial: the rate of combination of primary end point and stroke in the groups of intensive and standard blood pressure control (adapted according to NEJM 2010)



Note: SBP — systolic blood pressure; HR - hazard ratio.

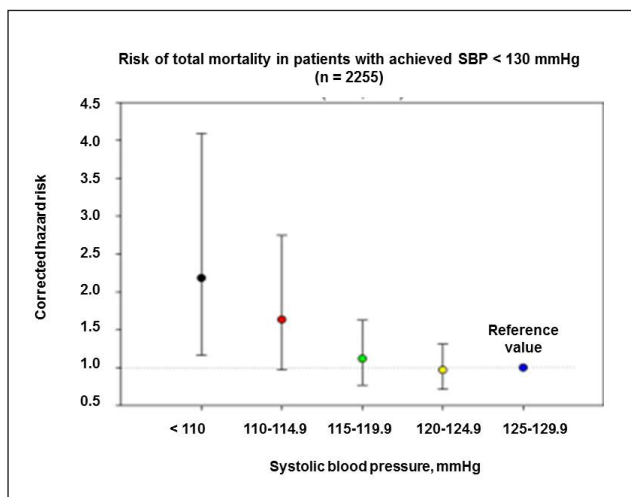
Unlike the ACCORD study, which included only patients with non-insulin dependent DM, the SPRINT study, where patients with non-insulin dependent DM were excluded, showed a 25%-reduction in the occurrence of myocardial infarction, stroke, heart failure and cardiovascular deaths when SBP was reduced <120 mm Hg [18]. What is the reason for these differences? Perhaps, it is due to the different capacity of these studies (the number of patients in ACCORD study is much smaller than in the SPRINT study: 4733 vs. 9361 subjects, respectively). There are probably other reasons related to the methodology of BP measurements and study design. In any case, while the analysis of this data is not completed, the extrapolation of the SPRINT study results to patients with non-insulin dependent DM is incorrect.

A more detailed analysis of the INVEST study [16] also provides doubts regarding the risks of reducing SBP below 130 mm Hg. In general, INVEST study demonstrated an increase in the overall mortality when SBP is reduced below 130 mm Hg. However, a sub-analysis of the group with non-insulin dependent DM showed that increase in mortality is associated with a reduction of SBP below 115 mm Hg, and the reduction within 130 to 120 mm Hg remains secure (Fig. 2).

Re-analysis of the INVEST study data also did not confirm the J-curve association between mortality risk and DBP. Thus, any J-shaped association disappeared when groups were matched by age, sex, smoking, previously existing cardiovascular events, renal failure, dyslipidemia and other risk factors [17].

A number of recently published studies and me-

Figure 2. The INVEST trial: sybanalysis of the group with type 2 diabetes mellitus (adapted according to JAMA 2010)



Note: SBP — systolic blood pressure.

ta-analyses also raise doubts regarding the decrease of BP targets in non-insulin dependent DM. Thus, the meta-analysis of Emdin C. A. and co-authors published in JAMA in 2015, including 100 354 patients with non-insulin dependent DM and arterial hypertension, showed the following:

- Decrease in systolic BP by each 10 mm Hg is accompanied by a decrease in overall mortality, cardiovascular events, stroke, occurrence of albuminuria and retinopathy;
- The rates of all events, including deaths, was lower when SBP was maintained at the level 130–140 mm Hg compared to SBP > 140 mm Hg;
- Further decrease in SBP below 130 mm Hg was accompanied by a reduction in the risk of stroke, development of retinopathy and progression of albuminuria.

Swedish researchers came to the same conclusion having conducted a population-based cohort study that included 187106 patients with non-insulin dependent DM, at the age <75 years old and without past cardiovascular events [20]. The mean follow-up was 5 years. Patients with low SBP (110–119 mm Hg) demonstrated a significant reduction in the risk of non-fatal MI (adjusted HR 0.76, 95% CI, 0.64–0.91; P = 0.003), AMI (fatal and non-fatal) (0.85, 0.72–0.99; P = 0.04), non-fatal cardiovascular events (0.82, 0.72–0.93; P = 0.002), all cardiovascular events (0.88, 0.79–0.99; P = 0.04) and non-fatal coronary heart disease (0.88, 0.78–0.99; P = 0.03), in comparison with comparison group of patients who achieved SBP 130–139 mm Hg. In addition, there was no J-shaped curve effect between SBP level and the endpoints, with the exception of heart failure and overall mortality.

Taking into consideration a J-shaped dependence of mortality on SBP and DBP, in 2015v the Russian Association of Endocrinologists (RAE) established a lower bound of target BP in DM to prevent negative effects of strict BP control (not below 120/70 with antihypertensive therapy) [13].

Therefore, the discussion about target BP values in DM is still far from complete. Lower BP values in non-insulin dependent DM should be achieved taken the adequate safety profile (in young patients, without pre-existing cardiovascular disease). The BP targets in non-insulin dependent DM seem to be re-evaluated in future based on the personalized approach depending on the patients' age (as already performed in many recommendations) and the pre-existing cardiovascular events.

Conflict of interest / The author declare no conflict of interest.

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