

# Stroke and Cognition



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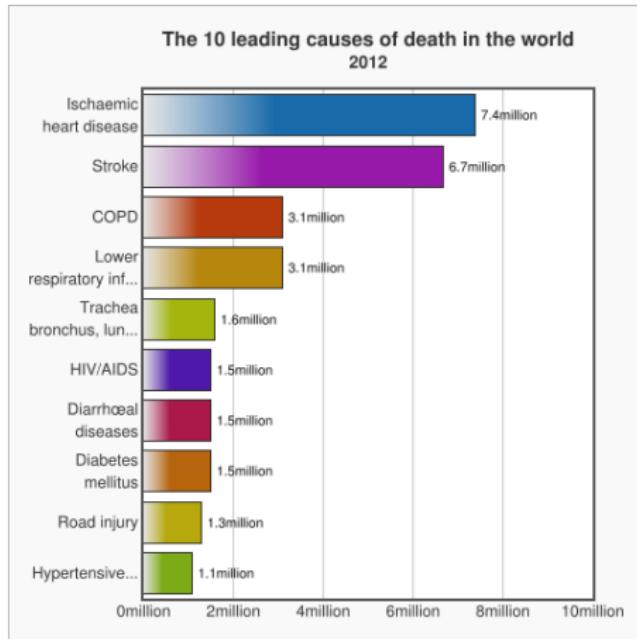
## ① Stroke in Korea

## ② Cognition in patients with stroke

- Choline alfoscerate
- ASCOMALVA study
- Choline alfoscerate after stroke

## ③ Summary

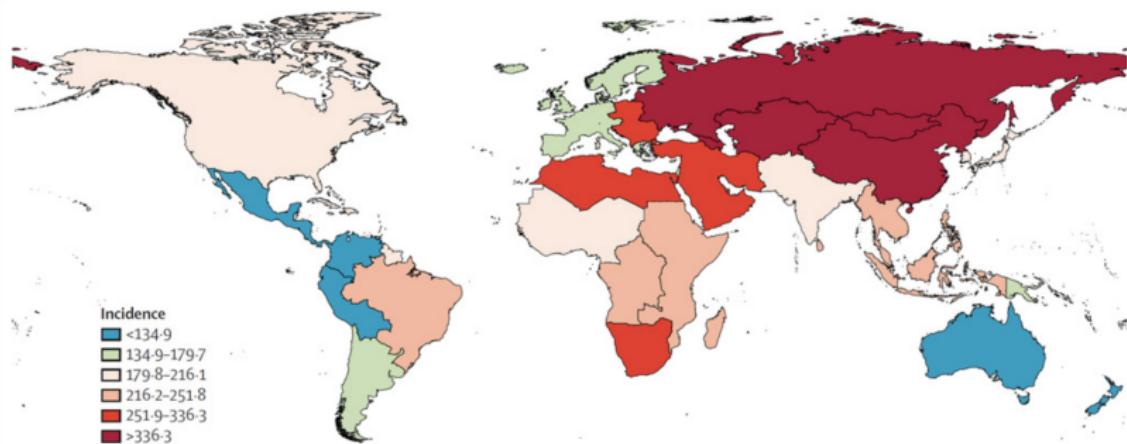
# Global burden of stroke



<http://www.who.int/mediacentre/factsheets/fs310/en/> accessed on Jan 16, 2016

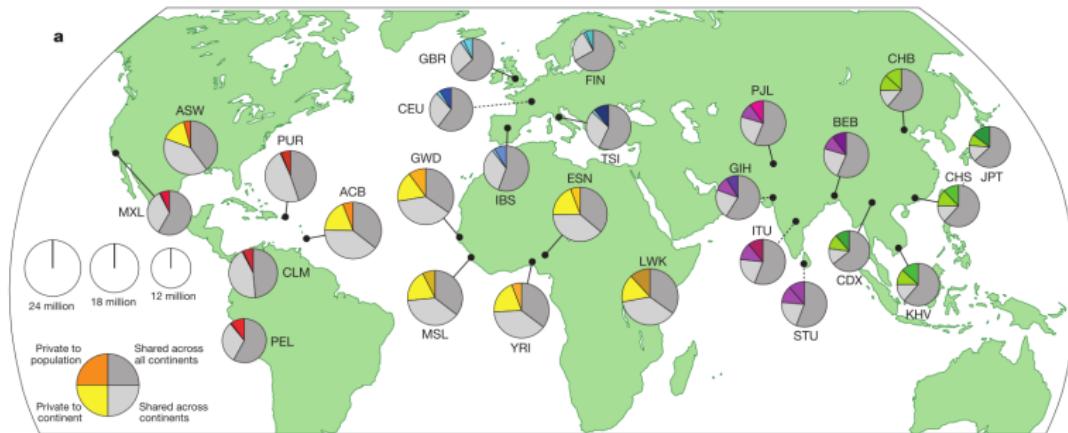
# Age-standardised stroke incidence

per 100 000 person-years for 2010



Lancet Neurol. 2014 383(9913): 245–254.

# A global reference for human genetic variation



The 1000 Genomes Project. Nature 2015

## Future life expectancy in 35 industrialised countries: projections with a Bayesian model ensemble

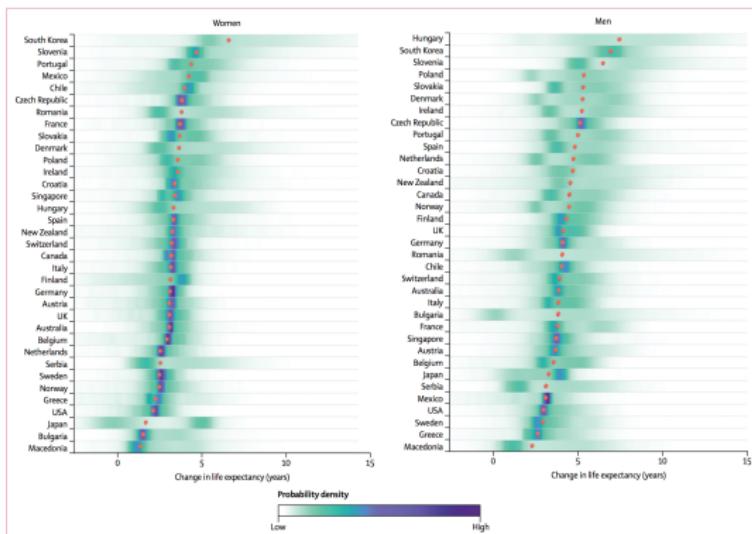


Vasilis Kontis\*, James E Bennett\*, Colin D Mathers, Guangxuan Li, Kyle Foreman, Majid Ezzati

### Summary

**Background** Projections of future mortality and life expectancy are needed to plan for health and social services and

Lancet 2017; 389: 1323–35

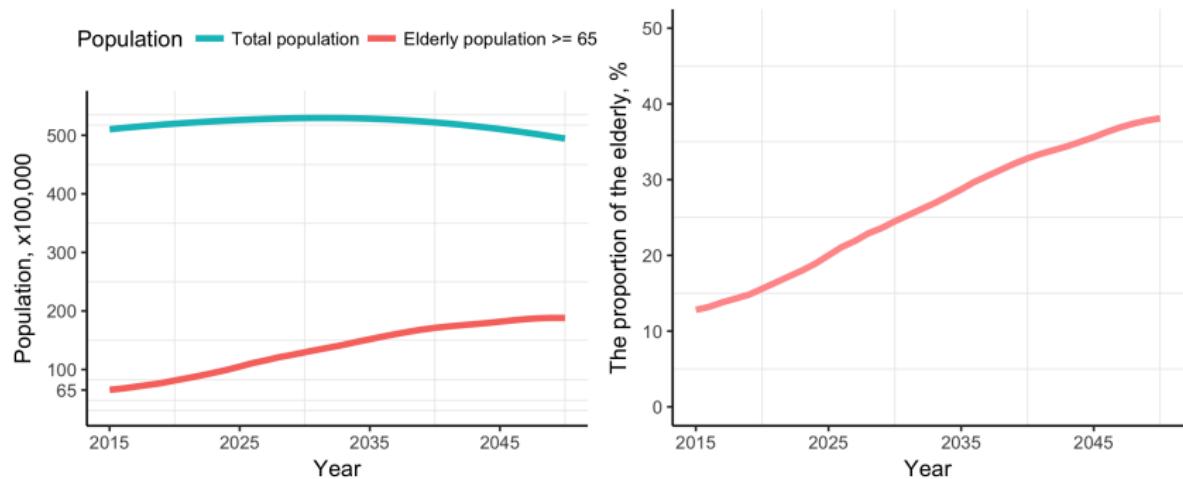


**Figure 1:** Posterior distribution of projected change in life expectancy at birth from 2010 to 2030  
Red dots show the posterior medians. Countries are ordered vertically by median projected increase from largest (at the top) to smallest (at the bottom).

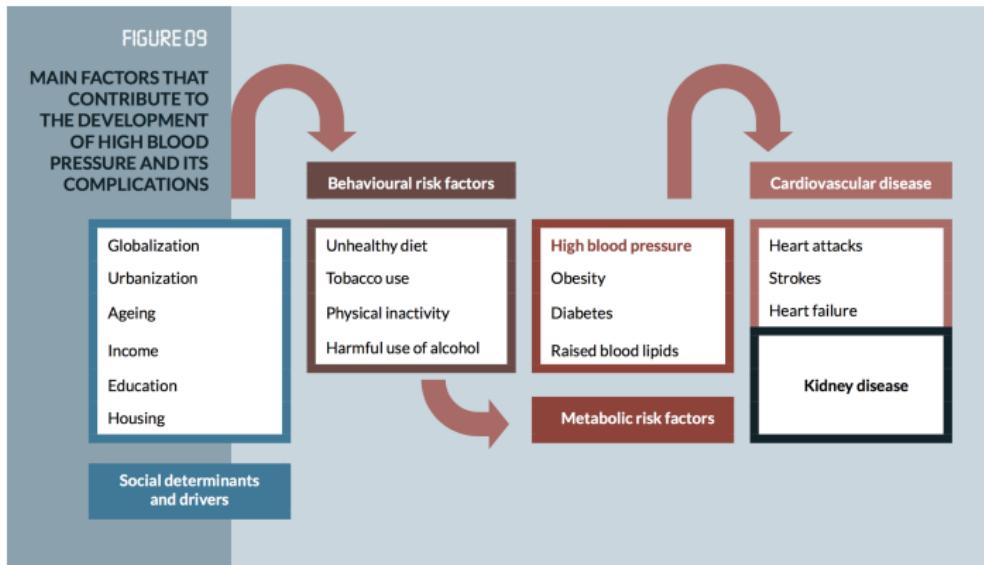
There is a 90% probability that life expectancy at birth among South Korean women in 2030 will be higher than 86.7 years, and a 57% probability that it will be higher than 90 years.

There is a greater than 95% probability that life expectancy at birth among men in South Korea, Australia, and Switzerland will surpass 80 years in 2030, and a greater than 27% probability that it will surpass 85 years.

# Rapid increase of Korean elderly population

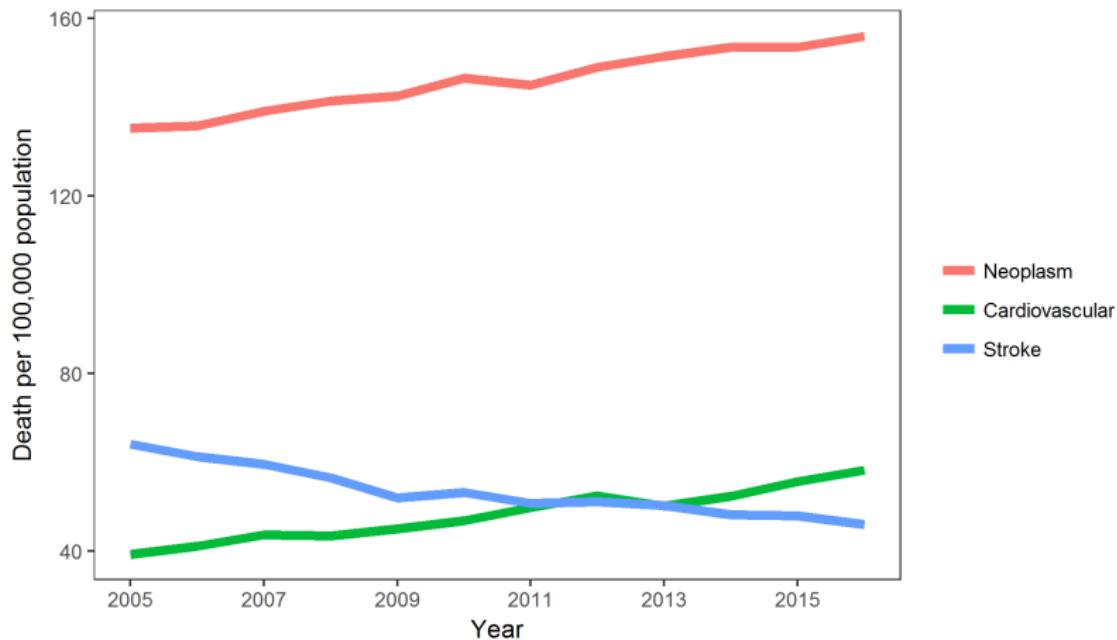


<http://kosis.kr/visual/populationKorea/>



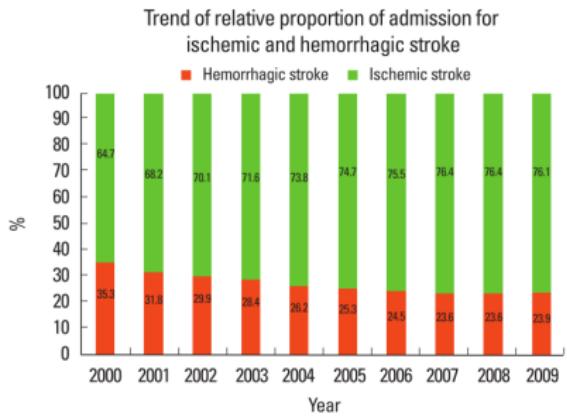
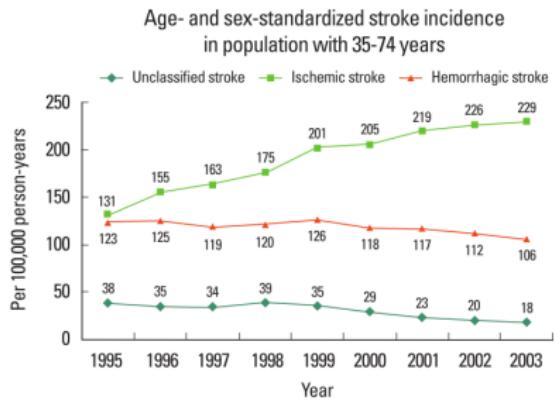
[http://www.who.int/cardiovascular\\_diseases/publications/global\\_brief\\_hypertension/en/](http://www.who.int/cardiovascular_diseases/publications/global_brief_hypertension/en/) accessed on May 07, 2017

# Secular trend of mortality in Korea



[http://www.index.go.kr/potal/main/EachDtlPageDetail.do?idx\\_cd=1012](http://www.index.go.kr/potal/main/EachDtlPageDetail.do?idx_cd=1012) accessed on June 6, 2018

# Incidence of stroke is increasing



# Etiologies of stroke

## Ischemic Stroke

- Atherosclerosis
- Small artery occlusion
- Cardiac disease causing embolism
- Other causes such as moyamoya disease

## Hemorrhagic Stroke

- Hypertensive hemorrhage
- Cerebral amyloid angiopathy
- Arteriovenous malformations
- Subarachnoid hemorrhage

The management should be based on the underlying etiologies.

# MRI findings of small vessel disease

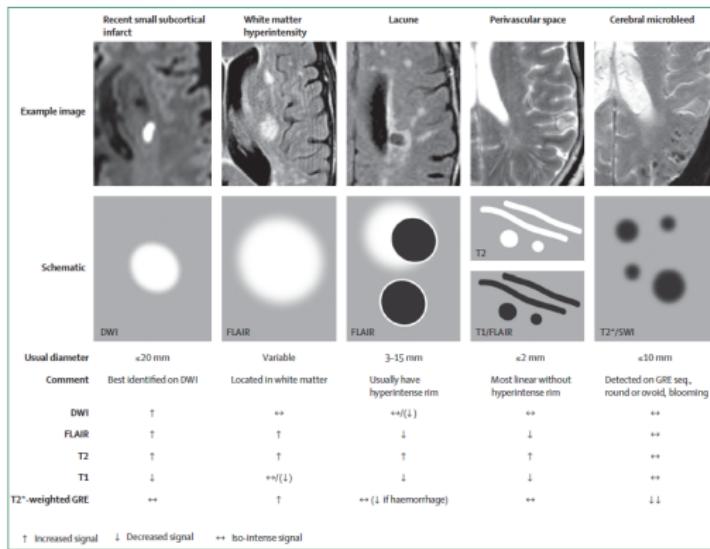
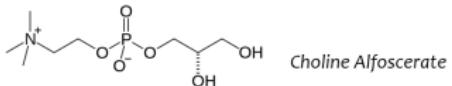


Figure 2: MRI findings for lesions related to small vessel disease

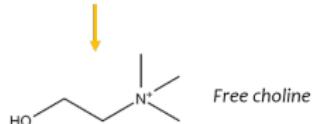
Wardlaw JM et al. Lancet Neurol 2013; 12: 822-38

# Choline alfoscerate

## Pharmacological Properties



Almost fully absorbed in oral administration(88%)



Cross blood-brain barrier

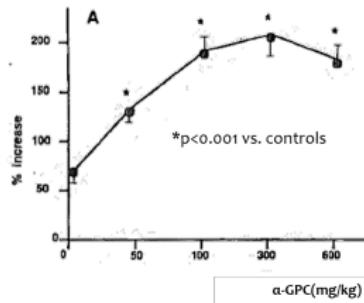
Increase the production of Acetylcholine(ACh)

primarily by facilitation of ACh release without an effect on the choline uptake process and without an inhibition of cholinesterase activity

# Choline alfoscerate

## In Preclinical Study

### Effects on Acetylcholine Release



Five groups of five rats each were treated with either saline or different doses (50- 600mg/kg p.o.) of choline alfoscerate( $\alpha$ -GPC) and killed by decapitation 3 h later. Hippocampal slices were preloaded with [ $^3$ H]choline and 30 mM potassium-stimulated [ $^3$ H]ACh release was determined.

# ASCOMALVA study

## ASCOMALVA trial

**ASCOMALVA (Association between the cholinesterase inhibitor donepezil and the cholinergic precursor choline alfoscerate in Alzheimer's disease)**

**Design** Multicenter, randomized, placebo-controlled, double blind study

**Patients** Alzheimer's disease patients suffering from ischemic brain damage

### **Administration**

- Active treatment : donepezil 10mg/day + choline alfoscerate 1,200mg/day
- Reference treatment : donepezil 10mg/day + placebo
- Duration : 2 years of observation in 113 patients of the 210 planned

### **Assessment**

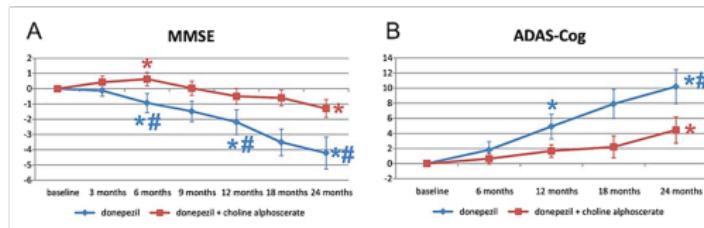
- Mini-Mental State Examination (MMSE)
- Alzheimer's Disease Assessment Scale Cognitive subscale (ADAS -cog)
- Basic Activities of Daily Living (BADL)
- Instrumental Activities of Daily Living (IADL)
- Neuropsychiatric Inventory frequency x severity (NPI-F)
- Neuropsychiatric Inventory distress of the caregiver (NPI-D)

# ASCOMALVA study

## ASCOMALVA trial

### Results

- Cognitive assessment



- In the control group, a progressive time-dependent worsening of MMSE and ADAS-cog scores was observed.
- The effect of association on psychometric tests was statistically significant after 12 and 24 months of treatment.

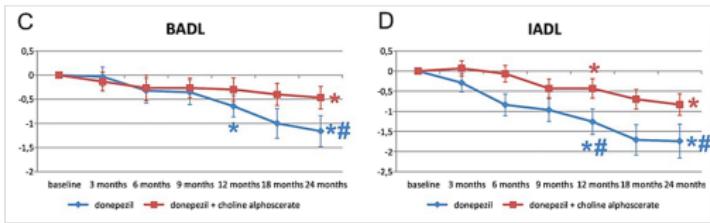
Abbr. ASCOMALVA, Association between the cholinesterase inhibitor donepezil and the cholinergic precursor choline alfoscerate in Alzheimer's disease; MMSE, Mini-Mental State Examination; ADAS-cog, Alzheimer's Disease Assessment Scale Cognitive subscale  
Ref. J Alzheimers Dis, 2014;42 Suppl 3:S281-8

# ASCOMALVA study

## ASCOMALVA trial

### Results

- Evaluation of basic and instrumental activity of daily living



Data are the means  $\pm$  S.E.M. \* $p < 0.05$  versus baseline; # $p < 0.05$  donepezil versus association therapy.

- BADL scores were significantly different between reference group and active treatment group after two years of treatment.
- IADL scores were improved in active treatment patients compared to the reference group at 12 and 24 months of observation.

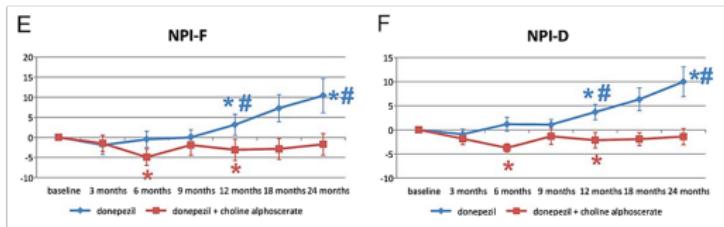
Abbr. ASCOMALVA, Association between the cholinesterase inhibitor donepezil and the cholinergic precursor choline alfoscerate in Alzheimer's disease; BADL, Basic Activities of Daily Living; IADL, Instrumental Activities of Daily Living  
Ref. J Alzheimers Dis, 2014;42 Suppl 3:S281-8

# ASCOMALVA study

## ASCOMALVA trial

### Results

- Analysis severity of neuropsychiatric symptoms and caregiver distress



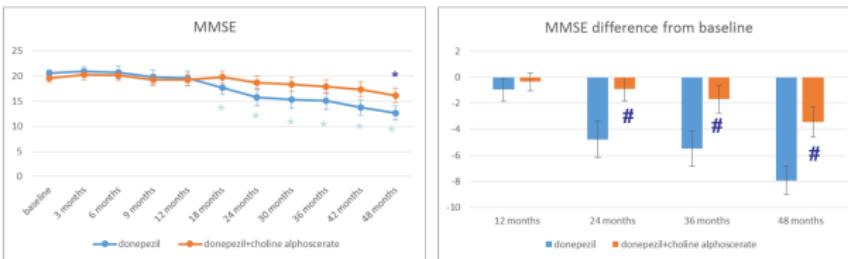
Data are the means  $\pm$  S.E.M. \*p < 0.05 versus baseline; #p < 0.05 donepezil versus association therapy.

- At 12 months of observation and after two years of treatment, revealed a significant decrease in NPI severity and distress of caregiver scores in active treatment group compared with reference group.

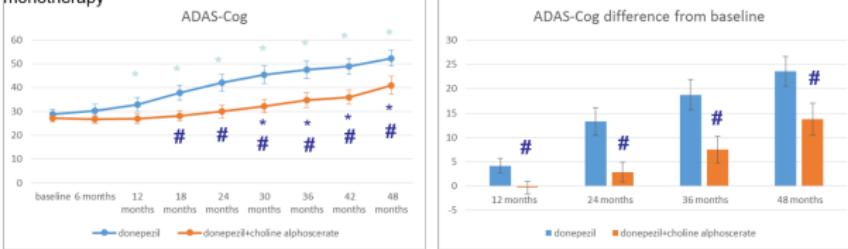
Abbr. ASCOMALVA, Association between the cholinesterase inhibitor donepezil and the cholinergic precursor choline alfoscerate in Alzheimer's disease; NPI-F, Neuropsychiatric Inventory frequency x severity; NPI-D, Neuropsychiatric Inventory distress of the caregiver  
Ref. J Alzheimers Dis, 2014;42 Suppl 3:S281-8

# ASCOMALVA study

## ASCOMALVA trial - 4 YEAR TREATMENT FIRST INTERIM RESULTS



Data are the mean  $\pm$  S.E.M.; \* = significant  $p < 0.05$  vs. baseline; # = significant  $p < 0.05$  vs. donepezil monotherapy



# ASCOMALVA study

## ASCOMALVA trial - 4 YEAR TREATMENT FIRST INTERIM RESULTS

### CONCLUSIONS

After two, 3 and 4 years of therapy, treatment with choline alboscerate and donepezil was effective in slowing the cognitive and functional decline in Alzheimer's disease

Results indicate that the treatment in association between donepezil and choline alboscerate is effective, mainly in people who start an MMSE less compromised, so the earlier the therapy begins, the greater will be the advantage in terms of improving cognitive parameters.

The association therapy has proven to be effective in limiting behavioral disorders both as regards the patient and caregiver stress, both in the first and in the second year of therapy.

These clinical observations support data of preclinical studies summarized here.

# ASCOMALVA study

## ASCOMALVA trial - 4 YEAR TREATMENT FIRST INTERIM RESULTS

### CONCLUSIONS

Morphometric analysis of brain volumes observed has shown that after two years, association therapy slow cortical and hippocampal atrophy; association therapy with choline alfoscerate limits at least in the first period the increase in the volume of CSF spaces. The white matter atrophy is reduced in the associative treatment from the first year of treatment.

Waiting for better therapeutic strategies, the association between ChE-I and choline alfoscerate, could represent a therapeutic option to be considered in the treatment of Alzheimer's disease associated with cerebrovascular damage.

The activity of the compound as an enhancer of cholinergic neurotransmission suggests to assess its effects also in MCI.

# Choline alfoscerate after stroke

## Mishchenko TS et al.

International Neurological Journal. 2016;82(4):25-31.

### Gliatilin in the Treatment of Post-stroke Patients

[Article in Ukrainian; Abstract in English, Russian, Ukrainian]

Mishchenko T.S.<sup>1</sup>, Mishchenko V.M.<sup>1</sup>, Lapshina I.A.<sup>1</sup>

<sup>1</sup>State Institution «Institute of Neurology, Psychiatry and Narcology of the National Academy of Medical Sciences of Ukraine», Kharkiv, Ukraine

**Abstract.** The paper presents the study on the effect of the drug Gliatilin on the severity of neurological deficit, activities of daily living performance and condition of the cognitive functions in patients in the recovery period of ischemic stroke. It was found that the use of Gliatilin at a dose of 1000 mg i.m. 1 time a day (duration of use is 14 days), and then 400 mg 2 times a day (duration of use is 2 months) in patients in the recovery period of ischemic stroke can reduce the severity of subjective and objective neurological symptoms. Patients showed improvement in cognitive impairment, in particular there is a restoration of concentration and memory, improvement in task and exercise performance, in emotional state of patients, which increases the effectiveness of rehabilitation measures.

**Key words:** ischemic stroke; recovery; Gliatilin; cognitive impairment; memory; attention

CKD\_MIPV\_P\_GLI-AIS\_201711

# Choline alfoscerate after stroke

## Mishchenko TS et al. - Aim & Method

### 연구목적

- 허혈성 뇌졸중의 회복단계에 있는 환자에서 신경학적 결함의 중증도, 일상생활 수행능력 및 인지기능에 대한 Gliatilin의 약효 연구

### 연구방법

- 다기관(multi-center), 공개(open-label)
- 연구대상 : 허혈성 뇌졸중의 회복단계에 있는 환자 255명(55~77세)
- 약물투여 :



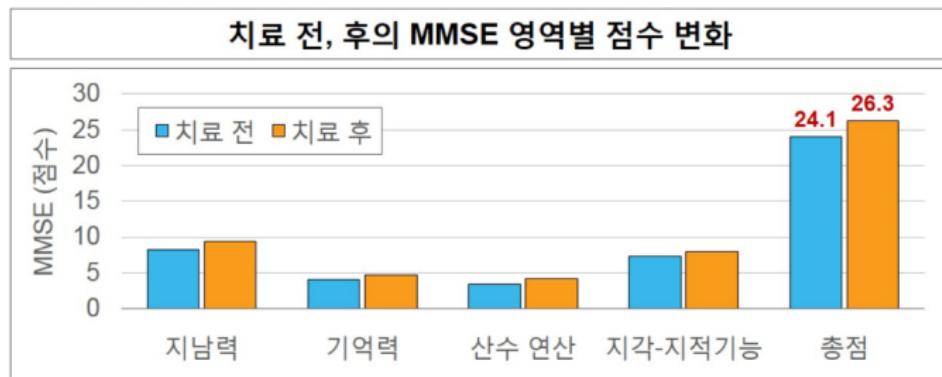
CKD\_MIPV\_P\_GLI-AIS\_201711

# Choline alfoscerate after stroke

## Mishchenko TS et al. - Result

### 결과 - MMSE를 바탕으로 한 인지기능에 미치는 효과의 평가

- 인지기능(기억력, 주의력, 지남력, 계산능력)의 유의한 개선



Abbr. MMSE, Mini-Mental State Examination

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# Choline alfoscerate after stroke

## Mishchenko TS et al. - Result

### 결과 - Rankin Scale 및 Barthel Index를 통한 일상생활 수행능력 평가

- 일상생활 수행에 있어 기능장애 수준과 기능상태 및 자립도의 개선



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# Choline alfoscerate after stroke

그러나 아래와 같이 결론을 내리기는 조금 어려워 보입니다.

## Mishchenko TS et al. - Conclusion

### 결론

- Gliatilin은 허혈성 뇌출증의 회복단계에 있는 환자에서 주관적이고 객관적인 신경학적 증상의 발현을 감소시킬 수 있었음
- Gliatilin의 치료는 손상된 인지기능의 개선을 목적으로 하며, 이러한 효과로 집중력과 기억력 회복되고, 정신적 및 신체적 수행능력이 개선되며, 환자의 정서상태가 개선되어 재활도구로서 효과를 높였음

효능과 안전성을 고려할 때, 허혈성 뇌출증 회복단계에 있는 환자에게 Gliatilin을 14일간 1일 1회 1000mg 근육주사로 투여한 후, 이후 2개월간 1일 2회 400mg 경구투여하는 처방이 권장됨

## Take-Home Message

- Stroke is one of the major causes of mortality and cognitive dysfunction in Korea.
  - Also, it is the leading cause of disability.
- 
- In patients with AD and ischemic brain injury, the addition of the cholinergic precursor **choline alfoscerate** to ChE-I brings about cognitive and behavioral improvements according to ASCOMALVA study.