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(Evidence Based Case Report)

STROKE RISK PROGNOSIS IN TYPE 2 DIABETES MELLITUS PATIENTS WITH HYPERTENSION

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ABSTRACT

Stroke is a leading cause of global morbidity and mortality, particularly among patients with type 2 diabetes mellitus (T2DM) and hypertension (HTN), where the combination of these conditions increases the risk of stroke. Several studies indicate that patients with both T2DM and HTN have a higher incidence of new stroke cases and recurrences compared to those with only one of these conditions. A prognosis-based evidence analysis was conducted using the Evidence-Based Case Report method, with article searches performed in the PubMed, Cochrane, and ProQuest databases. Articles were selected based on exclusion criteria and duplication, followed by a critical appraisal of three cohort studies using Sackett's (1996) prognosis worksheet. The study by Chang et al. (2022) showed that the incidence of new strokes in patients with T2DM and HTN within one year reached 15%, with a stroke risk 1.743 times higher than in patients without both conditions (95% CI: 1.216–2.499, p = 0.003). Meanwhile, Liu et al. (2021) found that the combination of T2DM and HTN further increased stroke risk (aHR = 2.620, 95% CI = 2.031 - 3.380, p < 0.0001). A long-term study by Hu et al. (2005) reported that patients with both conditions had up to 3.7 times higher stroke risk compared to patients without hypertension (HR = 3.7, 95% CI = 2.77 – 4.99). Based on these findings, it can be concluded that patients with T2DM and HTN have a higher risk of stroke than those with diabetes alone, emphasizing the importance of strict management of blood pressure and blood glucose levels in preventing stroke.

Keywords : Stroke, Type 2 Diabetes Mellitus, T2DM, Hypertension, HTN, Prognosis

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INTRODUCTION

Stroke is a major public health concern and one of the leading causes of morbidity and mortality worldwide. According to the World Health Organization (WHO), stroke accounts for approximately 11% of total deaths globally, making it the second leading cause of death after ischemic heart disease. The burden of stroke is particularly high in low- and middle-income countries, where limited access to healthcare and preventive measures contribute to increased stroke incidence and poor outcomes. Modifiable and non-modifiable risk factors, including hypertension, diabetes mellitus, dyslipidemia, and smoking, significantly influence the likelihood of stroke occurrence.[1] In Indonesia, stroke is the leading cause of disability and mortality, contributing to 11.2% of the total disability-adjusted life years (DALYs) and 18.5% of total deaths. Based on the 2023 Indonesian Health Survey (Survei Kesehatan Indonesia, SKI), the prevalence of stroke in Indonesia is recorded at 8.3 per 1,000 population. Additionally, stroke is classified as one of the catastrophic diseases with the third-highest healthcare costs, following heart disease and cancer, reaching IDR 5.2 trillion in 2023. Among the major risk factors for stroke, hypertension and type 2 diabetes mellitus (T2DM) are of particular concern due to their high prevalence and strong association with stroke pathogenesis. Data from SKI 2023 indicate that the prevalence of hypertension diagnosed by physicians is 19.64%, whereas blood pressure measurements reveal a prevalence of 31.67%.2 Meanwhile, the overall prevalence of diabetes mellitus is 14.53%, with T2DM specifically affecting 1.6% of the population.[2]

In Banten Province, the prevalence of stroke is 6.3%, slightly lower than the national figure. However, the prevalence of hypertension is significantly high, with 22.3% diagnosed by physicians and 35.6% identified through blood pressure measurements. This suggests that hypertension remains a pressing public health issue in this region. Additionally, the prevalence of T2DM in Banten is 1.6%, aligning with the national prevalence.[2] The interplay between hypertension and T2DM exacerbates vascular damage, increasing the risk of both ischemic and hemorrhagic strokes.[2,3] The underlying mechanisms linking hypertension and T2DM to stroke involve endothelial dysfunction, chronic inflammation, and accelerated atherosclerosis. Hyperglycemia contributes to vascular damage through oxidative stress and platelet aggregation, leading to atherosclerotic plaque formation. Meanwhile, hypertension promotes arterial stiffness and endothelial injury, exacerbating vascular complications. The combined effects of these conditions create a synergistic impact, significantly elevating stroke risk compared to individuals with only one of these risk factors.[3]

Several studies have highlighted the substantial contribution of hypertension and T2DM to stroke incidence. A study by Liu et al. reported that hypertension has a stronger association with stroke risk than T2DM, with hazard ratios (HR) of 4.543 and 1.584, respectively.[6] Meanwhile, a study by Chang et al. confirmed that patients with both HTN and T2DM have a higher risk of stroke compared to those with only one of these conditions.[5] However, most existing studies focus on the independent

effects of hypertension and diabetes on stroke rather than their combined impact. Furthermore, there is a lack of longitudinal studies examining the long-term consequences of having both conditions.

A case scenario involving a 40-year-old male patient with uncontrolled hypertension (160/95 mmHg) and poorly controlled diabetes (HbA1c 8.2%) raises concerns about an increased risk of stroke. The patient has reported dizziness and tingling sensations in his right hand, which may indicate early signs of vascular dysfunction. This case highlights the clinical importance of assessing stroke risk among individuals with both hypertension and T2DM. It also raises a crucial question for clinicians: to what extent does the combination of these two conditions increase the likelihood of stroke, and what prognostic factors can help predict future stroke events. This study aims to evaluate the combined impact of hypertension and T2DM on stroke risk, analyze their synergistic effects, and identify prognostic factors that may contribute to stroke occurrence. The findings will serve as a foundation for developing more effective preventive strategies and improving clinical management for patients at high risk of stroke.

METHODS

The article search was conducted using the PubMed, ProQuest, and Cochrane databases, each with specific search strategies tailored to their respective indexing systems. The search terms included variations of "Type 2 Diabetes Mellitus" (T2DM), "Hypertension" (HTN), "No comorbidity" (Non-hypertensive), and "Stroke" (Cerebrovascular Accident, CVA, Ischemic Stroke, Hemorrhagic Stroke). Detailed keyword usage and filtering criteria for each database are outlined in Table 1.

Table 1. Search database

Database	***Search strategy***	***Hits***	***Selected articles***
Pubmed	((((((((((((((((((Type 2 Diabetes Mellitus[Title/Abstract])) OR (type 2 diabetes mellitus[MeSH Terms])) OR (T2DM[Title/Abstract])) OR (T2DM[MeSH Terms])) OR (Diabetes mellitus [Title/Abstract])) OR (diabetes mellitus [MeSH Terms])) OR (diabetes mellitus[MeSH Terms])) AND (Hypertension[Title/Abstract])) OR (Hypertension[MeSH Terms])) OR (High blood pressure[Title/Abstract])) OR (high blood pressure[MeSH Terms])) OR (HTN[MeSH Terms])) OR (HTN[Title/Abstract])) OR (Hypertension [Title/Abstract])) OR (Hypertension [MeSH Terms])) AND (stroke[MeSH Terms])) OR (stroke[Title/Abstract])) OR (cerebral stroke[MeSH Terms])) OR (acute stroke[MeSH Terms]) AND ((y_10[Filter]) AND (ffrft [Filter]) AND (meta-analysis[Filter] OR review[Filter] OR systematicreview [Filter]) AND (female[Filter]) AND (english [Filter] OR indonesian [Filter])) Filters: in the last 10 years, Free full text, Meta-Alysis, Review, Systematic Review, English, Indonesian, Adult: 19+ years, Aged: 65+ years Sort by: Most Recent	1.171	16

Proquest	((“Type 2 Diabetes Mellitus” OR “Type 2 Diabetes Mellitus” OR “T2DM” OR “Adult-onset diabetes”) AND ("Hypertension" OR "High blood pressure" OR "HTN") AND ("No comorbidities" OR "Without comorbidities" OR "Non-hypertensive" OR "Isolated Diabetes Mellitus") AND ("Stroke" OR "Cerebrovascular accident" OR "CVA" OR "Brain ischemia" OR "Ischemic stroke" OR " Hemorrhagic stroke"))	517	4
Cochrane	#1 MeSH descriptor: [Diabetes Mellitus, Type 2] explode all trees #2 (Diabetes Mellitus, Type II): ti,ab,kw OR (" non insulin dependent diabetes"): ti,ab,kw OR ("type 2 diabetes mellitus"): ti,ab,kw #3 #1 OR #2 #4 MeSH descriptor: [Hypertension] explode all trees #5 (Blood Pressures, High): ti,ab,kw OR (High Blood Pressure): ti,ab,kw OR (High Blood Pressures): ti,ab,kw OR (Blood Pressure, High): ti,ab,kw #6 #4 OR #5 #7 MeSH descriptor: [Stroke] explode all trees #8 (Strokes): ti,ab,kw OR (Cerebrovascular Stroke): ti,ab,kw OR (Stroke, Cerebrovascular): ti,ab,kw OR (Cerebral Strokes): ti,ab,kw #9 #7 OR #8 #10 #3 AND #6 AND #9	129	1

Selected articles must fulfil criteria inclusion, namely a study that examines connection between hypertension and T2DM with risk of stroke, in the form of systematic review/meta analysis of cohort studies or cohort studies, as well as written in language English or Indonesia. On the other hand, the criteria exclusion covers studies with population that is not in a way specific own hypertension and/or T2DM, studies that did not evaluate effect second condition the to risk of stroke, as well as study that only discussing strokes due to other factors such as abnormality genetics or disturbance coagulation. The article selection process is illustrated in Figure 1, which provides a flowchart detailing the identification, screening, eligibility assessment, and final inclusion of studies. The flowchart outlines the number of articles retrieved, excluded, and those that met the criteria for final review.

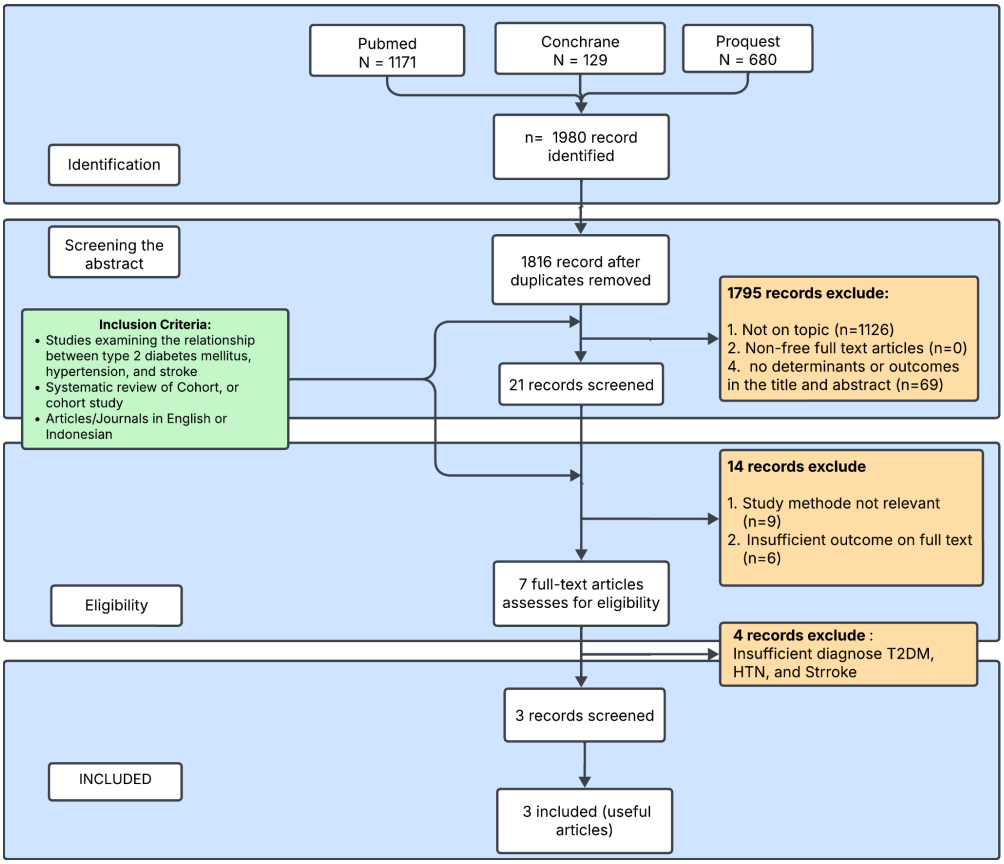

Figure 1. Flowchart

Determination eligibility studies based on the PICO criteria. Population (P) includes patients with T2DM aged ≥18 years, whose diagnosis confirmed through criteria laboratory or history therapy antidiabetic, record medical, and without previous history of stroke or disease other cerebrovascular. Intervention (I) covers patients with T2DM who have comorbid hypertension, with a diagnosis of hypertension based on pressure blood ≥140/90 mmHg or which has been diagnosed by the doctor who saw from record medical. Study not cover patients who are undergoing experimental therapy or their own hypotension weight. Group comparison (C) consists of patients with T2DM only without hypertension, with pressure blood <140/90 mmHg without therapy antihypertensive. Outcome (O) evaluated is ischemic stroke incidence or hemorrhagic during the action period continued, which was confirmed through record medical, examination imaging (CT scan or MRI), or improvement stroke score based on NIH Stroke Scale (NIHSS) or Modified Rankin Scale (mRS).

RESULTS

A literature search was conducted using cohort study designs to identify the connection between type 2 diabetes mellitus (T2DM), hypertension (HTN), and stroke. The search process was carried out through three major databases, namely PubMed (n = 1,171), Cochrane (n = 129), and ProQuest (n = 680), resulting in a total of 1,980 studies. After the duplication removal process, the number of

remaining studies was reduced to 1,816. At the abstract screening stage, a total of 1,795 studies were excluded because they were not relevant to the research topic, were not freely accessible, or did not list the determinant factors and relevant outcomes. From this process, 21 studies met the initial criteria. Next, a comprehensive full-text examination was conducted, and 14 articles were excluded due to the use of irrelevant methods or insufficient results for further evaluation. Of the 7 remaining studies, 4 were excluded because they did not provide sufficient data related to the diagnosis of T2DM, HTN, and stroke. Thus, only 3 articles met all the inclusion criteria and were included in the Evidence-Based Case Report (EBCR). A detailed description of the selected studies, including patient groups, outcomes, key results, and comments on the validity and limitations of each study, is presented in Table 2.

From the 3 selected studies, all were cohort study designs classified as level 2 evidence, according to the Oxford Centre for Evidence-Based Medicine 2011 levels of evidence, and were further critically reviewed using Sackett's (1996) prognosis worksheet (Centre for Evidence-Based Medicine [CEBM], 2011). The validity of the studies was assessed based on sample representation, duration and completeness of follow-up, and adjustments for prognostic factors. The first study by Chang Wei-wei et al. was a prospective cohort study with a follow-up period of 1 year, which was considered insufficient to reflect long-term risk. However, this study remained valid as it used multivariate Cox regression analysis to control for various risk factors, such as age, gender, smoking habits, and blood lipid levels.[5] The second study by Yan Liu et al. was a retrospective cohort study with a 4-year follow-up, utilizing a database that included more than 90 million patients in China. This study had a large sample size and a sufficient follow-up period to evaluate the incidence of cardiovascular events and stroke.[6] The third study by Gang Hu, PhD, et al. was a prospective cohort study with a mean follow-up of 19.1 years, allowing for long-term observation of stroke incidence and stroke-related mortality.[7] Although all these studies were valid in terms of design and analysis, they had limitations in blinding methods and validation in independent test groups. However, all three studies made adjustments for relevant prognostic factors, which strengthened the reliability of their findings.

In terms of clinical significance, the study by Chang WW et al. showed that patients with T2DM and HTN had a 1.743 times greater risk of stroke compared to T2DM patients without hypertension over a one-year period (aHR 1.743, 95% CI 1.216–2.499, $p<0.003$). The study by Yan Liu et al. further supported this finding, showing that the combination of T2DM and HTN increased the risk of stroke by 2.620 times (aHR 2.620, 95% CI 2.031–3.380, $p<0.0001$) compared to patients with T2DM alone. The study by Gang Hu, PhD, et al. provided a long-term perspective, demonstrating that the combination of T2DM and HTN increased the risk of ischemic and hemorrhagic stroke, as well as stroke-related mortality, by 2.5 times (aHR 2.50, 95% CI 1.61–4.01) over a period of more than a decade. These findings confirm that hypertension is a major risk factor that exacerbates the impact of T2DM on stroke incidence. This highlights the importance of managing hypertension in diabetic patients to reduce the risk of fatal cardiovascular complications. The results of these three studies can be applied in Indonesia, as the study populations remain relevant and the diagnostic methods used align with WHO guidelines,

which are also implemented in Indonesia.[12]

Table 2. The Answer and Description of Evidence

Author	Patient Group	Outcome	Key Result	Comments
Chang W-W, Fei S-Z, Pan N, Yao Y-S, Jin Y-L (2022)	Patients with Type 2 Diabetes Mellitus (T2DM) and/or Hypertension (HTN)	Incidence of New and Recurrent Stroke Within 1 Year	Type 2 Diabetes Mellitus (T2DM) and/or Hypertension (HTN) pose a high risk for both new-onset and recurrent stroke. Over a one-year follow-up period, the incidence rate of stroke in patients without a prior history of stroke was 12.1%, while the recurrence rate in patients with a history of stroke reached 26.5%. Multivariate analysis identified several significant risk factors contributing to new stroke events, including smoking (HR = 1.606, p = 0.030), abnormal total cholesterol (HR = 1.664, p = 0.007), abnormal LDL-C (HR = 2.368, p = 0.001), and the comorbidity of T2DM and HTN, which increased stroke risk compared to HTN alone (HR = 1.743, p = 0.003). Additionally, lack of physical activity was found to be a protective factor (HR = 0.359, p = 0.005), while moderate-to-severe carotid artery stenosis (CAS) and higher NIHSS scores were strongly associated with an increased risk of stroke. In patients with a history of stroke, CAS (HR = 2.560–3.825) and higher NIHSS scores were also identified as key factors that significantly increased the likelihood of stroke recurrence.	Among patients with DM and/or HTN followed for one year, 12.1% experienced a new stroke, while 26.5% had a recurrent stroke. Patients with a combination of DM and HTN had the highest risk compared to those with only one of these conditions. Strengths: Prospective analysis Limitations: Follow-up duration of only 1 year
Yan Liu, Jie Li, Ying Dou, Hongshan Ma (2021)	Patients with Type 2 Diabetes Mellitus (T2DM) and Hypertension (HTN)	Incidence of Combined Vascular Events (VEs) and Stroke	T2DM and HTN are strongly associated with the combined risk of vascular events (VEs) and stroke. However, the group with HTN alone had a higher combined risk of VEs and stroke compared to the group with T2DM alone. The study included 8,012 patients with T2DM, 9,653 patients with HTN, 3,592 patients with both T2DM and HTN, and 10,561 patients without T2DM or HTN. T2DM was significantly associated with the combined risk of VEs and stroke (HR 1.332, 95% CI 1.134–1.565 and HR 1.584, 95% CI 1.246–2.014). HTN was significantly associated with the combined risk of VEs and stroke (HR 3.244, 95% CI 2.946–3.572 and HR 4.543, 95% CI 3.918–5.268). T2DM with HTN was significantly associated with the combined risk of VEs and stroke (HR	Strengths: Retrospective cohort study design. Data collected from the SuValue database, which includes electronic medical records of >90 million patients from 161 hospitals across 18 provinces in China. Limitations: No access to patient mortality data.

			3.002, 95% CI 2.577–3.497 and HR 4.151, 95% CI 3.346–5.149, respectively). HTN alone was associated with a higher combined risk of VEs and stroke compared to T2DM alone (HR 2.435, 95% CI 2.113–2.805 and HR 2.868, 95% CI 2.341–3.513, respectively).	
Gang Hu, Cinzia Sarti, Pekka Jousilaht, Markku Peltone, Qing Qiao, Riitta Antikainen, Jaakko Tuomileh (2005)	Patients with Type 2 Diabetes Mellitus (T2DM) and/or Hypertension (HTN)	Stroke incidence (ischemic & hemorrhagic) and death due to stroke	The risk of stroke and death from stroke increases with hypertension and diabetes. Compared to the healthy group, the highest HR for stroke was found in hypertension II + diabetes (HR 4.50), while the highest HR for death from stroke was found in hypertension II + diabetes (HR 9.27)	Hypertension and type 2 diabetes increase the risk of stroke independently, but their combination drastically worsens the prognosis. Therefore, more aggressive prevention and control strategies are needed to reduce the incidence and mortality from stroke.

Source: Chang W-W et al., 2022; Yan Liu et al., 2021; Gang Hu et al., 2005

DISCUSSION

Based on the analysis of the three selected articles, the combination of type 2 diabetes mellitus (T2DM) and hypertension (HTN) significantly increases the risk of stroke compared to these conditions occurring separately. The risk escalates with the duration of hypertension and diabetes, emphasizing the necessity of comprehensive management for stroke prevention.[10] The study by Banerjee et al. (2012) reported that the risk of stroke increases by 3% annually after a diabetes diagnosis and triples if diabetes persists for more than 10 years.[9] The REGARDS study by Howard et al. (2024) further supports this, showing an increase in stroke risk associated with hypertension duration, with HR 1.31 (95% CI: 1.05–1.63) within the first five years and HR 1.67 (95% CI: 1.32–2.10) beyond 21 years.[10]

Pathophysiologically, the heightened stroke risk in T2DM and HTN patients is linked to excessive activation of the renin-angiotensin-aldosterone system (RAAS), chronic inflammation, and oxidative stress. Additionally, chronic hyperglycemia leads to the accumulation of advanced glycation end products (AGEs), promoting vascular stiffness and accelerating hypertension and stroke risk.[9] Long-term cohort studies provide robust evidence supporting this association. For example, the study by Hu et al. (2005) benefits from an extensive follow-up period and a large sample size, offering a comprehensive analysis of the long-term impact of T2DM and HTN on stroke risk. However, limitations exist in applying these findings to the Indonesian population due to socioeconomic factors, healthcare access disparities, and variations in chronic disease management. Methodologically, the three analyzed studies align with the prognosis study worksheet and PICO principles, demonstrating

validity through cohort designs and rigorous analysis of prognostic factors. Nonetheless, potential biases from self-reported data and differences in study populations remain challenges in generalizing the findings.

In clinical application, patients with T2DM and HTN should maintain strict blood sugar control (HbA1c <6.5%) and blood pressure <140/90 mmHg as primary measures for stroke prevention. The significantly increased stroke risk (3–4 times higher than the general population) underscores the importance of patient education. Lifestyle modifications, including smoking cessation and increased physical activity (3-5 times per week, totaling 150 minutes per week), are crucial, as these are independent stroke risk factors. Additionally, periodic screenings for carotid artery stenosis are recommended, particularly for patients with additional risk factors or a prior stroke history.[12]

CONCLUSION

Based on the review results from the three analyzed articles, it was consistently found that the combination of T2DM and HTN significantly increases the risk of stroke, both in the short and long term. Although all studies show similar results, this analysis primarily relies on findings from studies with the longest follow-up period as the basis for conclusions. The study by Hu et al. (2005) reported that patients with both T2DM and HTN had a stroke incidence of 19.7% over 19 years, with a nearly fourfold increased risk compared to the population without these conditions. Therefore, a more aggressive clinical approach is needed to manage blood pressure and blood sugar levels to reduce the risk of stroke. Strategies that can be applied include lifestyle modifications, such as maintaining a healthy diet, engaging in regular physical activity, quitting smoking, and using appropriate pharmacological therapy to ensure optimal blood pressure and glucose control.

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