**The effect of a structured clinical algorithm on glycemic control in patients with combined tuberculosis and diabetes in Indonesia: a randomized trial**

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**Abstract**

**Aims:** Diabetes mellitus (DM) is associated with worse tuberculosis (TB) treatment outcomes, especially among those with poor glycemic control. We examined whether a structured clinical algorithm can improve glycemic control in TB patients with DM.

**Methods:** Inan open label randomized trial,TB-DM patients in Bandung, Indonesia were randomized to regular scheduled counselling, glucose monitoring, and adjustment of glucose-lowering medication using a structured clinical algorithm (intervention arm) or routine DM management (control arm), with glycated hemoglobin (HbA1c) at month 6 as the primary end point.

**Results:** We randomized150 HIV-negative pulmonary TB-DM patients (92% culture positive, 51.3% male, mean age 53 years). DM was newly diagnosed in 28%, and previously known in 72%. Baseline mean HbA1c was 11.0% in the intervention arm (n=76) and 11.6% in the control arm (n=74). At 6 months, HbA1c had decreased more in the intervention arm (3.49; 95% CI: 2.88–4.10) than in the control arm (1.77; 95% CI: 0.97–2.57). Five patients were hospitalized in the intervention arm and seven in the control arm. There was more hypoglycemia (35.0% vs 11.8%; p=0.002) in the intervention arm. Two deaths occurred, both in the intervention arm, one as a result of cardiorespiratory failure and one because of suspected septic shock and multiorgan failure.

**Conclusion:** In Indonesianpatients with TB and DM, regular glucose monitoring and algorithmic adjustment of DM treatment led to improved glycemic control.

**Key words:** pulmonary tuberculosis; diabetes mellitus type 2; treatment adjustment

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1. **Introduction**

The prevalence of diabetes mellitus (DM) continues to increase globally. DM increases the risk of acquiring *Mycobacterium tuberculosis (Mtb)* infection and of developing tuberculosis (TB) disease.1 DM is also associated with poor TB treatment outcomes2, especially in patients with poor glycemic control.3,4 Better glycemic control in patients with concurrent TB and DM (TB-DM) may lead to better TB treatment outcomes,5,6 but several factors hamper glycemic control including TB-associated inflammation, food intake and physical activities that change during TB treatment, interactions of rifampicin with most oral anti-diabetic drugs, and lack of integration of TB and DM services.7

Recently published guidelines jointly agreed by the International Union Against Tuberculosis and Lung Disease and World Diabetes Federation suggest targets and approaches to DM management during TB treatment8. However, there are no published studies showing how to control hyperglycemia during TB treatment. We assessed whether a package of structured counselling, clinical monitoring, and formal algorithm-based DM treatment adjustments offers better glycemic control than routine care in TB-DM patients. We conducted a randomized trial in Indonesia, which has the third-highest TB incidence9 and sixth-highest DM prevalence worldwide.10

1. **Subjects**

Adult (>18 years of age) patients newly enrolled in TB treatment at outpatient TB clinics of two hospitals and 44 community health centers (CHC) in Bandung, Indonesia were screened for DM using a questionnaire and repeated laboratory-measured glycated hemoglobin (HbA1c). We also recruited DM patients diagnosed with pulmonary TB in a hospital endocrine clinic or CHC.

Patients with newly diagnosed pulmonary TB disease and either a previous diagnosis of DM, or a repeated laboratory HbA1c ≥6.5%12,13 on screening were eligible for randomization. Thirteen months after start of the study, the HbA1c threshold was raised to 7% to avoid misclassification due to TB-associated hyperglycemia. Patients were excluded if they were already on TB treatment for more than 72 hours, had steroid-dependent or gestational-DM, were HIV-infected, were living outside of Bandung city or had to be hospitalized or referred to the MDR-clinic because of proven drug-resistance.

1. **Methods**

*3.1 Trial design*

This open-label randomized clinical trial was registered at ClinicalTrials.gov number NCT02106039 as part of the TANDEM research project.11 The trial was originally intended to run in three countries: Peru, Romania, and Indonesia, but national guidelines ~~prohibited the use of metformin~~ recommended the use of insulin for combined TB and DM in Peru, and prohibited use of clinical DM algorithms in TB clinics in Romania.

*3.2 Participant consent and ethical approval*

Patients provided written informed consent prior to study enrolment. The study was approved by the Health Research Ethics Committee, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia (No: 05/UN6.C2.1.2/KEPK/PN/2014) and the Research Ethics Committee, London School of Hygiene and Tropical Medicine, London, UK (LSHTM ethics ref: 6449, LSHTM amendment no: A473). Participants could withdraw voluntarily from participation in the study at any time and for any reason.

*3.3 Randomization and blinding*

Randomization was carried out on-line using Research Electronic Data Capture (REDCap),14with permuted-block randomization (block sizes of 4, 6, and 8) generated using Stata v12.1 (Stata Corp, College Station, TX, USA). The randomization schedule was prepared and stored by TANDEM researchers in London, independent of the study site. The nature of the intervention precluded blinding of patients and treating physicians, but study physicians were blinded to the HbA1c results at 3-month follow-up, with adjustments of anti-DM medication done according to fasting and random blood glucose levels. Radiologists and laboratory staff were also blinded to the intervention.

*3.4 Procedures*

Patients randomized to the intervention arm were seen in the hospital research clinic at 1, 2, and 4 weeks after randomization and monthly thereafter until 6 months. Patients in the control arm were referred back to their original health care facility and asked to return to the research clinic for follow-up at month 2, 3, and 6. An educational flipchart was used to counsel patients in the intervention arm at each monthly follow-up visit regarding specific aspects of TB and DM (Text box 1), and a handout containing nutritional information was provided. All patients in the intervention arm were given a glucometer (Accu-check® active) and taught how to self-monitor and record their blood glucose (SMBG). Patients assigned to the control arm only received information about TB at time of randomization; they may have received other (i.e. DM) information from staff at their health care facilities.

Different monitoring and treatment algorithms were used in the intervention arm, taking DM medication history, HbA1c, estimated glomerular filtration rate (eGFR), glucose levels, and possible adverse drug effects into account (Supplementary figures 1–5). Patients with an HbA1c <10% at baseline received metformin (Flowchart A1 for known DM and A2 for newly diagnosed DM) at a starting dose of 500 mg once or twice daily, according to their eGFR, adjusted at weekly visits according to SMBG results and possible side effects. If glucose targets (i.e. average random blood glucose 100–180 mg/dl and/or fasting blood glucose 70–130 mg/dl) were not achieved using the safe maximum dose, long-acting insulin (Flowchart B) was added, or another oral DM drug (sulfonyl urea or DPP4 inhibitor) if the patient refused insulin (Flowchart D). Patients with an HbA1c ≥10% at baseline or a contraindication or intolerance for metformin were started on long-acting insulin once daily and short-acting insulin before meals (Flowchart C). Patients who were put on insulin were also asked to perform more intensive blood glucose monitoring at home, and their insulin dose was adjusted accordingly.

Monitoring and treatment of patients in the control arm was determined by their health care provider. Insulin, recommended for DM patients with TB according to national guidelines15, is not available in all CHCs. Instead, the main drugs used are metformin and glibenclamide. Several CHCs have programs for non-communicable diseases (NCDs), with regular group education, exercise, blood pressure measurement, and point of care glucose testing for patients with DM. Follow-up HbA1c results taken in the study clinic at month 3 and 6 were not available to the control group patient’s CHC clinician, but as usually done in Indonesia, blood glucose, sputum and chest x-ray findings were given to the patients with advice to share results with their doctors.

*3.5 Study outcomes*

The primary outcome of the study was change from baseline laboratory HbA1c 6 months after the start of TB treatment, as measured by Bio rad Variant II Hemoglobin A1C programme using HPLC in a NGSP certified laboratory. Secondary outcomes included change from baseline laboratory HbA1c at month 3, type of drugs prescribed, and adverse events. DM treatment was determined by study doctors in the intervention arm and assessed during follow-up at month 2, 3, and 6 in the control arm.

*3.6 Safety*

Adverse events (AE) grading used the Division of AIDS table for grading the severity of adult and pediatric adverse events version 2.0, 201416 and grading for hypoglycemia used Common Terminology Criteria for Adverse Events version 4.0, 2009.17 An action plan was developed to address any AE reported (Supplementary figure 6) in the intervention arm. Information regarding AE were collected at each follow-up visit. To reduce information bias, only self-reported AE in month 2, 3, and 6 were compared between arms. Information on serious adverse events (SAE) was reported at any time during the 6-months follow-up.

*3.7 Sample size and interim analysis*

A difference of 1.0% between groups in the 6-months change from baseline HbA1c was assumed to be clinically important. Based on the variation in the drop of HbA1c during TB treatment in a previous study from Indonesia,18 the required sample size was 350 to allow for potential clustering within countries and 150 patients were allocated to be recruited in the Indonesian site. After it became clear that Peru and Romania could not perform the trial, an interim analysis was performed to better estimate the standard deviation (SD) of the outcome, leading to the amended sample size estimate of 154 to achieve 80% power, at the 5% level of significance. To account for the interim analysis and to preserve the overall 5% level of significance, we used Pocock boundaries (each analysis assessed at p=0.0294). Indonesian investigators remained blinded to the results of the interim analysis.

* 1. *Data collection, variables, and statistical analyses*

Demographic and clinical data were entered in the electronic REDCap database by study physicians, except for the main outcome that was entered by a data entry officer to ensure blinding. Body mass index (BMI) was calculated and classified according to the Asia Pacific Criteria19; blood pressure according to the JNC VII.20

We performed a complete case analysis for the primary outcome. The change from baseline in HbA1c plasma-concentration at month 6 was compared between arms, using a linear regression model. Proportions of people achieving HbA1c concentration <8% as per recent recommendations8 at month 6 were compared using a logistic regression model. Adverse events were compared between arms using χ2 test. Data analyses were performed using Stata v13 (Stata Corp, College Station, TX, USA).

1. **Results**

*4.1 Baseline characteristics*

We identified 218 patients with concurrent TB and DM, with 94.5% being TB patients screened for DM, while the other 5.5% were DM patients screened for and identified with active, previously undiagnosed TB. One patient (HbA1c 6.8%) was included before the HbA1c criterion for inclusion was raised to 7%. We excluded 55 patients, mainly because of travelling distance (n=13) or patients were severely ill (n=12). Eleven patients refused participation, and 2 patients were not randomized without any documented reason, leaving 150 (68.8%) patients randomized (Figure 1) between 28 April 2014 to 21 February 2017. Compared to those included, patients who were excluded had a lower HbA1c (10.4 vs 11.3, p=0.027), more frequently used insulin (14.7% vs. 2.7%, p=0.001), and were more often treated in hospital instead of CHC (32.4% vs. 17.3%, p=0.046).

Patients included in the study (male 51.3%, mean age 53 years) mostly had positive sputum microscopy and culture and a chest x-ray suggestive of TB (Table 1). Most patients had a normal body weight or were mildly obese, while 20% were underweight. The overall mean HbA1c was 11.3% (SD: 2.5), 11.0% in the intervention arm and 11.6% in the control arm. No formal distinction was made between type 1 and type 2 diabetes but two patients using insulin had been diagnosed with diabetes before the age of 40 at study entry, and an additional seven patients were below 40 years of age, untreated, and with high HbA1c values (ranged from 8.4% to 17.0%), suggesting that at least 142 patients (94.0%) had type 2 DM. There were more patients in the control arm who were newly diagnosed DM (35.1% versus 21.0%). Insulin was used by 4 (5.3%) patients in the intervention arm and none in the control arm. No other significant differences in clinical characteristics were observed.

*4.2 Glycemic control*

In both groups, eight patients did not complete follow-up because of death, rifampicin resistance, drop-out, transfer-out, or withdrawal (Figure 1). Glycemic control was significantly better in the intervention arm, both at month 3 and 6, in terms of the median HbA1c (Figure 2) and the proportion of patients reaching the target HbA1c <8% (Figure 3). The drop in HbA1c was larger among patients with newly diagnosed DM in both arms. For those with known DM, the median HbA1c in the intervention arm dropped from 10.8% (IQR 9.1–12.7) to 7.5% (IQR 6.6–8.1) and from 11.4% (IQR 9.4–13.1) to 9.8% (IQR 7.4–12.0) in the control arm. For those with newly diagnosed DM, the median values dropped from 11.9% (IQR 8.6–13.0) to 7.3% (IQR 6.6–9.2) in the intervention arm and 11.8% (IQR 9.4–14.0) to 7.6% (IQR 7.1–10.2) in the control arm.

In a univariate linear regression analysis, the intervention arm was associated with a steeper drop in HbA1c (1.72%; 95% CI 0.72–2.71; p=0.001), which increased slightly after adjusting for the imbalance in known and newly diagnosed DM between groups (1.82%; 95% CI 0.82–2.83; p<0.001) (Table 2). The odds of achieving HbA1c below the target of 8% at month 6 in the intervention arm was 3.21 (95% CI: 1.58–6.51; p=0.001) compared to the control arm, and this became even stronger after adjustment for DM status (new or known DM) (AOR: 3.48, 95% CI: 1.67–7.21; p=0.001) (Table 2).

*4.3 Diabetes medication*

According to the algorithms, 35 patients (46.0%) in the intervention arm were started on metformin, 32 (42.1%) patients on long-acting insulin plus rapid-acting insulin, and 9 (11.8%) patients on metformin plus glibenclamide. Changes of the flowchart allocation over the treatment period were in accordance with the algorithm, except for one patient who was changed from insulin (Flowchart C) to metformin (Flowchart A1) after experiencing hypoglycemia. According to the flowcharts, insulin was added to oral treatment in three patients, insulin was replaced by metformin in three patients, six patients refusing insulin were treated with oral drugs, and two patients started insulin after some delay due to their initial refusal. At month 6, compared to the control arm, more patients in the intervention arm used insulin (51.5% vs 9.1%; p<0.001) and fewer used metformin (54.4% vs 80.3%; p=0.001) (Table 3).

*4.4 Serious adverse events (SAE) and adverse events (AE)*

There was no evidence for differences in the occurrence of SAE between arms (Table 4). However, there were two deaths in the intervention arm and none in the control arm. One death occurred in a 67-year old male patient admitted to another hospital three months after start of treatment with nausea and vomiting, progressive respiratory distress and finally cardiopulmonary failure. Another patient, a 60-year old female was admitted three weeks after starting treatment with presumed septic shock, acute kidney injury, and progressive multi-organ failure. The number of all AE combined was higher in the intervention arm, noting that patients in the intervention arm were seen more often. There was more grade 1 diarrhea (12.5% vs 2.9%; p=0.036) and hypoglycemia (35.0% vs 11.8%; p=0.002) in the intervention arm, while no significant difference was found for other adverse events.

1. **Discussion**

We report a randomized trial targeting better glycemic control among patients with combined TB and DM in Indonesia. Patients, both those previously diagnosed and newly diagnosed with DM, presented with severe hyperglycemia (mean HbA1c 11.3%). Regular scheduled counselling, glucose monitoring, and adjustment of glucose-lowering medication using a structured clinical algorithm led to much better glucose control, doubling the proportion of patients reaching the HbA1c target of 8% at month 6. TB patients with DM reasonably tolerated metformin, one third of patients in the intervention arm experienced hypoglycemia, and the intervention required multiple interactions with health care providers.

To our knowledge, this is the first trial of its type. Most studies have focused on the epidemiological associations between TB and DM1-4 and very few on patient management. Clinical trials have focused on giving supplementation to TB-DM patients.21,22 One trial investigating joint TB-DM management is currently recruiting participants in Mexico, but it is a non-randomized, community intervention trial.23 We therefore cannot compare the results of this study to another similar study.

With respect to the improved glycemic control in the control arm of our study, several observational studies in patients with TB and DM found that HbA1c level decreased with 6 months of anti-tuberculosis treatment alone, without any new DM treatmentintervention.24,25 As found in our study, Gupte et al23 showed that the decrease of HbA1c level was greater in those who were newly diagnosed, with a decrease from a median HbA1c of 10.1% to 8.7% for known DM (11.4% to 9.8% in our study) and from 8.5% to 7.3% in newly diagnosed DM (11.8% to 7.6% in our study). However, in our study, patients were given anti-DM treatment along with TB treatment due to their very high initial HbA1c levels. In a study in South India, HbA1c also declined after 3 months of anti-TB treatment in patients with DM, impaired glucose tolerance, and those who were normoglycemic.25 Similar to our study, the decline was also greatest in those who were newly diagnosed with DM. In an observational patient cohort in Peru, active diabetes management was associated with better treatment outcome.2 In Taiwan, patients who were enrolled in a pay-for-performance program for DM as part of their national health insurance were less likely to acquire TB, and if they developed TB had a better treatment outcome compared to DM patients who were not enrolled to the program.26

While we could not assess the efficacy of individual components of our intervention on glycemic control, education, monitoring and treatment adjustment are all likely to be necessary for optimal glycemic control. Patient education has been shown to be an important element of diabetes management.27 Self-monitoring blood glucose (SMBG) is recommended and is proven to be effective at improving glycemic control.28 The fact that one third of patients in the intervention arm failed to achieve the target of HbA1c <8%, as recently recommended in the IUALTD/WDF guidelines on TB and DM8, shows that controlling blood glucose in TB-DM patients is indeed an arduous task. Even in a high resource setting like the UK, almost one-fourth (23%) of DM patients at primary care level have a HbA1c >8% in a cohort of T2DM.29 While TB treatment is programmatic, DM treatment is recommended to be personalized, suggesting the need for special training for TB-DM management for the health care workers.

The mean HbA1c of TB-DM patients at baseline in this study was high and such levels of poor DM control in TB-DM patients (HbA1c >10%) were similar to findings from the other study sites (Romania, Peru, and South Africa),11 but much higher than DM patients without TB in the TANDEM study (median HbA1c varied from 7.7% in Peru, 8.3% in Indonesia, 9.5% in Romania, to 10.4% in South Africa).30 It is known that poor glycemic control in people with DM is associated with TB.31 Once a person living with DM acquires TB disease, the treatment outcome is poorer than those without DM,1–3 and even though not yet proven, better glycemic control during TB treatment is likely to lead to better TB treatment outcome and good glycemic control has been proven as beneficial to reduce cardiovascular complications.32

There was a higher proportion of AE in the intervention arm, especially mild diarrhea and hypoglycemia. Diarrhea is likely related to the use of metformin, which reached relatively high doses in the algorithms. However, there were no greater than grade 1 diarrhea reported in both arms. More grade 2 and 3 hypoglycemia episodes were reported in the intervention arm, likely due to frequent use of insulin. Two deaths occurred in the intervention arm, one as a result of cardiorespiratory failure and one because of suspected septic shock and multiorgan failure. Diabetes itself has a high mortality in Indonesia; 101 out of 590 people with diabetes in our setting had died after median 3.4 years follow-up.33 Even though there were no differences in SAE in both arms, there were more hospitalizations and disability in the control arm caused by DM complications which, at least in the case of hyperglycemia, could be related to inadequate DM treatment.

Long-term DM management is very challenging in Indonesia and other countries with similar settings. The effects of our intervention may wane after completion of TB treatment, especially for those treated with insulin, as (chronic) use of insulin requires trained professionals, time for intensive patient counselling, blood-glucose self-monitoring, and costs and possible reluctance from patients.7 Considering that insulin is relatively more expensive and less easy to use, optimizing the dose of metformin with the combination of sulphonyl urea in the CHCs may be a more feasible option. A study of nearly 2,000 DM patients managed in primary, secondary, and tertiary care facilities in Indonesia showed a mean HbA1c of 8.3% (SD: 2·2), with only 30.8% reaching the HbA1c target of 7%.34 Recently published studies in Indonesia also showed a high mortality and a high incidence of TB among DM patients33 and insufficient cardiovascular risk management.30

Our study has several strengths: randomization was carried out electronically by researchers far from the study site; the intervention followed specific algorithms and standard procedures; clinic staff were trained prior to recruitment and blinded to the primary outcome. We also had only just over 10% loss to follow-up, reducing the risk of bias. However, our study also has several limitations. With respect to generalizability, it was relatively small, was done at a single site, the intervention was applied in a research clinic, and severely ill (hospitalized patients) were excluded. Also, there were unavoidable differences in follow-up schedules between arms, and these could cause bias regarding frequency of adverse events, although we took this into account in the analysis.

In conclusion, our study showed that good glycemic control in TB-DM patients can be attained through a package of education and use of simple treatment algorithms. Even though TB treatment itself reduces inflammation-induced-hyperglycemia, extra intervention such as shown in our study may still be needed especially in settings where TB-DM patients have very high HbA1c levels during TB diagnosis. Moreover, referral of infectious TB-DM patients to DM clinics for their DM management is undesirable as this may fuel onward disease transmission8, therefore a structured algorithm for glycemic control is needed in TB clinics.Larger studies are needed to evaluate the best approach (and associated costs) of achieving glycemic control and implementing other essential components of DM management in patients with combined TB and DM, like cardiovascular risk management and other comorbidities.35

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**Text box 1. Educational topics in the intervention arm**

1. TB: cause, transmission, treatment compliance, possible side effects.

2. DM: what is DM? What are the symptoms? What can be done?

3. Glucose measurement and recording.

4. Importance of glycemic control.

5. Metformin and insulin (use, precautions, side effects).

6. Hyperglycemia and hypoglycemia.

7. The importance of smoking cessation for both TB and DM.

8. DM and TB together – more difficult to treat.

9. Healthy lifestyle: smoking, moderate exercise, diet.

10. Management after TB treatment is completed (long-term DM management)

Inspired by educational tools developed by Australian Respiratory Council. Key messages for TB and DM. 2012. <http://www.thearc.org.au/resources/flipchart>

**Figure 1. Flow chart of trial participants**

Patients with TB and DM

n=218

TB-DM patients randomized

n=150

Excluded (n=55)\*, refused (n=11), not randomized for unknown reason (n=2)

Intervention arm

n=76

Control arm

n=74

Did not wish to continue

n=2

Dropped out TB therapy

n=5

Moved to another city

n=1

Died

n=2

Dropped out TB therapy

n=3

Moved to another city

n=2

Completed follow-up

n=68

Completed follow-up

n=66

Became MDR-TB

n=1

\*TB-DM patients excluded: live outside Bandung City (n=13), severely ill (n=12), HbA1c<7 (n=8), study team was not ready for RCT (n=7), already took TB drugs prior to randomization (n=5), MDR-TB (n=4), on steroids (n=2), uncertain TB diagnosis (n=2), HIV (n=1), died before randomization (n=1).

Abbreviations: TB = tuberculosis; DM = diabetes mellitus

**Figure 2. Mean laboratory HbA1c values during TB treatment**

P-value was generated using repeated measures ANOVA (MANOVA) test.

Abbreviations: HbA1c=glycated haemoglobin; TB=tuberculosis

**Figure 3. Proportions of patients who reached target of HbA1c level < 8%**

Abbreviations: HbA1c=glycated haemoglobin

**Table 1. Baseline patient characteristics**

|  |  |  |  |
| --- | --- | --- | --- |
| Characteristics | Intervention arm(n=76) | Control arm(n=74) | Total (n=150) |
| Male sex – n (%) | 39 (51.3) | 38 (51.4) | 77 (51.3) |
| Mean age in years (SD)  | 53.7 (10.0) | 52.2 (8.9) | 53.0 (9.4) |
| Mean body mass index (SD) – kg/m2  | 21.5 (3.9) | 21.9 (3.6) | 21.7 (3.7) |
| Body mass index category (Asia Pacific) – kg/m2 |  |  |  |
|  Underweight (<18.5) | 18 (23.7) | 12 (16.2) | 30 (20.0) |
|  Normal (18.5–22.9) | 35 (46.0) | 36 (48.6) | 71 (47.3) |
|  Overweight (23.0–24.9) | 8 (10.5) | 11 (14.9) | 19 (12.7) |
|  Obese I (25.0–29.9) | 12 (15.8) | 14 (18.9) | 26 (17.3) |
|  Obese II (≥30) | 3 (34.0) | 1 (1.4) | 4 (2.7) |
| Blood pressure (JNC VII) – mmHg |  |  |  |
|  Normal (systole <120 and diastole <80) | 23 (30.3) | 28 (37.8) | 51 (34.0) |
|  Prehypertension (systole 120–129 or diastole 80–89) | 33 (43.4) | 29 (39.2) | 62 (41.3) |
|  Hypertension I (systole 140–159 or diastole 90–99) | 15 (19.7) | 10 (13.5) | 25 (16.7) |
|  Hypertension II (systole >160 or diastole >100) | 5 (6.6) | 7 (9.5) | 12 (8.0) |
| Mean laboratory HbA1c (SD) – %  | 11.0 (2.4) | 11.6 (2.5) | 11.3 (2.5) |
| Laboratory HbA1c (%) category – %  |  |  |  |
|  <7 | 1 (1.3) | 0 (0.0) | 1(0.7) |
|  7–9.9 | 26 (34.2) | 23 (31.1) | 49 (32.7) |
|  >10 | 49 (64.5) | 51 (68.9) | 100 (66.7) |
| DM duration – years  |  |  |  |
|  Newly diagnosed DM | 16 (21.0) | 26 (35.1) | 42 (28.0) |
|  <1  | 17 (22.4) | 13 (17.6) | 30 (20.0) |
|  1–5  | 23 (30.3) | 22 (29.7) | 45 (30.0) |
|  6–15  | 16 (21.0) | 11 (14.9) | 27 (18.0) |
|  >15  | 4 (5.3) | 2 (2.7) | 6 (4.0) |
| DM medication# |  |  |  |
|  No medication | 25 (32.9) | 32 (43.2) | 57 (38.0) |
|  Insulin | 4 (5.3) | 0 (0.0) | 4 (2.7) |
|  Metformin | 43 (56.6) | 35 (47.3) | 78 (52.0) |
|  Other oral anti-DM medication | 20 (26.3) | 17 (23.0) | 37 (24.7) |
| Sputum microscopy |  |  |  |
|  Negative | 6 (7.9) | 5 (6.8) | 11 (7.3) |
|  Scanty | 5 (6.6) | 4 (5.4) | 9 (6.0) |
|  1+ | 21 (27.6) | 12 (16.2) | 33 (22.0) |
|  2++ | 18 (23.7) | 23 (31.1) | 41 (27.3) |
|  3+++ | 26 (34.2) | 30 (40.5) | 56 (37.3) |
| *Mycobacterium tuberculosis* culture  |  |  |  |
|  Negative | 5 (6.6) | 3 (4.0) | 8 (5.3) |
|  Positive | 70 (92.1) | 68 (91.9) | 138 (92.0) |
|  No sample available  | 1 (1.3) | 3 (4.1) | 4 (2.6) |
| Chest X-ray |  |  |  |
|  Normal/Abnormal not TB | 2 (2.6) | 4 (5.4) |  6 (4.0) |
|  Possible/Probable TB | 74 (97.4) | 70 (94.6) | 144 (96.0) |
| Recruitment site |  |  |  |
|  Hasan Sadikin General Hospital | 10 (13.2) | 7 (9.5) | 17 (11.3) |
|  Kota Bandung District Hospital | 5 (6.6) | 4 (5.4) | 9 (6.0) |
|  Community Health Centre | 61 (80.3) | 63 (85.1) | 124 (82.7) |

#Patients may be in more than one category

Abbreviations: SD=standard deviation; JNC VII=Joint National Committee VII; HbA1c=glycated haemoglobin; DM=diabetes mellitus

**Table 2. Decrease of HbA1c from baseline to month 3 and 6**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Month/Arm |  | Mean decrease in HbA1c from baseline |  |  | Patients with HbA1c < 8% at month 6 |  |
| Crude decrease(95% CI) | Difference(95% CI) | p-value | Adjusted difference\* (95% CI) | p-value | n/total n (%) | OR (95% CI) | p-value | AOR\* (95% CI) | p-value |
| *Month 3*  |  |  |  |  |  |  |  |  |  |  |
| Control | 1.93 (1.28–2.59) |  |  |  |  | 23/67 (34.3) | Ref |  | Ref |  |
| Intervention | 2.87 (2.33–3.42) | 0.94 (0.10–1.78) | 0.028 | 1.11 (0.27–1.94) | 0.01 | 37/71 (52.1) | 2.08 (1.05–4.14) | 0.036 | 2.30 (1.13–4.69) | 0.02 |
| *Month 6* |  |  |  |  |  |  |  |  |  |  |
| Control | 1.77 (0.97–2.57) |  |  |  |  | 25/66 (37.9) | Ref |  | Ref |  |
| Intervention | 3.49 (2.88–4.10)  | 1.72 (0.72–2.71) | 0.001 | 1.82 (0.82–2.83) | <0.001 | 45/68 (66.2) | 3.21 (1.58–6.51) | 0.001 | 3.48 (1.67–7.21) | 0.001 |

\*Adjusted by diabetes (DM) diagnosis status (known vs. newly diagnosed DM)

Abbreviations: HbA1c=glycated haemoglobin

**Table 3. Diabetes medication at month 6**

|  |  |  |
| --- | --- | --- |
| Medication | Intervention arm(n=68)n (%) | Control arm(n=66)n (%) |
| *Oral anti diabetic drugs (OAD)* |  |  |
|  Metformin only | 32 (47.1) | 41 (62.1) |
|  Metformin and sulphonyl urea | 1 (1.5) | 13 (19.7) |
|  Sulphonyl urea only | 0 (0.0) | 3 (4.5) |
|  Acarbose only | 0 (0.0) | 1 (1.5) |
|  No medication | 0 (0.0) | 2 (3.0) |
| *Insulin only or in combination with OAD* |  |  |
|  Long-acting insulin and metformin  | 4 (5.9) | 0 (0.0) |
|  Long- and rapid- acting insulin | 26 (38.2) | 2 (3.0) |
|  Long- and rapid- acting insulin and metformin | 1 (1.5) | 0 (0.0) |
|  Long-acting insulin only | 4 (5.9) | 1 (1.5) |
|  Rapid-acting insulin only | 0 (0.0) | 1 (1.5) |
|  Rapid- and intermediate- acting insulin | 0 (0.0) | 1 (1.5) |
|  Long-acting insulin, acarbose, and sulphonyl urea | 0 (0.0) | 1 (1.5) |

**Table 4. Adverse events**

|  |  |  |  |
| --- | --- | --- | --- |
| Type of adverse event | Intervention armn (%) | Control armn (%) | P-value(χ2) |
| **Serious adverse events\*** | **(n=76)** | **(n=74)** |  |
|  *Hospitalisation*  | *5 (6*.*6)* | *7 (9*.*5)* | *0*.*52* |
|  Drug-induced liver injury | 3 (3.9) | 1 (1.4) |  |
|  Gastro-intestinal disturbance | 1 (1.3) | 2 (2.7) |  |
|  Grade 3 vertigo | 1 (1.3) | 0 (0.0) |  |
|  Severe cough and dyspnoea | 0 (0.0) | 1 (1.3) |  |
|  Hyperglycaemia | 0 (0.0) | 3 (4.0) |  |
|  *Disability* | *1 (1*.*3)* | *2 (2*.*7)* | *0*.*54* |
|  Vestibular disorder due to streptomycin | 1 (1.3) | 1 (1.3) |  |
|  Foot amputation | 0 (0.0) | 1 (1.4) |  |
|  *Death* | *2 (2*.*6)* | *0 (0*.*0)* | *0*.*16* |
| **Adverse events\*\*** | **(n=72)** | **(n=68)** |  |
|  None | 2 (0.0) | 8 (11.8) |  |
|  Any  | 72 (100.0) | 60 (88.2) | 0.003 |
| *Gastro-intestinal* |  |  |  |
| Nausea |  |  |  |
|  None | 27 (37.5) | 26 (38.2) |  |
|  Grade 1: minimal interference with oral intake | 36 (50.0) | 35 (51.5) |  |
|  Grade 2: decreased oral intake for 24 to 48 hours  | 9 (12.5) | 7 (10.3) | 0.92 |
| Vomiting |  |  |  |
|  None | 49 (68.1) | 49 (72.1) |  |
|  Grade 1: minimal interference with oral intake  | 19 (26.4) | 15 (22.1) |  |
|  Grade 2: frequent episodes, no or mild dehydration | 4 (5.6) | 3 (4.4) |  |
|  Grade 3: persistent, orthostatic hypotension or  aggressive rehydration required | 0 (0.0) | 1 (1.5) | 0.68 |
| Diarrhoea |  |  |  |
|  None | 63 (87.5) | 66 (97.1) |  |
|  Grade 1: transient or increase of <3 stools per 24 hours  | 9 (12.5) | 2 (2.9) | 0.04 |
| Epigastric pain  | 16 (22.2) | 12 (17.6) | 0.50 |
| Persistent gastro intestinal symptoms  | 14 (19.4) | 10 (14.7) | 0.46 |
| *Musculoskeletal* |  |  |  |
| Arthralgia/myalgia |  |  |  |
|  None | 17 (23.6) | 19 (27.9) |  |
|  Grade 1: no/minimal interference with usual social & functional activities | 53 (73.6) | 48 (70.6) |  |
|  Grade 2: more than minimal interference with usual  social & functional activities | 2 (2.8) | 1 (1.5) | 0.75 |
| Leg swelling  | 5 (6.9) | 3 (4.4) | 0.52 |
| *Neurologic* |  |  |  |
| Headache |  |  |  |
|  None | 37 (51.4) | 46 (67.6) |  |
|  Grade 1: no/minimal interference with usual social & functional activities | 34 (47.2) | 22 (32.4) |  |
|  Grade 2: more than minimal interference with usual  social & functional activities | 1 (1.4) | 0 (0.0) | 0.11 |
| *Dermatologic* |  |  |  |
| Itching |  |  |  |
|  None | 37 (51.4) | 35 (51.5) |  |
|  Grade 1: no/minimal interference with usual social & functional activities | 30 (41.7) | 30 (44.1) |  |
|  Grade 2: more than minimal interference with usual  social & functional activities | 5 (6.9) | 3 (4.4) | 0.80 |
| *Cardiopulmonary* |  |  |  |
| Dyspnoea |  |  |  |
|  None | 67 (93.1) | 61 (89.7) |  |
|  Grade 1: no/minimal interference with usual social & functional activities or wheezing or  minimal increase of respiratory rate for age | 5 (6.9) | 6 (8.8) |  |
|  Grade 2: more than minimal interference with usual social & functional activities or nasal flaring  or pulse oximetry 90-<95% | 0 (0.0) | 1 (1.5) | 0.53 |
| Chest pain  | 3 (4.2) | 1 (1.5) | 0.34 |
| *Hypoglycaemia* |  |  |  |
|  None | 47 (65.3) | 60 (88.2) |  |
|  Grade 1: 55 to 64 mg/dL | 12 (16.8) | 8 (11.8) |  |
|  Grade 2: 40 to <55 mg/dL | 12 (16.8) | 0 (0.0) |  |
|  Grade 3: 30 to <40 mg/dL | 1 (1.4) | 0 (0.0) | 0.002 |

\*SAE were recorded at any time during 6 months follow up.

\*\* AEs were recorded at months 2, 3, and 6.