# Management and Outcomes of Perioperative Care among European Diabetic Patients (MOPED)


## Steering Committee

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## Statistical Analysis Plan (SAP)

### Design

MOPED is a prospective, observational, international, multicentre cohort study, supported by the *European Society of Anaesthesiology & Intensive Care* (ESAIC). It has been registered on clinicaltrials.gov, NCT04511312.

### Participants

Diabetic patients (all classes except gestational diabetes) undergoing surgery with a substantive anaesthetic technique. This is defined as requiring any general anaesthesia technique or any specific regional anaesthetic technique or a combination. Ambulatory, elective or emergency surgery and patients who receive postoperative care in intensive care or high dependency units will be included.

### Setting

Any hospital in Europe (as defined by the World Health Organisation) is welcome to participate as a study centre. Non-European centres may be accepted upon request to the Steering Committee. Centres will be asked to enrol a minimum of 45 patients over a recruitment period of up to 18 months.

### Objectives

1. What is the epidemiology of diabetic patients undergoing surgery across Europe: Are there major variations in perioperative glycaemic control? Does management practice vary between centres and between nations?

2. What is the extent and patient-centred impact of postoperative complications among diabetic patients up to 30 days after surgery in Europe?

3. To undertake sub-group analysis comparing these outcomes among:

a. Type 1, Type 2, and other diabetic patients.

b. Patients with different strata (levels) of glycaemic control, i.e. HbA1c <53, HbA1c 53-69 and HbA1c >69 mmol.mol.

c. Patients who received different anaesthetic techniques: volatile versus total intravenous anaesthesia; regional versus general anaesthesia (GA).

d. Diabetics of longer duration have higher risk of intraoperative hypotension due to autonomic neuropathy.

**Primary Outcome**

Descriptive epidemiology of the perioperative management and postoperative morbidity of Diabetic patients across the different countries in Europe. Morbidity and mortality will be assessed using Days at Home at 30 days (DAH-30) as the primary outcome.

**Secondary Outcomes**

Secondary outcomes will be morbidity as assessed by the Comprehensive Complications Index (CCI) score, based on Clavien-Dindo scale and additional hypotheses of interest as listed in Table 1.

**Table 1. Secondary outcomes and hypotheses of interest.**

| Hypothesis | Variables |
|---|---|
| There are major differences in perioperative management of diabetic patients in different nations in Europe | Insulin dose<br>Methods of insulin admin<br>Oral hypoglycaemic use |
| There are major differences in postoperative morbidity and outcomes among diabetic patients in different nations in Europe | DAH-30<br>CCI |
| Outcomes among patients with different strata of glycaemic control, i.e.<br>HbA1c <53,<br>HbA1c 53-69 and<br>HbA1c >69 mmol.mmol will be different; | Preop HbA1c and glucose<br>DAH-30<br>CCI |
| Diabetic patient outcomes differ depending on anaesthetic technique:<br>Volatile versus total intravenous anaesthesia;<br>Regional versus general anaesthesia (GA)<br>Combined GA and regional anaesthesia versus patients receiving GA alone. | DAH30<br>CCI<br>All secondary outcomes |
| Diabetic Patients receiving liberal fluids perioperatively have better outcomes than patients receiving restrictive fluids, compared to their body weight | DAH-30, CCI<br>crystalloid and colloid totals up to PACU |

| | |
|---|---|
| Type 2 DM patients have worse outcomes than Type 1 | DAH-30, CCI |
| Patients where a consultant /senior surgeon and senior anaesthesiologist is present have better outcomes than when not present | Personnel tracking<br>All Outcomes |
| Diabetic patients of longer duration experience more hypotension duration/episodes due to autonomic neuropathy and have worse outcomes than diabetic patients with shorter duration | Intraop and PACU hypotension and use vasopressors and outcomes;<br>Duration of DM |
| NSAID use perioperatively worsens outcomes especially AKI | DAH30,CCI<br>AKI |
| Risk factors for higher morbidity in diabetic patients undergoing surgery | All factors,<br>All outcomes<br>Multivariable analysis |
| Patients with preoperative GLP-1 use have better perioperative glucose control (and outcome) as compared to other oral hypoglycaemics | PreOp medication use DAH30<br>CCI |
| There is no association between metformin use and perioperative lactic acidosis | Preop medication use<br>Incidence of DKA<br>DAH-30<br>CCI |
| Patients with known preoperative susceptibility for hypoglycaemia/DKA are more prone for perioperative hypoglycaemia/DKA | PreOK hypoglycaemia/DKA<br>PeriOK hypoglycaemia/DKA |
| Surgery in DM will lead to dysglycaemia up to 30 days | DM medication at 30 days |

**Sample size estimation**

Up to 5% of the population of Europe is thought to have diabetes. About 30 million surgeries are performed in Europe per annum, therefore perhaps 1.5 million diabetics have surgery in Europe each year. It is proposed to evaluate a pragmatic sample of 5,000 European diabetic patients across at least 50 centres in a minimum of 15 nations. It is expected that this should be sufficient for the main epidemiological aspects of this study. It is envisaged that this target number would be enrolled over a two-year period from initial roll-out, with up to a further 12 months needed for final data acquisition, data cleaning and analysis. A sample size of 5,000 should be sufficient to avoid over-fitting and variance inflation for 50 to 70 factors and interactions based on the conventional square root or 100 values per variable respectively. In addition, a sample size of 5,000 will have at least 90% power to find a standardized difference of 0.15 as significant at $P<0.05$ (Bonferroni corrected at $P<0.0007$) for up to 70 independent hypotheses and in comparing subsets of interest.

**Primary Statistical Analysis**

The aim of this research is the describe and quantify the epidemiology of the perioperative management and perioperative complications of diabetic patients in Europe. Descriptive statistics such as mean (SD), median [interquartiles, range] and frequencies (%) with be presented as appropriate. Gaussian distributions will be assessed using frequency histograms, normality plots and the Shapiro-Wilks statistic. The precision of the estimates will be reported as 95% confidence

intervals to show the prevalence and incidence rates of diabetic phenotypes and major adverse events and complications.

Continuous data will be analysed using Student *t*-, Welch *t-,* Mann-Whitney *U*-, one-way analysis of variance (ANOVA) and Kruskal-Wallis *H*- statistics. Categorical data will be analysed using chi-square independence and expanded Fisher exact statistics. Hierarchical nesting of patients in hospitals and countries will be entered as random effects in multilevel mixed-effects regression models. Effect sizes will be presented as mean or median differences, odds, risk or hazard ratios, with 95% confidence intervals. Multiple hypothesis or comparison testing will be addressed using Tukey-Kramer and Bonferroni corrections and overall statistical significance will be defined at $P<0.05$ (two-sided).

Repeated measurements in patients will be analysed using multilevel mixed-effects regression with maximum likelihood estimation (MLE) using appropriate link functions: Gaussian, Poisson, Negative Binomial and Logit. Robust multivariable linear, logistic, proportional hazards and quantile regression models will be constructed to identify significant independent risk factors for adverse outcomes. Variables with $P<0.15$ on bivariate analysis, or that are clinically relevant, will be entered. Multicollinearity will be assessed using variance inflation factors.

**Secondary Statistical Analysis**

Exploratory post-hoc analyses may be performed to gain further information about the cohort and to assess clinical outcomes with respect to participating countries and hospitals. Any post-hoc analyses will be identified as such in any reports. Participating institutions can request data extraction for further analysis and quality improvement, subject to approval of the Steering Committee. As the primary purpose of this project is epidemiological, missing data will not be replaced or imputed.

Analyses will be conducted with missing data as missing for primary outcomes. Missing data in secondary multivariable analyses will be analysed in order as missing, case-wise deletion and multiple imputation with propensity scores.

**Software**

Data will be analysed using Stata 16.1, StataCorp Inc., College Station, TX and Number Cruncher Statistical Systems 2020 (NCSS), NCSS Inc., Kaysville, UT.