Efficiency and effectiveness of intensive multidisciplinary follow-up of patients with stroke/TIA or myocardial infarction compared to usual monitoring: protocol of a pragmatic randomised clinical trial. DiVa (Dijon vascular) study

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ABSTRACT

Introduction The ongoing ageing population is associated with an increase in the number of patients suffering a stroke, transient ischaemic attack (TIA) or myocardial infarction (MI). In these patients, implementing secondary prevention is a critical challenge and new strategies need to be developed to close the gap between clinical practice and evidence-based recommendations. We describe the protocol of a randomised clinical trial that aims to evaluate the efficiency and effectiveness of an intensive multidisciplinary follow-up of patients compared with standard care.

Methods and analysis The DiVa study is a randomised, prospective, controlled, multicentre trial including patients >18 years old with a first or recurrent stroke (ischaemic or haemorrhagic) or TIA, or a type I or II MI, managed in one of the participating hospitals of the study area, with a survival expectancy >12 months. Patients will be randomised with an allocation ratio of 1:1 in two parallel groups: one group assigned to a multidisciplinary, nurse-based and pharmacist-based 2-year follow-up in association with general practitioners, neurologists and cardiologists versus one group with usual follow-up. In each group for each disease (stroke/TIA or MI), 430 patients will be enrolled (total of 1720 patients) over 3 years. The primary outcome will be the incremental cost-utility ratio at 24 months between intensive and standard follow-up in a society perspective. Secondary outcomes will include the incremental cost-utility ratio at 6 and 12 months, the incremental cost-effectiveness ratio at 24 months, reduction at 6, 12 and 24 months of the rates of death, unscheduled rehospitalisation and iatrogenic complications, changes in quality of life, net budgetary impact at 5 years of the intensive follow-up on the national health insurance perspective and analysis of factors having positive or negative effects on the implementation of the project in the study area.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This trial falls within the scope of a national policy led by the Ministry of Health and the National Health Insurance to experiment original care pathways in France.
⇒ The efficiency and effectiveness of an intensive multidisciplinary follow-up of patients will be compared with standard care using a robust methodology based on a randomised, prospective, controlled, multicentre trial.
⇒ The trial design considers the optimisation of healthcare expenses in the implementation of such an innovative strategy.
⇒ The generalisation of the findings of this study outside France will remain questionable because of large differences in the organisation of healthcare systems worldwide.

Ethics and dissemination Ethical approval was obtained and all patients receive information about the study and give their consent to participate before randomisation. Results of the main trial and each of the secondary analyses will be submitted for publication in a peer-reviewed journal.

Trial registration number ClinicalTrials.gov Identifier: NCT04188457. Registered on 6 December 2019.

INTRODUCTION

Stroke and myocardial infarction (MI) are responsible for the first cause of death and disability in adults worldwide.1,3 The acute management of these diseases improved dramatically over the past decades, thus leading to a decrease in early case fatality.4,5 Concomitantly, the ongoing
ageing population has been associated with an increase in the number of patients suffering a stroke or a MI each year. As a result, the number of stroke and heart attack survivors is increasing, thus making critical the issue of secondary prevention and management of disease-related complications. It has been shown that up to 30% of patients with stroke or MI will be readmitted to hospital within 1 year after the initial event. Major efforts are needed to reduce unscheduled rehospitalisations since they are associated with poor patients’ outcome, and substantial costs. To achieve this goal, new strategies need to be developed to close the gap between clinical practice and evidence-based recommendations in implementation of secondary prevention. One of the current limitations is a lack of medical time for cardiologists and neurologists in the French healthcare system due to unfavourable demographics, thus limiting patients’ access to these professionals. Therefore, the involvement of other health professionals could be an alternative to this problem in order to improve the follow-up of patients. Although some studies have demonstrated the central role that nurses and pharmacists can play in monitoring vascular risk factors, improving patients’ adherence to treatment or reducing iatrogenic complications, an overall medico-economic evaluation of the impact of such a multi-intervention approach remains to be performed.

As part of a national policy led by the French Ministry of Health and the National Health Insurance to experiment original care pathways in France, the DiVa (Dijon Vascular project) study aims to evaluate the efficiency and effectiveness of an intensive multidisciplinary follow-up of patients suffering from stroke, transient ischaemic attack (TIA) or MI, compared with standard care. The primary objective is to evaluate, at 24 months, the cost-utility impact of intensive versus standard follow-up of patients with stroke/TIA or MI, in a society perspective. The secondary objectives are to evaluate the cost-utility impact at 6 and 12 months in a society perspective; the cost-effectiveness impact at 24 months in a society perspective; the effectiveness of the intensive follow-up on the reduction at 6, 12 and 24 months on the rates of death, of the unscheduled rehospitalisations and of iatrogenic complications; the changes in quality of life; the net budgetary impact at 5 years of the intensive follow-up on the national health insurance perspective. Finally, the study aims to analyse the individual, structural and conjunctural factors having positive or negative effects on the implementation of the project in the territory.

METHODS

Trial design

The DiVa study is a randomised, prospective, controlled, multicentre study comparing two parallel groups with an allocation ratio of 1:1 including patients with stroke/TIA or MI.

Participants

Patients are included in seven hospitals from two administrative French regions, where they are managed for their acute vascular event, including one University Hospital, five general public hospital and one private hospital. Patients in the experimental group receive 2 years of intensive follow-up involving hospital pharmacists, hospital and private nurses, in association with general practitioners (GPs), cardiologists and neurologists. Patients in the control group receive standard follow-up according to current practice.

Inclusion criteria

Patients over 18 years of age, with a first confirmed or recurrent stroke (ischaemic stroke, International Classification of Diseases, 10th revision (ICD-10) code: I63; or intracerebral haemorrhage, ICD-10 code: I61), TIA (ICD-10 code: G45) or type I or II MI (ICD-10 code: I21–I22), living in the geographical areas of interest and managed in one of the participating hospitals, with a survival expectancy of more than 12 months, who are affiliated to the National Health Insurance, and who have given oral informed consent, are eligible.

Exclusion criteria

Patients with stroke leading to a severe handicap defined by a modified Rankin Scale (mRS) score ≥5, pregnant woman, patients with cerebral inflammatory, tumorous brain disease or chronic heart failure are excluded.

Interventions

Participating hospitals were included in DiVa with respect to the use of common procedures after a specific training on stroke/TIA and MI management. Nurses and pharmacists were trained in the recommended secondary prevention guidelines, the study protocol, the use of electronic Case Report Form (eCRF) and the electronic recording of data collected at each hospital, practice, or home visit.

Patients with stroke/TIA or MI are recruited during their hospital stay. After a complete diagnostic work-up and the introduction of secondary prevention therapy according to the current guidelines, they are invited to participate in the trial. Once they have given their consent, the randomisation procedure takes place. For all included patients, a letter summarising the hospital stay, and providing information about the DiVa protocol and patient’s personalised pathway, is sent to the GP and other specialists contributing to the DiVa care network.

In the French primary healthcare system, the acute management of stroke or MI is done in inpatient. When the patient is discharged after the acute stay (or after a stay in rehabilitation in approximately a third of stroke patients), a prescription for medication is issued and a discharge letter is sent to the GP and other specialists who previously followed the patient. The patient goes to the private pharmacist who ensures the delivery of prescribed drugs, can detect possible interferences, but currently has little intervention targeted on patient compliance.
or education. A private nurse can intervene on medical prescription in the patient’s home to provide specific care or to distribute medication, particularly for patients with cognitive disorders that may induce medication errors. For patients with stroke, physiotherapy and/or speech therapy can be prescribed too when needed. A specialised follow-up visit is scheduled and most often, this consultation takes place in the hospital by the team that took care of the patient during the acute phase. In this case, it is usually between 1 and 3 months after MI and between 3 and 9 months after stroke. If the patient was followed by a private cardiologist or neurologist before the event, the visit is usually done by them. Subsequent visits are scheduled according to clinical need from one consultation to the next. There are no formal scheduled GP visits as part of the usual follow-up after hospitalisation. A visit to GP is made at the request of the patient, in case of an intercurrent health problem or for the renewal of the prescription of medication (usually every 3 months).

Participant timeline according to arm assignment is shown in figure 1. Patients with stroke/TIA assigned to the standard follow-up have a scheduled outpatient visit with a hospital neurologist and a nurse at 6 and 24 months, and patients with MI have a scheduled visit with a cardiologist, either a private or a hospital-based at 3, 6, 12 and 24 months. In addition, all patients are called by a clinical research assistant at 3, 6, 9, 12 and 18 months to collect interim information on recurrence of vascular events, possible complications, rehospitalisations and to carry out a quality of life assessment. Patients in the intensive follow-up group have additional visits from a nurse at home at 1, 2 and 3 weeks, 6, 12 and 18 months and in hospital at 1, 3, 9 and 24 months after discharge. They also have an additional visit to a hospital pharmacist before discharge and 3 months afterwards, and to their local pharmacist at 6 and 12 months. In addition, patients with MI receive an extra visit from a hospital cardiologist at 1 month. During the visits, the nurse assesses the quality of return at home, checks blood pressure and glycaemia where indicated, and patient’s adherence to treatments, and identifies adverse events and complications. A report is sent to the GP and the specialist, and the nurse is invited to call them directly if there is a serious medical problem. In both arms an additional visit to the specialist may be arranged if the patient’s clinical condition requires it. During the pharmacist’s visit, patient’s adherence to treatment is evaluated and side-effects are assessed using a structured questionnaire for each disease (stroke/TIA or MI), and reported in the medical record.

During visits, clinical data, information about patients’ outcome, recurrence of cardiovascular events and quality of life are collected and reported in the eCRF. An electronic platform, called e-TICSS, which allows the sharing of secure medical information into care network of DiVa, collects anonymised clinical data, the number of scheduled or unscheduled consultations, the number and cause of re-hospitalisation as well as all the information necessary for the medico-economic evaluation.

Randomisation procedure

Eligible patients are randomised by the hospital practitioners from the participating centres. The randomisation procedure is generated by the digital system CleanWeb and stratified for each disease (Stroke/TIA or MI) by centre, and for stroke/TIA by residual disability based on the mRS score dichotomised into two groups: mRS score 0–2, corresponding to patients with no or minor disability who are able to look after own affairs without assistance, and mRS score 3 or 4 corresponding to patients with moderate to moderately severe disability.
Outcomes

Primary outcomes
The primary outcome is the incremental cost–utility ratio at 24 months between intensive and standard follow-up of patients with stroke/TIA or MI.

Secondary outcomes
1. Incremental cost–utility ratio at 6 and 12 months between intensive and standard follow-up.
2. Incremental cost-effectiveness ratio at 24 months between intensive and standard follow-up.
3. Effectiveness of the intensive follow-up on the reduction at 6, 12 and 24 months of the rates of death, unscheduled rehospitalisation and iatrogenic complications.
5. Net budgetary impact at 5 years of the intensive follow-up on the national health insurance perspective.
6. Analysis of the individual, structural and conjunctural factors having positive or negative effects on the implementation of the project in the study area and the unexpected effects of the project.

Medico-economic outcomes measure

Cost–utility analysis at 24 months
The choice of the cost–utility analysis (CUA) in a primary objective is justified because of the importance of the quality of life after a stroke/TIA, or a MI. For each of the two diseases, an incremental cost–utility ratio at 24 months associated with the intensive follow-up when compared with the usual follow-up will be estimated and expressed in terms of cost per quality-adjusted life year (cost/QALY) gained. The analyses will adopt a society perspective since they will be conducted from the point of view of hospitals, health insurance agencies, patients, Health Ministry as it is the current payer of the intensive posthospitalisation follow-up. The time horizon (24 months) corresponds to the expected duration of intensive posthospitalisation follow-up for patients after stroke or MI. It also corresponds to the period of maximum risk of recurrence.

Cost-measurement
For each of the two diseases (stroke/TIA and MI), the total costs of each follow-up strategy (usual and intensive) will be evaluated. Direct costs associated to scheduled visits (nurse, neurologist, cardiologist, pharmacist, GP) will be included, as well as all unscheduled care consumption over the 24 months of follow-up in relation to the evolution of the patient’s health condition (additional consultations; any rehospitalisations; drugs and medical devices dispensed; imaging and biological examinations performed; and any admission to institutions). Finally, all the patient travel costs will be considered. Indirect costs will be also taken into account in a further analysis, corresponding to the loss of productivity attributed to the absence from work of patients who were active at the time of their illness. The digital e-TICSS platform will allow to identify all the patients included in each arm and their care consumption during 24 months posthospitalisation. These data will be completed by an anonymised linkage with the French National Health Data System (Système National des Données de Santé—SNDS), including all individual data of care reimbursed, hospital stays and sick leave. For each of the two diseases and each arm, all scheduled visits will be valued by their current rates, except those with private/hospital nurses and local/hospital pharmacists, which benefit from a special pricing system in the context of the experimentation of the intensive follow-up. The cost of complications leading to hospital readmissions over the 2 years of follow-up will be calculated from a national survey on hospital production costs per Diagnosis Related Group, including a representative sample of public and private hospitals in France (Échelle Nationale des Coûts à Méthodologie Commune—ENCC). The cost of complications leading to unscheduled medical and paramedical procedures in the outpatient sector will be valued by their current rates. Finally, according to the societal perspective, a loss of national productivity will be estimated for each patient, per day of work stoppage. This estimate will be based on the gross domestic product (GDP) and the labour force statistics, annually published by the National Institute for Statistics and Economic Studies (Institut National de la Statistique et des Études Économiques—Insee).

QALY estimation
The utility scores will be estimated by using the generic questionnaire EQ-5D-5L, commonly used in medico-economic analyses and validated in France. This questionnaire assesses patients on five dimensions (mobility; autonomy; ability to carry out daily activities; pain and discomfort; anxiety or depression). It will be administered to patients in the intensive post-stroke/TIA and post-MI follow-up at M0, M3, M6, M9, M12, M18 and M24. It will be administered to patients in the post-stroke/TIA and post-MI usual follow-up at the same intervals, during consultation or by telephone. For each patient, a utility score will be calculated for each of these measures. A final utility score at 24 months, representing the number of QALYs gained, will be then calculated by taking into account the period between two measures.

Discount rate
In accordance with the methodology recommendations of the High Health Authority in France (Haute Autorité de Santé—HAS), the costs and the QALYs at 24 months will be discounted at 4% as the time horizon is greater than 12 months.

Incremental cost–utility ratio
For each of the two diseases (stroke/TIA and MI), an incremental cost–utility ratio at 24 months will be calculated by relating the difference in mean costs to the difference in mean QALYs between the intensive and usual follow-up. The result will be interpreted as the potential incremental cost associated with an additional QALY.
gained under the intensive follow-up compared with the usual follow-up.

**Sensitivity analyses**
For each of the two diseases, a non-parametric bootstrap analysis of the cost and QALY differential observed between the two follow-ups will be carried out. It enables to study the uncertainty associated with the study sample and construct a 95% CI for the incremental cost–utility ratio. In order to test the robustness of the conclusion drawn, univariate sensitivity analysis will be performed and represented in the form of a Tornado diagram. Sensitivity analyses will also concern the discount rate, by testing at least a higher rate (4.5%) and a zero rate. The sensitivity analysis on the discount rate will be performed simultaneously on the costs and the health outcomes.32

**Cost–utility analyses at 6 months and 12 months**
For each of the two diseases, a CUA at 6 and 12 months will be performed. Costs at 6 and 12 months will be evaluated in the same way as in the primary CUA, in a society perspective. A final utility score at 6 and 12 months will be then calculated. Incremental cost–utility ratios will be then calculated. No discount will be performed as the time horizons are less than 12 months. Similar sensitivity analyses will be performed.

**Cost-effectiveness analysis at 24 months**
For each of the two diseases, a cost-effectiveness analysis at 24 months will be performed, based on the ratio of the difference in mean costs to the difference in mean survival time between the two follow-ups. Costs will be evaluated in the same way as the primary CUA, in a society perspective. Results of costs and effectiveness at 24 months will be discounted at 4% as the time horizon is greater than 12 months. Deterministic and stochastic sensitivity analyses will be performed to the cost-effectiveness ratio.

**Budgetary impact analysis**
For each of the two diseases, a Budgetary Impact Analysis (BIA) will be performed35 to estimate the net annual financial impact (costs incurred and avoided) of the routine adoption of the intensive post-stroke/TIA and post-MI follow-up in the study area, from hospital discharge and for 24 months. The impact will be evaluated on the budget of the National Health Insurance (Assurance Maladie Obligatoire—AMO), the main funder of the medical management of these patients. This will inform about the budget affordability and anticipate the financial means needed for the years to come. The time horizon of the BIA will be 5 years as it is recommended by the HAS,32 and is justified by the maximum duration of the experimentation. The target population and the reached population will be defined and estimated. Deterministic and stochastic sensitivity analyses will be performed. The results of this BIA conducted in study area will also make it possible to anticipate the budgetary impact of the intensive follow-up strategy if it were generalised to other French departments with similar characteristics, or even the whole of France.

**Clinical outcomes measure**
For each of the two diseases, decrease of death rates, cerebral, cardiac and iatrogenic complications, recurrent events and unscheduled rehospitalisations, and the improvement of quality of life will be estimated.

**Statistical analyses**
All analyses will be carried out according to intention to treat. Description of the population, then of the clinical results, quality of life and costs will be performed. Qualitative variable will be described in terms of numbers and percentages and quantitative variables in terms of means and SD or median and IQR. For each of the two diseases, the two groups (intensive and standard follow-up) will be compared in terms of patient characteristics. Comparison on quantitative variables will be performed using a Student’s t-test or its non-parametric equivalent. In case of clinically significant imbalance between the two groups, a multivariate multiple linear regression model will be performed and the estimate of the effect of follow-up pathway will be adjusted on these parameters. Comparison on qualitative variables will be performed using a χ² test. In case of clinically significant imbalance between the two groups, the variables appearing unbalanced will be taken into account by a multivariate analysis using a logistic regression.

**Implementation study**
As part of the DiVa pragmatic trial, we will conduct an implementation study, including a process evaluation during the roll-out of the intervention. We will assess acceptability, as well as determinants of adherence to the follow-up protocol by patients, caregivers and payers. We will also assess protocol uptake, defined as the proportion of patients who fully completed the programme of scheduled hospital and home visits, fidelity, that is, the ability of the follow-up programme to be effectively deployed as planned, and the maintenance of the effects of the intervention over time.

**Sample size**
The sample size was calculated on the primary medico-economic judgement criteria according to the formula of Glick23 and was applied for the two diseases (stroke/TIA and MI). From the hypothesis of a willingness-to-pay (WTP) threshold of €36 000/QALY gained, an incremental effect of 0.05 QALY±0.1, a difference in costs of €1020±€1020, a correlation of 0.5, an alpha risk at 5% and a beta risk at 10 %, it is necessary to recruit a total of 430 patients in both arms (considering 15% attrition). This calculation leads to a total of 860 patients post-stroke and patients with TIA (430+430) and 860 patients post-MI (430+430). In the absence of a threshold value for the community’s WTP per additional QALY in France, we chose to refer to the GDP/capita as it can be suggested by international recommendations.34 35 For the design of this
Study development and Committee
The three trial coprincipal investigators (MG, YB, YC) designed the study while A-LS and MarcB built the methodological plan. The Steering Committee is responsible for the scientific coordination and is organised around the principal investigators, cardologists, neurologists, methodologists and biostatistician experts in clinical trials. An external Adjudication Committee validates reported outcome events. A Data Monitoring Committee is appointed to ensure the quality and the exhaustiveness of the date capture. A Publication Committee is organised around the steering committee members and will coordinate all manuscripts before submission.

Ethics and dissemination
The study is approved by French ethic committee (CCP; approval 2019-A02299-48) and the Commission Nationale Informatique et Liberté (CNIL, French data protection authority). Patients receive information about the study and give their consent to participate according to the French legislation (online supplemental material). Results of the main trial and each of the secondary analyses will be submitted for publication in a peer-reviewed journal following the CONSORT statement for reporting of pragmatic trials (online supplemental material).

Patient and public involvement
Patients or the public were not involved in the design, or conduct, or reporting or dissemination plans of our research.

DISCUSSION
In a context of increasing number of patients suffering a stroke/TIA or MI each year, partly because of the ageing of the population, innovative approaches to reduce the risk and cost of unexpected rehospitalisations are needed, while being sustainable from a balanced healthcare spending perspective. This trial aims to assess whether intensive, multidisciplinary, nurse-based and pharmacist-based, long-term follow-up after stroke/TIA or MI, in association with GPs, neurologists and cardiologists, has a beneficial impact on cost and utility compared with standard follow-up.

Previous studies have incompletely demonstrated the role of nurses in the control of vascular risk factors and the outcome of patients with stroke and MI. In addition, some other studies on this topic are in progress including the French CEOPS (Controlled Education Of Patients after Stroke) study that is based on a nurse-led multimodal randomised and controlled interventional programme involving a patient’s caregiver to optimise the control of blood pressure after ischaemic stroke. Our trial proposes an alternative and original patient care pathway based on multidisciplinary follow-up, thus contributing to breaking down the barriers sometimes observed between hospital and private care on the one hand, and between the different health professionals involved on the other. By assessing medico-economic aspect as primary endpoint, in a context of shortage in resources and increasing demand, this trial emphasises the need for considering optimisation of healthcare expenses in the implementation of innovative strategies aiming at improving outcome of patients with stroke/TIA or MI. Finally, several studies pointed out a worse outcome and higher mortality after stroke or MI in women compared with men. Subgroup analyses of our results by gender will help to understand the extent to which variations in follow-up of patients may contribute to these observed gender differences.

The major strength of this study is the use of a robust methodology based on a randomised, prospective, controlled, multicentre trial to compare the efficiency and effectiveness of an innovative intensive multidisciplinary follow-up of patients to standard care. Although the call for experimentation of original care pathways in France conducted by the Ministry of Health and the National Health Insurance did not require this type of evaluation, we chose this scientific approach to guarantee the reliability of the results. Several limitations must be acknowledged. This trial is based on a patient-centred approach, and we do not consider the issue of quality of life of next of kin although it could be impacted by the intervention. Information about the socioeconomic status of patients is not collected. However, in France, patients with either stroke or MI are eligible for full coverage of medical expenses by the national health insurance system, which minimises the risk of an effect of individual socioeconomic status on the study results. Some other health professionals including physiotherapists, occupational therapists or speech therapists were not involved in the study because only a limited proportion of patients with stroke discharged home receive their care, and adding an additional health professional would have increased the burden of the follow-up protocol for patients included in the intensive arm, with a risk of poor acceptance, and the costs. In addition, because of a follow-up of patients restricted to 2 years, it could be assumed that a beneficial effect of the intensive intervention on long-term survival could be missed. However, in patients with either stroke or MI, the risk of death is the highest during the first 2 years, that is, the majority of deaths occurs within this time frame. Therefore, we think that if the intervention has a beneficial effect on mortality, a 2year follow-up would be sufficient to capture it. Finally, the generalisation of
the findings of this study outside France will remain questionable because of large differences in the organisation of healthcare systems worldwide.

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