Meta-Analysis of the Quantitative Relation Between Pulse Pressure and Mean Arterial Pressure and Cardiovascular Risk in Patients With Diabetes Mellitus

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Results of epidemiologic studies that investigated the significance of pulse pressure (PP) and mean arterial pressure (MAP) in terms of risk of cardiovascular disease (CVD) in patients with diabetes mellitus are inconsistent. We performed a quantitative meta-analysis to estimate CVD risk in relation to PP or MAP. Electronic literature search was conducted for prospective studies providing data on CVD risk for an increment in baseline MAP or PP in patients with diabetes mellitus. The pooled CVD risk for a 10-mm Hg increase in each blood pressure (BP) index was estimated with a random-effects model. There were 17 eligible studies consisting of 52,647 patients and 5,112 CVD cases. The pooled relative risk (95% confidence interval) of CVD for an increment of 10 mm Hg was 1.10 (1.04 to 1.16) for PP and 1.09 (0.98 to 1.21) for MAP. Significant between-study heterogeneity was observed (I^2 [p value]; 76.5% [p <0.001] for PP, 67.8% [p = 0.005] for MAP). In studies concurrently investigating CVD risk for the 4 indexes (i.e., PP, MAP, systolic BP, and diastolic BP), the pooled relative risk (95% confidence interval) was 1.17 (1.09 to 1.26) for PP, 1.11 (1.06 to 1.15) for MAP, 1.14 (1.06 to 1.22) for systolic BP, and 1.06 (0.94 to 1.19) for diastolic BP. In conclusion, the current meta-analysis suggested that PP was the strongest indicator among the 4 commonly used BP indexes. However, the large heterogeneity urged cautious interpretation of the study results. **(Am J Cardiol 2014;113:1058−1065)**

There has been a well-established relation between blood pressure (BP), in particular systolic BP, and risk of cardiovascular disease (CVD) in patients with diabetes mellitus (DM) as well as in the general population. Recently, attention has been paid to 2 other indexes, mean arterial pressure (MAP) and pulse pressure (PP), whose components include both systolic and diastolic BP; MAP is calculated as$1/3 \times SBP + 2/3 \times DBP$, and PP is calculated as SBP − DBP, where SBP denotes systolic BP and DBP denotes diastolic BP. In the general population, compared with systolic and diastolic BP, PP has a lower predictive value for CVD whereas MAP has a comparable or greater predictive value.[1] However, the relative magnitude among the BP indexes in terms of CVD risk is hypothesized to be specific for DM, considering that in subjects at high risk for CVD, systolic BP is higher and diastolic BP is lower (i.e., PP, but not necessarily MAP, is enlarged) in those with DM compared with those without DM.[2] However, results of epidemiologic studies that investigated the significance of PP and MAP in terms of CVD risk in patients with DM are inconsistent. The aim of this meta-analysis is to comprehensively estimate CVD risk in relation to PP or MAP based on previously published prospective studies.

Methods

An electronic literature search using MEDLINE (from January 1, 1950 to April 2, 2013) and EMBASE (from January 1, 1974 to April 2, 2013) was conducted for studies providing data on future CVD risk in relation to baseline MAP or PP values in patients with DM. Study keywords were text words related to DM, MAP, PP, and CVD or thesaurus terms registered in MEDLINE (MeSH) or EMBASE (Emtree) related to DM (i.e., "diabetes mellitus, type 2" OR "diabetes mellitus" OR "diabetes mellitus, type 1" [in MeSH] and "insulin-dependent diabetes mellitus" OR "juvenile diabetes mellitus" OR "diabetes mellitus" OR "maturity-onset diabetes mellitus" OR "non−insulin-dependent diabetes mellitus" [in Emtree]) and CVD (i.e., "coronary disease" OR "coronary artery disease" OR "myocardial ischemia" OR "myocardial infarction" OR "cerebrovascular disorders" OR "brain ischemia" OR "stroke" OR "intracranial embolism and

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See page 1064 for disclosure information.

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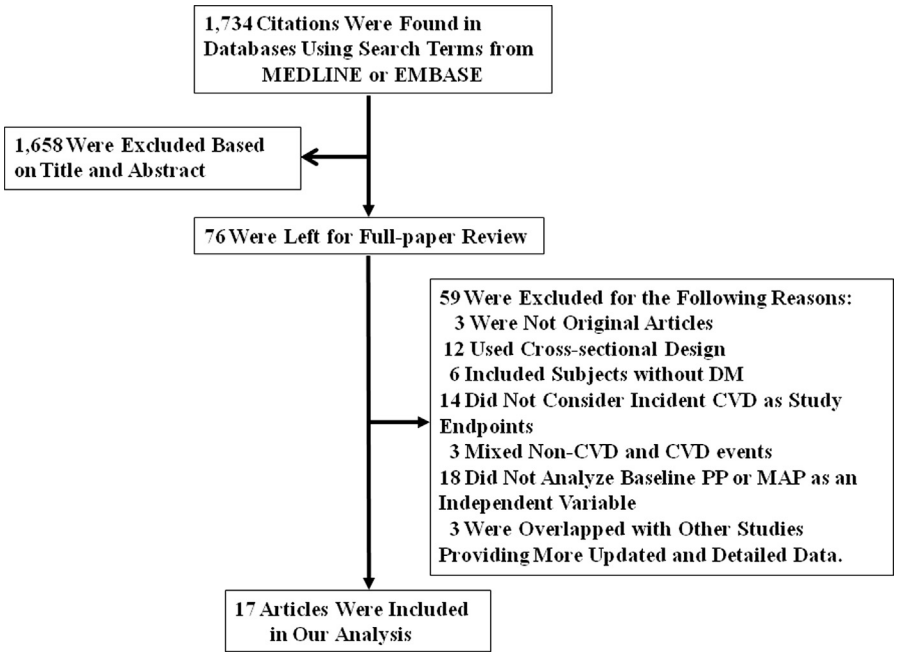

Figure 1. Flow chart of literature search for eligible studies.

thrombosis" OR "intracranial hemorrhages" OR "brain infarction" OR "cerebral infarction" OR "subarachnoid hemorrhage" [in MeSH] and "acute coronary syndrome" OR "ischemic heart disease" OR "acute heart infarction" OR "heart infarction" OR "stroke" OR "brain ischemia" OR "subarachnoid hemorrhage" OR "brain hemorrhage" OR "transient ischemic attack" OR "brain ventricle hemorrhage" OR "cerebellum hemorrhage" OR "cerebrovascular disease" OR "cardiovascular disease" [in Emtree]). The 3 key concepts (i.e., DM, MAP or PP, or CVD) were combined using the Boolean operator "AND" after combining MAP and PP using the Boolean operator "OR." Manual searches for relevant reports were added from examination of reference lists of the identified reports. No language restriction was imposed. Studies were included if (1) all participants had diabetes regardless of the type of diabetes; (2) incident CVDs were prospectively followed-up; (3) baseline values at cohort entry were presented for either PP or MAP or both PP and MAP; and (4) data on the relative risk (RR) of CVD for an increment in PP or MAP at cohort entry were provided.

The CVD end points included CVDs, coronary heart diseases (CHDs), and stroke that were symptomatic. Studies that investigated CHD or stroke apart from CVDs were included. Studies considering only fatal CVD as the study end point were also included. In studies that not only included data on risk of fatal CVD but also provided data on both fatal and nonfatal CVD, priority was given to data on risk of outcome that included both fatal and nonfatal events. If studies separately investigated fatal and nonfatal CVD, we chose the data on fatal CVD risk because it was the more serious event. Studies regarding peripheral vascular disease as a part of total CVD were also included. However, studies that mixed microvascular diseases (e.g., end-stage renal disease) and CVDs as study end points were excluded because these 2 end points involved entirely different concepts.

Two authors (SK and HS) independently extracted data, and discrepancies were solved by discussion. Data extracted from each study included the following: geographic region, type of DM (type 1, type 2, or nonspecified), definition of CVD outcomes, methods for ascertainment of CVD, mean age, gender, mean systolic BP, mean diastolic BP, proportion of patients taking antihypertensive drugs, duration of DM, follow-up periods, whether patients who already had CVD were excluded (yes or no), study covariates, and risk estimates for CVD. If the study reported multiple RRs for the same increment of BP, the most adjusted RR was used. For 1 study, in which the most adjusted RR could not be specified,[3] we chose the RR adjusted for age, gender, and antihypertensive drugs. Study quality was assessed by modifying the Newcastle-Ottawa Quality Assessment Scale[4] so that it was applicable to our theme. In summary, the Newcastle-Ottawa Quality Assessment Scale consists of 3 major items: S (selection, 3 questions), C (comparability, 2 questions), and O (outcome, 3 questions). For each "yes" answer, 1 point was awarded.

Data syntheses were separated by each combination of outcomes (i.e., CVD, CHD, or stroke) and by the BP indexes (i.e., PP, MAP, systolic BP, and diastolic BP). The RRs were transformed into natural logarithms—ln(RR)—and standardized into those for a 10-mm Hg increment. Each standardized ln(RR) was pooled with a random-effects model[5] and the final RR was calculated by exponentiation of the pooled ln(RR). For PP and MAP, the data syntheses were conducted by each combination of outcomes (i.e., CVD, CHD, or stroke). Between-study heterogeneity was assessed by I^2.[6]

We compared the magnitude of CVD risk in relation to an increment in any 2 of the 4 BP indexes, limiting the analysis to studies that provided data on the RR for systolic